Appendix E: Evidence Tables

E.1 Review question 1: Which pharmacological blood glucose lowering therapies should be used to control blood glucose levels in people with type 2 diabetes?

E.1.1 Initial therapy

Table 1: Abbatecola et al. (2006)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** Italy **Authors' conclusions:** Exaggerated postprandial glucose excursions are associated with a derangement of both global, executive and attention functioning. A tighter PPG control may prevent cognitive decline in older diabetic individuals **Source of funding:** finded by the Second University of Naples **Comments:** parallel, randomised open-study. No details of randomisation methods and allocation concealment reported. Initially all statistical analysis were made by a physician who was unaware of patient treatment categorisation
Number and characteristics of patients	**Total number of patients:** 156 **Inclusion criteria:** older adults (aged 60-78 years) with type 2 diabetes volunteered for the study who had not previously undergone antidiabetic drug treatment. Enrolled participants were considered poorly controlled with diet/exercise alone. **Exclusion criteria:** All participants were selected after exclusion of severe macro and microangiopathy, CHD, heart failure, medium/severe hypertension, cancer, COPD, upper limb paresis or paralysis and dementia Pre-randomisation phase: there was a 3 week pre trial period when titration adjustments were made and study protocol started at time 0 (after titration period). Graphs indicate that baseline measurements were taken at time 0 (change from baseline is 52 weeks)
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** All treatment naive/ no OADs at screening **Details of washout period:** N/A
Lifestyle advice	all patients were instructed to maintain their degree of physical activity and to consume the same diet (which was individualised at the beginning of the study) throughout the study period
Follow-up	**Total follow-up (wks):** 55 **Length of titration period (wks):** 3 **Length of maintenance period (wks):** 52 **Frequency of monitoring appointments:** at time 0, study protocol began with a full diabetic ambulatory control and was repeated on a monthly basis
Arms	**(1) Repaglinide** N: 77 Treatment duration (wks): - Washout period (d): - Treatment(s): repaglinide (Oral) – flexible-dose (dose-adjusted) Minimum dose (mg/d): 2 Frequency of dosing: twice a day

Details of dosing regimen: doses initially started with 1 mg twice daily. All agents were given up to 30 minutes before daily meals. To achieve target glycaemic control, titration adjustments were made acording to WHO recommendations over an initial 3 week period prior to the beginning of the study protocol

(2) Glibenclamide

N: 79

Treatment duration (wks): -
Washout period (d): -

Treatment(s): Sulfonylurea (Oral) – flexible-dose (dose-adjusted)

Minimum dose (mg/d): 5
Frequency of dosing: twice a day
Details of dosing regimen: Glibenclamide was initally started with 2.5 mg twice daily. All agents were given up to 30 minutes before daily meals. To achieve target glycaemic control, titration adjustments were made acording to WHO recommendations over an initial 3 week period prior to the beginning of the study protocol

Outcomes

General

12 (15.6%) patients in the repaglinide group and 16 (20%) in the glibenclamide group discontinued the study

Outcomes not reported in this evidence table include intima-media thickness and measures of cognitive performance

Analyses were performed according to ITT principle, this included all patients regardless of adherence, noncompliance and withdrawal.

Hypoglycaemic events were not reported in the study

Hypoglycaemic events

Major/severe hypoglycaemic event (major hypoglycaemic events were considered events having severe CNS symptoms consistent with hypoglycaemia in which the subject was unable to treat him/herself, blood glucose level readings were <3 mmol/l or reversal of symptoms by food intake)

Baseline characteristics

		Repaglinide			Glibenclamide			Δ	p
		N	k	mean	N	k	mean		
Demographics: Age (years)	Continuous	77		74.5 (SD 2.5)	79		74.3 (SD 2.3)		
Sex (n male)	Dichotomous	77	38	(49.4%)	79	38	(48.1%)		
Duration of diabetes (yrs)	Continuous	77		1.3 (SD 0.6)	79		1.1 (SD 0.4)		
Blood glucose: HbA1c (%) – 0mo	Continuous	77		7.3 (SD 0.8)	79		7.2 (SD 0.7)		
Fasting plasma glucose (mmol/l) – 0mo	Continuous	77		8.9 (SD 0.4)	79		9 (SD 0.3)		
Body weight: BMI (kg/m2)	Continuous	77		27.1 (SD 0.2)	79		26.7 (SD 0.4)		
Lipids: Total cholesterol (mmol/l)	Continuous	77		5 (SD 0.4)	79		5.1 (SD 0.3)		
HDL cholesterol (mmol/l)	Continuous	77		1.25 (SD 0.07)	79		1.26 (SD 0.08)		
Triglycerides (mmol/l)	Continuous	77		1.98 (SD 0.16)	79		1.95 (SD 0.18)		
LDL cholesterol (mmol/l)	Continuous	77		3.16 (SD 0.5)	79		3.14 (SD 0.41)		

Results

		Repaglinide			Glibenclamide			Δ	p
		N	k	mean	N	k	mean		
Blood glucose: HbA1c (%) – 3moa	Continuous	77		6.825 (SD 0.877)	79		6.94 (SD 1.33)		
HbA1c (%) – 6moa	Continuous	77		6.755 (SD 0.877)	79		6.9 (SD 1.78)		
HbA1c (%) – 12moa	Continuous	77		6.55 (SD 0.877)	79		6.7 (SD 1.78)		NS

	Fasting plasma glucose (mmol/l) – 3moa	Continuous	77		8.1 (SD 1.75)	79		7.85 (SD 1.33)		
	Fasting plasma glucose (mmol/l) – 6moa	Continuous	77		7.85 (SD 1.75)	79		7.45 (SD 1.33)		
	Fasting plasma glucose (mmol/l) – 12moa	Continuous	77		7.4 (SD 1.75)	79		6.95 (SD 1.78)		NS
	Hypoglycaemic events: Major/severe hypoglycaemic event – 12mo	Dichotomous	77			79				NR
	Dropouts: Total dropouts – 12mo	Dichotomous	77	12	(15.6%)	79	16	(20.3%)		

[a] Data extracted from graph; SD calculated from assumed SE

For the primary efficacy endpoints (Hba1c and cognition composite score) the change from baseline to the last visit of the maintenance period was evaluated by ANOVA. In these analyses the last last observation carried over method was used. The effects of the antidiabetic agents during the course of 4 follow-up visits was analysed by repeated measures ANOVA. Data were analysed for the changeover time during the course of the various visits (within group comparisons)a nd for differences between the 2 groups as regards these time related changes, that is for the interaction between drug and time. ANCOVA allowed adjustments for metabolic parameters.

Table 2: Alba et al. (2013)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** - **Authors' conclusions:** - **Source of funding:** - **Comments:** -
Number and characteristics of patients	**Total number of patients:** 211 **Inclusion criteria:** Adults (30-65 years) diagnosed with T2DM in the previous 5 years Drug naïve with HbA1c >= 7% and <=10% or on antihyperglycaemic monotherapy or lose dose combination therapy with HbA1c >= 6.5% and <=9% **Exclusion criteria:** - Pre-randomisation phase: 1 week screening period 8 week washout period: 6 week diet/exercise and washout if discontinuing antihyperglycaemic medication + 2 weeks single blind run in period
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** some on oral hypoglycaemic drugs and/or insulin **Details of washout period:** 8 week washout period: 6 week diet/exercise and washout if discontinuing antihyperglycaemic medication + 2 weeks single blind run in period
Lifestyle advice	6 week wash out period consisting of diet/exercise (details not provided)
Follow-up	**Total follow-up (wks):** 21 **Length of titration period (wks):** - **Length of maintenance period (wks):** 12 **Frequency of monitoring appointments:** Outcomes assessed at baseline and 12 weeks post-treatment
Arms	**(1) Sitagliptin 100mg** N: 52 Treatment duration (wks): 12 Washout period (d): 56 Comments: 1 week screening period, followed by 6 week diet/exercise period (and wash out if discontinuing previous AHAs), folllwed by 2 weeks single blind placebo run in, then a 12 week double blind treatment period

Treatment(s): Sitagliptin (Oral) – fixed-dose
Set dose (mg/d):100
Frequency of dosing: once a day
Details of dosing regimen: Once daily before morning meal

(2) Pioglitazone 30mg

N: 54

Treatment duration (wks): 12
Washout period (d): 56
Comments: 1 week screening period, followed by 6 week diet/exercise period (and wash out if discontinuing previous AHAs), folllwed by 2 weeks single blind placebo run in, then a 12 week double blind treatment period

Treatment(s): Pioglitazone (Oral) – fixed-dose
Set dose (mg/d):30
Frequency of dosing: once a day
Details of dosing regimen: Once daily before morning meal

(3) Placebo

N: 53

Treatment duration (wks): 12
Washout period (d): 56
Comments: 1 week screening period, followed by 6 week diet/exercise period (and wash out if discontinuing previous AHAs), folllwed by 2 weeks single blind placebo run in, then a 12 week double blind treatment period

Treatment(s): Placebo (Oral)
Frequency of dosing: once a day
Details of dosing regimen: Once daily before morning meal

Outcomes

General

Data from 4th arm in trial receiving sitagliptin plus pioglitazone were not extracted as it does not provide any relevant comparisons

Baseline characteristics

		Sitagliptin 100mg			Pioglitazone 30mg				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years) – 0wk	Continuous	52		54.6 (SD 7.6)	54		53.4 (SD 7.8)		
Sex (n male) – 0wk	Dichotomous	52	28	(53.8%)	54	23	(42.6%)		
Duration of diabetes (yrs) – 0wk	Continuous	52		2.4 (SD 1.6)	54		2.4 (SD 1.4)		
Blood glucose: HbA1c (%) – 12wk	Continuous	52		7.7 (SD 0.8)	54		7.9 (SD 0.9)		
Fasting plasma glucose (mmol/l) – 12wk	Continuous	52		9.6 (SD 2.1)	54		9.6 (SD 2.4)		
Body weight: BMI (kg/m2) – 0wk	Continuous	52		30.8 (SD 4.6)	54		31.4 (SD 5.3)		
Weight (kg) – 0wk	Continuous	52		85.7 (SD 14.1)	54		86.6 (SD 17.5)		
Previous blood glucose lowering drugs: Diet alone (i.e. drug naïve) – 0wk	Dichotomous	52	17	(32.7%)	54	18	(33.3%)		

		Sitagliptin 100mg			Placebo				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years) – 0wk	Continuous	52		54.6 (SD 7.6)	53		53.3 (SD 7.7)		
Sex (n male) – 0wk	Dichotomous	52	28	(53.8%)	53	32	(60.4%)		
Duration of diabetes (yrs) – 0wk	Continuous	52		2.4 (SD 1.6)	53		2.3 (SD 1.6)		
Blood glucose: HbA1c (%) – 12wk	Continuous	52		7.7 (SD 0.8)	53		8 (SD 1.1)		
Fasting plasma glucose (mmol/l) – 12wk	Continuous	52		9.6 (SD 2.1)	53		10 (SD 2.7)		

Body weight: BMI (kg/m2) – 0wk	Continuous	52		30.8 (SD 4.6)	53		30.1 (SD 5.2)		
Weight (kg) – 0wk	Continuous	52		85.7 (SD 14.1)	53		83.6 (SD 16.7)		
Previous blood glucose lowering drugs: Diet alone (i.e. drug naïve) – 0wk	Dichotomous	52	17	(32.7%)	53	17	(32.1%)		

		Pioglitazone 30mg			Placebo				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years) – 0wk	Continuous	54		53.4 (SD 7.8)	53		53.3 (SD 7.7)		
Sex (n male) – 0wk	Dichotomous	54	23	(42.6%)	53	32	(60.4%)		
Duration of diabetes (yrs) – 0wk	Continuous	54		2.4 (SD 1.4)	53		2.3 (SD 1.6)		
Blood glucose: HbA1c (%) – 12wk	Continuous	54		7.9 (SD 0.9)	53		8 (SD 1.1)		
Fasting plasma glucose (mmol/l) – 12wk	Continuous	54		9.6 (SD 2.4)	53		10 (SD 2.7)		
Body weight: BMI (kg/m2) – 0wk	Continuous	54		31.4 (SD 5.3)	53		30.1 (SD 5.2)		
Weight (kg) – 0wk	Continuous	54		86.6 (SD 17.5)	53		83.6 (SD 16.7)		
Previous blood glucose lowering drugs: Diet alone (i.e. drug naïve) – 0wk	Dichotomous	54	18	(33.3%)	53	17	(32.1%)		

Results

		Sitagliptin 100mg			Pioglitazone 30mg				
		N	k	mean	N	k	mean	Δ	p
Hypoglycaemic events: All hypoglycaemic events (no patients) – 12wk	Dichotomous	52	0	(0.0%)	54	2	(3.7%)		
Adverse events: GI: nausea – 12wk	Dichotomous	52	1	(1.9%)	54	0	(0.0%)		
Dropouts: Total dropouts – 12wk	Dichotomous	52	6	(11.5%)	54	2	(3.7%)		
Dropout due to AEs – 12wk	Dichotomous	52	3	(5.8%)	54	0	(0.0%)		

		Sitagliptin 100mg			Placebo				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 12wk	Continuous	52			53			MD=-0.790 (CI: -1.080, -0.500)	a
Fasting plasma glucose (mmol/l) – 12wk	Continuous	52			53			MD=-1.500 (CI: -2.200, -0.800)	a
Hypoglycaemic events: All hypoglycaemic events (no patients) – 12wk	Dichotomous	52	0	(0.0%)	53	0	(0.0%)		
Adverse events: GI: nausea – 12wk	Dichotomous	52	1	(1.9%)	53	0	(0.0%)		
Dropouts: Total dropouts – 12wk	Dichotomous	52	6	(11.5%)	53	5	(9.4%)		

Dropout due to AEs – 12wk	Dichotomous	52	3	(5.8%)	53	2	(3.8%)		

[a] SD calculated from 95% CI; LS means

		Pioglitazone 30mg			Placebo				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 12wk	Continuous	54			53			MD=-0.560 (CI: -0.850, -0.270)	a
Fasting plasma glucose (mmol/l) – 12wk	Continuous	54			53			MD=-1.900 (CI: -2.600, -1.200)	a
Hypoglycaemic events: All hypoglycaemic events (no patients) – 12wk	Dichotomous	54	2	(3.7%)	53	0	(0.0%)		
Adverse events: GI: nausea – 12wk	Dichotomous	54	0	(0.0%)	53	0	(0.0%)		
Dropouts: Total dropouts – 12wk	Dichotomous	54	2	(3.7%)	53	5	(9.4%)		
Dropout due to AEs – 12wk	Dichotomous	54	0	(0.0%)	53	2	(3.8%)		

[a] SD calculated from 95% CI; LS means

Table 3: Arjona et al. (2013)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** - **Authors' conclusions:** - **Source of funding:** - **Comments:** -
Number and characteristics of patients	**Total number of patients:** 423 **Inclusion criteria:** Adults (at least 30 years old) with T2DM and moderate to severe chronic renal insufficiency (eGFR < 50ml/min/1.73m2 using Modification of Diet in Renal Disease equation) not requiring dialysis for study duration and HbA1c between 7 and 9% inclusive **Exclusion criteria:** - Pre-randomisation phase: 1 week screening period, up to 14 week wash out period comprising diet/exercise and OADs wash out period and 2 week single blind placebo run in period
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** some on oral hypoglycaemic drugs and/or insulin **Details of washout period:** Up to 14 week wash out period comprising diet/exercise and OADs wash out period and 2 week single blind placebo run in period Patients not on AHAs for at least 12 weeks at screening with HbA1c between 7 and 9%: 2 week single blind placebo run in period Patients not on AHAs for at least 12 weeks at screening with HbA1c >9%: 6 week diet/exercise wash out period Patients on non-thiazolidinediones AHAs at screening with HbA1c between 7 and 9%: 8 week diet/exercise wash out period Patients on thiazolidinediones AHAs at screening with HbA1c between 7 and 9%: 10 week diet/exercise wash out period Patients on non-thiazolidinediones AHAs at screening with HbA1c 6.5 to <7%: 8-12 week diet/exercise wash out period Patients on thiazolidinediones AHAs at screening with HbA1c 6.5 to <7%: 10-14 week diet/exercise wash out

	period All patients received 2 week single blind placebo run in period
Lifestyle advice	All patients received diet and counselling advice throughout the study (details not reported except that recommendations were based on ADA and appropriate for patients with renal insufficiency)
Follow-up	**Total follow-up (wks):** 54 **Length of titration period (wks):** - **Length of maintenance period (wks):** 54 **Frequency of monitoring appointments:** Assessments were undertaken every 6 weeks
Arms	**(1) Sitagliptin 25mg/50mg + placebo** N: 211 Treatment duration (wks): 54 Washout period (d): 98 Comments: Up to 14 week wash out period comprising diet/exercise and OADs wash out period and 2 week single blind placebo run in period Patients not on AHAs for at least 12 weeks at screening with HbA1c between 7 and 9%: 2 week single blind placebo run in period Patients not on AHAs for at least 12 weeks at screening with HbA1c >9%: 6 week diet/exercise wash out period Patients on non-thiazolidinediones AHAs at screening with HbA1c between 7 and 9%: 8 week diet/exercise wash out period Patients on thiazolidinediones AHAs at screening with HbA1c between 7 and 9%: 10 week diet/exercise wash out period Patients on non-thiazolidinediones AHAs at screening with HbA1c 6.5 to <7%: 8-12 week diet/exercise wash out period Patients on thiazolidinediones AHAs at screening with HbA1c 6.5 to <7%: 10-14 week diet/exercise wash out period All patients received 2 week single blind placebo run in period Treatment(s): Sitagliptin (Oral) – fixed-dose Set dose (mg/d):25 Maximum dose (mg/d): 50 Frequency of dosing: once a day Details of dosing regimen: Patients with moderate renal insufficiency received 50mg per day (2 tablets per day) Patients with severe renal insufficiency received 25mg per day (1 tablet per day) Dose was changed from 50mg to 25mg per day for patients whose renal status changed from moderate to severe during the study. **(2) Glipizide flexi dose** N: 212 Treatment duration (wks): 54 Washout period (d): 98 Comments: Up to 14 week wash out period comprising diet/exercise and OADs wash out period and 2 week single blind placebo run in period Patients not on AHAs for at least 12 weeks at screening with HbA1c between 7 and 9%: 2 week single blind placebo run in period Patients not on AHAs for at least 12 weeks at screening with HbA1c >9%: 6 week diet/exercise wash out period Patients on non-thiazolidinediones AHAs at screening with HbA1c between 7 and 9%: 8 week diet/exercise wash out period Patients on thiazolidinediones AHAs at screening with HbA1c between 7 and 9%: 10 week diet/exercise wash out period Patients on non-thiazolidinediones AHAs at screening with HbA1c 6.5 to <7%: 8-12 week diet/exercise wash out period Patients on thiazolidinediones AHAs at screening with HbA1c 6.5 to <7%: 10-14 week diet/exercise wash out period All patients received 2 week single blind placebo run in period Treatment(s): Sulfonylurea (Oral) – flexible-dose (dose-adjusted) Minimum dose (mg/d): 2.5 Maximum dose (mg/d): 10 Frequency of dosing: once a day Details of dosing regimen: Administered at a starting dose of 2.5mg day prior to the morning meal and electively titrated to a maximum of 20mg day as considered appropriate by the investgator based on the patient's glycaemic control
Outcomes	**General** All efficacy and safety analyses included data up to the point of initiation of rescue medication.

Baseline characteristics

		Sitagliptin 25mg/50mg + placebo			Glipizide flexi dose				
		N	k	mean	N	k	mean	Δ	p
PP									
Demographics:									
Age (years)	Continuous	135		64.8 (SD 10.6)	142		64.3 (SD 9.2)		
Sex (n male)	Dichotomous	135	80	(59.3%)	142	78	(54.9%)		
Duration of diabetes (yrs)	Continuous	135		10.7 (SD 7.5)	142		10.1 (SD 7.8)		
Blood glucose:									
HbA1c (%) – 54wka	Mean change	135		-0.8 (SD 0.593)	142		-0.6 (SD 1.22)		
HbA1c (%) – 54wk	Continuous	135		7.8 (SD 0.7)	142		7.8 (SD 0.7)		
Fasting plasma glucose (mg/dl) – 54wka	Mean change	136		-17.5 (SD 41.7)	142		-24.6 (SD 42)		
Fasting plasma glucose (mg/dl) – 54wk	Continuous	135		148.1 (SD 40.1)	142		143.9 (SD 35.7)		
Body weight:									
BMI (kg/m2)	Continuous	135		26.5 (SD 4.8)	142		27 (SD 4.8)		
Weight (kg) – 0wkb	Continuous	135		74.7936 (SD 13.5)	142		76.2048 (SD 13.5)		
Weight (kg) – 12wkc	Mean change	135		-0.4 (SD 2.32)	142		0.4 (SD 1.79)		
Weight (kg) – 12wk	Continuous	135		68 (SD 14.8)	142		70.2 (SD 15.9)		
Previous blood glucose lowering drugs:									
Diet alone (i.e. drug naïve)	Dichotomous	135	41	(30.4%)	142	49	(34.5%)		

[a] Least squares mean reported, SD calculated from reported 95% CI
[b] estimated from BMI assuming mean height of 1.68m
[c] Data extracted from graphs; least squares mean, SD calculated from estimated SE

Results

		Sitagliptin 25mg/50mg + placebo			Glipizide flexi dose				
		N	k	mean	N	k	mean	Δ	p
Hypoglycaemic events:									
Symptomatic hypoglycaemia – 54wk	Dichotomous	210	13	(6.2%)	212	36	(17.0%)		
Dropouts:									
Total dropouts – 54wk	Dichotomous	211	47	(22.3%)	212	42	(19.8%)		
Dropout due to AEs – 54wka	Dichotomous	211	16	(7.6%)	212	18	(8.5%)		
PP									
Blood glucose:									
HbA1c (%) – 12wkb	Mean change	135		-0.56 (SD 0.813)	142		-0.56 (SD 0.834)		
HbA1c (%) – 24wkb	Mean change	135		-0.67 (SD 0.813)	142		-0.55 (SD 0.834)		
HbA1c (%) – 54wkc	Mean change	135		-0.8 (SD 0.593)	142		-0.6 (SD 1.22)		
HbA1c (%) – 54wk	Continuous	135		7.8 (SD 0.7)	142		7.8 (SD 0.7)		
Fasting plasma glucose (mmol/l) – 12wkb	Mean change	135		-1.9 (SD 1.74)	142		-1.39 (SD 1.79)		
Fasting plasma glucose (mmol/l) – 24wkb	Mean change	135		-0.92 (SD 2.09)	142		-1.17 (SD 2.14)		
Fasting plasma glucose (mg/dl) – 54wkc	Mean change	136		-17.5 (SD 41.7)	142		-24.6 (SD 42)		
Fasting plasma glucose (mg/dl) – 54wk	Continuous	135		148.1 (SD 40.1)	142		143.9 (SD 35.7)		
Body weight:									
Weight (kg) – 12wkb	Mean change	135		-0.4 (SD 2.32)	142		0.4 (SD 1.79)		

Weight (kg) – 12wk	Continuous	135		68 (SD 14.8)	142		70.2 (SD 15.9)		
Weight (kg) – 24wkb	Mean change	135		-0.65 (SD 2.9)	142		0.9 (SD 2.38)		
Weight (kg) – 54wkb	Mean change	135		-0.6 (SD 3.49)	142		1.15 (SD 3.57)		

[a] Data derived from flow diagram in supplementary information. Table provided in full text contains more detailed information on withdrawals due to AE, SAE, AR and SAR but unclear whether these were mutually exclusive
[b] Data extracted from graphs; least squares mean, SD calculated from estimated SE
[c] Least squares mean reported, SD calculated from reported 95% CI

Table 4: Aronoff et al. (2000)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** USA **Authors' conclusions:** Pioglitazone monotherapy significantly improves Hba1c and FBG while producing beneficial effects on serum lipids in patients with type 2 diabetes with no evidence of drug induced hepatoxicity **Source of funding:** Takeda **Comments:** Double-blind
Number and characteristics of patients	**Total number of patients:** 408 **Inclusion criteria:** patients with type 2 diabetes, with Hba1c >=7% FBG>=140 mg/dl and fasting c-peptide >1 ng/ml **Exclusion criteria:** patients with chronic insulin use, history of ketoacidosisunstable or rapidly progressive diabetic retinopathy, nephropathy or neuropathy, impaired liver or renal function, patients with myocardial infarction, TIA or cerebrovascular event within 6 months were excluded Pre-randomisation phase: There was a 6 to 8 week single blind washout phase
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** some on oral hypoglycaemic drugs and/or insulin **Details of washout period:** patients who were receiving antidiabetic medicine were required to discontinue at the start of the washout period (8 weeks before starting treatment)
Lifestyle advice	There were no required modifications of current dietary regimens during the study
Follow-up	**Total follow-up (wks):** 26 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 26 **Frequency of monitoring appointments:** Patients were seen every 2 weeks for the first 6 weeks and every 4 weeks for the remaining 20 weeks
Arms	**(1) Placebo** N: 79 Treatment duration (wks): 26 Washout period (d): 56 Comments: patients who were receiving antidiabetic medicine were required to discontinue at the start of the washout period (8 weeks before starting treatment) Treatment(s): Placebo (Oral) **(2) Pioglitazone (15 mg)** N: 81 Treatment duration (wks): 26 Washout period (d): 56 Comments: patients who were receiving antidiabetic medicine were required to discontinue at the start of the washout period (8 weeks before starting treatment)

Treatment(s): Pioglitazone (Oral) – fixed-dose
Set dose (mg/d):15
Details of dosing regimen: 15mg/d

(3) Pioglitazone (30 mg)

N: 87

Treatment duration (wks): 26
Washout period (d): 56
Comments: patients who were receiving antidiabetic medicine were required to discontinue at the start of the washout period (8 weeks before starting treatment)

Treatment(s): Pioglitazone (Oral) – fixed-dose
Set dose (mg/d):30
Details of dosing regimen: 30 mg/day

(4) Pioglitazone (45 mg)

N: 80

Treatment duration (wks): 26
Washout period (d): 56
Comments: patients who were receiving antidiabetic medicine were required to discontinue at the start of the washout period (8 weeks before starting treatment)

Treatment(s): Pioglitazone (Oral) – fixed-dose
Set dose (mg/d):45
Details of dosing regimen: 45 mg/day

(5) Pioglitazone (7.5mg)

N: 81

Treatment duration (wks): 26
Washout period (d): 56
Comments: patients who were receiving antidiabetic medicine were required to discontinue at the start of the washout period (8 weeks before starting treatment)

Treatment(s): Pioglitazone (Oral) – fixed-dose
Set dose (mg/d):7.5
Details of dosing regimen: 7.5mg/day

(6) Any pioglitazone

N: 329

Treatment duration (wks): 26
Washout period (d): 56
Comments: patients who were receiving antidiabetic medicine were required to discontinue at the start of the washout period (8 weeks before starting treatment)

Treatment(s): Pioglitazone (Oral) – fixed-dose
Details of dosing regimen: 7.5, 15, 30 or 45mg/d

Outcomes

General

Total dropouts not reported

Baseline characteristics

		All study participants		
		N	**k**	**mean**
Demographics:				
Age (years)	Continuous	329		54
Sex (n male)	Dichotomous	329	191a	(58.1%)
Duration of diabetes (yrs)	Continuous	329		b
Body weight:				
BMI (kg/m2)	Continuous	329		b
Weight (kg) – 0wk	Continuous	329		c
Weight (kg) – 0wk	Continuous	329		c

[a] approximated to nearest integer (percentages only presented in text)
[b] NR
[c] NR; estimated from BMI assuming mean height of 1.68m

		Placebo			Pioglitazone (15 mg)				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Blood glucose:									
HbA1c (%) – 0wk	Continuous	79		10.4 (SD 2)	81		10.2 (SD 1.8)		

Fasting plasma glucose (mmol/l) – 0wk	Continuous	79		14.87955 (SD 3.91)	81		14.8185 (SD 3.97)		
Body weight: Weight (kg) – 0wk	Continuous	79		90.4 (SD 13.1)	81		91.2 (SD 16.2)		
Lipids: Total cholesterol (mmol/l) – 0wk	Continuous	79		5.808156 (SD 1.25)	81		5.6892 (SD 1.27)		
HDL cholesterol (mmol/l) – 0wk	Continuous	79		1.078362 (SD 0.285)	81		1.044744 (SD 0.289)		
Triglycerides (mmol/l) – 0wk	Continuous	79		2.967012 (SD 3.45)	81		3.204102 (SD 3.5)		
LDL cholesterol (mmol/l) – 0wk	Continuous	79		3.589368 (SD 1.04)	81		3.410934 (SD 1.08)		

		Placebo			Pioglitazone (30 mg)				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 0wk	Continuous	79		10.4 (SD 2)	87		10.2 (SD 1.9)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	79		14.87955 (SD 3.91)	87		14.9517 (SD 4)		
Body weight: Weight (kg) – 0wk	Continuous	79		90.4 (SD 13.1)	87		90.3 (SD 14.7)		
Lipids: Total cholesterol (mmol/l) – 0wk	Continuous	79		5.808156 (SD 1.25)	87		5.759022 (SD 1.28)		
HDL cholesterol (mmol/l) – 0wk	Continuous	79		1.078362 (SD 0.285)	87		1.055088 (SD 0.292)		
Triglycerides (mmol/l) – 0wk	Continuous	79		2.967012 (SD 3.45)	87		2.947819 (SD 3.52)		
LDL cholesterol (mmol/l) – 0wk	Continuous	79		3.589368 (SD 1.04)	87		3.506616 (SD 1.04)		

		Placebo			Pioglitazone (45 mg)				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 0wk	Continuous	79		10.4 (SD 2)	80		10.3 (SD 1.9)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	79		14.87955 (SD 3.91)	80		15.29025 (SD 4)		
Body weight: Weight (kg) – 0wk	Continuous	79		90.4 (SD 13.1)	80		90.8 (SD 14)		
Lipids: Total cholesterol (mmol/l) – 0wk	Continuous	79		5.808156 (SD 1.25)	80		5.526282 (SD 1.28)		
HDL cholesterol (mmol/l) – 0wk	Continuous	79		1.078362 (SD 0.285)	80		1.052502 (SD 0.289)		
Triglycerides (mmol/l) – 0wk	Continuous	79		2.967012 (SD 3.45)	80		2.932013 (SD 3.52)		
LDL cholesterol (mmol/l) – 0wk	Continuous	79		3.589368 (SD 1.04)	80		3.279048 (SD 1.06)		

	Pioglitazone (15 mg)			Pioglitazone (30 mg)				
	N	k	mean	N	k	mean	Δ	p

Blood glucose: HbA1c (%) – 0wk	Continuous	81		10.2 (SD 1.8)	87		10.2 (SD 1.9)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	81		14.8185 (SD 3.97)	87		14.9517 (SD 4)		
Body weight: Weight (kg) – 0wk	Continuous	81		91.2 (SD 16.2)	87		90.3 (SD 14.7)		
Lipids: Total cholesterol (mmol/l) – 0wk	Continuous	81		5.6892 (SD 1.27)	87		5.759022 (SD 1.28)		
HDL cholesterol (mmol/l) – 0wk	Continuous	81		1.044744 (SD 0.289)	87		1.055088 (SD 0.292)		
Triglycerides (mmol/l) – 0wk	Continuous	81		3.204102 (SD 3.5)	87		2.947819 (SD 3.52)		
LDL cholesterol (mmol/l) – 0wk	Continuous	81		3.410934 (SD 1.08)	87		3.506616 (SD 1.04)		

		Pioglitazone (15 mg)			Pioglitazone (45 mg)				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 0wk	Continuous	81		10.2 (SD 1.8)	80		10.3 (SD 1.9)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	81		14.8185 (SD 3.97)	80		15.29025 (SD 4)		
Body weight: Weight (kg) – 0wk	Continuous	81		91.2 (SD 16.2)	80		90.8 (SD 14)		
Lipids: Total cholesterol (mmol/l) – 0wk	Continuous	81		5.6892 (SD 1.27)	80		5.526282 (SD 1.28)		
HDL cholesterol (mmol/l) – 0wk	Continuous	81		1.044744 (SD 0.289)	80		1.052502 (SD 0.289)		
Triglycerides (mmol/l) – 0wk	Continuous	81		3.204102 (SD 3.5)	80		2.932013 (SD 3.52)		
LDL cholesterol (mmol/l) – 0wk	Continuous	81		3.410934 (SD 1.08)	80		3.279048 (SD 1.06)		

		Pioglitazone (15 mg)			Pioglitazone (7.5mg)				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 0wk	Continuous	81		10.2 (SD 1.8)	81		10 (SD 1.8)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	81		14.8185 (SD 3.97)	81		14.6076 (SD 3.95)		
Body weight: Weight (kg) – 0wk	Continuous	81		91.2 (SD 16.2)	81		93.5 (SD 14.3)		
Lipids: Total cholesterol (mmol/l) – 0wk	Continuous	81		5.6892 (SD 1.27)	81		5.54697 (SD 1.26)		
HDL cholesterol (mmol/l) – 0wk	Continuous	81		1.044744 (SD 0.289)	81		1.04733 (SD 0.289)		
Triglycerides (mmol/l) – 0wk	Continuous	81		3.204102 (SD 3.5)	81		3.60151 (SD 3.48)		
LDL cholesterol (mmol/l) – 0wk	Continuous	81		3.410934 (SD 1.08)	81		3.178194 (SD 1.05)		

	Pioglitazone (30 mg)	Pioglitazone (45 mg)	Δ	p

		N	k	mean	N	k	mean		
Blood glucose: HbA1c (%) – 0wk	Continuous	87		10.2 (SD 1.9)	80		10.3 (SD 1.9)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	87		14.9517 (SD 4)	80		15.29025 (SD 4)		
Body weight: Weight (kg) – 0wk	Continuous	87		90.3 (SD 14.7)	80		90.8 (SD 14)		
Lipids: Total cholesterol (mmol/l) – 0wk	Continuous	87		5.759022 (SD 1.28)	80		5.526282 (SD 1.28)		
HDL cholesterol (mmol/l) – 0wk	Continuous	87		1.055088 (SD 0.292)	80		1.052502 (SD 0.289)		
Triglycerides (mmol/l) – 0wk	Continuous	87		2.947819 (SD 3.52)	80		2.932013 (SD 3.52)		
LDL cholesterol (mmol/l) – 0wk	Continuous	87		3.506616 (SD 1.04)	80		3.279048 (SD 1.06)		

		Pioglitazone (45 mg)			Pioglitazone (7.5mg)				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 0wk	Continuous	80		10.3 (SD 1.9)	81		10 (SD 1.8)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	80		15.29025 (SD 4)	81		14.6076 (SD 3.95)		
Body weight: Weight (kg) – 0wk	Continuous	80		90.8 (SD 14)	81		93.5 (SD 14.3)		
Lipids: Total cholesterol (mmol/l) – 0wk	Continuous	80		5.526282 (SD 1.28)	81		5.54697 (SD 1.26)		
HDL cholesterol (mmol/l) – 0wk	Continuous	80		1.052502 (SD 0.289)	81		1.04733 (SD 0.289)		
Triglycerides (mmol/l) – 0wk	Continuous	80		2.932013 (SD 3.52)	81		3.60151 (SD 3.48)		
LDL cholesterol (mmol/l) – 0wk	Continuous	80		3.279048 (SD 1.06)	81		3.178194 (SD 1.05)		

Results

		Any pioglitazone		
		N	k	mean
Hypoglycaemic events: All hypoglycaemic events (no patients) – 26wk	Dichotomous	329	4	(1.2%)
Adverse events: Any adverse event(s) – 26wk	Dichotomous	329	250	(76.0%)
cardiovascular AE – 26wk	Dichotomous	329	12	(3.6%)
Edema peripheral – 26wk	Dichotomous	329	12a	(3.6%)
Headache – 26wk	Dichotomous	329	41a	(12.5%)
Infection (upper airway or other common) – 26wk	Dichotomous	329	50	(15.2%)

[a] approximated to nearest integer (percentages only presented in text)

		Placebo			Pioglitazone (15 mg)				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 14wka	Mean change	79		0.7 (SD 0.889)	81		-0.12 (SD 0.99)		
HbA1c (%) – 26wk	Mean change	79		0.7 (SD 1.51)	81		-0.3 (SD 1.51)		

HbA1c (%) – 26wk	Continuous	79		11.1 (SD 2.31)	81		9.9 (SD 2.43)		
Fasting plasma glucose (mmol/l) – 14wka	Mean change	79		0.6105 (SD 2.47)	81		-1.8315 (SD 2.5)		
Fasting plasma glucose (mmol/l) – 26wk	Mean change	79		0.5217 (SD 3.4)	81		-1.6428 (SD 3.38)		
Body weight: Weight (kg) – 26wkb	Mean change	79		-1.3 (SD 3.2)	79		1.3 (SD 2.97)		
Dropouts: Dropout due to AEs – 26wkc	Dichotomous	79	2	(2.5%)	81	3	(3.7%)		
Lipids: Total cholesterol (mmol/l) – 26wk	Continuous	79		5.984004 (SD 1.2)	81		5.852118 (SD 1.16)		
Total cholesterol (mmol/l) – 26wk	Mean change	79		0.113784 (SD 0.356)	81		0.118956 (SD 0.363)		
HDL cholesterol (mmol/l) – 26wk	Continuous	79		1.145598 (SD 0.287)	81		1.174044 (SD 0.277)		
HDL cholesterol (mmol/l) – 26wk	Mean change	79		0.209466 (SD 0.467)	81		0.364626 (SD 0.477)		
Triglycerides (mmol/l) – 26wk	Mean change	79		0.054192 (SD 0.472)	81		-0.10161 (SD 0.482)		
Triglycerides (mmol/l) – 26wk	Continuous	79		2.852983 (SD 2.08)	81		2.55154 (SD 2.05)		
LDL cholesterol (mmol/l) – 26wk	Mean change	79		0.124128 (SD 0.602)	81		0.186192 (SD 0.621)		
LDL cholesterol (mmol/l) – 26wk	Continuous	79		3.669534 (SD 1.17)	81		3.573852 (SD 1.05)		
Aranoff (2000) & drug naive									
Blood glucose: HbA1c (%) – 14wka	Mean change	25		0.45 (SD 1)	26		-0.6 (SD 1.02)		
HbA1c (%) – 26wk	Mean change	25		0.6 (SD 1.45)	26		-0.8 (SD 1.43)		
Aranoff (2000) & previous OADs									
Blood glucose: HbA1c (%) – 14wka	Mean change	54		0.8 (SD 0.882)	53		0 (SD 0.946)		
HbA1c (%) – 26wk	Mean change	54		0.8 (SD 1.47)	53		-0.1 (SD 1.48)		

[a] extracted from graph
[b] SD calculated from reported SE
[c] approximated to nearest integer (percentages only presented in text)

		Placebo			Pioglitazone (30 mg)				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 14wka	Mean change	79		0.7 (SD 0.889)	87		-0.12 (SD 1.03)		
HbA1c (%) – 26wk	Mean change	79		0.7 (SD 1.51)	87		-0.3 (SD 1.57)		
HbA1c (%) – 26wk	Continuous	79		11.1 (SD 2.31)	87		9.9 (SD 2.7)		
Fasting plasma glucose (mmol/l) – 14wka	Mean change	79		0.6105 (SD 2.47)	87		-2.22 (SD 2.59)		
Fasting plasma glucose (mmol/l) – 26wk	Mean change	79		0.5217 (SD 3.4)	87		-1.7649 (SD 16.5)		
Body weight: Weight (kg) – 26wkb	Mean change	79		-1.3 (SD 3.2)	87		1.3 (SD 3.54)		
Dropouts: Dropout due to AEs – 26wk	Dichotomous	79	2c	(2.5%)	87	4d	(4.6%)		
Lipids: Total cholesterol (mmol/l) – 26wk	Continuous	79		5.984004 (SD 1.2)	87		5.88315 (SD 1.3)		
Total cholesterol (mmol/l) – 26wk	Mean change	79		0.113784 (SD 0.356)	87		0.085338 (SD 0.371)		

HDL cholesterol (mmol/l) – 26wk	Continuous	79		1.145598 (SD 0.287)	87		1.1637 (SD 0.302)		
HDL cholesterol (mmol/l) – 26wk	Mean change	79		0.209466 (SD 0.467)	87		0.315492 (SD 0.492)		
Triglycerides (mmol/l) – 26wk	Mean change	79		0.054192 (SD 0.472)	87		-0.108384 (SD 0.49)		
Triglycerides (mmol/l) – 26wk	Continuous	79		2.852983 (SD 2.08)	87		2.542508 (SD 2.61)		
LDL cholesterol (mmol/l) – 26wk	Mean change	79		0.124128 (SD 0.602)	87		0.134472 (SD 0.596)		
LDL cholesterol (mmol/l) – 26wk	Continuous	79		3.669534 (SD 1.17)	87		3.604884 (SD 1.23)		
Aranoff (2000) & drug naive									
Blood glucose: HbA1c (%) – 14wka	Mean change	25		0.45 (SD 1)	26		-0.6 (SD 1.02)		
HbA1c (%) – 26wk	Mean change	25		0.6 (SD 1.45)	26		-0.6 (SD 1.48)		
Aranoff (2000) & previous OADs									
Blood glucose: HbA1c (%) – 14wka	Mean change	54		0.8 (SD 0.882)	58		0.1 (SD 1.07)		
HbA1c (%) – 26wk	Mean change	54		0.8 (SD 1.47)	58		0 (SD 1.45)		

[a] extracted from graph
[b] SD calculated from reported SE
[c] approximated to nearest integer (percentages only presented in text)
[d] approximated to nearest integer (percentages only presented in text); approximated to nearest integer (percentages only presented in text)

		Placebo			Pioglitazone (45 mg)				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Blood glucose: HbA1c (%) – 14wka	Mean change	79		0.7 (SD 0.889)	80		-0.6 (SD 1.07)		
HbA1c (%) – 26wk	Mean change	79		0.7 (SD 1.51)	80		-0.9 (SD 1.57)		
HbA1c (%) – 26wk	Continuous	79		11.1 (SD 2.31)	80		9.4 (SD 2.59)		
Fasting plasma glucose (mmol/l) – 14wka	Mean change	79		0.6105 (SD 2.47)	80		-3.219 (SD 2.98)		
Fasting plasma glucose (mmol/l) – 26wk	Mean change	79		0.5217 (SD 3.4)	80		-3.10245 (SD 3.31)		
Body weight: Weight (kg) – 26wkb	Mean change	79		-1.3 (SD 3.2)	79		2.8 (SD 3.49)		
Dropouts: Dropout due to AEs – 26wk	Dichotomous	79	2c	(2.5%)	80	4	(5.0%)		
Lipids: Total cholesterol (mmol/l) – 26wk	Continuous	79		5.984004 (SD 1.2)	80		5.849532 (SD 1.22)		
Total cholesterol (mmol/l) – 26wk	Mean change	79		0.113784 (SD 0.356)	80		0.165504 (SD 0.368)		
HDL cholesterol (mmol/l) – 26wk	Continuous	79		1.145598 (SD 0.287)	80		1.236108 (SD 0.361)		
HDL cholesterol (mmol/l) – 26wk	Mean change	79		0.209466 (SD 0.467)	80		0.493926 (SD 0.479)		
Triglycerides (mmol/l) – 26wk	Mean change	79		0.054192 (SD 0.472)	80		-0.104997 (SD 0.486)		
Triglycerides (mmol/l) – 26wk	Continuous	79		2.852983 (SD 2.08)	80		2.471381 (SD 1.44)		
LDL cholesterol (mmol/l) – 26wk	Mean change	79		0.124128 (SD 0.602)	80		0.15516 (SD 0.622)		
LDL cholesterol (mmol/l) – 26wk	Continuous	79		3.669534 (SD 1.17)	80		3.50403 (SD 1.02)		

Aranoff (2000) & drug naive									
Blood glucose: HbA1c (%) – 14wka	Mean change	25		0.45 (SD 1)	21		-1.45 (SD 1.15)		
HbA1c (%) – 26wk	Mean change	25		0.6 (SD 1.45)	21		-1.9 (SD 1.51)		
Aranoff (2000) & previous OADs									
Blood glucose: HbA1c (%) – 14wka	Mean change	54		0.8 (SD 0.882)	55		-0.35 (SD 1.04)		
HbA1c (%) – 26wk	Mean change	54		0.8 (SD 1.47)	55		-0.6 (SD 1.48)		

[a] extracted from graph
[b] SD calculated from reported SE
[c] approximated to nearest integer (percentages only presented in text)

		Pioglitazone (15 mg)			Pioglitazone (30 mg)				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Blood glucose: HbA1c (%) – 14wka	Mean change	81		-0.12 (SD 0.99)	87		-0.12 (SD 1.03)		
HbA1c (%) – 26wk	Mean change	81		-0.3 (SD 1.51)	87		-0.3 (SD 1.57)		
HbA1c (%) – 26wk	Continuous	81		9.9 (SD 2.43)	87		9.9 (SD 2.7)		
Fasting plasma glucose (mmol/l) – 14wka	Mean change	81		-1.8315 (SD 2.5)	87		-2.22 (SD 2.59)		
Fasting plasma glucose (mmol/l) – 26wk	Mean change	81		-1.6428 (SD 3.38)	87		-1.7649 (SD 16.5)		
Body weight: Weight (kg) – 26wkb	Mean change	79		1.3 (SD 2.97)	87		1.3 (SD 3.54)		
Dropouts: Dropout due to AEs – 26wk	Dichotomous	81	3c	(3.7%)	87	4d	(4.6%)		
Lipids: Total cholesterol (mmol/l) – 26wk	Continuous	81		5.852118 (SD 1.16)	87		5.88315 (SD 1.3)		
Total cholesterol (mmol/l) – 26wk	Mean change	81		0.118956 (SD 0.363)	87		0.085338 (SD 0.371)		
HDL cholesterol (mmol/l) – 26wk	Continuous	81		1.174044 (SD 0.277)	87		1.1637 (SD 0.302)		
HDL cholesterol (mmol/l) – 26wk	Mean change	81		0.364626 (SD 0.477)	87		0.315492 (SD 0.492)		
Triglycerides (mmol/l) – 26wk	Mean change	81		-0.10161 (SD 0.482)	87		-0.108384 (SD 0.49)		
Triglycerides (mmol/l) – 26wk	Continuous	81		2.55154 (SD 2.05)	87		2.542508 (SD 2.61)		
LDL cholesterol (mmol/l) – 26wk	Mean change	81		0.186192 (SD 0.621)	87		0.134472 (SD 0.596)		
LDL cholesterol (mmol/l) – 26wk	Continuous	81		3.573852 (SD 1.05)	87		3.604884 (SD 1.23)		
Aranoff (2000) & drug naive									
Blood glucose: HbA1c (%) – 14wka	Mean change	26		-0.6 (SD 1.02)	26		-0.6 (SD 1.02)		
HbA1c (%) – 26wk	Mean change	26		-0.8 (SD 1.43)	26		-0.6 (SD 1.48)		
Aranoff (2000) & previous OADs									
Blood glucose: HbA1c (%) – 14wka	Mean change	53		0 (SD 0.946)	58		0.1 (SD 1.07)		
HbA1c (%) – 26wk	Mean change	53		-0.1 (SD 1.48)	58		0 (SD 1.45)		

[a] extracted from graph
[b] SD calculated from reported SE
[c] approximated to nearest integer (percentages only presented in text)
[d] approximated to nearest integer (percentages only presented in text); approximated to nearest integer (percentages only presented in text)

		Pioglitazone (15 mg)			Pioglitazone (45 mg)				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 14wka	Mean change	81		-0.12 (SD 0.99)	80		-0.6 (SD 1.07)		
HbA1c (%) – 26wk	Mean change	81		-0.3 (SD 1.51)	80		-0.9 (SD 1.57)		
HbA1c (%) – 26wk	Continuous	81		9.9 (SD 2.43)	80		9.4 (SD 2.59)		
Fasting plasma glucose (mmol/l) – 14wka	Mean change	81		-1.8315 (SD 2.5)	80		-3.219 (SD 2.98)		
Fasting plasma glucose (mmol/l) – 26wk	Mean change	81		-1.6428 (SD 3.38)	80		-3.10245 (SD 3.31)		
Body weight: Weight (kg) – 26wkb	Mean change	79		1.3 (SD 2.97)	79		2.8 (SD 3.49)		
Dropouts: Dropout due to AEs – 26wk	Dichotomous	81	3c	(3.7%)	80	4	(5.0%)		
Lipids: Total cholesterol (mmol/l) – 26wk	Continuous	81		5.852118 (SD 1.16)	80		5.849532 (SD 1.22)		
Total cholesterol (mmol/l) – 26wk	Mean change	81		0.118956 (SD 0.363)	80		0.165504 (SD 0.368)		
HDL cholesterol (mmol/l) – 26wk	Continuous	81		1.174044 (SD 0.277)	80		1.236108 (SD 0.361)		
HDL cholesterol (mmol/l) – 26wk	Mean change	81		0.364626 (SD 0.477)	80		0.493926 (SD 0.479)		
Triglycerides (mmol/l) – 26wk	Mean change	81		-0.10161 (SD 0.482)	80		-0.104997 (SD 0.486)		
Triglycerides (mmol/l) – 26wk	Continuous	81		2.55154 (SD 2.05)	80		2.471381 (SD 1.44)		
LDL cholesterol (mmol/l) – 26wk	Mean change	81		0.186192 (SD 0.621)	80		0.15516 (SD 0.622)		
LDL cholesterol (mmol/l) – 26wk	Continuous	81		3.573852 (SD 1.05)	80		3.50403 (SD 1.02)		
Aranoff (2000) & drug naive Blood glucose: HbA1c (%) – 14wka	Mean change	26		-0.6 (SD 1.02)	21		-1.45 (SD 1.15)		
HbA1c (%) – 26wk	Mean change	26		-0.8 (SD 1.43)	21		-1.9 (SD 1.51)		
Aranoff (2000) & previous OADs Blood glucose: HbA1c (%) – 14wka	Mean change	53		0 (SD 0.946)	55		-0.35 (SD 1.04)		
HbA1c (%) – 26wk	Mean change	53		-0.1 (SD 1.48)	55		-0.6 (SD 1.48)		

[a] extracted from graph
[b] SD calculated from reported SE
[c] approximated to nearest integer (percentages only presented in text)

		Pioglitazone (15 mg)			Pioglitazone (7.5mg)				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 14wka	Mean change	81		-0.12 (SD 0.99)	81		0.25 (SD 0.9)		
HbA1c (%) – 26wk	Mean change	81		-0.3 (SD 1.51)	81		0.2 (SD 1.52)		
HbA1c (%) – 26wk	Continuous	81		9.9 (SD 2.43)	81		10.2 (SD 2.25)		
Fasting plasma glucose (mmol/l) – 14wka	Mean change	81		-1.8315 (SD 2.5)	81		-1.11 (SD 2.5)		
Fasting plasma glucose (mmol/l) – 26wk	Mean change	81		-1.6428 (SD 3.38)	81		-1.00455 (SD 3.36)		

Body weight: Weight (kg) – 26wkb	Mean change	79		1.3 (SD 2.97)	81		-0.6 (SD 2.61)		
Dropouts: Dropout due to AEs – 26wkc	Dichotomous	81	3	(3.7%)	81	2	(2.5%)		
Lipids: Total cholesterol (mmol/l) – 26wk	Continuous	81		5.852118 (SD 1.16)	81		5.593518 (SD 1.17)		
Total cholesterol (mmol/l) – 26wk	Mean change	81		0.118956 (SD 0.363)	81		0.059478 (SD 0.363)		
HDL cholesterol (mmol/l) – 26wk	Continuous	81		1.174044 (SD 0.277)	81		1.122324 (SD 0.305)		
HDL cholesterol (mmol/l) – 26wk	Mean change	81		0.364626 (SD 0.477)	81		0.204294 (SD 0.477)		
Triglycerides (mmol/l) – 26wk	Mean change	81		-0.10161 (SD 0.482)	81		0.100481 (SD 0.481)		
Triglycerides (mmol/l) – 26wk	Continuous	81		2.55154 (SD 2.05)	81		2.981689 (SD 3.36)		
LDL cholesterol (mmol/l) – 26wk	Mean change	81		0.186192 (SD 0.621)	81		0.02586 (SD 0.621)		
LDL cholesterol (mmol/l) – 26wk	Continuous	81		3.573852 (SD 1.05)	81		3.289392 (SD 0.856)		
Aranoff (2000) & drug naive									
Blood glucose: HbA1c (%) – 14wka	Mean change	26		-0.6 (SD 1.02)	27		0.07 (SD 1.04)		
HbA1c (%) – 26wk	Mean change	26		-0.8 (SD 1.43)	27		0 (SD 1.45)		
Aranoff (2000) & previous OADs									
Blood glucose: HbA1c (%) – 14wka	Mean change	53		0 (SD 0.946)	53		0.4 (SD 1.09)		
HbA1c (%) – 26wk	Mean change	53		-0.1 (SD 1.48)	53		0.3 (SD 1.46)		

[a] extracted from graph
[b] SD calculated from reported SE
[c] approximated to nearest integer (percentages only presented in text)

		Pioglitazone (30 mg)			Pioglitazone (45 mg)				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Blood glucose: HbA1c (%) – 14wka	Mean change	87		-0.12 (SD 1.03)	80		-0.6 (SD 1.07)		
HbA1c (%) – 26wk	Mean change	87		-0.3 (SD 1.57)	80		-0.9 (SD 1.57)		
HbA1c (%) – 26wk	Continuous	87		9.9 (SD 2.7)	80		9.4 (SD 2.59)		
Fasting plasma glucose (mmol/l) – 14wka	Mean change	87		-2.22 (SD 2.59)	80		-3.219 (SD 2.98)		
Fasting plasma glucose (mmol/l) – 26wk	Mean change	87		-1.7649 (SD 16.5)	80		-3.10245 (SD 3.31)		
Body weight: Weight (kg) – 26wkb	Mean change	87		1.3 (SD 3.54)	79		2.8 (SD 3.49)		
Dropouts: Dropout due to AEs – 26wk	Dichotomous	87	4c	(4.6%)	80	4	(5.0%)		
Lipids: Total cholesterol (mmol/l) – 26wk	Continuous	87		5.88315 (SD 1.3)	80		5.849532 (SD 1.22)		
Total cholesterol (mmol/l) – 26wk	Mean change	87		0.085338 (SD 0.371)	80		0.165504 (SD 0.368)		
HDL cholesterol (mmol/l) – 26wk	Continuous	87		1.1637 (SD 0.302)	80		1.236108 (SD 0.361)		
HDL cholesterol (mmol/l) – 26wk	Mean change	87		0.315492 (SD 0.492)	80		0.493926 (SD 0.479)		
Triglycerides (mmol/l) – 26wk	Mean change	87		-0.108384 (SD 0.49)	80		-0.104997 (SD 0.486)		

Triglycerides (mmol/l) – 26wk	Continuous	87		2.542508 (SD 2.61)	80		2.471381 (SD 1.44)		
LDL cholesterol (mmol/l) – 26wk	Mean change	87		0.134472 (SD 0.596)	80		0.15516 (SD 0.622)		
LDL cholesterol (mmol/l) – 26wk	Continuous	87		3.604884 (SD 1.23)	80		3.50403 (SD 1.02)		
Aranoff (2000) & drug naive									
Blood glucose: HbA1c (%) – 14wka	Mean change	26		-0.6 (SD 1.02)	21		-1.45 (SD 1.15)		
HbA1c (%) – 26wk	Mean change	26		-0.6 (SD 1.48)	21		-1.9 (SD 1.51)		
Aranoff (2000) & previous OADs									
Blood glucose: HbA1c (%) – 14wka	Mean change	58		0.1 (SD 1.07)	55		-0.35 (SD 1.04)		
HbA1c (%) – 26wk	Mean change	58		0 (SD 1.45)	55		-0.6 (SD 1.48)		

[a] extracted from graph
[b] SD calculated from reported SE
[c] approximated to nearest integer (percentages only presented in text); approximated to nearest integer (percentages only presented in text)

		Pioglitazone (45 mg)			**Pioglitazone (7.5mg)**				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Blood glucose: HbA1c (%) – 14wka	Mean change	80		-0.6 (SD 1.07)	81		0.25 (SD 0.9)		
HbA1c (%) – 26wk	Mean change	80		-0.9 (SD 1.57)	81		0.2 (SD 1.52)		
HbA1c (%) – 26wk	Continuous	80		9.4 (SD 2.59)	81		10.2 (SD 2.25)		
Fasting plasma glucose (mmol/l) – 14wka	Mean change	80		-3.219 (SD 2.98)	81		-1.11 (SD 2.5)		
Fasting plasma glucose (mmol/l) – 26wk	Mean change	80		-3.10245 (SD 3.31)	81		-1.00455 (SD 3.36)		
Body weight: Weight (kg) – 26wkb	Mean change	79		2.8 (SD 3.49)	81		-0.6 (SD 2.61)		
Dropouts: Dropout due to AEs – 26wk	Dichotomous	80	4	(5.0%)	81	2c	(2.5%)		
Lipids: Total cholesterol (mmol/l) – 26wk	Continuous	80		5.849532 (SD 1.22)	81		5.593518 (SD 1.17)		
Total cholesterol (mmol/l) – 26wk	Mean change	80		0.165504 (SD 0.368)	81		0.059478 (SD 0.363)		
HDL cholesterol (mmol/l) – 26wk	Continuous	80		1.236108 (SD 0.361)	81		1.122324 (SD 0.305)		
HDL cholesterol (mmol/l) – 26wk	Mean change	80		0.493926 (SD 0.479)	81		0.204294 (SD 0.477)		
Triglycerides (mmol/l) – 26wk	Mean change	80		-0.104997 (SD 0.486)	81		0.100481 (SD 0.481)		
Triglycerides (mmol/l) – 26wk	Continuous	80		2.471381 (SD 1.44)	81		2.981689 (SD 3.36)		
LDL cholesterol (mmol/l) – 26wk	Mean change	80		0.15516 (SD 0.622)	81		0.02586 (SD 0.621)		
LDL cholesterol (mmol/l) – 26wk	Continuous	80		3.50403 (SD 1.02)	81		3.289392 (SD 0.856)		
Aranoff (2000) & drug naive									
Blood glucose: HbA1c (%) – 14wka	Mean change	21		-1.45 (SD 1.15)	27		0.07 (SD 1.04)		
HbA1c (%) – 26wk	Mean change	21		-1.9 (SD 1.51)	27		0 (SD 1.45)		
Aranoff (2000) & previous OADs									
Blood glucose: HbA1c (%) – 14wka	Mean change	55		-0.35 (SD 1.04)	53		0.4 (SD 1.09)		

	HbA1c (%) – 26wk	Mean change	55		-0.6 (SD 1.48)	53		0.3 (SD 1.46)		

[a] extracted from graph
[b] SD calculated from reported SE
[c] approximated to nearest integer (percentages only presented in text)

Table 5: Aschner et al. (2006)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** Australia, South America, Europe including UK, New Zealand, Hong Kong and other countries **Authors' conclusions:** In this 24-week study, once-daily sitagliptin monotherapy improved glycemic control in the fasting and postprandial states, improved measures of beta-cell function, and was well tolerated in patients with type 2 diabetes. **Source of funding:** sponsored by Merck **Comments:** multinational, randomized, double-blind, placebo-controlled study.
Number and characteristics of patients	**Total number of patients:** 741 **Inclusion criteria:** Patients, 18–75 years of age, on and not on an OHA were eligible. **Exclusion criteria:** Patients with type 1 diabetes, unstable cardiac disease, significant renal impairment, or elevated (more than twofold the upper limit of normal) alanine aminotransferase, aspartate aminotransferase, or creatine phosphokinase were excluded. Pre-randomisation phase: At screening, patients with an A1C of 7–10% and not on an OHA for >=8 weeks were eligible to directly enter a 2-week single-blind placebo run-in period; patients with A1C >10% and not on an OHA entered a run-in period of up to 6 weeks; patients with an A1C of 6–10% and on an OHA discontinued the agent and entered a wash-out period of 6–10 weeks (8–12 weeks for those on thiazolidinediones). If A1C was 7–10% after the wash-out period, patients were eligible to enter the placebo run-in period. Patients with adequate compliance (>=75%) during the placebo run-in period underwent baseline evaluation and were randomised
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** some on oral hypoglycaemic drugs and/or insulin **Details of washout period:** washout of 6-10 weeks (8-12 weeks for pioglitazone)
Lifestyle advice	Patients received counseling on exercise and a weight-maintenance diet consistent with American Diabetes Association recommendations throughout the study
Follow-up	**Total follow-up (wks):** 24 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 24 **Frequency of monitoring appointments:** Not reported
Arms	**(1) Sitagliptin 100 mg** N: 238 Treatment duration (wks): 24 Washout period (d): 84 Comments: Max washout was 12 weeks (for thiazolidinediones) Treatment(s): Sitagliptin (Oral) – fixed-dose Set dose (mg/d):100 Frequency of dosing: once a day Details of dosing regimen: During the study, patients not meeting progressively stricter glycemic goals were provided rescue therapy (metformin) until study completion. Glycemic rescue criteria were FPG >15.0 mmol/l (270 mg/dl) between randomization (day 1) and week 6, FPG >13.3 mmol/l (240 mg/dl) after week 6 through week 12, or FPG >11.1 mmol/l (200 mg/dl) after week 12 through week 24. **(2) Placebo** N: 253

Treatment duration (wks): 24
Washout period (d): 84
Comments: Max washout was 12 weeks (for thiazolidinediones)
Treatment(s): Placebo (Oral) – fixed-dose
Frequency of dosing: once a day

Outcomes

General

Only data from 2/3 arms were extracted as one arm related to sitagliptin 200 mg which is above the recommended dose in the SPC. Outcomes not extracted in this evidence table include Insulin, c-peptides, insulin/glucose AUC ratio and measures of insulin resistance

Efficacy analyses were based on the allpatients- treated (APT) population, consisting of all randomized patients who received at least one dose of study treatment and who had both a baseline and at least one postbaseline measurement. Safety and tolerability were assessed

in patients who received at least one dose of study medication by review of safety parameters. To avoid the confounding influence of rescue therapy on efficacy comparisons, data collected after initiation of rescue therapy were treated as missing.

14.7% patients in placebo and 12.2% in sitagliptin 100 mg discontinued

Baseline characteristics

		Sitagliptin 100 mg			Placebo			Δ	p
		N	k	mean	N	k	mean		
Demographics: Age (years)	Continuous	238		53.4 (SD 9.5)	253		54.3 (SD 10.1)		
Sex (n male)	Dichotomous	238	136	(57.1%)	253	130	(51.4%)		
Duration of diabetes (yrs)	Continuous	238		4.3 (SD 4.9)	253		4.6 (SD 4.7)		
Ethnicity-White	Dichotomous	238	122	(51.3%)	253	127	(50.2%)		
Ethnicity-Black	Dichotomous	238	10	(4.2%)	253	16	(6.3%)		
Ethnicity-Asian	Dichotomous	238	32	(13.4%)	253	34	(13.4%)		
Ethnicity-Hispanic	Dichotomous	238	58	(24.4%)	253	64	(25.3%)		
Ethnicity-Other	Dichotomous	238	16	(6.7%)	253	12	(4.7%)		
Blood glucose: HbA1c (%) – 0wk	Continuous	238		8 (SD 0.9)	253		8 (SD 0.8)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	238		9.5 (SD 2.4)	253		9.8 (SD 2.3)		
Body weight: BMI (kg/m2)	Continuous	238		30.3 (SD 5.2)	253		30.8 (SD 5.5)		
Weight (kg) – 0wk	Continuous	238		85 (SD 18.4)	253		85 (SD 18.1)		
Previous blood glucose lowering drugs: Diet alone (i.e. drug naïve)	Dichotomous	238	124	(52.1%)	253	129	(51.0%)		

Results

		Sitagliptin 100 mg			Placebo			Δ	p
		N	k	mean	N	k	mean		
Blood glucose: HbA1c (%) – 12wka	Continuous	229		7.43 (SD 0.757)	244		8.2 (SD 1.09)		
HbA1c (%) – 24wk	Mean change	229		-0.61 (SD 1)	244		0.18 (SD 0.956)		<=0.001
HbA1c (%) – 24wka	Continuous	229		7.4 (SD 0.757)	244		8.2 (SD 1.25)		
HbA1c < 7% or <=7% – 24wkb	Dichotomous	229	94	(41.0%)	244	41	(16.8%)		

Fasting plasma glucose (mmol/l) – 24wk	Mean change	234		-0.7 (SD 2.34)	247		0.3 (SD 2.41)		<=0.001
2-h post prandial glucose (mmol/l) – 24wk	Mean change	201		-2.7 (SD 3.62)	204		-0.1 (SD 3.64)		<=0.001
Body weight: Weight (kg) – 24wkc	Mean change	238		-0.2 (SD 3.09)	253		-1.1 (SD 3.18)		
Hypoglycaemic events: All hypoglycaemic events (no patients) – 24wk	Dichotomous	238	2	(0.8%)	253	2	(0.8%)		d
Adverse events: GI: nausea – 24wk	Dichotomous	238	5	(2.1%)	253	3	(1.2%)		NS
Any adverse event(s) – 24wk	Dichotomous	238	157	(66.0%)	253	167	(66.0%)		
Any serious adverse event(s) – 24wk	Dichotomous	238	12	(5.0%)	253	9	(3.6%)		
Serious AE drug related – 24wk	Dichotomous	238	2	(0.8%)	253	1	(0.4%)		
Study drug-related adverse event – 24wk	Dichotomous	238	23	(9.7%)	253	19	(7.5%)		
Arthralgia – 24wk	Dichotomous	238	3	(1.3%)	253	7	(2.8%)		
Back pain – 24wk	Dichotomous	238	4	(1.7%)	253	11	(4.3%)		
Cough – 24wk	Dichotomous	238	6	(2.5%)	253	8	(3.2%)		
Dizziness – 24wk	Dichotomous	238	3	(1.3%)	253	4	(1.6%)		
Fatigue – 24wk	Dichotomous	238	3	(1.3%)	253	5	(2.0%)		
Gastrointestinal disorders (any) – 24wk	Dichotomous	238	39	(16.4%)	253	29	(11.5%)		d
GI: diarrhoea – 24wk	Dichotomous	238	11	(4.6%)	253	6	(2.4%)		NS
GI: vomiting – 24wk	Dichotomous	238	3	(1.3%)	253	3	(1.2%)		NS
GI: abdominal pain – 24wk	Dichotomous	238	5	(2.1%)	253	4	(1.6%)		NS
GI: constipation – 24wk	Dichotomous	238	9	(3.8%)	253	3	(1.2%)		d
Headache – 24wk	Dichotomous	238	11	(4.6%)	253	12	(4.7%)		
Hyperglycaemia – 24wk	Dichotomous	238	5	(2.1%)	253	5	(2.0%)		
Hypertension – 24wk	Dichotomous	238	6	(2.5%)	253	5	(2.0%)		
Infection (upper airway or other common) – 24wk	Dichotomous	238	21	(8.8%)	253	22	(8.7%)		
Nasopharyngitis – 24wk	Dichotomous	238	17	(7.1%)	253	12	(4.7%)		
Pain (extremity) – 24wk	Dichotomous	238	3	(1.3%)	253	6	(2.4%)		
Sinusitis or sinus abnormality – 24wk	Dichotomous	238	2	(0.8%)	253	6	(2.4%)		
Temperature/influenza – 24wk	Dichotomous	238	11	(4.6%)	253	12	(4.7%)		
UTI – 24wk	Dichotomous	238	5	(2.1%)	253	7	(2.8%)		
Dropouts: Total dropouts – 24wke	Dichotomous	238	29	(12.2%)	253	37	(14.6%)		
Dropout due to AEs – 24wke	Dichotomous	238	5	(2.1%)	253	5	(2.0%)		
drop out due to drug related AE – 24wk	Dichotomous	238	1	(0.4%)	253	2	(0.8%)		
drop out due to SAE – 24wk	Dichotomous	238	3	(1.3%)	253	3	(1.2%)		
drop out due to drug related SAE – 24wk	Dichotomous	238	0	(0.0%)	253	1	(0.4%)		
Other medication: Taking rescue medication – 24wk	Dichotomous	238	21	(8.8%)	253	52	(20.6%)		<0.001

	Baseline Hba1c <8% Blood glucose: HbA1c (%) – 24wk	Continuous	130			253			MD=-0.590 (CI: -0.825, -0.355)	a
	baseline Hba1c >=9% Blood glucose: HbA1c (%) – 24wk	Continuous	62			253			MD=-0.800 (CI: -1.133, -0.467)	a
	Baseline Hba1c 8% to <9% Blood glucose: HbA1c (%) – 24wk	Continuous	37			253			MD=-1.510 (CI: -1.902, -1.118)	a

[a] estimated from graph
[b] approximated to nearest integer (percentages only presented in text)
[c] SD calculated from reported SE
[d] not reported
[e] Extracted from supplementary online data

ANCOVA was used to compare treatment groups for continuous efficacy parameters, focusing on change from baseline at week 24, with baseline values and prior OHA status as covariates. Missing data were handled using the last observation carried forward meth

The between group differences for efficacy end points were assessed by testing the difference in the least-squares mean change (or percentage

of change) from baseline at week 24. The proportion of patients achieving A1C <7% was compared among groups using a logistic regression analysis. P-values for comparisons for adverse events other than specific GI events were not reported

Table 6: Aschner et al. (2010)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** conducted at 113 sites in 23 countries **Authors' conclusions:** in this 24 week monotherapy study, sitagliptin was non-inferior to metformin in improving Hba1c in treatment naïve patients with type 2 diabetes. Although both treatments were generally well tolerated, a lower incidence of gastrointestinal related adverse events were observed with sitagliptin **Source of funding:** funded by Merck & Co **Comments:** Multinational, double-blind randomsied active control study-randomisation using computer generated allocation schedule but no details of allocation concealment or blinding reported. ECG read by technicians blinded to treatment assignment.
Number and characteristics of patients	**Total number of patients:** 1050 **Inclusion criteria:** Men and women with type 2 diabetes (18-78 years of age) who were treatment naïve (i.e.not taking an antihyperglycaemic agent for at least 16 weeks prior to study entry) with Hba1c 6.5-9.0% were eligible to participate. **Exclusion criteria:** type 1 diabetes, FPG<120 mg/dl or >250 mg/dl, unstable cardiac disease, significant renal impairment, elevated aminotransferase, aspartate aminotransferase, or creatinine phosphokinase or tryglycerides >600 mg/dl were excluded. Patients were discontinued for lack of efficacy based on progressively stricter glycaemic criteria: from randomisation to week 6 FPG>270 (15 mmol/l); from >week 6 to week 12 FPG>240 mg/dl (13.3 mmol/l); and from >week 12 to week 24 FPG>210 mg/dl (11.7 mmol/l) Pre-randomisation phase: 2-week placebo run-in period before randomisation. Baseline measurements were taken after placebo run-in period. Assumed titration occurs during maintenance period.
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** some on oral hypoglycaemic drugs and/or insulin **Details of washout period:** Drug naïve was defined as those not receiving AHAs 16 weeks prior to enrollment. No specific details provided regarding proportion on individuals who were previously on AHAs. 2 week placebo run in period
Lifestyle advice	patients were expected to follow a recommended regimen of diet and exercise for the duration of the study
Follow-up	**Total follow-up (wks):** 26

	Length of titration period (wks): 0 **Length of maintenance period (wks):** 24 **Frequency of monitoring appointments:** No details reported
Arms	**(1) Sitagliptin** N: 528 Treatment duration (wks): 24 Washout period (d): 0 Treatment(s): Sitagliptin (Oral) – fixed-dose Set dose (mg/d):100 Frequency of dosing: once a day **(2) Metformin** N: 522 Treatment duration (wks): 24 Washout period (d): 0 Treatment(s): Metformin (Oral) – forced titration Minimum dose (mg/d): 1000 Maximum dose (mg/d): 2000 Participants achieving full dose (n): 386 Frequency of dosing: variable Details of dosing regimen: Metformin 500 mg (or matching placebo) was intiated at a dose of one tablet daily and uptitrated to two 500 mg tablets twice daily (1000 mg bid) over a maximum 5 week period. Down titration of metformin was permitted for intolerance to a minimum allowed dose of 1000 mg/day. The mean dose of metformin after week 6 in the PP population was 1903 mg/day. During the course of the study. 96.4% of patients in the PP population reached a maximum dose of metformin of 2000 mg, and 88% of patients in the PP population were on the maximum dose of 2000 mg at week 24
Outcomes	**General** Per protocol population (PP) consisted of patients who completed the study and did not have any reasons for exclusion from this population, including absence of baseline or on-treatment data at the week 24 visit or major protocol violations [sitagliptin n=455 and metformin n=439]. The primary efficacy analysis used the PP population. Additional efficacy analyses for Hba1c were performed on the full analysis set (FAS) cohort that consisted of all randomised patients who had received at least one dose of the study treatment and who had both a baseline and at leats one postbaseline efficacy measurement. Missing values were imputed using the last observation carried forward approach. The safety analysis was based on 24 week results for the all patients as treated (ApaT) population, which consisted of all randomised patients who received at least one dose of study medication Outcomes not reported in this evidence table include fasting insulin, proinsulin, HOMA-IR, HOMA-beta, proinsulin/insulin ratio, non HDL cholesterol 61 (12%) patients in sitagliptin and 75 (14%) in metformin group discontinued the study
Baseline characteristics	

		Sitagliptin			Metformin				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
PP									
Demographics:									
Age (years)	Continuous	455		56.3 (SD 10.7)	439		55.7 (SD 10.3)		
Sex (n male)	Dichotomous	455	217	(47.7%)	439	194	(44.2%)		
Duration of diabetes (yrs)	Continuous	455		2.6 (SD 3.9)	439		2.1 (SD 3.5)		
Blood glucose:									
HbA1c (%) – 0wk	Continuous	455		7.2 (SD 0.7)	439		7.2 (SD 0.7)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	455		7.9032 (SD 1.77)	439		7.87545 (SD 1.84)		
Body weight:									
BMI (kg/m2)	Continuous	455		30.7 (SD 4.7)	439		30.9 (SD 4.9)		
Weight (kg) – 0wka	Continuous	455		86.64768 (SD 13.3)	439		87.21216 (SD 13.8)		

[a] estimated from BMI assuming mean height of 1.68m

Results		Sitagliptin			Metformin				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**

Blood glucose: HbA1c (%) – 24wk	Mean change	455			439			MD=0.140 (CI: 0.060, 0.220)	a
HbA1c < 7% or <=7% – 24wk	Dichotomous	455			439			MD=-7.100 (CI: -12.900, -1.300)	b
Hba1c <6.5% – 24wk	Dichotomous	455			439			MD=-5.600 (CI: -11.800, 0.600)	c
Fasting plasma glucose (mmol/l) – 24wk	Mean change	455			439			MD=0.444 (CI: 0.250, 0.638)	d
Body weight: Weight (kg) – 24wk	Mean change	458			446				<0.001
Hypoglycaemic events: Symptomatic hypoglycaemia – 24wk	Dichotomous	528	9	(1.7%)	522	17e	(3.3%)		
Symptomatic hypoglycaemia – 24wkf	Count	83580	17		81396	23			
Adverse events: GI: nausea – 24wk	Dichotomous	528	6	(1.1%)	522	16	(3.1%)	MD=-1.900 (CI: -3.900, 0.100)	g
Any adverse event(s) – 24wkh	Dichotomous	528	198	(37.5%)	522	215	(41.2%)		
Any serious adverse event(s) – 24wk	Dichotomous	528	10	(1.9%)	522	8	(1.5%)		
Study drug-related adverse event – 24wk	Dichotomous	528	31	(5.9%)	522	87	(16.7%)		
Arthralgia – 24wk	Dichotomous	528	5	(0.9%)	522	5	(1.0%)	MD=0.000 (CI: -1.400, 1.400)	i
Back pain – 24wk	Dichotomous	528	9	(1.7%)	522	9	(1.7%)	MD=0.000 (CI: -1.700, 1.700)	j
Bronchitis – 24wk	Dichotomous	528	4	(0.8%)	522	7	(1.3%)	MD=-0.600 (CI: -2.100, 0.900)	k
Cough – 24wk	Dichotomous	528	1	(0.2%)	522	8	(1.5%)	MD=-1.300 (CI: -2.800, 0.200)	l
Death – 24wk	Dichotomous	528	1m	(0.2%)	522	0	(0.0%)		
Dizziness – 24wk	Dichotomous	528	9	(1.7%)	522	5	(1.0%)	MD=0.700 (CI: -0.800, 2.200)	n
Dyspepsia – 24wk	Dichotomous	528	1	(0.2%)	522	7	(1.3%)	MD=-1.200 (CI: -2.600, 0.200)	o
Fatigue – 24wk	Dichotomous	528	6	(1.1%)	522	6	(1.1%)	MD=0.000 (CI: -1.500, 1.500)	p

Gastrointestinal disorders (any) – 24wk	Dichotomous	528	61q	(11.6%)	522	108	(20.7%)	MD=-9.100 (CI: -13.600, -4.600)	r
GI: diarrhoea – 24wk	Dichotomous	528	19	(3.6%)	522	57	(10.9%)	MD=-7.300 (CI: -10.600, -4.000)	<0.001s
GI: vomiting – 24wk	Dichotomous	528	2	(0.4%)	522	7	(1.3%)	MD=-1.000 (CI: -2.400, 0.400)	t
GI: abdominal pain – 24wk	Dichotomous	528	11	(2.1%)	522	20	(3.8%)	MD=-1.700 (CI: -4.000, 0.600)	u
GI: gastritis – 24wk	Dichotomous	528	6	(1.1%)	522	11	(2.1%)	MD=-1.000 (CI: -2.700, 0.700)	v
GI: constipation – 24wk	Dichotomous	528	9	(1.7%)	522	5	(1.0%)	MD=0.700 (CI: -0.800, 2.200)	n
Headache – 24wk	Dichotomous	528	17	(3.2%)	522	17	(3.3%)	MD=0.000 (CI: -2.300, 2.300)	w
Hypertension – 24wk	Dichotomous	528	12	(2.3%)	522	4	(0.8%)	MD=1.500 (CI: 0.000, 3.000)	x
Infection (upper airway or other common) – 24wk	Dichotomous	528	5	(0.9%)	522	11	(2.1%)	MD=-1.200 (CI: -2.900, 0.500)	y
Nasopharyngitis – 24wk	Dichotomous	528	10	(1.9%)	522	17	(3.3%)	MD=-1.400 (CI: -3.400, 0.600)	z
Osteoarthritis – 24wk	Dichotomous	528	1	(0.2%)	522	5	(1.0%)	MD=-0.800 (CI: -2.000, 0.400)	aa
Pain (extremity) – 24wk	Dichotomous	528	7	(1.3%)	522	2	(0.4%)	MD=0.900 (CI: -0.300, 2.100)	bb
Temperature/influenza – 24wk	Dichotomous	528	0	(0.0%)	522	5	(1.0%)	MD=-1.000 (CI: -2.200, 0.200)	cc
UTI – 24wk	Dichotomous	528	3	(0.6%)	522	13	(2.5%)	MD=-1.900 (CI: -3.700, -0.100)	dd
Dropouts:									
Total dropouts – 24wk	Dichotomous	528	61	(11.6%)	522	75	(14.4%)		
Dropout due to AEs – 24wk	Dichotomous	528	9	(1.7%)	522	19	(3.6%)		
drop out due to drug related AE – 24wk	Dichotomous	528	3	(0.6%)	522	12	(2.3%)		
drop out due to SAE – 24wk	Dichotomous	528	3	(0.6%)	522	3	(0.6%)		
Drop out due to unsatisfactory effect – 24wk	Dichotomous	528	10	(1.9%)	522	1	(0.2%)		

Lipids: Total cholesterol (mmol/l) – 24wk	Mean change	455			439			MD=0.085 (CI: 0.023, 0.147)	ee
HDL cholesterol (mmol/l) – 24wk	Mean change	455			439			MD=-0.021 (CI: -0.078, 0.036)	ff
Triglycerides (mmol/l) – 24wk	Mean change	455			439			MD=-0.043 (CI: -0.093, 0.007)	gg
LDL cholesterol (mmol/l) – 24wk	Mean change	455			439			MD=0.225 (CI: 0.106, 0.344)	hh
PP Blood glucose: HbA1c (%) – 12wkii	Continuous	455		6.78 (SD 0.213)	439		6.76 (SD 0.21)		
HbA1c (%) – 24wk	Continuous	455		6.8 (SD 0.7)	439		6.7 (SD 0.6)		
HbA1c (%) – 24wk	Mean change	455		-0.43 (SD 0.544)	439		-0.57 (SD 0.535)		
HbA1c < 7% or <=7% – 24wkq	Dichotomous	455	155	(34.1%)	439	334	(76.1%)		
Hba1c <6.5% – 24wkq	Dichotomous	455	155	(34.1%)	439	171	(39.0%)		
Fasting plasma glucose (mmol/l) – 12wkii	Continuous	455		7.271286 (SD 0.592)	439		6.827238 (SD 0.581)		
Fasting plasma glucose (mmol/l) – 24wk	Mean change	455		-0.63825 (SD 1.45)	439		-1.0767 (SD 1.48)		
Fasting plasma glucose (mmol/l) – 24wk	Continuous	446		7.26495 (SD 1.75)	435		6.8154 (SD 1.54)		
Body weight: Weight (kg) – 24wk	Mean change	458		-0.6 (SD 3.26)	446		-1.9 (SD 3.23)		
Lipids: Total cholesterol (mmol/l) – 24wk	Mean change	455		0.14223 (SD 0.478)	439		0.056892 (SD 0.498)		
HDL cholesterol (mmol/l) – 24wk	Mean change	455		0.160332 (SD 0.422)	439		0.18102 (SD 0.442)		
Triglycerides (mmol/l) – 24wk	Mean change	455		med: -0.041773jj	439		med: -0.013548kk		
LDL cholesterol (mmol/l) – 24wk	Mean change	455		0.289632 (SD 0.901)	439		0.06465 (SD 0.912)		
Compliance: Compliance – 24wkll	Continuous	455		98.6	439		98.6		
Baseline Hba1c <7% Blood glucose: HbA1c (%) – 24wkii	Mean change	199		-0.2 (SD 0.423)	182		-0.26 (SD 0.405)		
baseline Hba1c between 7 and 8% Blood glucose: HbA1c (%) – 24wkii	Mean change	182		-0.4 (SD 0.675)	184		-0.62 (SD 0.543)		
Baseline Hba1c >=8 Blood glucose: HbA1c (%) – 24wkii	Mean change	74		-1.14 (SD 0.86)	73		-1.25 (SD 1.03)		

[a] 95% CI 0.06 to 0.21
[b] difference in proportions 95% CI -12.9 to -1.2%
[c] differnce in proportions 95% CI -11.8 to 0.8%

	[d] 95% CI 4.5 to 11.4 [e] 2 in sitagliptin group required medical assistance [f] (Used in the analysis); Patient days estimated assuming dropouts halfway through the study [g] 95% CI -3.9 to -0.2% [h] one or more AE [i] 95% CI -1.4 to 1.4% [j] 95% CI -1.7 to 1.7% [k] 95% CI -2.1 to 0.8% [l] 95% CI -2.8 to -0.2% [m] lung cancer and not due to study drug [n] 95% CI -0.8 to 2.3% [o] 95% CI -2.6 to -0.0% [p] 95% CI -1.5 to 1.4% [q] approximated to nearest integer (percentages only presented in text) [r] 95% CI -13.6 to -4.7% [s] 95% CI -10.6 to -4.2% [t] 95% CI -2.4 to 0.2% [u] 95% CI -4.0 to 0.3% [v] 95% CI -2.7 to 0.6% [w] 95% CI -2.3 to 2.2% [x] 95% CI -0.0 to 3.2% [y] 95% CI -2.9 to 0.4% [z] 95% CI -3.4 to 0.6% [aa] 95% CI -2.0 to 0.3% [bb] 95% CI -0.3 to 2.4% [cc] 95% CI -2.2 to -0.1% [dd] 95% CI -3.7 to -0.4% [ee] 95% CI 0.9 to 5.8 [ff] 95% CI -3.0 to 1.4 [gg] 95% CI -8.2 to 0.5 (median) [hh] 95% CI 4.1 to 13.3 [ii] estimated from graph [jj] 95% CI -7.2 to -0.2 [kk] 95% CI -5.2 to 2.7 [ll] mean %
	Least squares mean change (LS) were estimated using ANCOVA model with terms for treatment and baseline Hba1c. Other efficcy endpoints were also analysed for the PP poulation using the same ANCOVA model. A non-paramateric approach was used for triglycerides, within treatment effects were estimated using medians. Between treatment differences in clinical AEs of interest (hypoglycaemia and GI events) were evaluated using Fisher's exact test and Wilson score method respectively. For triglycerides, between treatment effects were estimated using the Hodges-Lehmann estimate with a 95% CI based on Wilcoxon's rank sum test.

Table 7: Barnett et al. (2012)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** - **Country:** - **Authors' conclusions:** - **Source of funding:** - **Comments:** Study include participants for whome metformin was not indicated
Number and characteristics of patients	**Total number of patients:** 227 **Inclusion criteria:** Adults (18-80 years) with T2DM, were treatment naïve with HbA1c 7-10% or had previously received oral antidiabetic medication with HbA1c 6.5-9%, ineligible for metformin therapy and had a BMI <=40kg/m2 Treatment naïve = no previous glucose lowering medication or washout period of at least 10 weeks **Exclusion criteria:** -
Previous glucose-lowering	**Any participants previously taking glucose-lowering therapy?** some on oral hypoglycaemic drugs and/or insulin **Details of washout period:** 2 to 6 weeks

therapy	Patients previously on OAD had 4 weeks washout followed by 2 weeks open label placebo treatment Treatment naïve patients had 2 weeks open label placebo treatment
Lifestyle advice	Not reported
Follow-up	**Total follow-up (wks):** 52 **Length of titration period (wks):** - **Length of maintenance period (wks):** 52 **Frequency of monitoring appointments:** Assessments at baseline, 18 weeks (Stage 1), 52 weeks (Stage 2 - 34 week extension trial) Stage 1: linagliptin vs placebo (18 weeks) Stage 2: linagliptin vs placebo/glimepiride (34 weeks extension following 18 weeks) Stage 2 data not extracted as groups are not equivalent
Arms	**(1) Linagliptin** N: 151 Treatment duration (wks): 18 Washout period (d): 42 Comments: Linagliptin dose = 5mg once a day 44.9% had received OADs Washout period variable depending on previous OAD. Treatment naïve = 2 weeks washout, Previous OAD = 6 weeks washout During Stage 1 (first 18 weeks), 17 people received rescue medication (mean days = 43) Treatment(s): Linagliptin (Oral) – fixed-dose Set dose (mg/d):5 Frequency of dosing: once a day **(2) Placebo** N: 76 Treatment duration (wks): 18 Washout period (d): 42 Comments: 48% had received OAD's Washout period variable depending on previous OAD. Treatment naïve = 2 weeks washout, Previous OAD = 6 weeks washout During Stage 1 (first 18 weeks), 13 people received rescue medication (mean days = 39) Treatment(s): Placebo Frequency of dosing: once a day
Outcomes	

Baseline characteristics

		Linagliptin			Placebo				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years) – 0wk	Continuous	151		56.4 (SD 10.6)	76		56.7 (SD 9.7)		
Sex (n male) – 0wk	Dichotomous	151	55	(36.4%)	76	33	(43.4%)		
Blood glucose: HbA1c (%) – 12wk	Continuous	151		8.1 (SD 1)	76		8.1 (SD 0.9)		
Fasting plasma glucose (mg/dl) – 0wk	Continuous	151		183 (SD 46)	76		181 (SD 45)		
Body weight: BMI (kg/m2) – 0wk	Continuous	151		29.1 (SD 5.6)	76		30.2 (SD 5)		
Weight (kg) – 0wk	Continuous	151		77 (SD 18.8)	76		80.9 (SD 19.1)		
Full analysis set (FAS) or efficacy analysis pop Previous blood glucose lowering drugs: Diet alone (i.e. drug naïve) – 0wk	Dichotomous	147	81	(55.1%)	73	38	(52.1%)		

Results

	Linagliptin			Placebo				
	N	k	mean	N	k	mean	Δ	p

	Hypoglycaemic events: All hypoglycaemic events (no events) – 18wk	Count	18144	2		8820	0			
	Dropouts: Total dropouts – 18wka	Dichotomous	151	14	(9.3%)	76	12	(15.8%)		
	Dropout due to AEs – 18wk	Dichotomous	151	1b	(0.7%)	76	0a	(0.0%)		
	Randomised set/treated set Blood glucose: HbA1c (%) – 12wkc	Mean change	129		-0.56667 (SD -0.757)	57		0.24444 (SD 1.07)		

[a] Data taken from flow diagram
[b] Data taken from flow diagram. Discrepancy with data in Table
[c] Estimated from graph. SD estimated from SE

Table 8: Barzilai et al. (2011)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** USA **Authors' conclusions:** In this study, sitagliptin treatment significantly and rapidly improved glycaemic measures and was well tolerated in patients aged 65 years and older with type 2 diabetes **Source of funding:** funded by Merck & Co **Comments:** Randomised, double-blind, placebo-controlled trial. A computer generated schedule was used for randomisation sequence but details of allocation concealment and blinding were not reported
Number and characteristics of patients	**Total number of patients:** 206 **Inclusion criteria:** Eligible patients were of either gender, community dwelling, at least 65 years of age, and had type 2 diabetes that was inadeqautely controlled by diet and exercise alone (Hba1c 7-10%). Patients on oral antihyperglycaemic agent (AHA) monotherapy or low-dose combination therapy at the time of screening were eligible to participate if Hba1c following washout of therapy was between 7 and 10% **Exclusion criteria:** Patients who received insulin or exenatide within 8 weeks prior to screening were excluded. Also excluded were patients with type 1 diabetes, active liver disease, a recent change in cardiovascular status (such as ACS) or an estimated creatinine clearance (eCrCl) <35 ml/min. Following randomisation, patients were discontinued if they did not meet progressively lower limits for FPG: <=270 mg/dl through week 6, <=240 mg/dl after week 6 through week 12 and <=200 mg/dl thereafter Pre-randomisation phase: Randomisation was preceded by an 8-10 week period of AHA washout and /or adjustment of blood pressure, lipid altering, or thyroid medication that included the 2-week placebo (single blind) run-in period. Patients who required no washout or adjustment of medications entered directly into the 2 week placebo run-in period approx 1 week after screening. For patients who had taken AHA therapy other than Thiazolinediones within 8 weeks prior to screening, the washout period was 6 weeks. For patients who had taken a Thiazolidinedione within 8 weeks prior to screening, the duration of the washout/dose adjustment period was 8 weeks. Thus the combined washout/dose adjustment and placebo run-in periods were 8 weeks in those who discontinued other AHA therapies and 10 weeks in patients who discontinued therapy with a thiazolidinedione. To qualify for randomisation, patients were required to have a Hba1c between 7 and 10% at the time of entry into the placebo run-in periodand a fingerstick fasting blood glucose <=260 mg/dl upon completion of the run-in period
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** some on oral hypoglycaemic drugs and/or insulin **Details of washout period:** washout varied between 8-10 weeks (see pre-randomisation for more details of washout)
Lifestyle advice	Not reported
Follow-up	**Total follow-up (wks):** 34 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 24 **Frequency of monitoring appointments:** Physical examinations were performed at the screening visit, the

	randomisation visit and the final study visit (week 24). No further details reported.
Arms	**(1) Sitagliptin** N: 102 Treatment duration (wks): 24 Washout period (d): 70 Comments: Washout 6-8 weeks and 2 week placebo run-in period Treatment(s): Sitagliptin (Oral) – fixed-dose Set dose (mg/d):100 Frequency of dosing: once a day Compliance: compliance was assessed by counting the remaining tablets Details of dosing regimen: patients took 2 tablets of 50 mg sitagliptin (100 mg/day) once daily if their current eCrCl was >=50 and one tablet if their eCrCl was <50 and >=30 ml/min. It was prespecified that a decline to <30 ml/min would result in discontinuation **(2) Placebo** N: 104 Treatment duration (wks): 24 Washout period (d): 70 Comments: Washout 6-8 weeks and 2 week placebo run-in period Treatment(s): Placebo
Outcomes	**General** Efficacy outcomes were analysed using populations defined for each endpoint as the set of all randomised patients who received at least one dose of study medication and had both a baseline measurement and at least one post-randomisation measurement of the respective end-point. Safety and tolerability were analysed using all randomised patients who received at least one dose of the double-blind study medication (placebo n=104, sitagliptin n=102) Outcomes not reported in this evidence table include fasting insulin, proinsulin to insulin ratio, c-peptide, HOMA-beta, HOMA-IR, QUICKI, 1,5-anhydroglucitol. Analyses from pre-specified subgroups were only extracted if measures of dispersion were reported 47 (45%) in placebo group and 32 (31%) in sitagliptin group discontinued the study

Baseline characteristics

		Sitagliptin			Placebo				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	102		71.6 (SD 6.1)	104		72.1 (SD 6)		
Sex (n male)	Dichotomous	102	48	(47.1%)	104	49	(47.1%)		
Duration of diabetes (yrs)	Continuous	102		7.2 (SD 7.3)	104		7 (SD 7.5)		
Ethnicity-White	Dichotomous	102	76	(74.5%)	104	86	(82.7%)		
Ethnicity-Black	Dichotomous	102	10	(9.8%)	104	9	(8.7%)		
Ethnicity-Asian	Dichotomous	102	3	(2.9%)	104	3	(2.9%)		
Ethnicity-Hispanic	Dichotomous	102	9	(8.8%)	104	6	(5.8%)		
Ethnicity-Other	Dichotomous	102	4	(3.9%)	104	0	(0.0%)		
Blood glucose: HbA1c (%) – 0wk	Continuous	102		7.8 (SD 0.8)	104		7.8 (SD 0.7)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	102		9.768 (SD 2.72)	104		9.3795 (SD 2.11)		
Body weight: BMI (kg/m2)	Continuous	102		30.8 (SD 5.9)	104		31.1 (SD 7.2)		
Weight (kg) – 0wk	Continuous	102		85.6 (SD 16.6)	104		85.8 (SD 16.5)		
Previous blood glucose lowering drugs: Oral antidiabetic medication	Dichotomous	102	59	(57.8%)	104	64	(61.5%)		

Results

	Sitagliptin			Placebo				
	N	k	mean	N	k	mean	Δ	p

Blood glucose: HbA1c (%) – 12wka	Continuous	101		7.47 (SD 0.502)	91		8.06 (SD 0.763)		
HbA1c (%) – 24wk	Mean change	101		-0.5 (SD 1.03)	91		0.2 (SD 0.973)		0.043b
HbA1c (%) – 24wk	Mean change	101		-0.5 (SD 1.03)	91		0.2 (SD 0.973)	MD=-0.700 (CI: -0.900, -0.500)	<0.001
HbA1c (%) – 24wka	Continuous	101		7.51 (SD 0.703)	91		8.12 (SD 0.954)		
HbA1c < 7% or <=7% – 24wk	Dichotomous	101	35	(34.7%)	91	14	(15.4%)		<0.001c
Fasting plasma glucose (mmol/l) – 12wka	Continuous	101		8.658936 (SD 1.67)	91		9.71355 (SD 2.12)		
Fasting plasma glucose (mmol/l) – 24wka	Continuous	101		8.88096 (SD 1.95)	91		10.102092 (SD 2.65)		
Fasting plasma glucose (mmol/l) – 24wk	Mean change	96		-0.888 (SD 3.61)	88		0.6105 (SD 3.72)	MD=-1.499 (CI: -2.220, -0.777)	<0.001
2-h post prandial glucose (mmol/l) – 24wk	Mean change	74		-2.886 (SD 5.36)	68		0.4995 (SD 4.9)	MD=-3.386 (CI: -4.551, -2.220)	<0.001
0.5-h postprandial (mmol/l) – 24wkd	Continuous								
self-monitored BG level (mg/dl) – 24wk	Mean change	59		-25.7 (SD 33.3)	62		-2.1 (SD 34.5)	MD=-23.500 (CI: -32.600, -14.400)	<0.001
Body weight: Weight (kg) – 24wk	Mean change	101		-1.1	91		-1.7e		0.299
Hypoglycaemic events: All hypoglycaemic events (no patients) – 24wk	Dichotomous	102	0	(0.0%)	104	0	(0.0%)		
Adverse events: GI: nausea – 24wk	Dichotomous	102	0	(0.0%)	104	0	(0.0%)		
Any adverse event(s) – 24wk	Dichotomous	102	47	(46.1%)	104	55	(52.9%)	MD=-6.800 (CI: -20.000, 6.400)	
Any serious adverse event(s) – 24wk	Dichotomous	102	7	(6.9%)	104	14	(13.5%)	MD=-6.600 (CI: -15.200, 2.000)	
Serious AE drug related – 24wk	Dichotomous	102	0	(0.0%)	104	0	(0.0%)		
Study drug-related adverse event – 24wk	Dichotomous	102	11	(10.8%)	104	9	(8.7%)	MD=2.100 (CI: -6.300, 10.500)	
Bone fracture – 24wk	Dichotomous	102	0	(0.0%)	104	2	(1.9%)		f
cardiovascular AE – 24wk	Dichotomous	102	2	(2.0%)	104	6	(5.8%)		NS
confusion – 24wk	Dichotomous	102	0	(0.0%)	104	4	(3.8%)	MD=-3.800 (CI: -9.500, 1.900)	
GI: diarrhoea – 24wk	Dichotomous	102	1	(1.0%)	104	1	(1.0%)	MD=0.000 (CI: -4.300, 4.300)	
GI: vomiting – 24wk	Dichotomous	102	0	(0.0%)	104	1	(1.0%)	MD=-1.000 (CI: -5.200, 3.200)	
GI: abdominal pain – 24wk	Dichotomous	102	2	(2.0%)	104	0	(0.0%)	MD=2.000 (CI: -1.960, 5.960)	
GI: constipation – 24wk	Dichotomous	102	5	(4.9%)	104	0	(0.0%)	MD=4.900 (CI: 0.400, 9.400)	

	Infection (upper airway or other common) – 24wk	Dichotomous	102	3	(2.9%)	104	5	(4.8%)	MD=-1.900 (CI: -8.100, 4.300)	
	Laboratory adverse events – 24wk	Dichotomous	102	3	(2.9%)	104	2	(1.9%)		f
	Nasopharyngitis – 24wk	Dichotomous	102	4	(3.9%)	104	3	(2.9%)	MD=1.000 (CI: -4.700, 6.700)	
	Pain (extremity) – 24wk	Dichotomous	102	5	(4.9%)	104	3	(2.9%)	MD=2.000 (CI: -3.900, 7.900)	
	Sinusitis or sinus abnormality – 24wk	Dichotomous	102	4	(3.9%)	104	2	(1.9%)	MD=2.000 (CI: -3.400, 7.400)	
	UTI – 24wk	Dichotomous	102	4	(3.9%)	104	6	(5.8%)	MD=-1.800 (CI: -8.500, 4.900)	
	Dropouts: Total dropouts – 24wk	Dichotomous	102	32	(31.4%)	104	47	(45.2%)		
	Dropout due to AEs – 24wk	Dichotomous	102	5	(4.9%)	104	3	(2.9%)	MD=2.000 (CI: -3.900, 7.900)	
	Drop out due to unsatisfactory effect – 24wk	Count	102			104				0.068g
	Drop out due to unsatisfactory effect – 24wk	Dichotomous	102	11	(10.8%)	104	18	(17.3%)		
	Baseline Hba1c <8% Blood glucose: HbA1c (%) – 24wk	Mean change	68		-0.4 (SD 0.841)	64		0.2 (SD 1.22)	MD=-0.500 (CI: -0.800, -0.200)	
	baseline Hba1c >=8 to <9% Blood glucose: HbA1c (%) – 24wk	Mean change	20		-0.6 (SD 0.913)	22		0.4 (SD 0.957)	MD=-0.900 (CI: -1.400, -0.400)	
	baseline Hba1c >=9% Blood glucose: HbA1c (%) – 24wk	Mean change	13		-0.8 (SD 0.92)	5		0.8 (SD 0.799)	MD=-1.600 (CI: -2.400, -0.800)	

[a] estimated from graph
[b] for interaction of treatment by hba1c subgroup
[c] no other details reported
[d] graph
[e] No SD reported
[f] not reported
[g] Kaplan-Meier

Least squares mean (LS-mean) changes from baseline in continuous efficacy variables and between group differences were evaluated using an ANCOVA model. This model included terms for treatment, prior AHA status (on or not on AHA therapy within 8 weeks prior to screening visit), age and baseline eCrCl. When endpoint data was missing, last measurements were carried forward. For AEs with an incidence of 4 or more patients in either group, between group differences were estimated with 95% CI using Wilson score method. Between group comparisons of five prespecified AEs were assessed using Fisher's exact test. Estimates for adverse events are difference in percentage.

Table 9: Bautista et al. (2003)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral

	Parallel / crossover: Parallel **Country:** USA (7 centres in California) **Authors' conclusions:** The results indicate that once daily glimpiride plus diet/exercise was effective in Mexican Americans with type 2 diabetes whose disease was inadequately controlled with diet/exercise alone. It appeared to be well tolerated in the population studied. More weight gain was seen with glimepiride compared with placebo. **Source of funding:** funded by a research grant from Aventis Pharmaceuticals **Comments:** Multicentre, randomised, double-blind placebo controlled trial but no details of randomisation methods, allocation concelament or blinding
Number and characteristics of patients	**Total number of patients:** 70 **Inclusion criteria:** Mexican American men and women aged 35-80 years were eligible to participate if they had uncontrolled type 2 diabetes, with an FPG level between 120 and 225 mg/dl and a Hba1c value of 8 to 10.5%. Patients must have attempted glycaemic control for at least 3 months with diet/exercise alone. **Exclusion criteria:** A history of pharmacologic therapy for diabetes during the previous 3 months or over 6 months use of continuous or intermittent insulin therapy precluded participation. Additional exclusion criteria included clinically relevant medical or psychological condition, participation in an investigational drug study within 1 month of study entry and pregnancy or lactation. Patients were withdrawn from the study for severe hypoglycaemia Pre-randomisation phase: There was a 3 to 14 day screening period before randomisation. It has been assumed that baseline measurements were taken at the screening period and the endpoint measures were taken at approximately 16 weeks.
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** some on oral hypoglycaemic drugs and/or insulin **Details of washout period:** no AHAs in the previous 3 months
Lifestyle advice	continued diet and exercise
Follow-up	**Total follow-up (wks):** 16 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 14 **Frequency of monitoring appointments:** No details reported
Arms	**(1) Glimepiride** N: 48 Treatment duration (wks): 14 Washout period (d): 0 Treatment(s): Sulfonylurea (Oral) – flexible-dose (dose-adjusted) Minimum dose (mg/d): 1 Maximum dose (mg/d): 4 Participants achieving full dose (n): 25 Frequency of dosing: once a day Compliance: perecnt compliance with study medication was estimated by the number of dispensed versus returned capsules in each administration interval Details of dosing regimen: 1 mg once daily. All patients were instructed to take 1 capsule with breakfast or the first meal after study visits that required overnight fasting. Titration of glimepiride from 1 mg/day (level 1) to 2 mg/day (level 2) and 4 mg/day (level 3) was permitted at clinic visits 3 to 5 in patients with FPG level >120 mg/dl. In patients taking glimpiride for 91 and 120 days, maintenance doses were 1, 2 and 4mg once daily in 8%, 13% and 60% respectively (assumed ITT population used of 42 in glimpiride group) **(2) placebo** N: 22 Treatment duration (wks): 14 Washout period (d): 0 Treatment(s): Placebo (Oral) Frequency of dosing: once a day Compliance: see glimepiride Details of dosing regimen: Placebo was titrated accordingly for blinding purposes
Outcomes	**General** All analyses were performed in the ITT population comprising of all randomised patients who received study medication and had >=1 pretreatment and postrandomisation assessment. For variables that did not include analysis of change from baseline, the ITT analysis inluded all randomised patients in whom study medication exposure occurred and a postrandomisation assessment was recorded. A per protocol population consisting of ITT patients without any major protocol violations was used in a supportive analysis of the primary efficacy variable. 7 (15%) patient in the glimpiride and 7 (32%) patients in placebo group did not complete the study Outcomes not reported in this evidence table include fasting insulinfibrogen and PAI-1 levels

Blood glucose

Hba1c <=8% (excellent Hba1c defined as <7% and good Hba1c defined as 7-8%)

Hypoglycaemic events

Major/severe hypoglycaemic event (severe hypoglycaemia was defined as requiring assistance from another person for symptoms consistent with hypoglycaemia in conjunction with a blood glucose level <50 mg/dl or prompt recovery after oral carbohydrate, IV glucose or glucagon administration. Hypoglycaemia was also classed as severe if >=1 criterion for reporting a serious adverse event form was met (e.g. death, immediately life threatening))

Baseline characteristics

		All study participants		
		N	k	mean
Previous blood glucose lowering drugs:				
Metformin	Dichotomous	70	10a	(14.3%)
Sulfonylurea	Dichotomous	70	13a	(18.6%)
Other	Dichotomous	70	2a	(2.9%)
Insulin therapy	Dichotomous	70	3a	(4.3%)

[a] approximated to nearest integer (percentages only presented in text)

		Glimepiride			placebo				
		N	k	mean	N	k	mean	Δ	p
Demographics:									
Age (years) a	Continuous	48		48.4 (SD 11.7)	22		50.7 (SD 10)		
Sex (n male)	Dichotomous	48	27	(56.3%)	22	11	(50.0%)		
Duration of diabetes (yrs) a	Continuous	48		4.2 (SD 5.8)	22		5.7 (SD 8.4)		
Blood glucose:									
HbA1c (%) – 0wka	Continuous	48		10 (SD 1.8)	22		10.5 (SD 2.2)		
Fasting plasma glucose (mmol/l) – 0wka	Continuous	48		12.21 (SD 3.88)	22		12.432 (SD 4.16)		
Body weight:									
Weight (kg) – 0wka	Continuous	48		83.3 (SD 17)	22		76.3 (SD 18.5)		

[a] paper reports SE but these are assumed to be SD

Results

		Glimepiride			placebo				
		N	k	mean	N	k	mean	Δ	p
Blood glucose:									
HbA1c (%) – 16wka	Mean change	48		-2.3 (SD 0.3)	22		-0.7 (SD 0.3)	MD=-1.800 (CI: -2.584, -1.016)	<0.001b
HbA1c (%) – 16wka	Mean change	48		-2.3 (SD 0.3)	22		-0.7 (SD 0.3)	MD=-2.100 (CI: -2.884, -1.316)	<0.001c
Hba1c <=8% – 16wk	Dichotomous	42	37	(88.1%)	18	8	(44.4%)		<0.001
Fasting plasma glucose (mmol/l) – 16wka	Continuous	39		9.768 (SD 2.77)	15		11.8215 (SD 4.94)		
Fasting plasma glucose (mmol/l) – 16wk	Mean change	48			22			MD=-2.592 (CI: -4.408, -0.775)	0.007d
Body weight:									
Weight (kg) – 16wke	Continuous	42		2.3	18		-2.1		
Weight (kg) – 16wk	Mean change	42			18			MD=4.800 (CI: 2.644, 6.956)	<0.001f
Hypoglycaemic events:									
All hypoglycaemic events (no patients) – 16wk	Dichotomous	48	0	(0.0%)	22	0	(0.0%)		
Adverse events:									
Any adverse event(s) – 16wk	Dichotomous	48	27	(56.3%)	22	13	(59.1%)		

Any serious adverse event(s) – 16wk	Dichotomous	48	1	(2.1%)	22	1	(4.5%)		
Headache – 16wk	Dichotomous	48	4	(8.3%)	22	2	(9.1%)		
Dropouts: Total dropouts – 16wk	Dichotomous	48	7	(14.6%)	22	7	(31.8%)		
Compliance: Compliance – 16wk	Dichotomous	48	45g	(93.8%)	22	20h	(90.9%)		

[a] SE estimated from graph
[b] 95% CI -2.6 to -1.0 for ITT analysis
[c] per protocol analysis
[d] 95% CI -80 to -13
[e] No SD reported
[f] 95% CI 2.6 to 7.0
[g] approximated to nearest integer (percentages only presented in text); approximated to nearest integer (percentages only presented in text)
[h] approximated to nearest integer (percentages only presented in text)

Assumed SE reported in graphs

Changes in Hba1c, FPG and body weight from baseline to study endpoint were compared using ANCOVA with treatment group and study site as fixed main effects and baseline the covariate. Compliance was analysed and percent deviation from 100% using the Wilcoxon rank sum test. Between group comparison p-values were not reported for adverse events

Table 10: Birkeland et al. (1994)

General

Phase:
☑ monotherapy
☐ dual therapy
☐ triple therapy
☐ insulin monotherapy
☐ insulin+oral

Parallel / crossover: Parallel

Country: unclear but assumed Sweden

Authors' conclusions: Both glipizide and glyburide may achieve and maintain glycaemic reduction and stinulation of insulin secretion during long-term treatment. However, these agents do not prevent the gradual increase in overall glycaemia that develops over time in NIDDM patients

Source of funding: Supported by grant from Farmitalia Carlo Erba and Sweedish National Corporation of Pharmacies

Comments: Double-blind

Number and characteristics of patients

Total number of patients: 46

Inclusion criteria: patients with NIDDM, who were non-pharmacologically treated, Hba1c between 7 and 11%

Exclusion criteria: severe intercurrent illness or signs of chronic cardiac, hepatic, pulmonary or renal disease

Previous glucose-lowering therapy

Any participants previously taking glucose-lowering therapy? All treatment naive/ no OADs at screening

Details of washout period: -

Lifestyle advice

During the run-in period there was renewed ADA nutritional recommendations

Follow-up

Total follow-up (wks): 64

Length of titration period (wks): 0

Length of maintenance period (wks): 64

Frequency of monitoring appointments: -

Arms

(1) Glibenclamide

N: 15

Treatment duration (wks): 64
Washout period (d): 0
Comments: Treatment naïve

Treatment(s): Sulfonylurea (Oral) – flexible-dose (dose-adjusted)

Mean dose (mg/d): 5.5
Minimum dose (mg/d): 1.75
Details of dosing regimen: dose was adjusted weekly to achieve FBG <8.0 mmol/l and Hba1c <7.5%

(2) Placebo

N: 16

Treatment duration (wks): 60
Washout period (d): 0
Comments: Treatment naïve

Treatment(s): Placebo (Oral)

(3) Glipizide

N: 15

Treatment duration (wks): 60
Washout period (d): 0
Comments: Treatment naïve

Treatment(s): Sulfonylurea (Oral) – flexible-dose (dose-adjusted)
Mean dose (mg/d): 9.4
Details of dosing regimen: Glipizide, po. One tablet (2.5 mg/day), adjusted weekly by adding 1 tablet at the time to achieved target. Max dose was 6 tablets/day (4 before breakfast + 2 before dinner). The mean doses of glipizide were 5 and 9.4 mg/day at 3 and 15 months respectively.

(4) Any sulfonylurea

N: 30

Treatment duration (wks): -
Washout period (d): 0
Comments: Treatment naïve

Treatment(s): Sulfonylurea (Oral) – flexible-dose (dose-adjusted)
Details of dosing regimen: glibenclamide, po. One tablet (1.75 mg) in the morning, dose adjusted weekly by adding 1 tablet at the time. Max 6 tablets a day (4 before breakfast, 2 before dinner). Mean doses of glibenclamide at 3 and 15 months were 2.6 and 5.5 mg/day respectively.

Outcomes

General

Total dropouts not reported

Baseline characteristics

		All study participants		
		N	**k**	**mean**
Demographics:				
Age (years)	Continuous	46		59 (SD 7)
Sex (n male)	Dichotomous	46	22	(47.8%)
Body weight:				
BMI (kg/m2)	Continuous	46		26.4 (SD 3.9)
Weight (kg)	Continuous	46		74.51136 (SD 11.00736) a

[a] estimated from BMI assuming mean height of 1.68m

		Glibenclamide			Placebo				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Blood glucose:									
HbA1c (%) – 0moa	Continuous	15		8.3 (SD 1.4)	16		8.05 (SD 1)		
Fasting plasma glucose (mmol/l) – 0mo	Continuous	15		9.5 (SD 2.4)	16		9 (SD 2.4)		

[a] estimated from graph

		Glibenclamide			Glipizide				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Blood glucose:									
HbA1c (%) – 0moa	Continuous	15		8.3 (SD 1.4)	15		7.9 (SD 1)		
Fasting plasma glucose (mmol/l) – 0mo	Continuous	15		9.5 (SD 2.4)	15		10.1 (SD 2.7)		

[a] estimated from graph

		Placebo			Glipizide				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 0moa	Continuous	16		8.05 (SD 1)	15		7.9 (SD 1)		
Fasting plasma glucose (mmol/l) – 0mo	Continuous	16		9 (SD 2.4)	15		10.1 (SD 2.7)		

[a] estimated from graph

Results

		Glibenclamide			Placebo				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 3moa	Continuous	15		7.1 (SD 0.9)	16		8.1 (SD 1)		
HbA1c (%) – 6moa	Continuous	15		7.35 (SD 0.9)	16		8.1 (SD 1)		
HbA1c (%) – 12moa	Continuous	15		7.3 (SD 1.3)	16		8.5 (SD 0.95)		
HbA1c (%) – 15mo	Continuous	15		7.55 (SD 1.4) a	16		8.6 (SD 1)		
Fasting plasma glucose (mmol/l) – 12mo	Continuous	15		7.7 (SD 1.7)	16		9.8 (SD 3.1)		
Fasting plasma glucose (mmol/l) – 64mo	Continuous	15		8.4 (SD 3.1)	16		10.1 (SD 3)		

[a] estimated from graph

		Glibenclamide			Glipizide				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 3moa	Continuous	15		7.1 (SD 0.9)	15		7.2 (SD 0.9)		
HbA1c (%) – 6moa	Continuous	15		7.35 (SD 0.9)	15		7.5 (SD 1.1)		
HbA1c (%) – 12moa	Continuous	15		7.3 (SD 1.3)	15		7.6 (SD 0.7)		
HbA1c (%) – 15moa	Continuous	15		7.55 (SD 1.4)	15		7.75 (SD 0.8)		
Fasting plasma glucose (mmol/l) – 12mo	Continuous	15		7.7 (SD 1.7)	15		9.1 (SD 2.1)		
Fasting plasma glucose (mmol/l) – 64mo	Continuous	15		8.4 (SD 3.1)	15		9.3 (SD 2.4)		

[a] estimated from graph

		Glibenclamide			Any sulfonylurea				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 3mo	Continuous	15		7.1 (SD 0.9) a	30		7.6 (SD 1.1) b		
Fasting plasma glucose (mmol/l) – 64mo	Continuous	15		8.4 (SD 3.1)	30		8.9 (SD 2.8) c		

[a] estimated from graph
[b] from cochrane review
[c] from cochrane

		Placebo			Glipizide				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 3moa	Continuous	16		8.1 (SD 1)	15		7.2 (SD 0.9)		
HbA1c (%) – 6moa	Continuous	16		8.1 (SD 1)	15		7.5 (SD 1.1)		
HbA1c (%) – 12moa	Continuous	16		8.5 (SD 0.95)	15		7.6 (SD 0.7)		

HbA1c (%) – 15mo	Continuous	16		8.6 (SD 1)	15		7.75 (SD 0.8) a		
Fasting plasma glucose (mmol/l) – 12mo	Continuous	16		9.8 (SD 3.1)	15		9.1 (SD 2.1)		
Fasting plasma glucose (mmol/l) – 64mo	Continuous	16		10.1 (SD 3)	15		9.3 (SD 2.4)		

[a] estimated from graph

		Placebo			Any sulfonylurea				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 3mo	Continuous	16		8.1 (SD 1) a	30		7.6 (SD 1.1) b		
Fasting plasma glucose (mmol/l) – 64mo	Continuous	16		10.1 (SD 3)	30		8.9 (SD 2.8) c		
Hypoglycaemic events: Major/severe hypoglycaemic event – 64mo	Dichotomous	16	0	(0.0%)	30	0	(0.0%)		
Dropouts: Dropout due to AEs – 64mo	Dichotomous	16	4	(25.0%)	30	2	(6.7%)		

[a] estimated from graph
[b] from cochrane review
[c] from cochrane

		Glipizide			Any sulfonylurea				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 3mo	Continuous	15		7.2 (SD 0.9) a	30		7.6 (SD 1.1) b		
Fasting plasma glucose (mmol/l) – 64mo	Continuous	15		9.3 (SD 2.4)	30		8.9 (SD 2.8) c		

[a] estimated from graph
[b] from cochrane review
[c] from cochrane

Table 11: Bosi et al. (2009)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** over 250 centres in USA, Canada, Europe, South America and India **Authors' conclusions:** In treatment naïve patients, combinations of vildagliptin and both high dose and low dose metformin provide superior efficacy to monotherapy treatments with a comparable overall tolerability profile and low risk og hypoglycaemia. The potential dose sparing effect of adding vildagliptin to low-dose metformin in preference to the uptitration of metformin may allow patients to achieve equivalent or superior Hba1c lowering without the GI tolerability issues associated with higher odses of metformin **Source of funding:** Supported by Novartis Pharmaceuticals Corporation **Comments:** double-blind, randomised, active-controlled study-no details of randomisation methods, allocation concealment or blinding
Number and characteristics of patients	**Total number of patients:** 1179 **Inclusion criteria:** patients diagnosed with type 2 diabetes for >= 4 weeks were screened and assessed for eligibility. Male and female (non-fertile or using a medically approved birth control method), treatment naïve patients aged 18-78 years with a BMI 22-40 kg/m2, FPG <15 mmol/l and Hba1c 7.5-11% could participate **Exclusion criteria:** pregnant or lactating women, patients with a history of type 1 diabetes, diabetes resulting from pancreatic injury, secondary forms of diabetes or acute metabolic diabetic complications within

	the past 6 months. Other exclusion criteria were evidence of significant diabetic complications, acute infections and other concurrent medication that might have affected interpretation of efficacy and safety data, myocardial infarction, coronary artery bypass surgery, unstable angina or stroke within the past 6 months, congestive heart failure requiring pharamcological treatment, ECG abnormalities, liver disease, chronic insulin treatment within the past 6 months, involvement in a previous vildagliptin or other DPP-4 inhibitor trial, use of investigational drugs within 30 days of visit 1, alanine aminotransferase or aspartate aminotransferase >2 times the upper limit of the normal range (ULN), total bilirubin > 2 times ULN or direct bilirunbin >ULN, clinically significantrenal dysfunction or any other clinically significant laboratory abnormalities. Patients who met all the inclusion criteria execpt for glycaemic parameters could participate in a 24 week open label, single arm substudy (data not extracted) Pre-randomisation phase: titrtaion periods for metformin were part of the main treatment period
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** some on oral hypoglycaemic drugs and/or insulin **Details of washout period:** No details provided but inclusion criteria allowed individuals with previous AHA provided none were taken at least 12 weeks prior to enrollment
Lifestyle advice	no details reported
Follow-up	**Total follow-up (wks):** 24 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 24 **Frequency of monitoring appointments:** The primary efficacy variable (hba1c) was assessed at weeks -2, 0 (baseline), 2, 4, 6, 12, 18 and 24
Arms	**(1) Metformin monotherapy (1000 mg bid)** N: 294 Treatment duration (wks): 24 Washout period (d): 0 Comments: Patients should not have received AHA in previous 12 weeks to enrollment Treatment(s): Metformin (Oral) – forced titration Set dose (mg/d):2000 Frequency of dosing: once a day Details of dosing regimen: To mimic clinical practice and avoid potential gastrointestinal Aes metformin was initiated at 500 mg once daily and increased to achieve optimal glycaemic control in 500 mg increments at weeks 2, 4 and 6 **(2) Vildagliptin monotherapy (50mg bid)** N: 300 Treatment duration (wks): 24 Washout period (d): 0 Comments: Patients should not have received AHA in previous 12 weeks to enrollment Treatment(s): Vildagliptin (Oral) – fixed-dose Set dose (mg/d):100 Frequency of dosing: twice a day
Outcomes	**General** The safety population included all patients who received at least one dose of study drug and had at least one post-baseline safety assessment. The ITT population included patients who received at least one dose of the study drug and had at least one post-bseline primary efficacy variable assessment. The primary analysis was based on the ITT population. The last observation carried forward method was usesd for patients missing a week 24 assessment. Discontinuation rates were 11.9% for vildagliptin + high dose metformin, 15.5% for vildagliptin + low dose metformin, 18.3% for vildagliptin and 16.7% for metformin Outcomes not extracted in this evidence table include data relating to an open label, single arm substudy where patients did not achieve glycaemic paramaters and were given vildagliptin + high dose metformin (100 mg od + 1000 mg tid). All other outcomes were extracted. Data from 2 arms have not been extracted as they are dose comparisons of 2 OADs (outside protocol for first intensification) **Hypoglycaemic events** Major/severe hypoglycaemic event (severe hypoglycaemia (episode required hospitalisation or assistance of a third party) were also recorded) symptomatic (confirmed) (Hypoglycaemic events (symptoms suggestive of hypoglycaemia and confirmed by self-monitored plasma glucose <56 mg/dl (3.1 mmol/l))
Baseline characteristics	

	All study participants		
	N	**k**	**mean**

Demographics:				
Age (years)	Continuous	1179		52.8 (SD 10.65)
Sex (n male)	Dichotomous	1179	684	(58.0%)
Duration of diabetes (months)	Continuous	1179		24.34 (SD 36.91)
Ethnicity-White	Dichotomous	1179	867	(73.5%)
Ethnicity-Black	Dichotomous	1179	48	(4.1%)
Ethnicity-Asian	Dichotomous	1179	122	(10.3%)
Ethnicity-Hispanic	Dichotomous	1179	113	(9.6%)
Ethnicity-Other – wk	Dichotomous	1179	29	(2.5%)
Blood glucose:				
Fasting plasma glucose (mmol/l) – wk	Continuous	1179		10.44 (SD 2.85)
Fasting plasma glucose (mmol/l) – wk	Continuous	1179		10.44 (SD 2.85)
Body weight:				
BMI (kg/m2)	Continuous	1179		31.25 (SD 4.76)
Weight (kg) – wk	Continuous	1179		88.25 (SD 17.68)
Weight (kg) – wk	Continuous	1179		88.25 (SD 17.68)
ITT				
Blood glucose:				
HbA1c (%) – wk	Continuous	1179		8.65 (SD 0.1)
HbA1c (%) – wk	Continuous	1179		8.65 (SD 0.1)

		Metformin monotherapy (1000 mg bid)			**Vildagliptin monotherapy (50mg bid)**				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Demographics:									
Age (years)	Continuous	294		52.4 (SD 10.7)	300		53.5 (SD 11)		
Sex (n male)	Dichotomous	294	171	(58.2%)	300	180	(60.0%)		
Duration of diabetes (months)	Continuous	294		26.26 (SD 39.9)	300		25.48 (SD 39.8)		
Ethnicity-White	Dichotomous	294	212	(72.1%)	300	225	(75.0%)		
Ethnicity-Black	Dichotomous	294	14	(4.8%)	300	8	(2.7%)		
Ethnicity-Asian	Dichotomous	294	30	(10.2%)	300	30	(10.0%)		
Ethnicity-Hispanic	Dichotomous	294	27	(9.2%)	300	31	(10.3%)		
Ethnicity-Other – 0wk	Dichotomous	294	11	(3.7%)	300	6	(2.0%)		
Blood glucose:									
Fasting plasma glucose (mmol/l) – 0wk	Continuous	294		10.48 (SD 2.77)	300		10.32 (SD 3)		
Body weight:									
BMI (kg/m2)	Continuous	294		31.31 (SD 4.58)	300		31.26 (SD 4.82)		
Weight (kg) – 0wk	Continuous	294		88.43 (SD 17.4)	300		87.84 (SD 17.9)		
ITT									
Blood glucose:									
HbA1c (%) – 0wk	Continuous	294		8.62 (SD 0.93)	300		8.68 (SD 1.02)		

Results

		Metformin monotherapy (1000 mg bid)			**Vildagliptin monotherapy (50mg bid)**				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Blood glucose:									
HbA1c (%) – 0wk	Continuous	294			300				a

HbA1c reduction >=1% – 0wk	Dichotomous	294			300				a
HbA1c reduction >=1% – 24wk	Dichotomous	285	175	(61.4%)	287	158	(55.1%)		
Hba1c reduction >=0.7% – 0wk	Dichotomous	294			300				a
Hba1c reduction >=0.7% – 24wk	Dichotomous	285	205	(71.9%)	287	188	(65.5%)		
HbA1c < 7% or <=7% – 0wk	Dichotomous	294			300				a
HbA1c <= 6.5% – 24wk	Dichotomous	285	76	(26.7%)	286	71	(24.8%)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	294			300				a
Fasting plasma glucose (mmol/l) – 24wk	Mean change	294		-1.92 (SD 2.23)	300		-1.26 (SD 2.25)		
Body weight:									
Weight (kg) – 0wk	Continuous	294			300				a
Weight (kg) – 24wkb	Mean change	294		-1.62 (SD 3.77)	300		-0.59 (SD 3.81)		
Hypoglycaemic events:									
symptomatic (confirmed) – 24wk	Count	45276	2		45780	2	c		
Dropouts:									
Total dropouts – 24wk	Dichotomous	294	49c	(16.7%)	300	55	(18.3%)		
Dropout due to AEs – 24wk	Dichotomous	294	13	(4.4%)	300	7	(2.3%)		
drop out due to SAE – 24wkd	Dichotomous	294	2	(0.7%)	300	4	(1.3%)		
Drop out due to unsatisfactory effect – 24wk	Dichotomous	294	5	(1.7%)	300	12	(4.0%)		
ITT									
Blood glucose:									
HbA1c (%) – 12wke	Continuous	285		7.33 (SD 1.35)	287		7.5 (SD 1.36)		
HbA1c (%) – 24wk	Mean change	285		-1.4 (SD 1.01)	287		-1.1 (SD 1.02)		
HbA1c < 7% or <=7% – 24wk	Dichotomous	283	123	(43.5%)	285	114	(40.0%)		
HbA1c <= 6.5% – 0wk	Dichotomous	294			300				a
Safety population									
Hypoglycaemic events:									
Major/severe hypoglycaemic event – 24wk	Dichotomous	292	1	(0.3%)	297	0	(0.0%)		
Adverse events:									
GI: nausea – 24wk	Dichotomous	292	17	(5.8%)	297	7	(2.4%)		
Any adverse event(s) – 24wk	Dichotomous	292	175	(59.9%)	297	153	(51.5%)		
Any serious adverse event(s) – 24wk	Dichotomous	292	12	(4.1%)	297	4d	(1.3%)		
Asthenia – 24wk	Dichotomous	292	4	(1.4%)	297	4	(1.3%)		
Back pain – 24wk	Dichotomous	292	11	(3.8%)	297	6	(2.0%)		
Cough – 24wk	Dichotomous	292	9	(3.1%)	297	8	(2.7%)		
Dizziness – 24wk	Dichotomous	292	12	(4.1%)	297	8	(2.7%)		
Dyspepsia – 24wk	Dichotomous	292	5	(1.7%)	297	3	(1.0%)		
Fatigue – 24wk	Dichotomous	292	15	(5.1%)	297	6	(2.0%)		
GI: diarrhoea – 24wk	Dichotomous	292	32	(11.0%)	297	7	(2.4%)		
GI: vomiting – 24wk	Dichotomous	292	7	(2.4%)	297	1	(0.3%)		
GI: abdominal pain – 24wk	Dichotomous	292	10	(3.4%)	297	6	(2.0%)		
GI: constipation – 24wk	Dichotomous	292	5	(1.7%)	297	10	(3.4%)		
Headache – 24wk	Dichotomous	292	13	(4.5%)	297	16	(5.4%)		
Hypertension – 24wk	Dichotomous	292	10	(3.4%)	297	7	(2.4%)		
Infection (upper airway or other common) – 24wk	Dichotomous	292	8	(2.7%)	297	10	(3.4%)		
Nasopharyngitis – 24wk	Dichotomous	292	14	(4.8%)	297	11	(3.7%)		
Pain (extremity) – 24wk	Dichotomous	292	7	(2.4%)	297	5	(1.7%)		

	Baseline Hba1c <=8% Blood glucose: HbA1c (%) – 24wk	Mean change	90		-0.8 (SD 0.854)	94		-0.8 (SD 1.07)		
	HbA1c < 7% or <=7% – 24wk	Dichotomous	90	46	(51.1%)	94	60	(63.8%)		
	Hba1c>9.0% Blood glucose: HbA1c reduction >=1% – 24wk	Dichotomous	86	73	(84.9%)	98	65	(66.3%)		
	Hba1c>=10% Blood glucose: HbA1c (%) – 24wk	Mean change			-2.6f			-1.5g		

[a] not reported
[b] SD calculated from reported SE
[c] (Used in the analysis)
[d] approximated to nearest integer (percentages only presented in text)
[e] estimated from graph; SD calculated from reported SE
[f] total n for subgroup not reported SE 0.26
[g] total n for subgroup not reported SE 0.24

	Change from baseline in Hba1c was analsyed using an ANCOVA model with treatment and pooled centre as classification variables and baseline Hba1c as covariate. Data are presented as least squares adjusted mean. To control for multiple type 1 errors, the min test and Hochberg's multiple testing step-up procedure was used. Between-group comparison p-values for adverse events and hypoglycaemia were not reported

Table 12: Braun D,Schonherr (1996)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** Germany **Authors' conclusions:** The anti-hyperglycaemic action of acarbose is sufficiemt to justify its use as a first line drug for patients with type 2 diabetes not adequately controlled by diet alone **Source of funding:** Unclear **Comments:** Double-blind
Number and characteristics of patients	**Total number of patients:** 152 **Inclusion criteria:** Patients with type 2 diabetes who are not adequatly controlled by diet alone, with diabetes for at least 2 months, FBG >=7.8 mmol/l, Hba1c >=8% and <=13% **Exclusion criteria:** Previous treatemnt with OADs or insulin, severe impairment of hepatic or renal function, severe intestinal disorders Pre-randomisation phase: There was a 4 week run-in period
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** All treatment naive/ no OADs at screening **Details of washout period:** 4 week run in period; all diet controlled only
Lifestyle advice	-
Follow-up	**Total follow-up (wks):** 24 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 24 **Frequency of monitoring appointments:** -
Arms	**(1) Placebo** N: 44 Treatment duration (wks): - Washout period (d): - Treatment(s): Placebo (Oral)

(2) Acarbose

N: 42

Treatment duration (wks): -

Washout period (d): -

Treatment(s): Acarbose (Oral) – fixed-dose

Set dose (mg/d):300

Details of dosing regimen: Braun (1996)-acarbose, week 1-2 50 mg TID, week 3-24 100 mg TID

Campbell (1998)- acarbose 100 mg TID

Chan (1998)-acarbose, week 1-4 50 mg TID, week 5-24 100 mg TID

Coniff (1995b)- acarbose 100 mg TID. The dosage was titrated at 2 week intervals depending on drug assignment

Fischer (1998)-acarbose 25 mg TID

Gentile (1999)-acarbose, week 1 50 mg TID, week 2-12 100 mg TID

Hanefeld (1991)-acarbose 100 mg TID

Hoffman (1990)-acarbose, week 1-4 50 mg TID, week 5-25 100 mg TID (for one patient dose reduced to 100 mg BID)

Hoffman (1994)-acarbose 100 mg TID

Hoffman (1997)-acarbose 100 mg TID

Holman (1999)-acarbose, 50 mg once, BID & TID at two-week intervals; 4 months after start dosage increased in 3 weeks period with 50 mg per step to 100 mg TID

Hotta (1993)- acarbose 100 mg TID

Meneilly (2000)-acarbose, week 1: 50 mg once daily, week 2: 50 mg BID, week 3: 50 mg TID, week 4-52 titrated upward to 100 mg TID when post-load blood glucose > 12 mmol/l, downtitrated in case of intolerance

Rosenthal (2002)-acarbose, 50 mg TID, uptitrated to 100 mg TID

Salman (2001)- acarbose, week 1 to 4 every week 50 mg increase to 100 mg BID, week 4-24 100 mg TID, dose reduced to 100 mg BID in case of adverse events

Santeusanio (1993)-acarbose 100 mg TID

Scott (1999)- acarbose, week 1-2 50 mg TID, wk 3-16 100 mg TID, dose reduced to 50 mg TID in case of adverse events

Spengler (1992)-acarbose, week 1-2 50 mg TID, week 3-24 100 mg TID

Outcomes

General

Dropouts (total and due to adverse events) not reported

Baseline characteristics

		Placebo			Acarbose				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	44		61 [rng 42–74]	42		60 [rng 47–75]		
Sex (n male)	Dichotomous	44	24	(54.5%)	42	26	(61.9%)		
Duration of diabetes (months)	Continuous	44		17 [rng 3–60]	42		16 [rng 3–48]		
Blood glucose: HbA1c (%) – 0wk	Continuous	44		9.9 (SD 1.5)	42		10 (SD 1.5)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	44		10 (SD 2.2)	42		9.9 (SD 2.2)		
Body weight: BMI (kg/m2)	Continuous	44		26 [rng 22–31]	42		26 [rng 20–32]		
Weight (kg) – 0wk	Continuous	44		76 (SD 8.6)	42		76.3 (SD 10.1)		
Lipids: Total cholesterol (mmol/l) – 0wk	Mean change	44		6.2 (SD 0.9)	42		6.2 (SD 1.2)		
HDL cholesterol (mmol/l) – 0wk	Mean change	44		1.2 (SD 0.5)	42		1.1 (SD 0.3)		
Triglycerides (mmol/l) – 0wk	Mean change	44		2.1 (SD 0.6)	42		2.1 (SD 0.5)		

Results

		Placebo			Acarbose			Δ	p
		N	k	mean	N	k	mean		
Blood glucose: HbA1c (%) – 16wka	Continuous	44		9 (SD 2)	42		8 (SD 2)		
HbA1c (%) – 24wk	Continuous	44		8.9 (SD 2.6)	42		7.5 (SD 2.1)		
Fasting plasma glucose (mmol/l) – 16wka	Continuous	44		9.5 (SD 2.1)	42		8 (SD 1.7)		
Fasting plasma glucose (mmol/l) – 24wk	Continuous	44		8.9 (SD 2.6)	42		7.5 (SD 2.1)		
Body weight: Weight (kg) – 16wka	Continuous	44		76 (SD 7.1)	42		76 (SD 9)		
Weight (kg) – 24wk	Continuous	44		76 (SD 7.9)	42		75.3 (SD 9.6)		
Adverse events: GI: nausea – 24wk	Dichotomous	44	1	(2.3%)	42	0	(0.0%)		
Lipids: Total cholesterol (mmol/l) – 24wk	Continuous	44		5.9 (SD 1)	42		5.3 (SD 0.8)		
HDL cholesterol (mmol/l) – 24wk	Continuous	44		1.3 (SD 0.4)	42		1.2 (SD 0.3)		
Triglycerides (mmol/l) – 24wk	Continuous	44		2 (SD 0.5)	42		1.9 (SD 0.5)		
Safety population Adverse events: Any adverse event(s) – 24wkb	Dichotomous	57	4	(7.0%)	55	21	(38.2%)		

[a] estimated from graph
[b] No of patients

Table 13: Bruce et al. (2006)

General

Phase:
☑ monotherapy
☐ dual therapy
☐ triple therapy
☐ insulin monotherapy
☐ insulin+oral

Parallel / crossover: Parallel

Country: unclear

Authors' conclusions: In this exploratory study the administration of metformin-glibenclamide combination tablets to patients hyperglycaemic despite treatment with diet and exercise was associated with an increased second-phase insulin response, compared with glibenclamide alone.

Source of funding: Funded by a grant from Bristol-Myers Squibb Pharmaceuticals

Comments: double-blind, randomised, multicentre, 3 arm trial. Matching placebos were used in a triple-dummy design but no other details of randomisation methods or allocation concealment

Number and characteristics of patients

Total number of patients: 50

Inclusion criteria: Patients were men or women aged 20-75 years, with a diagnosis of type 2 diabetes within the previous 5 years, and Hba1c >6.7% but <=9.5% on diet and exercise. Subjects were either drug naïve or id not receive any antihyperglycaemia therapy during the 8 weeks prior to screening.

Exclusion criteria: patients were excluded for BMI >40 kg/m2, symptomatic diabetes (marked polyuria and polydipsia with >10% weight loss within 3 months prior to screening), history of chronic insulin use, renal dysfunction, morbid cardiovascular events within 6 months of screening, or other signiifcant renal, hepatic, cardiac or psychiatric disease. Women of child-bearing potential were required to practice a reliable method of contraception

Pre-randomisation phase: A 1 week lead in on a eucaloric, weight maintaining diet was followed by randomisation.

Previous

Any participants previously taking glucose-lowering therapy? All treatment naive/ no OADs at screening

glucose-lowering therapy	**Details of washout period:** No details provided but inclusion criteria stipulated that any participants with AHA must have stopped at least 8 weeks prior to enrollment
Lifestyle advice	At enrolment patients received instructions on miantaining a eucaloric diet for the duration of the study.
Follow-up	**Total follow-up (wks):** 20 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 20 **Frequency of monitoring appointments:** no details reported
Arms	**(1) Metformin** N: 15 Treatment duration (wks): 20 Washout period (d): 0 Comments: Subjects were either drug naïve or id not receive any antihyperglycaemia therapy during the 8 weeks prior to screening Treatment(s): Metformin (Oral) Mean dose (mg/d): 1500 Minimum dose (mg/d): 500 Maximum dose (mg/d): 2000 Frequency of dosing: variable Compliance: Compliance was assessed by interveiw with the participant, review of the study medication that was dispensed and returned, and via a pharmokinetic sample collected during week 2 of the trial. Details of dosing regimen: metformin 500 mg tablets were used. Patients started treatment with one tablet of study therapy daily, with the morning meal. The dosage could be increased by a single tablet at weeks 2, 4, 8, 12 or 16 if the self-monitored mean blood glucose (measured 3-5 days before a study visit) was >=7 mmol/l. In addition, study therapy could be titrated at weeks 12 or 16 if Hba1c >7%. The maximum permitted dose of study treatment was four tablets per day. Dosages of more than one tablet/day were divided between the morning and evening meals. Study treatment was reduced by one tablet if fasting blood glucose was <2.8 mmol/l with symptoms suggestive of hypoglycaemia in the absence of environmental factors known to contribute to hypoglycaemia. Patients with documented hypoglycaemia on one tablet/day were withdrawn form the study **(2) Glibenclamide** N: 17 Treatment duration (wks): 20 Washout period (d): 0 Comments: Subjects were either drug naïve or id not receive any antihyperglycaemia therapy during the 8 weeks prior to screening Treatment(s): Sulfonylurea (Oral) – flexible-dose (dose-adjusted) Mean dose (mg/d): 6.6 Minimum dose (mg/d): 2.5 Maximum dose (mg/d): 10 Frequency of dosing: variable Details of dosing regimen: Glibenclamide 2.5 mg tablets were used. Patients started treatment with one tablet of study therapy daily, with the morning meal. The dosage could be increased by a single tablet at weeks 2, 4, 8, 12 or 16 if the self-monitored mean blood glucose (measured 3-5 days before a study visit) was >=7 mmol/l. In addition, study therapy could be titrated at weeks 12 or 16 if Hba1c >7%. The maximum permitted dose of study treatment was four tablets per day. Dosages of more than one tablet/day were divided between the morning and evening meals. Study treatment was reduced by one tablet if fasting blood glucose was <2.8 mmol/l with symptoms suggestive of hypoglycaemia in the absence of environmental factors known to contribute to hypoglycaemia. Patients with documented hypoglycaemia on one tablet/day were withdrawn form the study
Outcomes	**General** Due to the exploratory nature of this study, no adjustments were made for pair-wise comparisons The primary outcome was the change in second phase insulin response after 20 weeks of double-blind treatment. Outcomes not extracted in this evidence table include insulin, C-peptide, insulin sensitivity measures and glcose turnover during the OGTT 1 (7%) patient in the metformin group and 2 (12%) in the glibenclamide group disontinued the study prematurely Data from the third trial arm was not extracted (combination of metformin and glibenclamide) as this comparison was outside the protocol.

Baseline characteristics

		Metformin			Glibenclamide				
		N	k	mean	N	k	mean	Δ	p
Demographics:									
Age (years)	Continuous	15		48 (SD 9)	17		51 (SD 8)		
Sex (n male)	Dichotomous	15	47	(313.3%)	17	29	(170.6%)		
Duration of diabetes (yrs)	Continuous	15		2.7 (SD 2.2)	17		2.4 (SD 1.6)		
Blood glucose:									
HbA1c (%) – 0wk	Continuous	15		7.6 (SD 1)	17		8 (SD 1.3)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	15		9.6 (SD 2.6)	17		9.8 (SD 2.7)		
Body weight:									
BMI (kg/m2)	Continuous	15		33 (SD 6)	17		36 (SD 4)		

Results

		Metformin			Glibenclamide				
		N	k	mean	N	k	mean	Δ	p
Blood glucose:									
HbA1c (%) – 20wka	Mean change	14		-0.24 (SD 1.31)	15		-0.7 (SD 1.12)		
Fasting plasma glucose (mmol/l) – 20wka	Mean change	14		-1.5 (SD 3.37)	15		-1.8 (SD 2.32)		
Hypoglycaemic events:									
All hypoglycaemic events (no events) – 20wkb	Count	2030	0		2240	13			
All hypoglycaemic events (no patients) – 20wk	Dichotomous	15	0	(0.0%)	17	5	(29.4%)		
Adverse events:									
Any adverse event(s) – 20wk	Dichotomous	15	13	(86.7%)	17	11	(64.7%)		
Death – 20wk	Dichotomous	15	0	(0.0%)	17	0	(0.0%)		
Gastrointestinal disorders (any) – 20wk	Dichotomous	15	8	(53.3%)	17	4	(23.5%)		
Dropouts:									
Total dropouts – 20wk	Dichotomous	15	1	(6.7%)	17	2	(11.8%)		
Dropout due to AEs – 20wk	Dichotomous	15	0	(0.0%)	17	1	(5.9%)		

[a] estimated from graph
[b] reviewer estimated patient days

ANCOVA of log-transformed post to pretreatment ratios of the measurements was completed with main effect terms of treatment and baseline measurement, and age and BMI as covariates. No between group p-values were reported for the outcomes extracted

Table 14: Buchanan et al. (1988)

General

Phase:
☑ monotherapy
☐ dual therapy
☐ triple therapy
☐ insulin monotherapy
☐ insulin+oral

Parallel / crossover: Parallel

Country: UK

Authors' conclusions: The study suggests that acarbose was not an effective substitute for sulfonylureas in non-obese type 2 diabetes uncontrolled by diet alone

Source of funding: Bayer UK

Comments: Double-blind

Number and characteristics of patients

Total number of patients: 20
Inclusion criteria: Non-obese patients with NIDDM, treated with refined carbohydrate/high complex carbohydrate/low fat diet and a sulfonylurea (which had been previously withdrawn)
Exclusion criteria: Pregnant patients, had received insulin or biguanide or were taking drugs with a known diabetogenic effect

Previous glucose-lowering therapy

Any participants previously taking glucose-lowering therapy? all on oral hypoglycaemic drugs and/or insulin
Details of washout period: patients were previously taking sulfonylurea (this had been previously withdrawn) and maintained on diet alone for 8 week run in period

Lifestyle advice

No dietary modifications were introduced (already on low fat diet)

Follow-up

Total follow-up (wks): 24
Length of titration period (wks): 0
Length of maintenance period (wks): 16
Frequency of monitoring appointments: -

Arms

(1) Placebo
N: 9
Treatment duration (wks): 16
Washout period (d): 0
Comments: Treatment naïve
Treatment(s): Placebo (Oral)

(2) Acarbose
N: 11
Treatment duration (wks): 16
Washout period (d): 0
Comments: Treatment naïve
Treatment(s): Acarbose (Oral) – fixed-dose
Set dose (mg/d):300
Frequency of dosing: twice a day
Details of dosing regimen: Acarbose, week 0-2 50 mg TID, week 3-8 100 mg TID, week 9-12: 200-100-100 mg, week 13-16 200-100-200 mg, in case of adverse effects patients were instructed to reduce the dosage of acarbose to that which could be tolerated.

Outcomes

General
Extractable dropout (total, due to adverse events) data not reported.

Baseline characteristics

		Placebo			Acarbose				
		N	k	mean	N	k	mean	Δ	p
Demographics:									
Age (years)	Continuous	11		57.6 (SD 8.2)	9		60.1 (SD 6.8)		
Sex (n male)	Dichotomous	11	8	(72.7%)	9	6	(66.7%)		
Duration of diabetes (months)	Continuous	11		50.6 (SD 30.1)	9		44.9 (SD 28.6)		
Blood glucose:									
HbA1c (%) – 0wk	Continuous	11		10.6 (SD 2.8)	9		11.3 (SD 2.7)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	11		11.6 (SD 3.9)	9		10.5 (SD 3.3)		
Body weight:									
Weight (kg) – 0wk	Continuous	11		69.5 (SD 9.9)	9		73.4 (SD 9.3)		
Lipids:									
Total cholesterol (mmol/l) – 0wk	Continuous	11		6.6 (SD 1.4)	9		7.3 (SD 1.1)		
Triglycerides (mmol/l) – 0wk	Continuous	11		1.9 (SD 1.8)	9		1.5 (SD 0.6)		

Results

	Placebo			Acarbose				
	N	k	mean	N	k	mean	Δ	p

	Blood glucose:									
	HbA1c (%) – 16wk	Continuous	11		12.2 (SD 4)	9		12.4 (SD 3.6)		
	Fasting plasma glucose (mmol/l) – 16wk	Continuous	11		10.9 (SD 5)	9		11.4 (SD 3.7)		
	Body weight:									
	Weight (kg) – 16wk	Continuous	11		67.2 (SD 9.8)	9		70.2 (SD 8.6)		
	Lipids:									
	Total cholesterol (mmol/l) – 16wk	Continuous	11		6.8 (SD 1.8)	9		7.2 (SD 1.1)		
	Triglycerides (mmol/l) – 16wk	Continuous	11		1.7 (SD 1.9)	9		1.7 (SD 0.5)		

Table 15: Campbell et al. (1994)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** Unclear but assumed UK **Authors' conclusions:** In conclusion, metformin gave better glycaemic control than glipizide, with weight loss rather than weight gain in obese type 2 patients **Source of funding:** Unclear **Comments:** Open label
Number and characteristics of patients	**Total number of patients:** 48 **Inclusion criteria:** Patients uncontrolled by diet with no evidence of cardiac failure. **Exclusion criteria:** Unclear
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** All treatment naive/ no OADs at screening **Details of washout period:** -
Lifestyle advice	-
Follow-up	**Total follow-up (wks):** 52 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 52 **Frequency of monitoring appointments:** Patients were seen at 2,4,8,12,24,36 and 52 weeks
Arms	**(1) Metformin** N: 24 Treatment duration (wks): 52 Washout period (d): 0 Comments: All treatment naïve Treatment(s): Metformin (Oral) – flexible-dose (dose-adjusted) Mean dose (mg/d): 1.8 Maximum dose (mg/d): 3000 Details of dosing regimen: Metformin was started at 500mg BID with total daily dose increased in increments of 500 mg at each visit to a maximum of 3000 mg if FBG >8 mmol/l. The dose was reduced if FBG <=4 mmol/l. The mean dose at 24 weeks was 1.7 g and at 52 weeks was 1.8 g. **(2) Sulfonylurea** N: 24 Treatment duration (wks): 52 Washout period (d): 0 Comments: All treatment naïve Treatment(s): Sulfonylurea (Oral) – flexible-dose (dose-adjusted)

Minimum dose (mg/d): 5
Maximum dose (mg/d): 30
Details of dosing regimen: Glipizide was started at 5 mg od and increased in increments of 5 mg to a maximum divided dose of 30 mg if FBG > 8 mmol/l.

Outcomes

Baseline characteristics

		Metformin			Sulfonylurea				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	24		57 (SD 10)	24		57 (SD 9)		
Sex (n male)	Dichotomous	24	8	(33.3%)	24	8	(33.3%)		
Duration of diabetes (yrs)	Continuous	24		2.3 (SD 3.4)	24		2.8 (SD 3.9)		
Blood glucose: HbA1c (%) – 0wk	Continuous	24		11.46 (SD 1.92)	24		11.75 (SD 2.11)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	24		11.2 (SD 2.8)	24		12.2 (SD 3.3)		
Body weight: BMI (kg/m2)	Continuous	24		29.6 (SD 5.6)	24		31.2 (SD 6.6)		
Weight (kg) – 0wk	Continuous	24		78.2 (SD 15.7)	24		82.2 (SD 16.8)		
Lipids: Total cholesterol (mmol/l) – 0wk	Continuous	24		0.1686072 (SD 0.0328)	24		0.1652454 (SD 0.0359)		
HDL cholesterol (mmol/l) – 0wk	Continuous	24		0.0237912 (SD 0.0075)	24		0.0240498 (SD 0.00569)		
Triglycerides (mmol/l) – 0wk	Continuous	24		0.0242735 (SD 0.0166)	24		0.0232574 (SD 0.00779)		

Results

		Metformin			Sulfonylurea				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 12wka	Mean change	24		-2.27	24		-3.04		
HbA1c (%) – 12wkb	Continuous	24		9.15 (SD 0.98)	24		8.85 (SD 0.98)		
HbA1c (%) – 24wkb	Continuous	24		8.85 (SD 0.98)	24		8.9 (SD 1.47)		
HbA1c (%) – 24wka	Mean change	24		-2.7	24		-3.09		
HbA1c (%) – 52wk	Continuous	24		8.64 (SD 1.21)	24		9.72 (SD 1.91)		
HbA1c (%) – 52wka	Mean change	24		-2.57	24		-1.93		
Fasting plasma glucose (mmol/l) – 12wka	Mean change	24		-4.11	24		-4.37		
Fasting plasma glucose (mmol/l) – 12wkb	Continuous	24		7.15 (SD 1.47)	24		7.8 (SD 2.45)		
Fasting plasma glucose (mmol/l) – 24wkb	Continuous	24		7 (SD 1.47)	24		8.3 (SD 2.94)		
Fasting plasma glucose (mmol/l) – 24wka	Mean change	24		-4.25	24		-3.89		
Fasting plasma glucose (mmol/l) – 52wk	Continuous	24		7.1 (SD 1.47) b	24		9.23 (SD 3.69)		
Fasting plasma glucose (mmol/l) – 52wk	Continuous	24		7.11 (SD 1.28)	24		9.2 (SD 3.43) b		
Fasting plasma glucose (mmol/l) – 52wk	Continuous	24		7.11 (SD 1.28)	24		9.23 (SD 3.69)		

	Fasting plasma glucose (mmol/l) – 52wkb	Continuous	24		7.1 (SD 1.47)	24		9.2 (SD 3.43)		
	Fasting plasma glucose (mmol/l) – 52wka	Mean change	24		-4	24		-2.8		
	Body weight: Weight (kg) – 12wka	Mean change	24		-2.1	24		1.04		
	Weight (kg) – 12wk	Mean change	24		-2.1a	24		1.04 (SD 2.2) b		
	Weight (kg) – 12wkb	Mean change	24		-2.1 (SD 2.45)	24		1.04 (SD 2.2)		
	Weight (kg) – 12wk	Mean change	24		-2.1 (SD 2.45) b	24		1.04a		
	Weight (kg) – 24wk	Mean change	24		-2.33a	24		2.56 (SD 2.45) b		
	Weight (kg) – 24wk	Mean change	24		-2.33 (SD 2.94) b	24		2.56a		
	Weight (kg) – 24wkb	Mean change	24		-2.33 (SD 2.94)	24		2.56 (SD 2.45)		
	Weight (kg) – 24wka	Mean change	24		-2.33	24		2.56		
	Weight (kg) – 52wk	Continuous	24		76 (SD 12.3)	24		84.6 (SD 21.7)		
	Weight (kg) – 52wkc	Mean change	24		-1.97 (SD 3.43)	24		2.62 (SD 4.41)		
	Hypoglycaemic events: All hypoglycaemic events (no patients) – 52wk	Dichotomous	24	0	(0.0%)	24	0	(0.0%)		
	Dropouts: Total dropouts – 52wk	Dichotomous	24	0	(0.0%)	24	0	(0.0%)		
	Lipids: Total cholesterol (mmol/l) – 24wk	Continuous	24		6.56 (SD 1.36)	24		6.31 (SD 1.2)		
	Total cholesterol (mmol/l) – 52wk	Continuous	24		6.56 (SD 1.53)	24		6.97 (SD 1.3)		
	HDL cholesterol (mmol/l) – 24wk	Continuous	24		0.95 (SD 0.31)	24		0.94 (SD 0.26)		
	HDL cholesterol (mmol/l) – 52wk	Continuous	24		0.95 (SD 0.29)	24		0.93 (SD 0.22)		
	Triglycerides (mmol/l) – 24wk	Continuous	24		1.94 (SD 0.94)	24		2.14 (SD 1.01)		
	Triglycerides (mmol/l) – 52wk	Continuous	24		2.28 (SD 1.84)	24		2.31 (SD 1.22)		
	LDL cholesterol (mmol/l) – 24wk	Continuous	24		4.73 (SD 1.08)	24		4.41 (SD 0.99)		
	LDL cholesterol (mmol/l) – 52wk	Continuous	24		4.58 (SD 1.19)	24		4.99 (SD 1.16)		

[a] SD not reported in table
[b] estimated from graph
[c] SD calculated from SE extracted from graph

Table 16: Chan et al. (1998)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral

	Parallel / crossover: Parallel **Country:** Hong Kong, Taiwan, Philippines, Korea, Singapore, Malaysia **Authors' conclusions:** Acarbose 100 mg tid was an effective, safe and well tolerated therapy in Asian type 2 diabetic patients with dietary failure. In some patients with gastrointestinal symptoms, a lower dose may be necessary **Source of funding:** Bayer **Comments:** Double-blind
Number and characteristics of patients	**Total number of patients:** 126 **Inclusion criteria:** Patients with type 2 diabetes for at least 3 months, aged between 35 and 70 years, a stable BMI <35 kg/m2 and Hba1c 7-10% **Exclusion criteria:** Previous treatment with antidiabetic drugs, history of significant gastrointestinal, cardiovascular or renal disease
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** All treatment naive/ no OADs at screening **Details of washout period:** People on AHA were excluded
Lifestyle advice	-
Follow-up	**Total follow-up (wks):** 30 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 24 **Frequency of monitoring appointments:** 6 week screening period prior to randomisation. Patients were followed up at weeks 10,16 and 24.
Arms	**(1) Placebo** N: 63 Treatment duration (wks): 24 Washout period (d): 0 Comments: AHA naïve Treatment(s): Placebo (Oral) **(2) Acarbose** N: 63 Treatment duration (wks): 24 Washout period (d): 0 Comments: AHA naïve Treatment(s): Acarbose (Oral) – fixed-dose Set dose (mg/d):300 Frequency of dosing: three times a day Details of dosing regimen: Acarbose, week 1-4 50 mg TID, week 5-24 100 mg TID
Outcomes	

Baseline characteristics

		Placebo			Acarbose				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Demographics: Age (years)	Continuous	63		54 (SD 10)	63		52.8 (SD 10.2)		
Sex (n male)	Dichotomous	63	32	(50.8%)	63	32	(50.8%)		
Duration of diabetes (yrs)	Continuous	63		2.1 (SD 3.4)	63		2.7 (SD 3.5)		
Blood glucose: HbA1c (%) – 0wk	Continuous	63		8.6 (SD 1.1)	63		8.2 (SD 1)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	63		8.3 (SD 2.2)	63		8.4 (SD 1.8)		
Body weight: BMI (kg/m2) – 0wk	Continuous	63		25.6 (SD 3.8)	63		25.4 (SD 3.9)		
Weight (kg) – 0wk	Continuous	63		65.4 (SD 13.3)	63		64.1 (SD 10)		

Results

	Placebo	Acarbose	Δ	p

		N	k	mean	N	k	mean
Dropouts: Total dropouts – 24wk	Dichotomous	63	6	(9.5%)	63	11	(17.5%)
ITT Blood glucose: HbA1c (%) – 16wka	Continuous	62		8 (SD 1.31)	59		7.2 (SD 0.999)
HbA1c (%) – 24wkb	Mean change	62		-0.27 (SD 1.1)	59		-0.7 (SD 1.21)
HbA1c (%) – 24wka	Continuous	62		8 (SD 1.31)	59		7.2 (SD 0.999)
Fasting plasma glucose (mmol/l) – 24wk	Mean change	62		0.41 (SD 2)	59		-0.37 (SD 1.5)
Body weight: BMI (kg/m2) – 24wkc	Mean change	62		0.04 (SD 0.7)	59		-0.52 (SD 1.6)
Weight (kg) – 24wkc	Mean change	62		0.16 (SD 1.9)	59		-1.31 (SD 4.5)
Blood pressure: Systolic blood pressure (mmHg) – 12wk	Mean change	62		2.9 (SD 12.4)	59		2.73 (SD 12)
Diastolic blood pressure (mmHg) – 12wk	Mean change	62		0.67 (SD 8.72)	59		0.6 (SD 8.97)
Lipids: Total cholesterol (mmol/l) – 24wk	Mean change	62		-0.04 (SD 5.4)	59		0.13 (SD 0.5)
HDL cholesterol (mmol/l) – 24wk	Mean change	62		-0.03 (SD 0.3)	59		-0.02 (SD 0.3)
Triglycerides (mmol/l) – 24wk	Mean change	62		-0.06 (SD 1.2)	59		-0.05 (SD 0.5)
LDL cholesterol (mmol/l) – 24wk	Mean change	62		-0.02 (SD 0.7)	59		0.15 (SD 0.8)

[a] estimated from graph; SD calculated from assumed SE error bars
[b] SD calculated from reported Cis
[c] SD calculated from reported 95% CI

Table 17: Charbonnel et al. (2005)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** Australia, Europe, Canada, South Africa **Authors' conclusions:** The pioglitazone based regimens resulted in improved insulin sensitivity and more favourable insulin sensitiy related lipid profiles compared with gliclazide based therapy **Source of funding:** Employees of Takeda or Eli Lilly are authors **Comments:** Double-blind
Number and characteristics of patients	**Total number of patients:** - **Inclusion criteria:** - **Exclusion criteria:** -
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** - **Details of washout period:** -
Lifestyle advice	-

Follow-up

Total follow-up (wks): -
Length of titration period (wks): -
Length of maintenance period (wks): -
Frequency of monitoring appointments: -

Arms

(1) Pioglitazone
N: 624
Treatment duration (wks): -
Washout period (d): -
Treatment(s): Pioglitazone
Details of dosing regimen: Charbonnel (20050-pioglitazone, po., starting daily dose was 15 mg for 4 weeks (weeks 0 to 4), increased to 30 mg daily for the next 4 weeks (weeks 4 to 8), and, finally, to 45 mg daily for the subsequent 8 weeks (weeks 8 to 16) on the basis of tolerability. The dose of study drug was increased at each time point during titration unless the patient had not tolerated the previous dose or the investigator considered the patient at risk of experiencing hypoglycaemia or other tolerability issues should the dose of study drug be further increased.
Forst (2005)-pioglitazone, po., 45 mg in the morning
Nakamura (2004)-pioglitazone, po., 15 mg/day

(2) Gliclazide
N: 626
Treatment duration (wks): -
Washout period (d): -
Treatment(s): Sulfonylurea (Oral) – forced titration
Maximum dose (mg/d): 320
Frequency of dosing: twice a day

Outcomes

General
See Tan (2005) for study details and 2 year follow-up data

Baseline characteristics

		Pioglitazone			Gliclazide				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Blood glucose: HbA1c (%) – 4wk	Continuous	624		8.7 (SD 1)	626		8.7 (SD 1.1)		
Body weight: BMI (kg/m2)	Continuous	624		31.7 (SD 6)	626		30.6 (SD 5.1)		
Weight (kg) – 0wka	Continuous	624		89.47008 (SD 16.9)	626		86.36544 (SD 14.4)		
Weight (kg) – 4wk	Continuous	624		90.7 (SD 18.6)	626		88.1 (SD 16.9)		
2-year follow-up (reported in Tan et al. 2005) Demographics:									
Age (years)	Continuous	270		57 (SD 9.8)	297		56 (SD 9.9)		
Sex (n male)	Dichotomous	270	171	(63.3%)	297	182	(61.3%)		
Duration of diabetes (yrs)	Continuous	270		2.7 (SD 3.5)	297		2.9 (SD 3.8)		
Ethnicity-White	Dichotomous	270	253	(93.7%)	297	275	(92.6%)		
Ethnicity-Other	Dichotomous	270	17	(6.3%)	297	22	(7.4%)		
Blood glucose: HbA1c (%) – 0wkb	Continuous	270		8.6 (SD 1.03)	297		8.74 (SD 1.08)		
Fasting plasma glucose (mmol/l) – 0wkc	Continuous	270		10.9 (SD 1.64)	297		11.21 (SD 1.72)		
Body weight: BMI (kg/m2)	Continuous	270		32 (SD 6.4)	297		31 (SD 5.6)		
Weight (kg) – 0wk	Continuous	270		91.7 (SD 19.9)	297		89.2 (SD 18.2)		

[a] estimated from BMI assuming mean height of 1.68m
[b] SD calculated from standard errors estimated from graph
[c] estimated from graph

Results

{/i}{/s}

		Pioglitazone			Gliclazide				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Blood glucose: HbA1c (%) – 24wka	Continuous	624		7.125 (SD 1.12)	626		6.875 (SD 1.12)		
HbA1c (%) – 52wkb	Continuous	624		7.2 (SD 1.12)	626		7.3 (SD 1.12)		
Fasting plasma glucose (mmol/l) – 52wk	Continuous	624		8.7 (SD 3.5)	626		9.2 (SD 3)		
Body weight: Weight (kg) – 52wkc	Continuous	624		92.4 (SD 5)	626		91.4 (SD 5)		
Hypoglycaemic events: All hypoglycaemic events (no patients) – 52wk	Dichotomous	624	22	(3.5%)	626	63	(10.1%)		
Major/severe hypoglycaemic event – 52wk	Dichotomous	624	0	(0.0%)	626	1	(0.2%)		
Adverse events: GI: nausea – 52wk	Dichotomous	620	27	(4.4%)	618	32	(5.2%)		
Any adverse event(s) – 52wk	Dichotomous	624	468	(75.0%)	626	444	(70.9%)		
Dropouts: Total dropouts – 104wk	Dichotomous	624	477	(76.4%)	626	499	(79.7%)		
Dropout due to AEs – 52wk	Dichotomous	624	38	(6.1%)	626	39	(6.2%)		
2-year follow-up (reported in Tan et al. 2005) Blood glucose: HbA1c (%) – 104wkd	Continuous	261		7.35 (SD 1.21)	289		7.78 (SD 1.28)		
HbA1c (%) – 104wk	Mean change	270			297			MD=-0.450 (CI: -0.666, -0.234)	<0.05e
HbA1c < 7% or <=7% – 104wkf	Dichotomous	261	111	(42.5%)	289	81	(28.0%)		<0.001
Hba1c <8% – 104wk	Dichotomous	270	129	(47.8%)	297	110	(37.0%)		<0.001g
Fasting plasma glucose (mmol/l) – 16wkh	Continuous	261		8.6 (SD 1.62)	289		8.23 (SD 1.36)		
Fasting plasma glucose (mmol/l) – 24wkh	Continuous	261		8.3 (SD 1.62)	289		8.3 (SD 1.7)		
Fasting plasma glucose (mmol/l) – 52wkh	Continuous	261		8.55 (SD 1.62)	289		9.2 (SD 1.7)		
Fasting plasma glucose (mmol/l) – 104wkh	Continuous	261		8.7 (SD 1.62)	289		9.55 (SD 1.53)		
Fasting plasma glucose (mmol/l) – 104wk	Mean change	270			297			MD=-0.830 (CI: -1.261, -0.399)	<0.05i
Body weight: Weight (kg) – 16wkh	Continuous	261		92 (SD 1.62)	289		92 (SD 1.7)		
Weight (kg) – 24wkh	Continuous	261		92.1 (SD 1.62)	289		92.1 (SD 1.7)		
Weight (kg) – 52wkh	Continuous	261		94.2 (SD 1.62)	289		92.8 (SD 1.7)		
Weight (kg) – 104wkj	Continuous	146		95.6 (SD 6.79)	127		93.4 (SD 7.14)		<0.001

Weight (kg) – 104wk{i}j	Continuous	261		95.6 (SD 6.79)	289		93.4 (SD 7.14)		<0.001
Dropouts:									
Dropout due to AEs – 104wk	Dichotomous	270	33	(12.2%)	297	25	(8.4%)		
Drop out due to unsatisfactory effect – 104wk	Dichotomous	270	45	(16.7%)	297	86	(29.0%)		
drop out due to headache – 104wk	Dichotomous	270	0	(0.0%)	297	3	(1.0%)		
drop out due to increased weight – 104wk	Dichotomous	270	6	(2.2%)	297	1	(0.3%)		

{s}{i}a{/i} Estimated from graph
[b] SD extracted from graph
[c] estimated from graph; SD calculated from SE
[d] Mean estimated from graph. SD calculated from standard errors estimated from graph
[e] 95% CI -0.66 to -0.23, specific p-value not reported
[f] at least one post-baseline measurement
[g] log-rank test of difference between Kaplan Meier curves
[h] estimated from graph
[i] 95% CI -1.26 to -0.39, specific p-value not reported
[j] SD calculated from assumed reported SE

Table 18: Chiasson & (2001)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** Unclear **Authors' conclusions:** In type 2 diabetic patients, miglitol in combination with metformin gives greater glycaemic improvement than metformin monotherapy **Source of funding:** Bayer and Sanofi-Synthelabo **Comments:** Double-blind
Number and characteristics of patients	**Total number of patients:** 324 **Inclusion criteria:** Patients with type 2 diabetes, > 40 years in whom diabetes was inadeqautely controlled by diet alone (Hba1c between 7.2 and 9.5%) **Exclusion criteria:** Type 1 diabetes, major diseases, recent cardiovascular events, history of lactic acidosis Pre-randomisation phase: Single blind 8 week placebo run-in period. Those without adequate control were randomised
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** some on oral hypoglycaemic drugs and/or insulin **Details of washout period:** Patients taking either metformin or sulfonylurea discontinued this before taking part
Lifestyle advice	All patients were seen by a dietitian before the run-in period and were advised on eating a well-balanced, weight-reducing diet. They were also advised regarding exercise (walking 20-30 mins at least 3 times per week)
Follow-up	**Total follow-up (wks):** 36 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 36 **Frequency of monitoring appointments:** Patients were seen at weeks 4,8,12,16,20,28 and 36
Arms	**(1) Placebo**

N: 83
Treatment duration (wks): 36
Washout period (d): 56
Comments: Patients taking either metformin or sulfonylurea discontinued this before taking part. 8 week placebo run-in period
Treatment(s): Placebo

(2) Metformin

N: 83
Treatment duration (wks): 36
Washout period (d): 56
Comments: Patients taking either metformin or sulfonylurea discontinued this before taking part. 8 week placebo run-in period
Treatment(s): Metformin (Oral) – fixed-dose
Set dose (mg/d):1500
Frequency of dosing: three times a day
Details of dosing regimen: 500 mg/8h (i.e. 1500 mg/day)

Outcomes

General

Data for 2 trial arms were not extracted (miglitol and miglitol plus metformin).
Total dropouts not reported

Baseline characteristics

		Placebo			Metformin			Δ	p
		N	k	mean	N	k	mean		
Demographics: Age (years)	Continuous	83		57.7 (SD 9.9)	83		57.9 (SD 8.6)		
Sex (n male)	Dichotomous	83	56	(67.5%)	83	61	(73.5%)		
Duration of diabetes (yrs)	Continuous	83		5.1 (SD 4.9)	83		7.5 (SD 7.4)		
Blood glucose: HbA1c (%) – 0wk	Continuous	83		8.1 (SD 0.7)	83		8.2 (SD 0.9)		
Body weight: BMI (kg/m2)	Continuous	83		31.1 (SD 4.4)	83		30.7 (SD 5.1)		
Weight (kg) – 0wk	Continuous	83		88.6 (SD 14.1)	83		89 (SD 17.8)		
Previous blood glucose lowering drugs: Diet alone (i.e. drug naïve)	Dichotomous	83	48	(57.8%)	83	55	(66.3%)		

Results

		Placebo			Metformin			Δ	p
		N	k	mean	N	k	mean		
Hypoglycaemic events: All hypoglycaemic events (no patients) – 36wk	Dichotomous	83	7	(8.4%)	83	8	(9.6%)		
Adverse events: GI: nausea – 36wk	Dichotomous	83	2	(2.4%)	83	14	(16.9%)		
Any adverse event(s) – 36wk	Dichotomous	83	71	(85.5%)	83	78	(94.0%)		
Dyspepsia – 36wk	Dichotomous	83	2	(2.4%)	83	7	(8.4%)		
Flatulence – 36wk	Dichotomous	83	12	(14.5%)	83	24	(28.9%)		
Gastrointestinal disorders (any) – 36wk	Dichotomous	83	29	(34.9%)	83	50	(60.2%)		
GI: diarrhoea – 36wk	Dichotomous	83	9	(10.8%)	83	23	(27.7%)		
GI: abdominal pain – 36wk	Dichotomous	83	2	(2.4%)	83	5	(6.0%)		
GI: constipation – 36wk	Dichotomous	83	5	(6.0%)	83	7	(8.4%)		
Dropouts: Dropout due to AEs – 36wk	Dichotomous	83	2	(2.4%)	83	5	(6.0%)		

	ITT									
	Blood glucose: HbA1c (%) – 36wka	Mean change	82		0.38 (SD 1.09)	81		-0.85 (SD 1.18)		
	Fasting plasma glucose (mmol/l) – 36wk	Continuous	82		-0.0499554 (SD 2.86)	81		-1.1323224 (SD 2.55)		
	Body weight: Weight (kg) – 36wka	Continuous	82		-0.69 (SD 2.44)	81		-0.79 (SD 2.97)		
	[a] SD calculated from reported SE									

Table 19: Chiasson JL,Josse RG,Hunt JA,Palmason C,Rodger NW,Ross (1994)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** Canada **Authors' conclusions:** Acarbose impproved long-term glycaemic control in patients with NIDDM regardless of concomitant antidiabetic medication **Source of funding:** Miles Canada **Comments:** Double-blind
Number and characteristics of patients	**Total number of patients:** 354 **Inclusion criteria:** Patients with NIDDM for at least 6 months, patients may have been taking OAD or insulin at study entry (subgroup analyses for patients on diet alone were extracted only) with Hba1c >7% (>6.5% in those treated with diet alone). Patients with hypertension were included if their BP was well controlled with medication **Exclusion criteria:** Patients receiving therapy with beta-blockers or thiazide diuretics, and all patients with documented gastrointestinal disease
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** All treatment naive/ no OADs at screening **Details of washout period:** Some patients continued taking their pre-existing OADs but these data were not extracted Only data from patients who were solely on diet therapy were extracted
Lifestyle advice	All patients were placed on a weight maintaining diet
Follow-up	**Total follow-up (wks):** 52 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 52 **Frequency of monitoring appointments:** -
Arms	**(1) Placebo** N: 39 Treatment duration (wks): 52 Washout period (d): 0 Comments: Data only extracted for those treatment naïve Treatment(s): Placebo (Oral) **(2) Acarbose** N: 38 Treatment duration (wks): 52 Washout period (d): 0 Comments: Data only extracted for those treatment naïve Treatment(s): Acarbose (Oral) – flexible-dose (dose-adjusted) Minimum dose (mg/d): 150 Maximum dose (mg/d): 600 Frequency of dosing: three times a day Details of dosing regimen: Acarbose 50, 100 or 200 mg (max) TID, dose adjusted according to blood glucose values and / or tolerance, main target to achieve a postprandial

	blood glucose < 12 mmol/l.
Outcomes	**General** Data were only extracted for those treatment naïve (subgroup analyses)
Baseline characteristics	

		All study participants		
		N	**k**	**mean**
Demographics: Age (years)	Continuous	77		57.2 (SD 9.6524608261)
Sex (n male)	Dichotomous	77	48	(62.3%)
Duration of diabetes (yrs)	Continuous	77		5.2 (SD 5.2649786324)
Blood glucose: HbA1c (%) – 0wk	Continuous	77		6.7 (SD 0.2)
HbA1c (%) – 0wk	Continuous	77		6.7 (SD 0.2)
Body weight: BMI (kg/m2)	Continuous	77		29 (SD 2.63248931621764)
Weight (kg)	Continuous	77		81.8496 (SD 7.42993784609266) a

[a] estimated from BMI assuming mean height of 1.68m

		Placebo			Acarbose				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Blood glucose: Fasting plasma glucose (mmol/l) – 0wk	Continuous	37		10.3 (SD 3.04)	30		10.7 (SD 2.74)		

Results									
		Placebo			Acarbose				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Blood glucose: HbA1c (%) – 12wka	Mean change	37		0.1 (SD 1.24)	30		-0.45 (SD 1.4)		
HbA1c (%) – 26wka	Mean change	37		-0.15 (SD 0.931)	30		-0.9 (SD 1.4)		
HbA1c (%) – 52wkb	Mean change	37		0.4 (SD 1.09)	30		-0.5 (SD 1.54)		
Fasting plasma glucose (mmol/l) – 52wk	Continuous	37		11.6 (SD 3.04)	30		10 (SD 2.74)		
Fasting plasma glucose (mmol/l) – 52wk	Mean change	37		1.4 (SD 2.4)	30		-0.7 (SD 2.2)		

[a] estimated from graph
[b] Extracted from graph; SD estimated from 95% CI

Table 20: Collier A,Watson HH,Patrick AW,Ludlam (1989)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral

	Parallel / crossover: Parallel **Country:** Unclear but assumed UK **Authors' conclusions:** Metformin and gliclazide were equally effective in the glycaemic control of non-insulin dependent diabetes, and there was no difference in the platelet variables measured in the two groups. **Source of funding:** Lipha Pharmaceuticals **Comments:** Open label
Number and characteristics of patients	**Total number of patients:** 24 **Inclusion criteria:** Patients were newly diagnosed, non-obese, type 2 diabetes patients. All patients had Hba1c >9% after the dietary period. No patients had retinopathy and none were taking medication at entry into the study **Exclusion criteria:** Unclear Pre-randomisation phase: There was a 3-6 week dietary run-in period prior to randomisation.
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** All treatment naive/ no OADs at screening **Details of washout period:** Unclear whether patients were AHA naïve
Lifestyle advice	Patients were instructed to have a diet low in refined carbohydrates content, moderate in fibre and low in saturated fat
Follow-up	**Total follow-up (wks):** 24 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 24 **Frequency of monitoring appointments:** patients were studied at baseline and 6 months
Arms	**(1) Metformin** N: 12 Treatment duration (wks): 24 Washout period (d): 42 Comments: Patients had run in between 3 and 6 weeks. States that none were on medication at enrollment but unclear whether all were AHA naïve Treatment(s): Metformin (Oral) Minimum dose (mg/d): 1500 Maximum dose (mg/d): 3000 Details of dosing regimen: 1.5 to 3 g/day (median 2g/day) **(2) Sulfonylurea** N: 12 Treatment duration (wks): 24 Washout period (d): 42 Comments: Patients had run in between 3 and 6 weeks. States that none were on medication at enrollment but unclear whether all were AHA naïve Treatment(s): Sulfonylurea (Oral) Minimum dose (mg/d): 80 Maximum dose (mg/d): 240 Details of dosing regimen: gliclazide 80-240 mg/day (median 160 mg/day)
Outcomes	**General** Dropouts were not reported
Baseline characteristics	

		Metformin			Sulfonylurea				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	12		53.1 (SD 5.1)	12		55.5 (SD 5.1)		
Sex (n male)	Dichotomous	12	6	(50.0%)	12	6	(50.0%)		
Blood glucose: HbA1c (%) – 0wk	Continuous	12		12.1 (SD 2.4)	12		11.7 (SD 1.5)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	12		11.8 (SD 3.1)	12		12.2 (SD 2.4)		
Body weight: BMI (kg/m2) – 0wk	Continuous	12		24.3 (SD 1.4)	12		23.1 (SD 1.3)		
Lipids: Total cholesterol (mmol/l) – 0wk	Mean change	12		6.5 (SD 0.9)	12		7 (SD 0.7)		

	Triglycerides (mmol/l) – 0wk	Mean change	12		1.6 (SD 0.5)	12		1.9 (SD 0.6)			
Results			**Metformin**			**Sulfonylurea**					
			N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
	Blood glucose: HbA1c (%) – 24wk	Continuous	12		7.4 (SD 0.8)	12		7 (SD 0.8)		
	Fasting plasma glucose (mmol/l) – 24wk	Continuous	12		7.5 (SD 1.7)	12		6.4 (SD 1.5)		
	Body weight: BMI (kg/m2) – 24wk	Continuous	12		24.5 (SD 1.6)	12		23.6 (SD 1.4)		
	Hypoglycaemic events: minor hypoglycaemic events – 24wk	Dichotomous	12	0	(0.0%)	12	2	(16.7%)		
	Adverse events: GI: nausea – 24wk	Dichotomous	12	3	(25.0%)	12	0	(0.0%)		
	Lipids: Total cholesterol (mmol/l) – 24wk	Mean change	12		5.8 (SD 0.7)	12		6.3 (SD 0.8)		
	Triglycerides (mmol/l) – 24wk	Mean change	12		1.3 (SD 0.4)	12		1.6 (SD 0.5)		

Table 21: Coniff et al. (1995)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** USA **Authors' conclusions:** Acarbose was effective and well controlled in the treatment of NIDDM. Control of glycaemia was significantly better with acarbose compared with diet alone. Acarbose plus tolbutamide was superior to tolbutamide alone **Source of funding:** Miles Inc **Comments:** Double-blind
Number and characteristics of patients	**Total number of patients:** 290 **Inclusion criteria:** Patients with NIDDM, at least 18 years old, with a stable bodyweight and FBG>=140 mg/dl on diet alone (patients on sulfonylureas and insulins had medications discontinued at least 4 weeks prior to enrollment) **Exclusion criteria:** Significant diseases or conditions, gastrointestinal disease, severely and poorly controlled diabetes, impaired hepatic and/or renal function Pre-randomisation phase: 6 week run in period where participants were on diet alone
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** some on oral hypoglycaemic drugs and/or insulin **Details of washout period:** Patients on AHA discontinued medication 4 weeks prior to enrollment 6 week wash out period where patients were on diet only
Lifestyle advice	All patients were advised to follow a standard diabetic diet
Follow-up	**Total follow-up (wks):** 36 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 24

	Frequency of monitoring appointments: Patients were measured for Hba1c at weeks 6,12,18 and 24 (there was also a 6 week follow-up after double-blind treatment period) 6 week run in, 24 week treatment, 6 week follow up
Arms	**(1) Acarbose (200 mg TID)** N: 67 Treatment duration (wks): 24 Washout period (d): 42 Treatment(s): Acarbose (Oral) – fixed-dose Set dose (mg/d):600 Frequency of dosing: three times a day Details of dosing regimen: Acarbose 200 mg TID with meals **(2) sulfonylurea (Tolbutamide)** N: 66 Treatment duration (wks): 24 Washout period (d): 42 Treatment(s): Sulfonylurea (Oral) – flexible-dose (dose-adjusted) Minimum dose (mg/d): 250 Maximum dose (mg/d): 1000 Frequency of dosing: three times a day Details of dosing regimen: Tolbutamide, started at 250 mg TID and was individually adjusted in steps of 250 mg TID if 1 hour PPG >=200 mg/dl **(3) Placebo** N: 62 Treatment duration (wks): 24 Washout period (d): 42 Treatment(s): Placebo (Oral)
Outcomes	**General** Data not available on numbers originally randomised
Baseline characteristics	

		Acarbose (200 mg TID)			sulfonylurea (Tolbutamide)			Δ	p
		N	k	mean	N	k	mean		
Demographics:									
Age (years) a	Continuous	67		56.2	66		55.4		
Sex (n male)	Dichotomous	67	26b	(38.8%)	66	37	(56.1%)		
Duration of diabetes (yrs) a	Continuous	67		5.1	66		5.6		
Blood glucose:									
HbA1c (%) – 0wka	Continuous	67		6.88	66		6.95		
Fasting plasma glucose (mg/dl) a	Continuous	67		219	66		217		
Body weight:									
BMI (kg/m2)	Continuous	67		29.7	66		29.5		
Weight (kg) – 0wka	Continuous	67		81.6	66		84.8		
Height (cm) a	Continuous	67		166.1	66		169.8		

[a] SD not reported
[b] approximated to nearest integer (percentages only presented in text)

		Acarbose (200 mg TID)			Placebo			Δ	p
		N	k	mean	N	k	mean		
Demographics:									
Age (years) a	Continuous	67		56.2	62		56.3		
Sex (n male) b	Dichotomous	67	26	(38.8%)	62	32	(51.6%)		
Duration of diabetes (yrs) a	Continuous	67		5.1	62		5.5		
Blood glucose:									
HbA1c (%) – 0wka	Continuous	67		6.88	62		7.1		
Fasting plasma glucose (mg/dl) a	Continuous	67		219	62		227		

Body weight: BMI (kg/m2)	Continuous	67		29.7	62		29.9		
Weight (kg) – 0wka	Continuous	67		81.6	62		85.8		
Height (cm) a	Continuous	67		166.1	62		169.5		

[a] SD not reported
[b] approximated to nearest integer (percentages only presented in text)

		sulfonylurea (Tolbutamide)			Placebo				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years) a	Continuous	66		55.4	62		56.3		
Sex (n male)	Dichotomous	66	37	(56.1%)	62	32b	(51.6%)		
Duration of diabetes (yrs) a	Continuous	66		5.6	62		5.5		
Blood glucose: HbA1c (%) – 0wka	Continuous	66		6.95	62		7.1		
Fasting plasma glucose (mg/dl) a	Continuous	66		217	62		227		
Body weight: BMI (kg/m2)	Continuous	66		29.5	62		29.9		
Weight (kg) – 0wka	Continuous	66		84.8	62		85.8		
Height (cm) a	Continuous	66		169.8	62		169.5		

[a] SD not reported
[b] approximated to nearest integer (percentages only presented in text)

Results

		Acarbose (200 mg TID)			sulfonylurea (Tolbutamide)				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 12wka	Continuous	74		-0.52 (SD 0.688)	71		-0.77 (SD 0.758)		
HbA1c (%) – 24wk	Mean change	65		-0.54 (SD 1.05)	67		-0.99 (SD 1.04)		
Fasting plasma glucose (mmol/l) – 24wk	Mean change	67		-1.11 (SD 3.17)	66		-2.02 (SD 3.13)		
Body weight: Weight (kg) – 12wka	Mean change	74		-0.95 (SD 1.72)	71		1.1 (SD 2.02)		
Weight (kg) – 24wk	Mean change	66		-1.42 (SD 2.84)	66		1.84 (SD 2.76)		
Hypoglycaemic events: All hypoglycaemic events (no patients) – 24wkb	Dichotomous	74	6	(8.1%)	71	11	(15.5%)		
Adverse events: GI: nausea – 24wkc	Dichotomous	74	6	(8.1%)	71	7	(9.9%)		
Any adverse event(s) – 24wkc	Dichotomous	74	67	(90.5%)	71	42	(59.2%)		
Death (disease related) – 24wkc	Dichotomous	67	0	(0.0%)	66	1	(1.5%)		
Death – 24wkc	Dichotomous	67	0	(0.0%)	66	1	(1.5%)		
Flatulence – 24wkc	Dichotomous	74	59	(79.7%)	71	24	(33.8%)		
Gastrointestinal disorders (any) – 24wkc	Dichotomous	74	59	(79.7%)	71	24	(33.8%)		
GI: diarrhoea – 24wkc	Dichotomous	74	20	(27.0%)	71	4	(5.6%)		
GI: vomiting – 24wkc	Dichotomous	74	2	(2.7%)	71	2	(2.8%)		
Lipids: Total cholesterol (mmol/l) – 24wk	Mean change	64		-0.21 (SD 0.79)	61		0.05 (SD 0.77)		
HDL cholesterol (mmol/l) – 24wk	Mean change	58		0.07 (SD 0.23)	54		0.08 (SD 0.23)		
Triglycerides (mmol/l) – 24wk	Mean change	64		-0.49 (SD 1.87)	61		-0.03 (SD 1.84)		

LDL cholesterol (mmol/l) – 24wk	Mean change	48		-0.09 (SD 0.67)	47		-0.1 (SD 0.68)		

[a] estimated from graph
[b] Assumed group numbers same as safety analysis
[c] No of patients

		Acarbose (200 mg TID)			Placebo			Δ	p
		N	k	mean	N	k	mean		
Blood glucose: HbA1c (%) – 12wka	Continuous	74		-0.52 (SD 0.688)	72		0.14 (SD 0.764)		
HbA1c (%) – 24wk	Mean change	65		-0.54 (SD 1.05)	62		0.04 (SD 1.02)		
Fasting plasma glucose (mmol/l) – 24wk	Mean change	67		-1.11 (SD 3.17)	62		0.12 (SD 3.24)		
Body weight: Weight (kg) – 12wka	Mean change	74		-0.95 (SD 1.72)	72		-0.8 (SD 2.12)		
Weight (kg) – 24wk	Mean change	66		-1.42 (SD 2.84)	62		-1.4 (SD 2.91)		
Hypoglycaemic events: All hypoglycaemic events (no patients) – 24wkb	Dichotomous	74	6	(8.1%)	72	4	(5.6%)		
Adverse events: GI: nausea – 24wkc	Dichotomous	74	6	(8.1%)	72	2	(2.8%)		
Any adverse event(s) – 24wkc	Dichotomous	74	67	(90.5%)	72	31	(43.1%)		
Death – 24wkc	Dichotomous	67	0	(0.0%)	62	0	(0.0%)		
Flatulence – 24wkc	Dichotomous	74	59	(79.7%)	72	25	(34.7%)		
Gastrointestinal disorders (any) – 24wkc	Dichotomous	74	59	(79.7%)	72	25	(34.7%)		
GI: diarrhoea – 24wkc	Dichotomous	74	20	(27.0%)	72	4	(5.6%)		
GI: vomiting – 24wkc	Dichotomous	74	2	(2.7%)	72	0	(0.0%)		
Lipids: Total cholesterol (mmol/l) – 24wk	Mean change	64		-0.21 (SD 0.79)	58		-0.13 (SD 0.8)		
HDL cholesterol (mmol/l) – 24wk	Mean change	58		0.07 (SD 0.23)	51		0.06 (SD 0.24)		
Triglycerides (mmol/l) – 24wk	Mean change	64		-0.49 (SD 1.87)	58		-0.31 (SD 1.9)		
LDL cholesterol (mmol/l) – 24wk	Mean change	48		-0.09 (SD 0.67)	45		-0.25 (SD 0.69)		

[a] estimated from graph
[b] Assumed group numbers same as safety analysis
[c] No of patients

		sulfonylurea (Tolbutamide)			Placebo			Δ	p
		N	k	mean	N	k	mean		
Blood glucose: HbA1c (%) – 12wka	Continuous	71		-0.77 (SD 0.758)	72		0.14 (SD 0.764)		
HbA1c (%) – 24wk	Mean change	67		-0.99 (SD 1.04)	62		0.04 (SD 1.02)		
Fasting plasma glucose (mmol/l) – 24wk	Mean change	66		-2.02 (SD 3.13)	62		0.12 (SD 3.24)		
Body weight: Weight (kg) – 12wka	Mean change	71		1.1 (SD 2.02)	72		-0.8 (SD 2.12)		
Weight (kg) – 24wk	Mean change	66		1.84 (SD 2.76)	62		-1.4 (SD 2.91)		
Hypoglycaemic events: All hypoglycaemic events (no patients) – 24wkb	Dichotomous	71	11	(15.5%)	72	4	(5.6%)		

Adverse events:										
GI: nausea – 24wkc	Dichotomous	71	7	(9.9%)	72	2	(2.8%)		
Any adverse event(s) – 24wkc	Dichotomous	71	42	(59.2%)	72	31	(43.1%)		
Death – 24wkc	Dichotomous	66	1	(1.5%)	62	0	(0.0%)		
Flatulence – 24wkc	Dichotomous	71	24	(33.8%)	72	25	(34.7%)		
Gastrointestinal disorders (any) – 24wkc	Dichotomous	71	24	(33.8%)	72	25	(34.7%)		
GI: diarrhoea – 24wkc	Dichotomous	71	4	(5.6%)	72	4	(5.6%)		
GI: vomiting – 24wkc	Dichotomous	71	2	(2.8%)	72	0	(0.0%)		
Lipids:									
Total cholesterol (mmol/l) – 24wk	Mean change	61		0.05 (SD 0.77)	58		-0.13 (SD 0.8)		
HDL cholesterol (mmol/l) – 24wk	Mean change	54		0.08 (SD 0.23)	51		0.06 (SD 0.24)		
Triglycerides (mmol/l) – 24wk	Mean change	61		-0.03 (SD 1.84)	58		-0.31 (SD 1.9)		
LDL cholesterol (mmol/l) – 24wk	Mean change	47		-0.1 (SD 0.68)	45		-0.25 (SD 0.69)		

[a] estimated from graph
[b] Assumed group numbers same as safety analysis
[c] No of patients

Table 22: Coniff et al. (1995)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** Unclear but assumed USA **Authors' conclusions:** Acarbose at doses of 100, 200 and 300 mg administered three times daily for 16 weeks significantly reduced Hba1c levels and postprandial hyperglycaemia. Treatment with acarbose is safe and effective adjunct to dietary therapy for the treatmetn of NIDDM **Source of funding:** Unclear but some authors from Bayer **Comments:** Double-blind
Number and characteristics of patients	**Total number of patients:** 290 **Inclusion criteria:** patients over 30 years of age with NIDDM for at least 3 months, patients could have previously been treated with sulfonylureas if these had been discontinued at least 6 weeks before screening visit and if the patients had achieved stable fasting glucose levels **Exclusion criteria:** significant disease or condition that is likely to alter the course of diabetes, documented gastrointestinal disease, severe and poorly controlled diabetes, therapy with insulin, impaired liver or kidney function Pre-randomisation phase: there was a 4 week placebo run-in phase
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** some on oral hypoglycaemic drugs and/or insulin **Details of washout period:** there was a 4 week placebo run-in phase but participants were also required to be AHA free at least 6 weeks prior to screening
Lifestyle advice	During the run-in phase patients were maintained on a diet recommended by the ADA
Follow-up	**Total follow-up (wks):** 22 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 16 **Frequency of monitoring appointments:** 2 week screening, 4 week placebo run in, 16 week treatment phase. There were 9 visits in total (including screening and run-in period)

Arms

(1) Placebo

N: 73

Treatment duration (wks): 16
Washout period (d): 28
Comments: 4 week placebo run-in

Treatment(s): Placebo (Oral)

(2) Acarbose (100 mg TID)

N: 73

Treatment duration (wks): 16
Washout period (d): 28
Comments: 4 week placebo run-in

Treatment(s): Acarbose (Oral) – fixed-dose
Set dose (mg/d):300
Details of dosing regimen: Acarbose 100 mg TID. The dosage was titrated at 2 week intervals depending on drug assignment

(3) Acarbose (200 mg TID)

N: 72

Treatment duration (wks): 16
Washout period (d): 28
Comments: 4 week placebo run-in

Treatment(s): Acarbose (Oral) – fixed-dose
Set dose (mg/d):600
Details of dosing regimen: Acarbose, week 1-2 100 mg TID, week 3-16 200 mg TID. The dosage was titrated at 2 week intervals depending on drug assignment

Outcomes

General

Data from 3/4 arms have been extracted in this evidence table (data relating to acarbose 300 mg TID or 900 mg/day is over the maximum licensed dose)

Total dropouts not reported

Baseline characteristics

		Placebo			Acarbose (100 mg TID)				
		N	k	mean	N	k	mean	Δ	p
Safety population									
Demographics:									
Age (years)	Continuous	73		55	73		54		
Sex (n male) a	Dichotomous	73	41	(56.2%)	73	40	(54.8%)		
Duration of diabetes (yrs)	Continuous	73		5	73		6		
Body weight:									
BMI (kg/m2)	Continuous	73		31	73		30		
Weight (kg) – 0wkb	Continuous	73		87.4944	73		84.672		
Weight (kg) – 16wk	Continuous	73		91	73		87		
Height (cm)	Continuous	73		170	73		169		
Full analysis set (FAS) or efficacy analysis pop									
Blood glucose:									
HbA1c (%) – 0wk	Continuous	62		8.67	57		8.69		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	62		202.5	57		202.3		
Body weight:									
BMI (kg/m2)	Continuous	64		32	58		31		
Weight (kg) – 0wkb	Continuous	64		90.3168	58		87.4944		
Weight (kg) – 16wkc	Mean change	62		-0.37	57		-0.19		
Weight (kg) – 16wk	Continuous	64		93	58		86		
Height (cm)	Continuous	64		171	58		168		
Lipids:									
Total cholesterol (mmol/l) – 0wk	Continuous	62		5.368536	57		5.593518		
Triglycerides (mmol/l) – 0wk	Continuous	62		2.274935	57		2.312192		

[a] approximated to nearest integer (percentages only presented in text)
[b] estimated from BMI assuming mean height of 1.68m

[c] from full paper; SD not reported

		Placebo			Acarbose (200 mg TID)			Δ	p
		N	k	mean	N	k	mean		
Safety population									
Demographics:									
Age (years)	Continuous	73		55	72		57		
Sex (n male) a	Dichotomous	73	41	(56.2%)	72	42	(58.3%)		
Duration of diabetes (yrs)	Continuous	73		5	72		5		
Body weight:									
BMI (kg/m2)	Continuous	73		31	72		31		
Weight (kg) – 0wkb	Continuous	73		87.4944	72		87.4944		
Weight (kg) – 16wk	Continuous	73		91	72		90		
Height (cm)	Continuous	73		170	72		171		
Full analysis set (FAS) or efficacy analysis pop									
Blood glucose:									
HbA1c (%) – 0wk	Continuous	62		8.67	54		8.96		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	62		202.5	54		238		
Body weight:									
BMI (kg/m2)	Continuous	64		32	54		31		
Weight (kg) – 0wkb	Continuous	64		90.3168	54		87.4944		
Weight (kg) – 16wkc	Mean change	62		-0.37	54		-0.8		
Weight (kg) – 16wk	Continuous	64		93	54		89		
Height (cm)	Continuous	64		171	54		170		
Lipids:									
Total cholesterol (mmol/l) – 0wk	Continuous	62		5.368536	54		5.4306		
Triglycerides (mmol/l) – 0wk	Continuous	62		2.274935	54		2.13381		

[a] approximated to nearest integer (percentages only presented in text)
[b] estimated from BMI assuming mean height of 1.68m
[c] from full paper; SD not reported

		Acarbose (100 mg TID)			Acarbose (200 mg TID)			Δ	p
		N	k	mean	N	k	mean		
Safety population									
Demographics:									
Age (years)	Continuous	73		54	72		57		
Sex (n male) a	Dichotomous	73	40	(54.8%)	72	42	(58.3%)		
Duration of diabetes (yrs)	Continuous	73		6	72		5		
Body weight:									
BMI (kg/m2)	Continuous	73		30	72		31		
Weight (kg) – 0wkb	Continuous	73		84.672	72		87.4944		
Weight (kg) – 16wk	Continuous	73		87	72		90		
Height (cm)	Continuous	73		169	72		171		
Full analysis set (FAS) or efficacy analysis pop									
Blood glucose:									
HbA1c (%) – 0wk	Continuous	57		8.69	54		8.96		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	57		202.3	54		238		
Body weight:									
BMI (kg/m2)	Continuous	58		31	54		31		
Weight (kg) – 0wkb	Continuous	58		87.4944	54		87.4944		

Weight (kg) – 16wkc	Mean change	57		-0.19	54		-0.8		
Weight (kg) – 16wk	Continuous	58		86	54		89		
Height (cm)	Continuous	58		168	54		170		
Lipids:									
Total cholesterol (mmol/l) – 0wk	Continuous	57		5.593518	54		5.4306		
Triglycerides (mmol/l) – 0wk	Continuous	57		2.312192	54		2.13381		

[a] approximated to nearest integer (percentages only presented in text)
[b] estimated from BMI assuming mean height of 1.68m
[c] from full paper; SD not reported

Results

		Placebo			Acarbose (100 mg TID)			Δ	p
		N	k	mean	N	k	mean		
Safety population									
Adverse events:									
GI: nausea – 16wk	Dichotomous	73	0	(0.0%)	73	4	(5.5%)		
Any adverse event(s) – 16wk	Dichotomous	73	59	(80.8%)	73	70	(95.9%)		
Flatulence – 16wk	Dichotomous	73	18	(24.7%)	73	56	(76.7%)		
GI: diarrhoea – 16wk	Dichotomous	73	7	(9.6%)	73	26	(35.6%)		
GI: abdominal pain – 16wk	Dichotomous	73	4	(5.5%)	73	13	(17.8%)		
Headache – 16wk	Dichotomous	73	5	(6.8%)	73	11	(15.1%)		
Dropouts:									
Dropout due to AEs – 16wk	Dichotomous	73	3a	(4.1%)	73	12b	(16.4%)		
Full analysis set (FAS) or efficacy analysis pop									
Blood glucose:									
HbA1c (%) – 16wkc	Mean change	62		0.31 (SD 1.02)	57		-0.48 (SD 0.981)		
Fasting plasma glucose (mmol/l) – 16wkd	Mean change	62		1.0989	57		-0.406815		
Body weight:									
Weight (kg) – 16wkd	Mean change	62		-0.37	57		-0.19		
Weight (kg) – 16wk	Continuous	64		93	58		86		
Lipids:									
Total cholesterol (mmol/l) – 16wkd	Mean change	62		-0.0537888	57		0.0843036		
Triglycerides (mmol/l) – 16wkd	Mean change	62		0.2987334	57		0.1026261		

[a] approximated to nearest integer (percentages only presented in text)
[b] approximated to nearest integer (percentages only presented in text); approximated to nearest integer (percentages only presented in text)
[c] from full paper; SD estimated from graph; ANCOVA with baseline Hba1c
[d] from full paper; SD not reported

		Placebo			Acarbose (200 mg TID)			Δ	p
		N	k	mean	N	k	mean		
Safety population									
Adverse events:									
GI: nausea – 16wk	Dichotomous	73	0	(0.0%)	72	6	(8.3%)		
Any adverse event(s) – 16wk	Dichotomous	73	59	(80.8%)	72	69	(95.8%)		
Flatulence – 16wk	Dichotomous	73	18	(24.7%)	71	62	(87.3%)		
GI: diarrhoea – 16wk	Dichotomous	73	7	(9.6%)	72	24	(33.3%)		
GI: abdominal pain – 16wk	Dichotomous	73	4	(5.5%)	72	11	(15.3%)		
Headache – 16wk	Dichotomous	73	5	(6.8%)	72	3	(4.2%)		
Dropouts:									
Dropout due to AEs – 16wk	Dichotomous	73	3a	(4.1%)	72	15b	(20.8%)		

Full analysis set (FAS) or efficacy analysis pop								
Blood glucose: HbA1c (%) – 16wkc	Mean change	62		0.31 (SD 1.02)	54		-0.4 (SD 1.1)	
Fasting plasma glucose (mmol/l) – 16wkd	Mean change	62		1.0989	54		-1.060605	
Body weight: Weight (kg) – 16wkd	Mean change	62		-0.37	54		-0.8	
Weight (kg) – 16wk	Continuous	64		93	54		89	
Lipids: Total cholesterol (mmol/l) – 16wkd	Mean change	62		-0.0537888	54		0.0069822	
Triglycerides (mmol/l) – 16wkd	Mean change	62		0.2987334	54		-0.0944973	

[a] approximated to nearest integer (percentages only presented in text)
[b] approximated to nearest integer (percentages only presented in text); approximated to nearest integer (percentages only presented in text)
[c] from full paper; SD estimated from graph; ANCOVA with baseline Hba1c
[d] from full paper; SD not reported

		Acarbose (100 mg TID)			Acarbose (200 mg TID)				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Safety population									
Adverse events: GI: nausea – 16wk	Dichotomous	73	4	(5.5%)	72	6	(8.3%)		
Any adverse event(s) – 16wk	Dichotomous	73	70	(95.9%)	72	69	(95.8%)		
Flatulence – 16wk	Dichotomous	73	56	(76.7%)	71	62	(87.3%)		
GI: diarrhoea – 16wk	Dichotomous	73	26	(35.6%)	72	24	(33.3%)		
GI: abdominal pain – 16wk	Dichotomous	73	13	(17.8%)	72	11	(15.3%)		
Headache – 16wk	Dichotomous	73	11	(15.1%)	72	3	(4.2%)		
Dropouts: Dropout due to AEs – 16wka	Dichotomous	73	12	(16.4%)	72	15	(20.8%)		
Full analysis set (FAS) or efficacy analysis pop									
Blood glucose: HbA1c (%) – 16wkb	Mean change	57		-0.48 (SD 0.981)	54		-0.4 (SD 1.1)		
Fasting plasma glucose (mmol/l) – 16wkc	Mean change	57		-0.406815	54		-1.060605		
Body weight: Weight (kg) – 16wkc	Mean change	57		-0.19	54		-0.8		
Weight (kg) – 16wk	Continuous	58		86	54		89		
Lipids: Total cholesterol (mmol/l) – 16wkc	Mean change	57		0.0843036	54		0.0069822		
Triglycerides (mmol/l) – 16wkc	Mean change	57		0.1026261	54		-0.0944973		

[a] approximated to nearest integer (percentages only presented in text); approximated to nearest integer (percentages only presented in text)
[b] from full paper; SD estimated from graph; ANCOVA with baseline Hba1c
[c] from full paper; SD not reported

data from the cochrane review were not consistent with data from the full study so cochrane data has not been extracted

Table 23: Damsbo et al. (1998)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** Denmark **Authors' conclusions:** Metformin and diet had no significant effect on GS activity. The added effect of metformin to that of a hypocaloric diet in improving insulin stimulated glucose utilisation is marginal when blood glucose reduction is obtained by weight loss **Source of funding:** Lipha Pharmaceuticals, Novo Nordisk and Danish Diabetes Association **Comments:** Double-blind
Number and characteristics of patients	**Total number of patients:** 18 **Inclusion criteria:** Obese patients newly diagnosed with type 2 diabetes who had not received antidiabetic drugs previously **Exclusion criteria:** Patients had no significant concurrent disease, no clinical or biochemical evidence of impaired renal, hepatic or cardiac function
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** All treatment naive/ no OADs at screening **Details of washout period:** All never received AHAs previously
Lifestyle advice	Not reported
Follow-up	**Total follow-up (wks):** 12 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 12 **Frequency of monitoring appointments:** Assessments at baseline, 1, 2 and 3 months
Arms	**(1) Placebo** N: 9 Treatment duration (wks): 12 Washout period (d): 0 Comments: All AHA naïve Treatment(s): Placebo **(2) Metformin** N: 9 Treatment duration (wks): 12 Washout period (d): 0 Comments: All AHA naïve Treatment(s): Metformin (Oral) – flexible-dose (dose-adjusted) Minimum dose (mg/d): 1000 Maximum dose (mg/d): 3000 Details of dosing regimen: 1 to 3 g/day. The initial dose of 1 g daily followed by increments of 0.5 g every week to a maximum of 3 g or a maximum tolerated dose aiming at a FBG <7.8 mmol/l. Tablets were taken at meals twice daily.
Outcomes	
Baseline characteristics	

		Placebo			Metformin				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Demographics: Age (years)	Continuous	9		53 [rng 40–63]	9		51 [rng 40–60]		
Sex (n male)	Dichotomous	9	6	(66.7%)	9	7	(77.8%)		
Blood glucose: HbA1c (%) – 0wka	Continuous	9		9.9 (SD 3.9)	9		9.5 (SD 1.8)		
Fasting plasma glucose (mmol/l) – 0wka	Continuous	9		10.9 (SD 2.7)	9		12.7 (SD 3.6)		
Body weight: BMI (kg/m2) – 0wka	Continuous	9		31.9 (SD 4.5)	9		31.6 (SD 3.6)		
Weight (kg) – 0wka	Continuous	9		93.6 (SD 8.4)	9		101.2 (SD 12)		

	[a] SD calculated from reported SE
Results	

		Placebo			Metformin				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 12wka	Continuous	9		6.6 (SD 1.5)	9		6.7 (SD 0.9)		
Fasting plasma glucose (mmol/l) – 12wka	Continuous	9		8 (SD 2.4)	9		8.1 (SD 3)		
Body weight: BMI (kg/m2) – 12wka	Continuous	9		29.7 (SD 4.5)	9		29.6 (SD 3.3)		
Weight (kg) – 12wka	Continuous	9		87.5 (SD 9.6)	9		94.7 (SD 10.5)		
Dropouts: Total dropouts – 12wk	Dichotomous	9	0	(0.0%)	9	0	(0.0%)		

[a] SD calculated from reported SE

Table 24: DeFronzo & (1995)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** USA **Authors' conclusions:** Metformin monotherapy is well tolerated and improves glycaemic control and lipid concentration in patients with NIDDM whose diabetes is poorly controlled with diet or sulfonylurea alone **Source of funding:** Lipha pharamceuticals **Comments:** Double-blind
Number and characteristics of patients	**Total number of patients:** 289 **Inclusion criteria:** obese patients **Exclusion criteria:** - Pre-randomisation phase: Diet alone for 8 weeks prior to randomisation
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** some on oral hypoglycaemic drugs and/or insulin **Details of washout period:** Unclear whether patients were all AHA naïve as patients who previously had insulin within the 6 months prior to enrollment were excluded
Lifestyle advice	Patients were instructed in a hypocaloric diet, which they were told to follow for 8 weeks before undergoing randomisation
Follow-up	**Total follow-up (wks):** 37 **Length of titration period (wks):** 5 **Length of maintenance period (wks):** 24 **Frequency of monitoring appointments:** 8 week pre-randomisation and 29 week treatment period. Measurements taken at weeks 9, 21 and 29
Arms	**(1) Placebo** N: 146 Treatment duration (wks): 29 Washout period (d): 56 Treatment(s): Placebo (Oral) **(2) Metformin** N: 143

Treatment duration (wks): 29
Washout period (d): 56
Treatment(s): Metformin (Oral) – flexible-dose (dose-adjusted)
Minimum dose (mg/d): 850
Maximum dose (mg/d): 2550
Participants achieving full dose (n): 122
Details of dosing regimen: 850 to 2550 mg/day. At the end of the 5 week titration phase 78% were taking maximal doses (2550 mg/day) and 85% eventually took this dose. Doses were titrated as long as FBG >140 mg/dl and side effects were tolerable

Outcomes

Baseline characteristics

		Placebo			Metformin				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years) a	Continuous	146		53 (SD 12.1)	143		53 (SD 12)		
Sex (n male)	Dichotomous	146	62	(42.5%)	143	62	(43.4%)		
Duration of diabetes (yrs) a	Continuous	146		6 (SD 7.25)	143		6 (SD 5.98)		
Blood glucose: HbA1c (%) – 0wka	Continuous	146		8.2 (SD 2.42)	143		8.4 (SD 1.2)		
Fasting plasma glucose (mmol/l) – 0wka	Continuous	146		13.209 (SD 4.02)	143		13.3755 (SD 3.32)		
Body weight: BMI (kg/m2) a	Continuous	146		29.2 (SD 3.62)	143		29.9 (SD 3.59)		
Weight (kg) – 0wka	Continuous	146		92.2 (SD 14.5)	143		94.4 (SD 13.2)		
Lipids: Total cholesterol (mmol/l) – 0wk	Continuous	146		5.48232 (SD 1.25)	143		5.45646 (SD 0.928)		
HDL cholesterol (mmol/l) – 0wk	Continuous	146		1.06026 (SD 0.312)	143		1.00854 (SD 0.309)		
Triglycerides (mmol/l) – 0wk	Continuous	146		2.08865 (SD 1.23)	143		2.35961 (SD 2.03)		
LDL cholesterol (mmol/l) – 0wk	Continuous	146		3.56868 (SD 0.937)	143		3.51696 (SD 0.928)		

[a] SD calculated from reported SE

Results

		Placebo			Metformin				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 13wka	Mean change	146		0.15 (SD 0.242)	143		-1.3 (SD 0.598)		
HbA1c (%) – 29wkb	Mean change	146		0.4 (SD 1.2)	143		-1.4 (SD 1.19)		
Fasting plasma glucose (mmol/l) – 13wka	Mean change	146		0.13875 (SD 1.68)	143		-3.0525 (SD 1.66)		
Fasting plasma glucose (mmol/l) – 29wkb	Continuous	146		13.7 (SD 3.62)	143		10.6 (SD 3.58)		
Fasting plasma glucose (mmol/l) – 29wkb	Mean change	146		0.3 (SD 3.62)	143		-2.9 (SD 3.59)		
Body weight: Weight (kg) – 29wkc	Mean change	146		-1.1 (SD 2.41)	143		-0.6 (SD 3.58)		
Dropouts: Total dropouts – 29wk	Dichotomous	146	41	(28.1%)	143	31	(21.7%)		
Dropout due to AEs – 29wk	Dichotomous	146	2	(1.4%)	143	14	(9.8%)		
Drop out due to unsatisfactory effect – 29wk	Dichotomous	146	18	(12.3%)	143	2	(1.4%)		
Lipids: Total cholesterol (mmol/l) – 29wkc	Mean change	146		0.02586 (SD 0.0233)	143		-0.28446 (SD 0.023)		
HDL cholesterol (mmol/l) – 29wkc	Mean change	146		-0.02586 (SD 0.00776)	143		0.02586 (SD 0.0075)		

	Triglycerides (mmol/l) – 29wkc	Mean change	146		0.06774 (SD 0.0105)	143		-0.19193 (SD 0.0177)		
	LDL cholesterol (mmol/l) – 29wkc	Mean change	146		-0.05172 (SD 0.0155)	143		-0.28446 (SD 0.023)		

[a] estimated from graph; unclear error bars
[b] SD calculated from reported SE
[c] reported in full paper

Table 25: Dejager et al. (2007)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** 134 centres in USA, Russia and Tunisia **Authors' conclusions:** In conclusion, vildagliptin monotherapy decreases Hba1c in drug naïve patients without weight gain and is well tolerated with minimal hypoglycaemia **Source of funding:** funded by Novartis Pharmaceuticals Corporation **Comments:** 24 week, double-blind, parallel group study. No details of randomisation procedure, blinding or allocation concealment
Number and characteristics of patients	**Total number of patients:** 632 **Inclusion criteria:** patients who were diagnosed with type 2 diabetes and who had Hba1c 7.5 to 10.0% at the screening visit while receiving no pharmacologic treatment. Patients who had taken no OAD for at least 12 weeks prior to screening and no OAD for >3 consecutive months at any time in the past were considered to be representative of a drug naïve population. Male and female patients aged 18-80 years, inclusive, with a BMI 22-45 kg/m2 and with a FPG <15 mmol/l were eligible to participate **Exclusion criteria:** history of type 1 or secondary diabetes, acute metabolic complications within the past 6 months, MI, unstable angina or coronary artery bypass surgery within the previous 6 months. CHF and liver disease also precluded participation. Patients with any of the followig laboratory abnormalities were also excluded: ALT or AST greater then 3 times the upper normal limit, direct bilirubin >1.3 times the ULN, serum creatinine >2.5 mg/dl, clinically abnormal TSH, or fasting triglycerides >700 mg/dl. During the study patients were discontinued due to unsatisfactory therapeutic effect if they experienced an FPG>15 mmol/l confirmed by repeat measurement in the absence of intercurrent illness, or symptoms of worsening hyperglycaemia in the absence of intercurrent illness, or other incidental circumstances potentially causing deterioration of glucose control. A patients could also be discontinued due to UTE without meeting these pre-specified criteria based soley on the investigators judgement. Pre-randomisation phase: Each patient attended one screening visit (week 2) during which inclusion/exclusion criteria were assessed. Eligible patients were randomised at visit 2 (baseline)
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** some on oral hypoglycaemic drugs and/or insulin **Details of washout period:** Drug naïve defined as those not previously taking AHA in the 12 weeks prior to enrollment
Lifestyle advice	no details reported
Follow-up	**Total follow-up (wks):** 24 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 24 **Frequency of monitoring appointments:** efficacy and tolerability were assessed during 5 additional visits at weeks 4, 8, 12, 16 and 24 of active treatment
Arms	**(1) Vildagliptin (50 mg qd)** N: 163 Treatment duration (wks): 24 Washout period (d): 0 Treatment(s): Vildagliptin (Oral) – fixed-dose Set dose (mg/d):50 Frequency of dosing: once a day

Details of dosing regimen: no other details reported

(2) Vildagliptin (50mg bid)

N: 152

Treatment duration (wks): 24
Washout period (d): 0

Treatment(s): Vildagliptin (Oral) – fixed-dose
Set dose (mg/d):100
Frequency of dosing: twice a day
Details of dosing regimen: no other details reported

(3) Vildagliptin (100 mg qd)

N: 157

Treatment duration (wks): 24
Washout period (d): 0

Treatment(s): Vildagliptin (Oral) – fixed-dose
Set dose (mg/d):100
Frequency of dosing: once a day
Details of dosing regimen: no other details reported

(4) placebo

N: 160

Treatment duration (wks): 24
Washout period (d): 0

Treatment(s): Placebo (Oral)
Details of dosing regimen: No details reported

Outcomes

General

The primary ITT population (n=380) consists of all randomised patients who had a screening Hba1c >=7.4%, received at least one dose of the study medication and had a baseline as well as at least one post-baseline Hba1c value. The ITT population (n=594) includes all patients in the primary ITT population as well as those patients who were inapproriately randomised (having baseline Hba1c <7.4%) and those without a baseline Hba1c value. The safety population (n=625) consists of all patients who received at least one dose of study drug and had at least one post-baseline safety assessment. Last observation carried forward method was used for patients who discontinued early. Efficacy analyses were performed with the primary ITT population.

33 (20.2%) patients in 50 mg qd, 24 (15.8%) in 50mg bid, 23 (14.6%) in 100 mg qd and 41 (25.6%) in placebo group discontinued the study.

All outcomes have been extracted in this evidence table

Hypoglycaemic events

Major/severe hypoglycaemic event (Severe hypoglycaemia was defined as any episode requiring the assistance of another party)

symptomatic (confirmed) (hypoglycaemia was defined as symptoms suggestive of low blood glucose confirmed by self monitored blood glucose (SMBG) <3.1 mmol/l.)

Baseline characteristics

		Vildagliptin (50 mg qd)			Vildagliptin (50mg bid)				
		N	k	mean	N	k	mean	Δ	p
Demographics:									
Ethnicity-White	Dichotomous	163	76	(46.6%)	152	66	(43.4%)		
Ethnicity-Black	Dichotomous	163	10	(6.1%)	152	9	(5.9%)		
Ethnicity-Hispanic	Dichotomous	163	14	(8.6%)	152	12	(7.9%)		
Ethnicity-Other	Dichotomous	163	4	(2.5%)	152	3	(2.0%)		
ITT (primary) Demographics:									
Age (years)	Continuous	104		55.3 (SD 11.4)	90		52.8 (SD 9.6)		
Sex (n male)	Dichotomous	104	43	(41.3%)	90	42	(46.7%)		
Duration of diabetes (yrs)	Continuous	104		2.1 (SD 3.6)	90		2.1 (SD 3.3)		
Blood glucose:									
HbA1c (%) – 0wk	Continuous	104		8.2 (SD 0.8)	90		8.6 (SD 0.8)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	104		9.8 (SD 2.4)	90		10.1 (SD 2.2)		
Body weight:									
BMI (kg/m2)	Continuous	104		32.9 (SD 6)	90		33.3 (SD 4.8)		
Weight (kg) – 0wka	Continuous	104		92.85696 (SD 16.9)	90		93.98592 (SD 13.5)		

[a] estimated from BMI assuming mean height of 1.68m

		Vildagliptin (50 mg qd)			Vildagliptin (100 mg qd)			Δ	p
		N	k	mean	N	k	mean		
Demographics: Ethnicity-White	Dichotomous	163	76	(46.6%)	157	70	(44.6%)		
Ethnicity-Black	Dichotomous	163	10	(6.1%)	157	4	(2.5%)		
Ethnicity-Hispanic	Dichotomous	163	14	(8.6%)	157	14	(8.9%)		
Ethnicity-Other	Dichotomous	163	4	(2.5%)	157	4	(2.5%)		
ITT (primary) Demographics: Age (years)	Continuous	104		55.3 (SD 11.4)	92		53.6 (SD 10.8)		
Sex (n male)	Dichotomous	104	43	(41.3%)	92	49	(53.3%)		
Duration of diabetes (yrs)	Continuous	104		2.1 (SD 3.6)	92		2.4 (SD 4.2)		
Blood glucose: HbA1c (%) – 0wk	Continuous	104		8.2 (SD 0.8)	92		8.4 (SD 0.8)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	104		9.8 (SD 2.4)	92		9.9 (SD 2.3)		
Body weight: BMI (kg/m2)	Continuous	104		32.9 (SD 6)	92		32.4 (SD 6.1)		
Weight (kg) – 0wka	Continuous	104		92.85696 (SD 16.9)	92		91.44576 (SD 17.2)		

[a] estimated from BMI assuming mean height of 1.68m

		Vildagliptin (50 mg qd)			placebo			Δ	p
		N	k	mean	N	k	mean		
Demographics: Ethnicity-White	Dichotomous	163	76	(46.6%)	160	65	(40.6%)		
Ethnicity-Black	Dichotomous	163	10	(6.1%)	160	12	(7.5%)		
Ethnicity-Hispanic	Dichotomous	163	14	(8.6%)	160	11	(6.9%)		
Ethnicity-Other	Dichotomous	163	4	(2.5%)	160	6	(3.8%)		
ITT (primary) Demographics: Age (years)	Continuous	104		55.3 (SD 11.4)	94		52.2 (SD 11.2)		
Sex (n male)	Dichotomous	104	43	(41.3%)	94	45	(47.9%)		
Duration of diabetes (yrs)	Continuous	104		2.1 (SD 3.6)	94		1.6 (SD 2.5)		
Blood glucose: HbA1c (%) – 0wk	Continuous	104		8.2 (SD 0.8)	94		8.4 (SD 0.8)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	104		9.8 (SD 2.4)	94		9.9 (SD 2.5)		
Body weight: BMI (kg/m2)	Continuous	104		32.9 (SD 6)	94		32.6 (SD 5.6)		
Weight (kg) – 0wka	Continuous	104		92.85696 (SD 16.9)	94		92.01024 (SD 15.8)		

[a] estimated from BMI assuming mean height of 1.68m

		Vildagliptin (50mg bid)			Vildagliptin (100 mg qd)			Δ	p
		N	k	mean	N	k	mean		
Demographics: Ethnicity-White	Dichotomous	152	66	(43.4%)	157	70	(44.6%)		
Ethnicity-Black	Dichotomous	152	9	(5.9%)	157	4	(2.5%)		
Ethnicity-Hispanic	Dichotomous	152	12	(7.9%)	157	14	(8.9%)		
Ethnicity-Other	Dichotomous	152	3	(2.0%)	157	4	(2.5%)		

ITT (primary)									
Demographics:									
Age (years)	Continuous	90		52.8 (SD 9.6)	92		53.6 (SD 10.8)		
Sex (n male)	Dichotomous	90	42	(46.7%)	92	49	(53.3%)		
Duration of diabetes (yrs)	Continuous	90		2.1 (SD 3.3)	92		2.4 (SD 4.2)		
Blood glucose:									
HbA1c (%) – 0wk	Continuous	90		8.6 (SD 0.8)	92		8.4 (SD 0.8)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	90		10.1 (SD 2.2)	92		9.9 (SD 2.3)		
Body weight:									
BMI (kg/m2)	Continuous	90		33.3 (SD 4.8)	92		32.4 (SD 6.1)		
Weight (kg) – 0wka	Continuous	90		93.98592 (SD 13.5)	92		91.44576 (SD 17.2)		

[a] estimated from BMI assuming mean height of 1.68m

		Vildagliptin (50mg bid)			placebo				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Demographics:									
Ethnicity-White	Dichotomous	152	66	(43.4%)	160	65	(40.6%)		
Ethnicity-Black	Dichotomous	152	9	(5.9%)	160	12	(7.5%)		
Ethnicity-Hispanic	Dichotomous	152	12	(7.9%)	160	11	(6.9%)		
Ethnicity-Other	Dichotomous	152	3	(2.0%)	160	6	(3.8%)		
ITT (primary)									
Demographics:									
Age (years)	Continuous	90		52.8 (SD 9.6)	94		52.2 (SD 11.2)		
Sex (n male)	Dichotomous	90	42	(46.7%)	94	45	(47.9%)		
Duration of diabetes (yrs)	Continuous	90		2.1 (SD 3.3)	94		1.6 (SD 2.5)		
Blood glucose:									
HbA1c (%) – 0wk	Continuous	90		8.6 (SD 0.8)	94		8.4 (SD 0.8)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	90		10.1 (SD 2.2)	94		9.9 (SD 2.5)		
Body weight:									
BMI (kg/m2)	Continuous	90		33.3 (SD 4.8)	94		32.6 (SD 5.6)		
Weight (kg) – 0wka	Continuous	90		93.98592 (SD 13.5)	94		92.01024 (SD 15.8)		

[a] estimated from BMI assuming mean height of 1.68m

		Vildagliptin (100 mg qd)			placebo				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Demographics:									
Ethnicity-White	Dichotomous	157	70	(44.6%)	160	65	(40.6%)		
Ethnicity-Black	Dichotomous	157	4	(2.5%)	160	12	(7.5%)		
Ethnicity-Hispanic	Dichotomous	157	14	(8.9%)	160	11	(6.9%)		
Ethnicity-Other	Dichotomous	157	4	(2.5%)	160	6	(3.8%)		
ITT (primary)									
Demographics:									
Age (years)	Continuous	92		53.6 (SD 10.8)	94		52.2 (SD 11.2)		
Sex (n male)	Dichotomous	92	49	(53.3%)	94	45	(47.9%)		
Duration of diabetes (yrs)	Continuous	92		2.4 (SD 4.2)	94		1.6 (SD 2.5)		
Blood glucose:									
HbA1c (%) – 0wk	Continuous	92		8.4 (SD 0.8)	94		8.4 (SD 0.8)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	92		9.9 (SD 2.3)	94		9.9 (SD 2.5)		
Body weight:									
BMI (kg/m2)	Continuous	92		32.4 (SD 6.1)	94		32.6 (SD 5.6)		

Weight (kg) – 0wka	Continuous	92		91.44576 (SD 17.2)	94		92.01024 (SD 15.8)				

[a] estimated from BMI assuming mean height of 1.68m

Results

		Vildagliptin (50 mg qd)			Vildagliptin (50mg bid)				
		N	k	mean	N	k	mean	Δ	p
Dropouts:									
Total dropouts – 24wk	Dichotomous	163	33	(20.2%)	152	24	(15.8%)		
Dropout due to AEs – 24wk	Dichotomous	163	3	(1.8%)	152	2	(1.3%)		
Drop out due to unsatisfactory effect – 24wk	Dichotomous	163	6	(3.7%)	152	6	(3.9%)		
ITT (primary)									
Blood glucose:									
HbA1c (%) – 24wka	Mean change	104		-0.8 (SD 1.02)	90		-0.8 (SD 0.949)		
Fasting plasma glucose (mmol/l) – 24wkb	Mean change	104		-1	90		-0.8		
Body weight:									
Weight (kg) – 24wka	Mean change	104		-1.8 (SD 4.08)	90		-0.3 (SD 3.79)		
Blood pressure:									
Systolic blood pressure (mmHg) – 24wkb	Mean change	104		-1.4	90		-4.1		
Safety population									
Hypoglycaemic events:									
All hypoglycaemic events (no patients) – 24wk	Dichotomous	162	2	(1.2%)	151	0	(0.0%)		
Adverse events:									
GI: nausea – 24wk	Dichotomous	162	3	(1.9%)	151	4	(2.6%)		
Any adverse event(s) – 24wk	Dichotomous	162	108	(66.7%)	151	94	(62.3%)		
Any serious adverse event(s) – 24wk	Dichotomous	162	8	(4.9%)	151	6	(4.0%)		
Any serious adverse event(s) – 24wk	Dichotomous	162	8	(4.9%)	151	7	(4.6%)		
Any serious adverse event(s) – 24wk	Dichotomous	162	9	(5.6%)	151	6	(4.0%)		
Any serious adverse event(s) – 24wk	Dichotomous	162	9	(5.6%)	151	7	(4.6%)		
Study drug-related adverse event – 24wk	Dichotomous	162	18	(11.1%)	151	13	(8.6%)		
GI: diarrhoea – 24wk	Dichotomous	162	3	(1.9%)	151	6	(4.0%)		
Baseline Hba1c >8%									
Blood glucose:									
HbA1c (%) – 24wk	Mean change	56		-0.8 (SD 0.748)	58		-1.3 (SD 1.52)		
Fasting plasma glucose (mmol/l) – 24wk	Mean change	56		-1 (SD 2.99)	58		-1.3 (SD 3.05)		

[a] SD calculated from reported SE
[b] No SDs reported

		Vildagliptin (50 mg qd)			Vildagliptin (100 mg qd)				
		N	k	mean	N	k	mean	Δ	p
Dropouts:									
Total dropouts – 24wk	Dichotomous	163	33	(20.2%)	157	23	(14.6%)		
Dropout due to AEs – 24wk	Dichotomous	163	3	(1.8%)	157	6	(3.8%)		
Drop out due to unsatisfactory effect – 24wk	Dichotomous	163	6	(3.7%)	157	2	(1.3%)		
ITT (primary)									
Blood glucose:									
HbA1c (%) – 24wka	Mean change	104		-0.8 (SD 1.02)	92		-0.9 (SD 0.959)		
Fasting plasma glucose (mmol/l) – 24wkb	Mean change	104		-1	92		-0.8		

Body weight: Weight (kg) – 24wka	Mean change	104		-1.8 (SD 4.08)	92		-0.8 (SD 3.84)			
Blood pressure: Systolic blood pressure (mmHg) – 24wkb	Mean change	104		-1.4	92		-3			
Safety population Hypoglycaemic events: All hypoglycaemic events (no patients) – 24wk	Dichotomous	162	2	(1.2%)	155	1	(0.6%)			
Adverse events: GI: nausea – 24wk	Dichotomous	162	3	(1.9%)	155	2	(1.3%)			
Any adverse event(s) – 24wk	Dichotomous	162	108	(66.7%)	155	111	(71.6%)			
Any serious adverse event(s) – 24wk	Dichotomous	162	8	(4.9%)	155	3	(1.9%)			
Any serious adverse event(s) – 24wk	Dichotomous	162	8	(4.9%)	155	7	(4.5%)			
Any serious adverse event(s) – 24wk	Dichotomous	162	9	(5.6%)	155	3	(1.9%)			
Any serious adverse event(s) – 24wk	Dichotomous	162	9	(5.6%)	155	7	(4.5%)			
Study drug-related adverse event – 24wk	Dichotomous	162	18	(11.1%)	155	17	(11.0%)			
GI: diarrhoea – 24wk	Dichotomous	162	3	(1.9%)	155	2	(1.3%)			
Baseline Hba1c >8% Blood glucose: HbA1c (%) – 24wk	Mean change	56		-0.8 (SD 0.748)	51		-1.4 (SD 1.43)			
Fasting plasma glucose (mmol/l) – 24wk	Mean change	56		-1 (SD 2.99)	51		-1.5 (SD 2.86)			

[a] SD calculated from reported SE
[b] No SDs reported

		Vildagliptin (50 mg qd)			placebo				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Blood glucose: Fasting plasma glucose (mmol/l) – 24wk	Continuous	163			160				0.021
Dropouts: Total dropouts – 24wk	Dichotomous	163	33	(20.2%)	160	41	(25.6%)		
Dropout due to AEs – 24wk	Dichotomous	163	3	(1.8%)	160	6	(3.8%)		
Drop out due to unsatisfactory effect – 24wk	Dichotomous	163	6	(3.7%)	160	15	(9.4%)		
ITT Blood glucose: HbA1c (%) – 24wk	Mean change	152			149			MD=-0.500 (CI: -0.696, -0.304)	<0.001
ITT (primary) Blood glucose: HbA1c (%) – 24wka	Mean change	104		-0.8 (SD 1.02)	94		-0.3 (SD 0.97)	MD=-0.500 (CI: -0.892, -0.108)	0.006
Fasting plasma glucose (mmol/l) – 24wkb	Mean change	104		-1	94		-0.1		
Body weight: Weight (kg) – 24wka	Mean change	104		-1.8 (SD 4.08)	94		-1.4 (SD 3.88)		
Blood pressure: Systolic blood pressure (mmHg) – 24wkb	Mean change	104		-1.4	94		-1.5		
Safety population Hypoglycaemic events: All hypoglycaemic events (no patients) – 24wk	Dichotomous	162	2	(1.2%)	157	0	(0.0%)		
Adverse events: GI: nausea – 24wk	Dichotomous	162	3	(1.9%)	157	6	(3.8%)		

Any adverse event(s) – 24wk	Dichotomous	162	108	(66.7%)	157	97	(61.8%)		
Any serious adverse event(s) – 24wk	Dichotomous	162	8	(4.9%)	157	5	(3.2%)		
Any serious adverse event(s) – 24wk	Dichotomous	162	8	(4.9%)	157	9	(5.7%)		
Any serious adverse event(s) – 24wk	Dichotomous	162	9	(5.6%)	157	5	(3.2%)		
Any serious adverse event(s) – 24wk	Dichotomous	162	9	(5.6%)	157	9	(5.7%)		
Study drug-related adverse event – 24wk	Dichotomous	162	18	(11.1%)	157	19	(12.1%)		
GI: diarrhoea – 24wk	Dichotomous	162	3	(1.9%)	157	5	(3.2%)		
>=3 months since diagnosis Blood glucose: HbA1c (%) – 24wk	Mean change	63			55			MD=-0.800 (CI: -1.192, -0.408)	<0.001
Baseline Hba1c >8% Blood glucose: HbA1c (%) – 24wk	Mean change	56		-0.8 (SD 0.748)	56		c		
Fasting plasma glucose (mmol/l) – 24wk	Mean change	56		-1 (SD 2.99)	56		d		

[a] SD calculated from reported SE
[b] No SDs reported
[c] not reported in text
[d] not reported

		Vildagliptin (50mg bid)			Vildagliptin (100 mg qd)				
		N	k	mean	N	k	mean	Δ	p
Dropouts: Total dropouts – 24wk	Dichotomous	152	24	(15.8%)	157	23	(14.6%)		
Dropout due to AEs – 24wk	Dichotomous	152	2	(1.3%)	157	6	(3.8%)		
Drop out due to unsatisfactory effect – 24wk	Dichotomous	152	6	(3.9%)	157	2	(1.3%)		
ITT (primary) Blood glucose: HbA1c (%) – 24wka	Mean change	90		-0.8 (SD 0.949)	92		-0.9 (SD 0.959)		
Fasting plasma glucose (mmol/l) – 24wkb	Mean change	90		-0.8	92		-0.8		
Body weight: Weight (kg) – 24wka	Mean change	90		-0.3 (SD 3.79)	92		-0.8 (SD 3.84)		
Blood pressure: Systolic blood pressure (mmHg) – 24wkb	Mean change	90		-4.1	92		-3		
Safety population Hypoglycaemic events: All hypoglycaemic events (no patients) – 24wk	Dichotomous	151	0	(0.0%)	155	1	(0.6%)		
Adverse events: GI: nausea – 24wk	Dichotomous	151	4	(2.6%)	155	2	(1.3%)		
Any adverse event(s) – 24wk	Dichotomous	151	94	(62.3%)	155	111	(71.6%)		
Any serious adverse event(s) – 24wk	Dichotomous	151	6	(4.0%)	155	3	(1.9%)		
Any serious adverse event(s) – 24wk	Dichotomous	151	6	(4.0%)	155	7	(4.5%)		
Any serious adverse event(s) – 24wk	Dichotomous	151	7	(4.6%)	155	3	(1.9%)		
Any serious adverse event(s) – 24wk	Dichotomous	151	7	(4.6%)	155	7	(4.5%)		
Study drug-related adverse event – 24wk	Dichotomous	151	13	(8.6%)	155	17	(11.0%)		
GI: diarrhoea – 24wk	Dichotomous	151	6	(4.0%)	155	2	(1.3%)		

Baseline Hba1c >8%										
Blood glucose: HbA1c (%) – 24wk	Mean change	58		-1.3 (SD 1.52)	51		-1.4 (SD 1.43)			
Fasting plasma glucose (mmol/l) – 24wk	Mean change	58		-1.3 (SD 3.05)	51		-1.5 (SD 2.86)			

[a] SD calculated from reported SE
[b] No SDs reported

		Vildagliptin (50mg bid)			placebo				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: Fasting plasma glucose (mmol/l) – 24wk	Continuous	152			160				0.093
Dropouts: Total dropouts – 24wk	Dichotomous	152	24	(15.8%)	160	41	(25.6%)		
Dropout due to AEs – 24wk	Dichotomous	152	2	(1.3%)	160	6	(3.8%)		
Drop out due to unsatisfactory effect – 24wk	Dichotomous	152	6	(3.9%)	160	15	(9.4%)		
ITT Blood glucose: HbA1c (%) – 24wk	Mean change	143			149			MD=-0.600 (CI: -0.796, -0.404)	<0.001
ITT (primary) Blood glucose: HbA1c (%) – 24wka	Mean change	90		-0.8 (SD 0.949)	94		-0.3 (SD 0.97)	MD=-0.500 (CI: -0.892, -0.108)	0.006
Fasting plasma glucose (mmol/l) – 24wkb	Mean change	90		-0.8	94		-0.1		
Body weight: Weight (kg) – 24wka	Mean change	90		-0.3 (SD 3.79)	94		-1.4 (SD 3.88)		
Blood pressure: Systolic blood pressure (mmHg) – 24wkb	Mean change	90		-4.1	94		-1.5		
Safety population Hypoglycaemic events: All hypoglycaemic events (no patients) – 24wk	Dichotomous	151	0	(0.0%)	157	0	(0.0%)		
Adverse events: GI: nausea – 24wk	Dichotomous	151	4	(2.6%)	157	6	(3.8%)		
Any adverse event(s) – 24wk	Dichotomous	151	94	(62.3%)	157	97	(61.8%)		
Any serious adverse event(s) – 24wk	Dichotomous	151	6	(4.0%)	157	5	(3.2%)		
Any serious adverse event(s) – 24wk	Dichotomous	151	6	(4.0%)	157	9	(5.7%)		
Any serious adverse event(s) – 24wk	Dichotomous	151	7	(4.6%)	157	5	(3.2%)		
Any serious adverse event(s) – 24wk	Dichotomous	151	7	(4.6%)	157	9	(5.7%)		
Study drug-related adverse event – 24wk	Dichotomous	151	13	(8.6%)	157	19	(12.1%)		
GI: diarrhoea – 24wk	Dichotomous	151	6	(4.0%)	157	5	(3.2%)		
>=3 months since diagnosis Blood glucose: HbA1c (%) – 24wk	Mean change	54			55			MD=-0.700 (CI: -1.092, -0.308)	0.003
Baseline Hba1c >8% Blood glucose: HbA1c (%) – 24wk	Mean change	58		-1.3 (SD 1.52)	56		c		

Fasting plasma glucose (mmol/l) – 24wk	Mean change	58		-1.3 (SD 3.05)	56		d		

[a] SD calculated from reported SE
[b] No SDs reported
[c] not reported in text
[d] not reported

		Vildagliptin (100 mg qd)			placebo				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: Fasting plasma glucose (mmol/l) – 24wk	Continuous	157			160				0.058
Dropouts: Total dropouts – 24wk	Dichotomous	157	23	(14.6%)	160	41	(25.6%)		
Dropout due to AEs – 24wk	Dichotomous	157	6	(3.8%)	160	6	(3.8%)		
Drop out due to unsatisfactory effect – 24wk	Dichotomous	157	2	(1.3%)	160	15	(9.4%)		
ITT Blood glucose: HbA1c (%) – 24wk	Mean change	150			149			MD=-0.600 (CI: -0.796, -0.404)	<0.001
ITT (primary) Blood glucose: HbA1c (%) – 24wka	Mean change	92		-0.9 (SD 0.959)	94		-0.3 (SD 0.97)	MD=-0.600 (CI: -0.992, -0.208)	0.001
Fasting plasma glucose (mmol/l) – 24wkb	Mean change	92		-0.8	94		-0.1		
Body weight: Weight (kg) – 24wka	Mean change	92		-0.8 (SD 3.84)	94		-1.4 (SD 3.88)		
Blood pressure: Systolic blood pressure (mmHg) – 24wkb	Mean change	92		-3	94		-1.5		
Safety population Hypoglycaemic events: All hypoglycaemic events (no patients) – 24wk	Dichotomous	155	1	(0.6%)	157	0	(0.0%)		
Adverse events: GI: nausea – 24wk	Dichotomous	155	2	(1.3%)	157	6	(3.8%)		
Any adverse event(s) – 24wk	Dichotomous	155	111	(71.6%)	157	97	(61.8%)		
Any serious adverse event(s) – 24wk	Dichotomous	155	3	(1.9%)	157	5	(3.2%)		
Any serious adverse event(s) – 24wk	Dichotomous	155	3	(1.9%)	157	9	(5.7%)		
Any serious adverse event(s) – 24wk	Dichotomous	155	7	(4.5%)	157	5	(3.2%)		
Any serious adverse event(s) – 24wk	Dichotomous	155	7	(4.5%)	157	9	(5.7%)		
Study drug-related adverse event – 24wk	Dichotomous	155	17	(11.0%)	157	19	(12.1%)		
GI: diarrhoea – 24wk	Dichotomous	155	2	(1.3%)	157	5	(3.2%)		
>=3 months since diagnosis Blood glucose: HbA1c (%) – 24wk	Mean change	59			55			MD=-0.900 (CI: -1.292, -0.508)	<0.001
Baseline Hba1c >8% Blood glucose: HbA1c (%) – 24wk	Mean change	51		-1.4 (SD 1.43)	56		c		

	Fasting plasma glucose (mmol/l) – 24wk	Mean change	51		-1.5 (SD 2.86)	56		d			

[a] SD calculated from reported SE
[b] No SDs reported
[c] not reported in text
[d] not reported

	Change from baseline in primary and secondary endpoints were analysed using an ANCOVA model treatment and pooled center as the classification variables and baseline as the covariate

Table 26: Del et al. (2003)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** International (France, Italy and Netherlands) **Authors' conclusions:** Benofluorex significantly reduces Hba1c and FBG when compared with placebo, has a good safety profile and has relatively less potency compared to metformin although the non-inferiority test was significant **Source of funding:** IRIS (Institut de Recherches Internationales Servier) **Comments:** Double-blind
Number and characteristics of patients	**Total number of patients:** 722 **Inclusion criteria:** Patients with type 2 diabetes aged 35-70 years with FBG 7.8-16.7 mmol/l on diet alone or 7.8-11.1 mmol/l ni patients receiving an oral agent and a BMI between 25-40 kg/m2 **Exclusion criteria:** - Pre-randomisation phase: 2 month placebo run-in with strict diet plan. Patients with FBG between 7.8-13.9 mmol/l and/or Hba1c 7.5-10% and compliance with placebo 80% or over were eligible for randomisation
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** some on oral hypoglycaemic drugs and/or insulin **Details of washout period:** At inclusion, patients stopped oral therapy and entered a 2 month placebo controlled run-in period + diet
Lifestyle advice	Strict diet plan during the run-in period. During the study patients met a dietitian on a regular basis
Follow-up	**Total follow-up (wks):** 29 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 29 **Frequency of monitoring appointments:** Patients were measured after 17 and 29 weeks
Arms	**(1) Placebo** N: 144 Treatment duration (wks): 29 Washout period (d): 60 Comments: At inclusion, patients stopped oral therapy and entered a 2 month placebo controlled run-in period + diet Treatment(s): Placebo (Oral) **(2) Metformin** N: 284 Treatment duration (wks): 29 Washout period (d): 60 Comments: At inclusion, patients stopped oral therapy and entered a 2 month placebo controlled run-in period + diet Treatment(s): Metformin (Oral) – flexible-dose (dose-adjusted) Mean dose (mg/d): 2125 Minimum dose (mg/d): 850 Maximum dose (mg/d): 2550 Details of dosing regimen: 5 week dose finding

Outcomes

General

Data from third trial arm not extracted (benfluorex).

Baseline characteristics

		Placebo			Metformin			Δ	p
		N	k	mean	N	k	mean		
Demographics: Age (years)	Continuous	144		56 (SD 9)	284		56 (SD 9)		
Sex (n male)	Dichotomous	144	91	(63.2%)	284	68	(23.9%)		
Blood glucose: HbA1c (%) – 0wk	Continuous	144		7.43 (SD 1.48)	284		7.79 (SD 1.61)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	144		9.74 (SD 2.28)	284		10.15 (SD 2.47)		
Body weight: BMI (kg/m2) – 0wk	Continuous	144		29.9 (SD 3.9)	284		29.7 (SD 4.2) a		
Weight (kg) – 0wk	Continuous	144		84.5 (SD 14.8)	284		82.6 (SD 14.6)		
Lipids: Total cholesterol (mmol/l) – 0wk	Mean change	144		5.26 (SD 0.94)	284		5.38 (SD 0.96)		
HDL cholesterol (mmol/l) – 0wk	Mean change	144		1.15 (SD 0.29)	284		1.14 (SD 0.3)		
Triglycerides (mmol/l) – 0wk	Mean change	144		1.56 (SD 0.99)	284		1.82 (SD 1.15)		
Previous blood glucose lowering drugs: Diet alone (i.e. drug naïve)	Dichotomous	144	55	(38.2%)	284	122	(43.0%)		
Oral antidiabetic medication	Dichotomous	144	89	(61.8%)	284	162	(57.0%)		

[a] Data extracted from baseline characteristics (slight inconsistency in other table i.e. 29.8 rather than 29.7)

Results

		Placebo			Metformin			Δ	p
		N	k	mean	N	k	mean		
Blood glucose: HbA1c (%) – 29wk	Continuous	144		7.91 (SD 1.86)	284		6.77 (SD 1.34)		
Fasting plasma glucose (mmol/l) – 29wk	Continuous	144		10.13 (SD 3.11)	284		8.16 (SD 1.9)		
Body weight: BMI (kg/m2) – 29wk	Continuous	144		29.6 (SD 4)	284		29.5 (SD 4.3)		
Weight (kg) – 29wk	Continuous	144		83.5 (SD 14.5)	284		81.9 (SD 15)		
Dropouts: Total dropouts – 29wk	Dichotomous	144	36	(25.0%)	284	45	(15.8%)		
Dropout due to AEs – 29wk	Dichotomous	144	6	(4.2%)	284	16	(5.6%)		
Drop out due to unsatisfactory effect – 29wk	Dichotomous	144	15	(10.4%)	284	3	(1.1%)		
Lipids: Total cholesterol (mmol/l) – 29wk	Mean change	144		5.44 (SD 1.04)	284		5.2 (SD 0.93)		
HDL cholesterol (mmol/l) – 29wk	Mean change	144		1.18 (SD 0.3)	284		1.23 (SD 0.35)		
Triglycerides (mmol/l) – 29wk	Mean change	144		1.83 (SD 1.71)	284		1.65 (SD 1.02)		

Table 27: Delgado et al. (2002)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** Switzerland/Spain **Authors' conclusions:** Our results show that treatment with acarbose is efficient even in diabetic patients presenting with good glucose control without any other associated treatment. By decreasing postprandial blood glucose, acarbose improves both insulin sensitivity and secretion **Source of funding:** Unclear but may not have received funding from pharmaceutical company **Comments:** Double-blind, randomised, placebo controlled trial
Number and characteristics of patients	**Total number of patients:** 17 **Inclusion criteria:** selected from those belonging to the outpatient pool of authors division. Included patients with type 2 diabetes (ADA definition), with stable body weight as well as capillary blood glucose readings for 2 months prior to study enrollment. All patients had received 2 week education programme. **Exclusion criteria:** patients with uncontrolled type 2 diabetes, presence of micro or macrovasular complications, treatment with insulin and/or other oral hypoglycaemic agents, dyslipidemia, hypertension and any drug known to affect insulin resistence/secretion Pre-randomisation phase: 2 week in hospital education programme. Titration was part of the maintenance period
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** some on oral hypoglycaemic drugs and/or insulin **Details of washout period:** Althought it states that 'patients were well controlled with diet alone', unclear whether any had history of AHAs
Lifestyle advice	all participants had received a two week in-hospital therapeutic education programme aimed at improving diabetes management skills, dietary knowledge and weight stabilsation strategies
Follow-up	**Total follow-up (wks):** 16 **Length of titration period (wks):** 2 **Length of maintenance period (wks):** 14 **Frequency of monitoring appointments:** No details reported
Arms	**(1) Acarbose** N: 9 Treatment duration (wks): 16 Washout period (d): 0 Treatment(s): Acarbose (Oral) – forced titration Minimum dose (mg/d): 50 Maximum dose (mg/d): 100 Details of dosing regimen: patients received 50mg acarbose once daily for 2 weeks then 100 mg (2 tablets daily) for remaining 14 weeks **(2) Placebo** N: 8 Treatment duration (wks): 16 Washout period (d): 0 Treatment(s): Placebo (Oral) – forced titration Details of dosing regimen: patients received placebo (1 tablet daily) for two weeks then placebo (2 tablets daily) for remaining 14 weeks
Outcomes	**General** Outcomes not extracted in this evidence tble include fat mass, lean mass, insulin resistence measures, fat oxidation, carbohydrate oxidation and c-peptide. Fasting blood glucose following Ravens triple infusion was also not extracted. Drop outs not reported so assumed all completed study No details of ITT analysis reported
Baseline characteristics	

	Acarbose	Placebo	Δ	p

			N	k	mean	N	k	mean		
Demographics: Sex (n male)		Dichotomous	9	6	(66.7%)	8	3	(37.5%)		
Blood glucose: HbA1c (%) – 0wka		Continuous	9		6.8 (SD 1.5)	8		7.5 (SD 1.7)		
Fasting plasma glucose (mmol/l) – 0wka		Continuous	9		7.8 (SD 3.6)	8		7.5 (SD 1.7)		
Body weight: BMI (kg/m2) – 0wka		Continuous	9		36.1 (SD 4.5)	8		34.4 (SD 7.92)		
Weight (kg) – 0wka		Continuous	9		103.8 (SD 8.7)	8		90.6 (SD 25.2)		
Blood pressure: Systolic blood pressure (mmHg) – 0wk		Continuous	9		142 (SD 9)	8		149 (SD 11.3)		
Diastolic blood pressure (mmHg) – 0wk		Continuous	9		84 (SD 9)	8		91 (SD 8.49)		
Lipids: Total cholesterol (mmol/l) – 0wk		Continuous	9		5.2 (SD 1.2)	8		5.4 (SD 0.849)		
HDL cholesterol (mmol/l) – 0wk		Continuous	9		1.1 (SD 0.3)	8		1.1 (SD 0.283)		
Triglycerides (mmol/l) – 0wk		Continuous	9		2 (SD 0.9)	8		2.6 (SD 2.55)		

[a] SD calculated from reported SE

Results

		Acarbose			Placebo			Δ	p
		N	k	mean	N	k	mean		
Blood glucose: HbA1c (%) – 16wka	Continuous	9		6.7 (SD 0.9)	8		7.5 (SD 3.11)		NS
Fasting plasma glucose (mmol/l) – 16wka	Continuous	9		7.3 (SD 2.1)	8		8.4 (SD 1.98)		
Body weight: BMI (kg/m2) – 16wka	Continuous	9		36.3 (SD 4.8)	8		34.5 (SD 7.35)		b
Weight (kg) – 16wka	Continuous	9		104.6 (SD 8.7)	8		91.1 (SD 24.3)		b
Adverse events: Gastrointestinal disorders (any) – 16wk	Dichotomous	9	7	(77.8%)	8	0c	(0.0%)		b
Blood pressure: Systolic blood pressure (mmHg) – 16wk	Continuous	9		135 (SD 18)	8		143 (SD 12.7)		b
Diastolic blood pressure (mmHg) – 16wk	Continuous	9		84 (SD 6)	8		89 (SD 9.9)		b
Lipids: Total cholesterol (mmol/l) – 16wk	Continuous	9		5.4 (SD 0.9)	8		5.9 (SD 1.13)		b
HDL cholesterol (mmol/l) – 16wk	Continuous	9		1.1 (SD 0.3)	8		1.2 (SD 0)		b
Triglycerides (mmol/l) – 16wk	Continuous	9		1.8 (SD 0.6)	8		2.6 (SD 1.7)		b

[a] SD calculated from reported SE
[b] not reported
[c] assumed 0 although this is not explicitly reported

SD converted from SE
Data analysed using a two-way ANOVA

Table 28: Derosa et al. (2003)

General

Phase:
☑ monotherapy

	☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** Italy **Authors' conclusions:** Repaglinide and glimpiride improved glycaemic control and reduced levels of other metabolic parameters of interest in this population of patients with type 2 diabetes **Source of funding:** Unclear **Comments:** Randomised, double-blind, placebo controlled trial. Randomisation codes were prepared by a statistician and placed in envelopes, the statistician subsequently carried out randomisation by drawing envelopes. Blinding was maintained through the use of identical numbered bottles prepared by the hospital pharmacy
Number and characteristics of patients	**Total number of patients:** 132 **Inclusion criteria:** patients with a diagnosis of type 2 diabetes for 6 months or longer were eligible for participation. Eligible participants were to be non-smokers with normal blood pressure, no coronary heart disease and normal renal function (serum creatinine <1.5 mg/dl). Patients were receiving no anti diabetic medication at the time of enrollment and had not achieved satisfactory glycaemic control (Hba1c <7%) with diet and exercise. All patients had LDL cholesterol >=100 mg/dl and thus were at increased risk of vascular disease. Patients were taking no hypoglycaemic drugs, dieuretics, beta blockers or thyroxin **Exclusion criteria:** see inclusion criteria for details Pre-randomisation phase: After an initial 4 week placebo washout period, patients were randomised
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** some on oral hypoglycaemic drugs and/or insulin **Details of washout period:** Unclear whether all participants were completely naïve. Patients were not on OADs at enrollment
Lifestyle advice	Patients were on diet and exercise at enrollment (it was recommended that patients ride a stationary bicycle for at least 30 minutes 3 to 4 times per week). Standardised meals based on a controlled eneregy diet were used. Patients were instructed to maintain this diet throughout the study. As part of a behaviour-modification programme, patients kept food diaries and had tri-monthly visits with a dietician.
Follow-up	**Total follow-up (wks):** 64 **Length of titration period (wks):** 8 **Length of maintenance period (wks):** 52 **Frequency of monitoring appointments:** Outcomes were measured at the end of the placebo washout period (baseline) and at 6 and 12 months during active treatment
Arms	**(1) Repaglinide** N: 66 Treatment duration (wks): 60 Washout period (d): 28 Comments: 4 week placebo washout period Treatment(s): repaglinide (Oral) Mean dose (mg/d): 2.5 Minimum dose (mg/d): 1 Compliance: assessed by counting the number of tablets returned Details of dosing regimen: started on 1 mg/day. This dose was optimised over an 8 week titration period **(2) Glimepiride** N: 66 Treatment duration (wks): 60 Washout period (d): 28 Comments: 4 week placebo washout period Treatment(s): Sulfonylurea (Oral) Mean dose (mg/d): 3 Minimum dose (mg/d): 1 Details of dosing regimen: glimpiride 1 mg/day. The dose of the study drug was optimised over an 8 week titration period
Outcomes	**General** 4 (6%) patients in the glimepiride group and 4 (6%) in the repaglinide group discontinued the study Outcomes not extracted in this evidence table include fasting insulin, lipoprotein, PAI-1, homocysteine, fibrinogen and apolipoprotein No details of ITT analysis reported

Baseline characteristics

		Repaglinide			Glimepiride				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: Postprandial plasma glucose (mmol/l) – 0wk	Continuous	62		10.767 (SD 1.66)	62		10.434 (SD 1.78)		
Body weight: Height (cm) a	Continuous	62		171 (SD 5)	62		172 (SD 6)		
Blood pressure: Systolic blood pressure (mmHg) – 0wk	Continuous	62		129 (SD 4)	62		128 (SD 5)		
Diastolic blood pressure (mmHg) – 0wk	Continuous	62		85 (SD 4)	62		85 (SD 3)		
Lipids: Total cholesterol (mmol/l) – 0wk	Continuous	62		5.5599 (SD 0.983)	62		5.6892 (SD 1.11)		
HDL cholesterol (mmol/l) – 0wk	Continuous	62		1.11198 (SD 0.181)	62		1.13784 (SD 0.129)		
Triglycerides (mmol/l) – 0wk	Continuous	62		1.72737 (SD 0.361)	62		1.9193 (SD 0.406)		
LDL cholesterol (mmol/l) – 0wk	Continuous	62		3.59454 (SD 0.569)	62		3.67212 (SD 0.621)		
PP Demographics: Age (years)	Continuous	62		56 (SD 9)	62		54 (SD 10)		
Sex (n male)	Dichotomous	62	31	(50.0%)	62	30	(48.4%)		
Blood glucose: HbA1c (%) – 0wk	Continuous	62		8 (SD 1.1)	62		7.8 (SD 1.2)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	62		8.769 (SD 1.22)	62		9.102 (SD 0.999)		
Body weight: BMI (kg/m2) – 0wk	Continuous	62		26.1 (SD 1.2)	62		26.4 (SD 1)		
Weight (kg) – 0wk	Continuous	62		76.4 (SD 5.2)	62		77.1 (SD 5.9)		

[a] Assumed metres reported in table

Results

		Repaglinide			Glimepiride				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 60wk	Continuous	62			62				NS
Fasting plasma glucose (mmol/l) – 60wk	Continuous	62			62				NS
Fasting plasma glucose (mmol/l) – 60wk	Mean change	62		-2.109 (SD 5.35)	62		-2.1645 (SD 8.25)		
Fasting plasma glucose (mg/dl) – 60wk	Continuous	62		120 (SD 24)	62		125 (SD 19)		
Postprandial plasma glucose (mmol/l) – 60wk	Mean change	62		-2.553 (SD 4.01)	62		-1.1655 (SD 6.02)		
Postprandial plasma glucose (mmol/l) – 60wk	Continuous	62			62				<0.05
Body weight: BMI (kg/m2) – 60wk	Continuous	62			62				NS
Weight (kg) – 60wk	Continuous	62			62				NS
Dropouts: Total dropouts – 60wk	Dichotomous	66	4	(6.1%)	66	4	(6.1%)		
Dropout due to AEs – 60wk	Dichotomous	66	0	(0.0%)	66	2	(3.0%)		
Drop out due to unsatisfactory effect – 60wk	Dichotomous	62	3	(4.8%)	62	2	(3.2%)		NR
Blood pressure: Systolic blood pressure (mmHg) – 34wk	Continuous	62		131 (SD 3)	62		130 (SD 4)		

	Systolic blood pressure (mmHg) – 60wk	Continuous	62		128 (SD 5)	62		129 (SD 4)	NS
	Diastolic blood pressure (mmHg) – 34wk	Continuous	62		84 (SD 5)	62		86 (SD 4)	
	Diastolic blood pressure (mmHg) – 34wk	Continuous	62		85 (SD 5)	62		86 (SD 4)	
	Diastolic blood pressure (mmHg) – 60wk	Continuous	62			62			NS
	Lipids: Total cholesterol (mmol/l) – 34wk	Continuous	62		5.172 (SD 1.03)	62		5.5599 (SD 1.03)	
	Total cholesterol (mmol/l) – 60wk	Continuous	62		5.09442 (SD 0.931)	62		5.19786 (SD 0.828)	NS
	HDL cholesterol (mmol/l) – 34wk	Continuous	62		1.13784 (SD 0.155)	62		1.1637 (SD 0.129)	
	HDL cholesterol (mmol/l) – 60wk	Continuous	62		1.1637 (SD 0.181)	62		1.11198 (SD 0.155)	NS
	Triglycerides (mmol/l) – 34wk	Continuous	62		1.60318 (SD 0.418)	62		1.85156 (SD 0.395)	
	Triglycerides (mmol/l) – 60wk	Continuous	62		1.52415 (SD 0.406)	62		1.74995 (SD 0.44)	NS
	LDL cholesterol (mmol/l) – 34wk	Continuous	62		3.46524 (SD 0.672)	62		3.6204 (SD 0.698)	
	LDL cholesterol (mmol/l) – 60wk	Continuous	62		3.41352 (SD 0.465)	62		3.51696 (SD 0.646)	NS
	PP Blood glucose: HbA1c (%) – 60wk	Continuous	62		6.8 (SD 0.8)	62		6.7 (SD 0.9)	
	HbA1c (%) – 60wka	Mean change	62		-1.2	62		-1.1	
	Body weight: BMI (kg/m2) – 34wk	Continuous	62		25.7 (SD 1.1)	62		26.1 (SD 1.1)	
	BMI (kg/m2) – 60wk	Continuous	62		26.2 (SD 0.8)	62		25.9 (SD 1.2)	
	Weight (kg) – 34wk	Continuous	62		75.8 (SD 5)	62		76.8 (SD 5.6)	
	Weight (kg) – 60wk	Continuous	62		76.5 (SD 5.3)	62		76.6 (SD 5.3)	
	[a] SD calculated from reported 95% CI implausible and therefore not used								
	One way ANOVA was used to compare baseline data and to assess significance within and between groups. One sample t-tests were used to compared values obtained before and after treatment, two sample t-tests were used for between group comparisons.								

Table 29: Derosa et al. (2011)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** Italy **Authors' conclusions:** Acarbose was more effective than placebo in reducing the post-OFL peaks of the various parameters including the inflammatory markers, after 7 months of therapy **Source of funding:** Authors certify no affliation with or financial involvement in any organisation with a direct financial interest in the subject matter or materials discussed in the manuscript **Comments:** Multicentre, randomised, double-blind controlled study. Both drugs were supplied as identical, opaque, white capsules in coded bottles to ensure blinding. Randomisation was done using a drawing of envelopes containing randomisation codes prepared by a statistician. A copy of the code was provided to the responsible person performing statistical analysis. The code was only broken after databse lock.
Number and	**Total number of patients:** 188

characteristics of patients

Inclusion criteria: caucasian type 2 diabetic patients aged 18 years and over, of either sex and with controlled diabetes (Hba1c<7%) in therapy with diet and physical activity.

Exclusion criteria: history of ketoacidosis or unstable or rapidly progressive retinopathy, nephropathy, or neuropathy, impaired hepatic function, impaired renal function, or severe anaemia. Patients with serious cardiovascular disease or cerebrovascular conditions within 6 months before study enrollment were also excluded. Patients with gastrointestinal disorders or intolerance to acarbose were excluded. Women who were pregnant or breastfeeding or of childbearing potential and not taking adequate contraceptive precautions were also excluded.

Pre-randomisation phase: assumed titration period was included as part of the maintenance period

Previous glucose-lowering therapy

Any participants previously taking glucose-lowering therapy? All treatment naive/ no OADs at screening

Details of washout period: All patients were only treated with diet and exercise

Lifestyle advice

participants began a controlled-energy diet based on ADA recommendations. Standard diet advice was given by a dietician and/or specialist doctor, who periodically provided instruction on dietary intake recording procedures as part of a behaviour modification program and then later used the subjects food diaries for counselling. Individuals were also encouraged to increase their physical activity by walking briskly for 20 to 30 minutes, 3-5 times a week, or by cycle.

Follow-up

Total follow-up (wks): 28

Length of titration period (wks): 0

Length of maintenance period (wks): 28

Frequency of monitoring appointments: Does not specify length of titration period

BMI, Hba1c, FPG, PPG, lipids and BP were evalauted at baseline and after 1, 2 and 7 months

Arms

(1) acarbose

N: 96

Treatment duration (wks): 28
Washout period (d): 0

Treatment(s): Acarbose (Oral) – forced titration
Set dose (mg/d):300
Frequency of dosing: three times a day
Compliance: assessed by counting the number of pills returned at the time of specified clinic visits
Details of dosing regimen: acarbose 50mg three times a day. After the first month acarbose was titrated to 100 mg three times a day.

(2) placebo

N: 92

Treatment duration (wks): -
Washout period (d): 0

Treatment(s): Placebo (Oral)
Frequency of dosing: three times a day
Details of dosing regimen: placebo three times daily

Outcomes

General

ITT analysis was conducted in patients who had received >= 1 dose of study medication and had a subsequent efficacy observation. Patients were included in the tolerability analysis sif they had received >= 1 dose of trial medication and had undergone subsequent tolerability observation.

Outcomes not reported in this evidence table include oral fat load, insulin resistance measures, c-reactive protein, interlukin-6 and other biochemical markers.

8 (9%) patients in acarbose and 5 (6%) in placebo group discontinued the study

Baseline characteristics

		All study participants		
		N	**k**	**mean**
Body weight: Height (cm)	Continuous	188		169 (SD 5)

	acarbose			placebo				
	N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**

Demographics: Sex (n male)	Dichotomous	96	47	(49.0%)	92	45	(48.9%)		
Blood glucose: HbA1c (%) – 0wk	Continuous	96		6.8 (SD 0.6)	92		6.7 (SD 0.5)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	96		8.214 (SD 0.944)	92		8.103 (SD 0.832)		
Body weight: BMI (kg/m2) – 0wk	Continuous	96		26.6 (SD 0.8)	92		26.8 (SD 0.9)		
Weight (kg) – 0wk	Continuous	96		75.1 (SD 7.7)	92		76.5 (SD 8.2)		
Blood pressure: Systolic blood pressure (mmHg) – 0wk	Continuous	96		132 (SD 5)	92		134 (SD 7)		
Diastolic blood pressure (mmHg) – 0wk	Continuous	96		87 (SD 4)	92		89 (SD 5)		
Lipids: Total cholesterol (mmol/l) – 0wk	Continuous	96		4.7841 (SD 0.207)	92		4.86168 (SD 0.259)		
HDL cholesterol (mmol/l) – 0wk	Continuous	96		1.13784 (SD 0.155)	92		1.11198 (SD 0.129)		
Triglycerides (mmol/l) – 0wk	Continuous	96		1.90801 (SD 0.474)	92		1.84027 (SD 0.429)		
LDL cholesterol (mmol/l) – 0wk	Continuous	96		2.81874 (SD 0.181)	92		2.92218 (SD 0.207)		

Results

		acarbose			placebo				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Blood glucose: HbA1c (%) – 28wk	Continuous	88		5.7 (SD 0.1)	87		6.4 (SD 0.3)		<0.01
Fasting plasma glucose (mmol/l) – 28wk	Continuous	88		6.6045 (SD 0.388)	87		7.3815 (SD 0.555)		<0.05
2-h post prandial glucose (mmol/l) – 28wk	Continuous	88		8.436 (SD 0.333)	87		9.2685 (SD 0.444)		<0.05
Body weight: BMI (kg/m2) – 28wk	Continuous	88		24.5 (SD 0.2)	87		25 (SD 0.3)		NS
Weight (kg) – 28wk	Continuous	88		69.2 (SD 5.8)	87		71.4 (SD 6.1)		NS
Hypoglycaemic events: All hypoglycaemic events (no patients) – 28wk	Dichotomous	88	0	(0.0%)	87	0	(0.0%)		a
Dropouts: Total dropouts – 28wk	Dichotomous	96	8	(8.3%)	92	5	(5.4%)		
Dropout due to AEs – 28wk	Dichotomous	88	8	(9.1%)	87	1	(1.1%)		a
Blood pressure: Systolic blood pressure (mmHg) – 28wk	Continuous	88		131 (SD 4)	87		134 (SD 7)		NS
Diastolic blood pressure (mmHg) – 28wk	Continuous	88		86 (SD 3)	87		87 (SD 4)		NS
Lipids: Total cholesterol (mmol/l) – 28wk	Continuous	88		4.44792 (SD 0.129)	87		4.70652 (SD 0.181)		<0.05
HDL cholesterol (mmol/l) – 28wk	Continuous	88		1.1637 (SD 0.181)	87		1.08612 (SD 0.103)		NS
Triglycerides (mmol/l) – 28wk	Continuous	88		1.34351 (SD 0.181)	87		1.49028 (SD 0.237)		<0.05
LDL cholesterol (mmol/l) – 28wk	Continuous	88		2.66358 (SD 0.155)	87		2.92218 (SD 0.207)		<0.05

[a] not reported

Continuous variables were tested using a two-way repeated measures ANOVA to assess overall differences in post-prandial responses. Intervention effects were adjusted for additional potential confounders (sex,

	smoking) using ANCOVA. ANOVA was also used to assess the significance within and between groups. The statistical significance of the independent effects of traetment on the other variables was determined using ANCOVA taking the baseline level of each parameter as a covariate.

Table 30: Ebeling et al. (2001)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** Helsinki **Authors' conclusions:** Inflammatory factors and complement activation are associated in patients with type 2 diabetes **Source of funding:** Takeda and Maud Kuistila Foundation **Comments:** Double-blind
Number and characteristics of patients	**Total number of patients:** 29 **Inclusion criteria:** patients with type 2 diabetes, treated with either diet alone or diet and one oral medication, BMI >=25 kg/m2, aged between 35 and 70 years, Hba1c >=7.5%, FBG >=7.8 mmol/l **Exclusion criteria:** No details reported Pre-randomisation phase: There was a 4 week period on diet alone before randomisation
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** some on oral hypoglycaemic drugs and/or insulin **Details of washout period:** There was a 4 week period on diet alone before randomisation
Lifestyle advice	Details not reported
Follow-up	**Total follow-up (wks):** 26 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 26 **Frequency of monitoring appointments:** Patients visited the outpatients clinic at 2-6 weekly intervals
Arms	**(1) Pioglitazone (30 mg)** N: 9 Treatment duration (wks): 26 Washout period (d): 28 Comments: There was a 4 week period on diet alone Treatment(s): Pioglitazone (Oral) – flexible-dose (dose-adjusted) Set dose (mg/d):30 Maximum dose (mg/d): 45 Frequency of dosing: once a day Details of dosing regimen: 30 mg/day od but if after 9 weeks Hba1c had not reduced by 0.3% pioglitazone was increased to 45mg/day. Dose increased for 4/9 **(2) Glibenclamide (2.5 mg/day)** N: 10 Treatment duration (wks): 26 Washout period (d): 28 Comments: There was a 4 week period on diet alone Treatment(s): Sulfonylurea (Oral) – flexible-dose (dose-adjusted) Minimum dose (mg/d): 2.5 Maximum dose (mg/d): 5 Frequency of dosing: once a day Details of dosing regimen: 2.5 mg/day od but if after 9 weeks Hba1c had not reduced by 0.3% glibenclamide was doubled to 5mg/day. Dose not increased for any of the patients receiving glibenclamide **(3) Placebo** N: 10 Treatment duration (wks): 26 Washout period (d): 28 Comments: There was a 4 week period on diet alone

	Treatment(s): Placebo (Oral)
Outcomes	**General** Dropouts not explicitly reported

Baseline characteristics

		All study participants		
		N	**k**	**mean**
Demographics:				
Age (years)	Continuous	29		55.2 (SD 9.69329665284211) a
Sex (n male)	Dichotomous	29	21	(72.4%)
Duration of diabetes (yrs)	Continuous	29		5.9 (SD 7.00071424927486) a
Body weight:				
BMI (kg/m2) – 0wk	Continuous	29		30.9 (SD 4.3081318457076) a
BMI (kg/m2) – 0wk	Continuous	29		30.9 (SD 4.3081318457076) a
Weight (kg)	Continuous	29		87.21216 (SD 12.1592713213251) b

[a] SD calculated from reported SE
[b] SD calculated from reported SE; estimated from BMI assuming mean height of 1.68m

		Pioglitazone (30 mg)			Glibenclamide (2.5 mg/day)				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Blood glucose:									
HbA1c (%) – 0wka	Continuous	9		9.1 (SD 0.9)	10		8.9 (SD 0.9)		
Fasting plasma glucose (mmol/l) – 0wka	Continuous	9		10.9 (SD 1.8)	10		11.6 (SD 1.58)		
Body weight:									
BMI (kg/m2) – 0wka	Continuous	9		30.5 (SD 3.9)	10		30.2 (SD 5.38)		
Lipids:									
Total cholesterol (mmol/l) – 0wk	Continuous	9		5.18 (SD 0.66)	10		5.37 (SD 0.569)		
HDL cholesterol (mmol/l) – 0wk	Continuous	9		1.19 (SD 0.21)	10		1.17 (SD 0.19)		
Triglycerides (mmol/l) – 0wk	Continuous	9		2.34 (SD 1.41)	10		2.05 (SD 1.11)		

[a] SD calculated from reported SE

		Pioglitazone (30 mg)			Placebo				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Blood glucose:									
HbA1c (%) – 0wka	Continuous	9		9.1 (SD 0.9)	10		8.6 (SD 0.6)		
Fasting plasma glucose (mmol/l) – 0wka	Continuous	9		10.9 (SD 1.8)	10		11.3 (SD 1.58)		
Body weight:									
BMI (kg/m2) – 0wka	Continuous	9		30.5 (SD 3.9)	10		31.9 (SD 4.74)		
Lipids:									
Total cholesterol (mmol/l) – 0wk	Continuous	9		5.18 (SD 0.66)	10		5.2 (SD 0.949)		
HDL cholesterol (mmol/l) – 0wk	Continuous	9		1.19 (SD 0.21)	10		1.22 (SD 0.253)		
Triglycerides (mmol/l) – 0wk	Continuous	9		2.34 (SD 1.41)	10		2.19 (SD 1.11)		

[a] SD calculated from reported SE

		Glibenclamide (2.5 mg/day)		Placebo			Δ	p

		N	k	mean	N	k	mean		
Blood glucose: HbA1c (%) – 0wka	Continuous	10		8.9 (SD 0.9)	10		8.6 (SD 0.6)		
Fasting plasma glucose (mmol/l) – 0wka	Continuous	10		11.6 (SD 1.58)	10		11.3 (SD 1.58)		
Body weight: BMI (kg/m2) – 0wka	Continuous	10		30.2 (SD 5.38)	10		31.9 (SD 4.74)		
Lipids: Total cholesterol (mmol/l) – 0wk	Continuous	10		5.37 (SD 0.569)	10		5.2 (SD 0.949)		
HDL cholesterol (mmol/l) – 0wk	Continuous	10		1.17 (SD 0.19)	10		1.22 (SD 0.253)		
Triglycerides (mmol/l) – 0wk	Continuous	10		2.05 (SD 1.11)	10		2.19 (SD 1.11)		

[a] SD calculated from reported SE

Results

		Pioglitazone (30 mg)			Glibenclamide (2.5 mg/day)			Δ	p
		N	k	mean	N	k	mean		
Blood glucose: HbA1c (%) – 26wka	Continuous	8		8 (SD 1.5)	10		7.7 (SD 0.63)		
Fasting plasma glucose (mmol/l) – 26wka	Continuous	9		9.5 (SD 2.4)	10		10.1 (SD 1.9)		
Body weight: BMI (kg/m2) – 26wka	Continuous	9		31.4 (SD 4.5)	10		31 (SD 5.06)		
Lipids: Total cholesterol (mmol/l) – 26wk	Continuous	9		5.83 (SD 0.63)	10		5.74 (SD 0.854)		
HDL cholesterol (mmol/l) – 26wk	Continuous	9		1.41 (SD 0.24)	10		1.15 (SD 0.221)		
Triglycerides (mmol/l) – 26wk	Continuous	9		1.97 (SD 0.87)	10		2.29 (SD 1.64)		

[a] SD calculated from reported SE

		Pioglitazone (30 mg)			Placebo			Δ	p
		N	k	mean	N	k	mean		
Blood glucose: HbA1c (%) – 26wka	Continuous	8		8 (SD 1.5)	10		8.4 (SD 0.95)		
Fasting plasma glucose (mmol/l) – 26wka	Continuous	9		9.5 (SD 2.4)	10		9.9 (SD 0.949)		
Body weight: BMI (kg/m2) – 26wka	Continuous	9		31.4 (SD 4.5)	10		31.3 (SD 4.11)		
Lipids: Total cholesterol (mmol/l) – 26wk	Continuous	9		5.83 (SD 0.63)	10		5.82 (SD 1.08)		
HDL cholesterol (mmol/l) – 26wk	Continuous	9		1.41 (SD 0.24)	10		1.25 (SD 0.285)		
Triglycerides (mmol/l) – 26wk	Continuous	9		1.97 (SD 0.87)	10		2.48 (SD 1.08)		

[a] SD calculated from reported SE

		Glibenclamide (2.5 mg/day)			Placebo			Δ	p
		N	k	mean	N	k	mean		
Blood glucose: HbA1c (%) – 26wka	Continuous	10		7.7 (SD 0.63)	10		8.4 (SD 0.95)		
Fasting plasma glucose (mmol/l) – 26wka	Continuous	10		10.1 (SD 1.9)	10		9.9 (SD 0.949)		

Body weight: BMI (kg/m2) – 26wka	Continuous	10		31 (SD 5.06)	10		31.3 (SD 4.11)		
Lipids: Total cholesterol (mmol/l) – 26wk	Continuous	10		5.74 (SD 0.854)	10		5.82 (SD 1.08)		
HDL cholesterol (mmol/l) – 26wk	Continuous	10		1.15 (SD 0.221)	10		1.25 (SD 0.285)		
Triglycerides (mmol/l) – 26wk	Continuous	10		2.29 (SD 1.64)	10		2.48 (SD 1.08)		

[a] SD calculated from reported SE

Table 31: Erdem et al. (2008)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** Turkey **Authors' conclusions:** Despite improvements in insulin sensitivity and glycaemic regulation, either pioglitazone or metformin treatment did not result in any effect on blood visfatin levels in patients with treatment naïve type 2 diabetes **Source of funding:** suported by the research committee of the Gulhane Schoold of Medicine **Comments:** No details reported relating to method of randomisation, allocation concealment or blinding
Number and characteristics of patients	**Total number of patients:** 53 **Inclusion criteria:** patients with type 2 diabetes were recruited from the outpatient department of internal medicine, Gulhane school of medicine. Patients were included if they were aged between 30 and 70 years with BMI <35 kg/m2. Described as treatment naïve but no details provided **Exclusion criteria:** patients should have no other illnesses including liver failure, renal failure, heart failure or other chronic disease as determined by history, physical exmaination and screening tests Pre-randomisation phase: Assumed titration occurred during the maintenance period.
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** All treatment naive/ no OADs at screening **Details of washout period:** States that all are treatment naïve but did not provide any details
Lifestyle advice	Along with medication, all patients were allocated to treatment with an intensive lifestyle intervention with modification (no further details reported).
Follow-up	**Total follow-up (wks):** 12 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 12 **Frequency of monitoring appointments:** 6 visits were applied to all patients (anthopometric measures and laboratory tests were performed for all patients at baseline and the end of the 12th week)
Arms	**(1) Pioglitazone** N: 26 Treatment duration (wks): 12 Washout period (d): 0 Treatment(s): Pioglitazone (Oral) – forced titration Minimum dose (mg/d): 15 Maximum dose (mg/d): 45 Details of dosing regimen: pioglitazone treatment was initiated with 15 mg/day and could be increased up to 45 mg/day in increments of 15 mg. The dose of medication was tittrated during on-therapy visits, based on failure to achieve a glycaemic target of mean daily glucose less than or equal to 110 mg/dl (this was calculated from daily patient-measured glucose levels 3 days prior to on-therapy visits). The dose was increased to the maximum tolerated dose unless the glycaemic target was achieved or there was a tolerability issue at

	the current dose level. **(2) Metformin** N: 27 Treatment duration (wks): 12 Washout period (d): 0 Treatment(s): Metformin (Oral) – forced titration Minimum dose (mg/d): 1000 Maximum dose (mg/d): 2000 Details of dosing regimen: Metformin treatment was started with a dose of 1000 mg/day and could be increased up to 2000 mg/day in increments of 500 mg. The dose of medication was titrated based on failure to achieve a glycaemic target (see pioglitazone for details). The dose was increased to the maximum tolerated dose unless the glycaemic target was achieved or there was a tolerability issue at the current dose level.
Outcomes	**General** 5 (19%) patients in the pioglitazone group and 4 (15%) in metformin group discontinued the study. Outcomes not extracted in this evidence table include insulin, HOMA-IR, adiponectin and visfatin ITT analysis not mentioned. Analysis has been conducted in those patients who completed.

Baseline characteristics

		Pioglitazone			Metformin				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	21		54.9 (SD 7.8)	23		55.09 (SD 9.9)		
Sex (n male)	Dichotomous	21	8	(38.1%)	23	9	(39.1%)		
Blood glucose: HbA1c (%) – 0wk	Continuous	21		6.34 (SD 1.2)	23		6.74 (SD 1.3)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	21		7.1151 (SD 1.3)	23		7.4148 (SD 2.03)		
Body weight: BMI (kg/m2) – 0wk	Continuous	21		30.41 (SD 4.2)	23		31.41 (SD 3.8)		
Waist circumference (cms) – 0wk	Continuous	21		103.57 (SD 8.2)	23		103.6 (SD 7)		
Blood pressure: Systolic blood pressure (mmHg) – 0wk	Continuous	21		130.95 (SD 9.4)	23		130.23 (SD 9.7)		
Diastolic blood pressure (mmHg) – 0wk	Continuous	21		82.61 (SD 4.4)	23		82.14 (SD 6.4)		
Lipids: Total cholesterol (mmol/l) – 0wk	Continuous	21		5.6250672 (SD 1.28)	23		5.373708 (SD 0.76)		
HDL cholesterol (mmol/l) – 0wk	Continuous	21		1.2423144 (SD 0.243)	23		1.2492966 (SD 0.339)		
Triglycerides (mmol/l) – 0wk	Continuous	21		2.0767955 (SD 1.19)	23		1.8747045 (SD 0.924)		
LDL cholesterol (mmol/l) – 0wk	Continuous	21		3.4305876 (SD 0.921)	23		3.4243812 (SD 0.799)		

Results

		Pioglitazone			Metformin				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 12wk	Continuous	21		5.6 (SD 0.7)	23		6.15 (SD 0.53)		NS
Fasting plasma glucose (mmol/l) – 12wk	Continuous	21		6.2493 (SD 0.855)	23		6.1605 (SD 0.899)		NS
Body weight: BMI (kg/m2) – 12wk	Continuous	21		30.33 (SD 4.4)	23		29.41 (SD 3.05)		0.002
Waist circumference (cms) – 12wk	Continuous	21		100.76 (SD 7.1)	23		98.45 (SD 8.9)		NS

Dropouts: Total dropouts – 12wk	Dichotomous	26	5	(19.2%)	27	4	(14.8%)		
Blood pressure: Systolic blood pressure (mmHg) – 12wk	Continuous	21		129.04 (SD 9.4)	23		124.25 (SD 12.5)		0.01
Diastolic blood pressure (mmHg) – 12wk	Continuous	21		81.1 (SD 6.3)	23		77.5 (SD 6.2)		0.004
Lipids: Total cholesterol (mmol/l) – 12wk	Continuous	21		5.6250672 (SD 1.28)	23		4.894005 (SD 0.613)		0.001
HDL cholesterol (mmol/l) – 12wk	Continuous	21		1.377045 (SD 0.277)	23		1.2767082 (SD 0.305)		0.01
Triglycerides (mmol/l) – 12wk	Continuous	21		1.8315767 (SD 0.955)	23		1.6940645 (SD 0.76)		NR
LDL cholesterol (mmol/l) – 12wk	Continuous	21		3.3261132 (SD 0.789)	23		2.9110602 (SD 0.721)		<0.001

Measurement of within group changes in parameters with normal distribution was performed by the paired sample t-test. Two-related-samples test was used for non-normally distributed parameters. Between group changes were tested with chi-squared test, Mann-Whitney U-test ot student's t-test

Table 32: Erem et al. (2014)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** - **Authors' conclusions:** - **Source of funding:** - **Comments:** -
Number and characteristics of patients	**Total number of patients:** 60 **Inclusion criteria:** Adults (30 to 70 years) with newly diagnosed uncontrolled T2DM who were OAD naïve **Exclusion criteria:** -
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** All treatment naive/ no OADs at screening **Details of washout period:** All were OAD naïve
Lifestyle advice	Diabetes education and individualised diet and physical activity advice which was monitored at each visit.
Follow-up	**Total follow-up (wks):** 52 **Length of titration period (wks):** 8 **Length of maintenance period (wks):** 44 **Frequency of monitoring appointments:** Drug titration: 4 to 8 weeks Total maintenance period including titration: 12 months (examined every 2 to 4 weeks) Assessments at baseline, 3, 6 and 12 months
Arms	**(1) Gliclazide MR** N: 19 Treatment duration (wks): 52 Washout period (d): 0 Treatment(s): Sulfonylurea (modified release) (Oral) – flexible-dose (dose-adjusted) Set dose (mg/d):30 Frequency of dosing: once a day

Details of dosing regimen: Starting dose 30mg/d
Increased to 60-120mg/d as needed

(2) Metformin

N: 19

Treatment duration (wks): 52
Washout period (d): 0

Treatment(s): Metformin (Oral) – flexible-dose (dose-adjusted)
Set dose (mg/d):500
Frequency of dosing: once a day
Details of dosing regimen: Starting dose 500mg/d
Increased to 2x1000mg/d at 1-2 week intervals if no side effects were observed

(3) Pioglitazone

N: 19

Treatment duration (wks): 52
Washout period (d): 0

Treatment(s): Pioglitazone (Oral) – flexible-dose (dose-adjusted)
Set dose (mg/d):15
Frequency of dosing: once a day
Details of dosing regimen: Starting dose 15mg/d
Increased to 45mg/d as needed

Outcomes

Baseline characteristics

		Gliclazide MR		
		N	**k**	**mean**
ITT				
Demographics:				
Age (years)	Continuous	19		55 (SD 8.7)
Sex (n male)	Dichotomous	19	7	(36.8%)
Blood glucose:				
HbA1c (%) – 0mo	Continuous	19		8.26 (SD 1.65)
HbA1c (%) – 0mo	Continuous	19		8.26 (SD 1.65)
Fasting plasma glucose (mg/dl) – 3mo	Continuous	19		172.2 (SD 55.2)
Fasting plasma glucose (mg/dl) – 3mo	Continuous	19		172.2 (SD 55.2)
Body weight:				
BMI (kg/m2)	Continuous	19		32.72 (SD 3.86)
Weight (kg) – 0mo	Continuous	19		90.06 (SD 18.1)
Weight (kg) – 0mo	Continuous	19		90.06 (SD 18.1)
Height (cm)	Continuous	19		165.7 (SD 9.4)

		Metformin		
		N	**k**	**mean**
ITT				
Demographics:				
Age (years)	Continuous	19		52.2 (SD 10.5)
Sex (n male)	Dichotomous	19	6	(31.6%)
Blood glucose:				
HbA1c (%) – 0mo	Continuous	19		7.62 (SD 1.06)
HbA1c (%) – 0mo	Continuous	19		7.62 (SD 1.06)
Fasting plasma glucose (mg/dl) – 3mo	Continuous	19		172.68 (SD 37.6)
Fasting plasma glucose (mg/dl) – 3mo	Continuous	19		172.68 (SD 37.6)
Body weight:				
BMI (kg/m2)	Continuous	19		33.56 (SD 4.56)
Weight (kg) – 0mo	Continuous	19		87.5 (SD 12.9)
Weight (kg) – 0mo	Continuous	19		87.5 (SD 12.9)

Height (cm)	Continuous	19		161.5 (SD 8.9)

		Pioglitazone		
		N	k	mean
ITT				
Demographics:				
Age (years)	Continuous	19		52.5 (SD 5.2)
Sex (n male)	Dichotomous	19	5	(26.3%)
Blood glucose:				
HbA1c (%) – 0mo	Continuous	19		8.03 (SD 1.7)
HbA1c (%) – 0mo	Continuous	19		8.03 (SD 1.7)
Fasting plasma glucose (mg/dl) – 3mo	Continuous	19		165.7 (SD 34.2)
Fasting plasma glucose (mg/dl) – 3mo	Continuous	19		165.7 (SD 34.2)
Body weight:				
BMI (kg/m2)	Continuous	19		31.31 (SD 4.69)
Weight (kg) – 0mo	Continuous	19		81.93 (SD 13.4)
Weight (kg) – 0mo	Continuous	19		81.93 (SD 13.4)
Height (cm)	Continuous	19		161.6 (SD 7.7)

Results

		Gliclazide MR		
		N	k	mean
Dropouts:				
Total dropouts – 12mo	Dichotomous	20	1	(5.0%)
ITT				
Blood glucose:				
HbA1c (%) – 3mo	Continuous	19		6.93 (SD 0.9)
HbA1c (%) – 3mo	Continuous	19		6.93 (SD 0.9)
HbA1c (%) – 6mo	Continuous	19		6.92 (SD 0.6)
HbA1c (%) – 6mo	Continuous	19		6.92 (SD 0.6)
HbA1c (%) – 12mo	Continuous	19		6.98 (SD 0.5)
HbA1c (%) – 12mo	Continuous	19		6.98 (SD 0.5)
Fasting plasma glucose (mg/dl) – 3mo	Continuous	19		123.8 (SD 23.3)
Fasting plasma glucose (mg/dl) – 3mo	Continuous	19		123.8 (SD 23.3)
Fasting plasma glucose (mg/dl) – 6mo	Continuous	19		122.9 (SD 31.6)
Fasting plasma glucose (mg/dl) – 6mo	Continuous	19		122.9 (SD 31.6)
Fasting plasma glucose (mg/dl) – 12mo	Continuous	19		109 (SD 13.4)
Fasting plasma glucose (mg/dl) – 12mo	Continuous	19		109 (SD 13.4)
Body weight:				
Weight (kg) – 3mo	Continuous	19		89.41 (SD 18.5)
Weight (kg) – 3mo	Continuous	19		89.41 (SD 18.5)
Weight (kg) – 6mo	Continuous	19		88.72 (SD 19.7)
Weight (kg) – 6mo	Continuous	19		88.72 (SD 19.7)
Weight (kg) – 12mo	Continuous	19		91 (SD 26.2)
Weight (kg) – 12mo	Continuous	19		91 (SD 26.2)
Hypoglycaemic events:				
All hypoglycaemic events (no patients) – 12mo	Dichotomous	19	0	(0.0%)
Adverse events:				
GI: nausea – 12mo	Dichotomous	19	0	(0.0%)

		Metformin		
		N	**k**	**mean**
Dropouts:				
Total dropouts – 12mo	Dichotomous	20	1	(5.0%)
ITT				
Blood glucose:				
HbA1c (%) – 3mo	Continuous	19		6.67 (SD 1.2)
HbA1c (%) – 3mo	Continuous	19		6.67 (SD 1.2)
HbA1c (%) – 6mo	Continuous	19		6.42 (SD 0.71)
HbA1c (%) – 6mo	Continuous	19		6.42 (SD 0.71)
HbA1c (%) – 12mo	Continuous	19		6.4 (SD 0.7)
HbA1c (%) – 12mo	Continuous	19		6.4 (SD 0.7)
Fasting plasma glucose (mg/dl) – 3mo	Continuous	19		114.6 (SD 25.9)
Fasting plasma glucose (mg/dl) – 3mo	Continuous	19		114.6 (SD 25.9)
Fasting plasma glucose (mg/dl) – 6mo	Continuous	19		119.3 (SD 28.2)
Fasting plasma glucose (mg/dl) – 6mo	Continuous	19		119.3 (SD 28.2)
Fasting plasma glucose (mg/dl) – 12mo	Continuous	19		113.45 (SD 19.6)
Fasting plasma glucose (mg/dl) – 12mo	Continuous	19		113.45 (SD 19.6)
Body weight:				
Weight (kg) – 3mo	Continuous	19		85.9 (SD 12.6)
Weight (kg) – 3mo	Continuous	19		85.9 (SD 12.6)
Weight (kg) – 6mo	Continuous	19		84.7 (SD 12.4)
Weight (kg) – 6mo	Continuous	19		84.7 (SD 12.4)
Weight (kg) – 12mo	Continuous	19		83.4 (SD 13.3)
Weight (kg) – 12mo	Continuous	19		83.4 (SD 13.3)
Weight (kg) – 12mo	Continuous	19		83.4 (SD 13.3)
Weight (kg) – 12mo	Continuous	19		83.4 (SD 13.3)
Hypoglycaemic events:				
All hypoglycaemic events (no patients) – 12mo	Dichotomous	19	0	(0.0%)
Adverse events:				
GI: nausea – 12mo	Dichotomous	19	0	(0.0%)

		Pioglitazone		
		N	**k**	**mean**
Dropouts:				
Total dropouts – 12mo	Dichotomous	20	1	(5.0%)
ITT				
Blood glucose:				
HbA1c (%) – 3mo	Continuous	19		6.9 (SD 1.1)
HbA1c (%) – 3mo	Continuous	19		6.9 (SD 1.1)
HbA1c (%) – 6mo	Continuous	19		6.85 (SD 1.15)
HbA1c (%) – 6mo	Continuous	19		6.85 (SD 1.15)
HbA1c (%) – 12mo	Continuous	19		6.46 (SD 0.56)
HbA1c (%) – 12mo	Continuous	19		6.46 (SD 0.56)
Fasting plasma glucose (mg/dl) – 3mo	Continuous	19		119.4 (SD 32.1)
Fasting plasma glucose (mg/dl) – 3mo	Continuous	19		119.4 (SD 32.1)
Fasting plasma glucose (mg/dl) – 6mo	Continuous	19		121.2 (SD 25.6)
Fasting plasma glucose (mg/dl) – 6mo	Continuous	19		121.2 (SD 25.6)
Fasting plasma glucose (mg/dl) – 12mo	Continuous	19		105.11 (SD 20.4)
Fasting plasma glucose (mg/dl) – 12mo	Continuous	19		105.11 (SD 20.4)

	Body weight:				
	Weight (kg) – 3mo	Continuous	19		78.79 (SD 13.8)
	Weight (kg) – 3mo	Continuous	19		78.79 (SD 13.8)
	Weight (kg) – 6mo	Continuous	19		77.33 (SD 14.3)
	Weight (kg) – 6mo	Continuous	19		77.33 (SD 14.3)
	Weight (kg) – 12mo	Continuous	19		76.8 (SD 14.7)
	Weight (kg) – 12mo	Continuous	19		76.8 (SD 14.7)
	Weight (kg) – 12mo	Continuous	19		76.8 (SD 14.7)
	Weight (kg) – 12mo	Continuous	19		76.8 (SD 14.7)
	Hypoglycaemic events:				
	All hypoglycaemic events (no patients) – 12mo	Dichotomous	19	0	(0.0%)
	Adverse events:				
	GI: nausea – 12mo	Dichotomous	19	0	(0.0%)

Table 33: Esposito et al. (2011)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** Italy **Authors' conclusions:** Compared with metformin, pioglitazone treatment improved the imbalance between endothelial damage and repair capacity and led to more favourable changes in coronary risk factors in patients with newly diagnosed type 2 diabetes **Source of funding:** Supported by the Second University of Naples and by an unconditional resaerch grant from Takeda Italia Farmaceutici **Comments:** Prospective, randomised, double-blind study. Patients were randomly assigned using a computer generated random number sequence (simple randomisation). Allocation was concealed in sealed study folders that were held in a central, secure location until after informed consent was obtained. The study medication was identified by pack numbers. Investigators and all study staff were blinded to treatment assignment until all study results were collected.
Number and characteristics of patients	**Total number of patients:** 110 **Inclusion criteria:** men and women with newly diagnosed type 2 diabetes according to the ADA criteria who have never been treated with antihyperglycaemic drugs from the clinical practice sof the trial investigators. Patients were included if they were aged 30-75 years, BMI >25 kg/m2 and Hba1c between 7 and 10%. Participants had no evidence of participation in weight-reduction programmes and a stable weight in the past 6 months **Exclusion criteria:** pregnancy or breastfeeding, use of any investigational drug in the previous 3 months, use of agents affecting glycaemic control, acute disease or infection, recent (within 3 months) cardiovascular events or surgery, immunological disorders and any condition that may compromise adherence to the study. Patients were also excluded if they had positive antibodies to glutamate decarboxylase or C-peptide levels less than 0.25 pmol and patients with abnormal laboratory test results including liver enzyme levels greater than 3 times the upper limit of normal and serum creatinine levels greater than 123.8 µmol/l Pre-randomisation phase: see follow-up for details of forced titration and maintenance period lengths
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** All treatment naive/ no OADs at screening **Details of washout period:** All AHA naïve and newly diagnosed
Lifestyle advice	participants were requested to adhere to pre-study lifestyle and dietary habits throughout the study
Follow-up	**Total follow-up (wks):** 24 **Length of titration period (wks):** 8

Length of maintenance period (wks): 16
Frequency of monitoring appointments: no details reported

Arms

(1) Pioglitazone

N: 55

Treatment duration (wks): 24
Washout period (d): 0

Treatment(s): Pioglitazone (Oral) – forced titration

Minimum dose (mg/d): 15
Maximum dose (mg/d): 45
Participants achieving full dose (n): 40
Frequency of dosing: once a day
Compliance: study drug adherence was assessed at each study visit by pill count and calculated as percentage of pills taken. The adherence rates were 94.5% for pioglitazone.
Details of dosing regimen: 15 mg (once daily) titrated to 30-45 mg (once daily). Dose levels were increased or maintained at 4, 6 and 8 weeks according to tolerability. The dose reached at week 8 was fixed for the rest of the study. At the end of the titration period 15 (27.2%) were on 30 mg/day and 40 (72.3%) were on 45 mg/day

(2) Metformin

N: 55

Treatment duration (wks): 24
Washout period (d): 0

Treatment(s): Metformin (Oral) – forced titration

Minimum dose (mg/d): 1000
Maximum dose (mg/d): 2000
Participants achieving full dose (n): 35
Frequency of dosing: twice a day
Compliance: The adherence rate for metformin was 92.7%
Details of dosing regimen: 500 mg twice daily, titrated to 1000 mg twice daily. Dose levels were increased or maintained at 4, 6 and 8 weeks according to tolerability. The dose reached at week 8 was fixed for the rest of the study. At the end of the titration period 20 (36.3%) were on 1500 mg/day and 35 (63.6%) were on 2000 mg/day

Outcomes

General

The primary outcome was the level of circulating EMPs. Data were analysed by intention-to-treat

The main outcome was the level of circulating EMPs (endothelial microparticles). Outcomes not extracted in this evidence table include EMPs, adiponectin, HOMA insulin sensitivity, C-reactive protein level and flow mediated dilation.

4 (7%) patients in each group discontinued

Baseline characteristics

		Pioglitazone			Metformin				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	55		54.2 (SD 6.1)	55		54.9 (SD 6.6)		
Sex (n male)	Dichotomous	55	30	(54.5%)	55	28	(50.9%)		
Blood glucose: HbA1c (%) – 0wk	Continuous	55		8 (SD 1)	55		8.1 (SD 1)		
Plasma glucose level (mmol/l) – 0wk	Continuous	55		8.2 (SD 1.3)	55		8.5 (SD 1.3)		
Body weight: BMI (kg/m2) – 0wk	Continuous	55		28.9 (SD 3.5)	55		29.1 (SD 3.3)		
Weight (kg) – 0wk	Continuous	55		84.5 (SD 8.6)	55		83.5 (SD 8.5)		
Waist circumference (cms) – 0wk	Continuous	55		95 (SD 7.5)	55		96 (SD 7.3)		
Blood pressure: Systolic blood pressure (mmHg) – 0wk	Continuous	55		134 (SD 10)	55		135 (SD 11)		
Diastolic blood pressure (mmHg) – 0wk	Continuous	55		86 (SD 7)	55		85 (SD 7)		
Lipids: Total cholesterol (mmol/l) – 0wk	Mean change	55		5.2 (SD 0.8)	55		5.1 (SD 0.7)		
HDL cholesterol (mmol/l) – 0wk	Mean change	55		1.1 (SD 0.2)	55		1.05 (SD 0.2)		
Triglycerides (mmol/l) – 0wk	Mean change	55		1.7 (SD 0.5)	55		1.7 (SD 0.5)		

Other medication:											
Anti-hypertensive		Dichotomous	55	15	(27.3%)	55	13	(23.6%)			
Lipid-lowering medication		Dichotomous	55	11	(20.0%)	55	13	(23.6%)			

Results

		Pioglitazone			Metformin				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 24wk	Mean change	55		-0.9 (SD 0.5)	55		-0.9 (SD 0.5)	MD=0.000 (CI: -0.300, 0.300)	NS
HbA1c < 7% or <=7% – 24wk	Dichotomous	55	30	(54.5%)	55	28	(50.9%)	MD=3.700 (CI: -2.100, 9.500)	NS
Plasma glucose level (mmol/l) – 24wk	Mean change	55		-1.9 (SD 1)	55		-2 (SD 1.1)	MD=0.100 (CI: -0.300, 0.500)	NS
Body weight: BMI (kg/m2) – 24wk	Mean change	55		0.5 (SD 0.4)	55		-0.1 (SD 0.1)	MD=0.600 (CI: 0.100, 1.100)	NR
Weight (kg) – 24wk	Mean change	55		1.4 (SD 0.9)	55		-0.2 (SD 0.2)	MD=1.600 (CI: 0.500, 2.700)	<0.05
Waist circumference (cms) – 24wk	Mean change	55		0.4 (SD 0.6)	55		-0.1 (SD 0.3)	MD=0.500 (CI: -0.300, 1.300)	NR
Adverse events: Any adverse event(s) – 24wka	Dichotomous	55	9	(16.4%)	55	12	(21.8%)		
Any serious adverse event(s) – 24wk	Dichotomous	55	0	(0.0%)	55	0	(0.0%)		
Bone fracture – 24wk	Dichotomous	55	0	(0.0%)	55	0	(0.0%)		
cardiovascular AE – 24wk	Dichotomous	55	0	(0.0%)	55	0	(0.0%)		
Death – 24wk	Dichotomous	55	0	(0.0%)	55	0	(0.0%)		
Dropouts: Total dropouts – 24wk	Dichotomous	55	4	(7.3%)	55	4	(7.3%)		
Blood pressure: Systolic blood pressure (mmHg) – 24wk	Mean change	55		-3 (SD 3)	55		-2 (SD 3)	MD=-1.000 (CI: -2.000, 0.000)	NS
Diastolic blood pressure (mmHg) – 24wk	Mean change	55		-2 (SD 2)	55		-2 (SD 2)	MD=0.000 (CI: -2.000, 2.000)	NS
BP <130/80 (mmHg) – 24wk	Dichotomous	55	33	(60.0%)	55	30	(54.5%)	MD=5.400 (CI: -3.100, 13.900)	NS
Lipids: Total cholesterol (mmol/l) – 24wk	Mean change	55		-0.08 (SD 0.1)	55		0.05 (SD 0.07)	MD=-0.130 (CI: -0.350, 0.090)	NS
HDL cholesterol (mmol/l) – 24wk	Mean change	55		0.1 (SD 0.1)	55		0 (SD 0.1)	MD=0.100 (CI: 0.020, 0.180)	<0.05
Triglycerides (mmol/l) – 24wk	Mean change	55		-0.25 (SD 0.19)	55		-0.03 (SD 0.1)	MD=-0.220 (CI: -0.400, -0.040)	<0.05
LDL cholesterol <2.6 mmol/l – 24wk	Dichotomous	55	22	(40.0%)	55	24	(43.6%)	MD=-3.500 (CI: -10.100, 3.100)	NS

[a] at least one event

Study variables were compared using a test based on values at the end of follow-up and a t-test based on differences from baseline. Fishers exact test was used to compare categorical safety variables

Table 34: Esteghamati et al. (2014)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** - **Authors' conclusions:** - **Source of funding:** - **Comments:** -
Number and characteristics of patients	**Total number of patients:** 98 **Inclusion criteria:** Adults with newly diagnosed T2DM, not currently or previously taking oral antihyperglycaemic medications **Exclusion criteria:** -
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** All treatment naive/ no OADs at screening **Details of washout period:** Participants were totally drug naïve - not previously taking any OADs for any condition
Lifestyle advice	-
Follow-up	**Total follow-up (wks):** - **Length of titration period (wks):** - **Length of maintenance period (wks):** - **Frequency of monitoring appointments:** -
Arms	**(1) Pioglitazone** N: 55 Treatment duration (wks): 12 Washout period (d): 0 Treatment(s): Pioglitazone (Oral) – fixed-dose Set dose (mg/d):30 Frequency of dosing: twice a day Details of dosing regimen: 15mg tablets twice daily **(2) Metformin** N: 43 Treatment duration (wks): 12 Washout period (d): 0 Treatment(s): Metformin (Oral) – fixed-dose Set dose (mg/d):1000 Frequency of dosing: twice a day Details of dosing regimen: 500mg tablets twice daily
Outcomes	

Baseline characteristics

		Pioglitazone		
		N	**k**	**mean**
PP				
Demographics:				
Age (years) – wk	Continuous	39		51.25 (SD 7.84)
Sex (n male) – wk	Dichotomous	39	14	(35.9%)
Blood glucose:				
HbA1c (%) – 12wk	Continuous	42		8.0982 (SD 1.50942)
HbA1c (%) – 12wk	Continuous	42		8.0982 (SD 1.50942)
Fasting plasma glucose (mmol/l) – 12wk	Continuous	42		9.4 (SD 2.09)
Fasting plasma glucose (mmol/l) – 12wk	Continuous	42		9.4 (SD 2.09)
Body weight:				
BMI (kg/m2) – 12wk	Continuous	42		30.12 (SD 4.47)
BMI (kg/m2) – 12wk	Continuous	42		30.12 (SD 4.47)
Weight (kg) – 12wk	Continuous	42		77.01 (SD 13.61)

Weight (kg) – 12wk	Continuous	42		77.01 (SD 13.61)

		Metformin		
		N	k	mean
PP				
Demographics:				
Age (years) – wk	Continuous	39		50.03 (SD 9.13)
Sex (n male) – wk	Dichotomous	39	20	(51.3%)
Blood glucose:				
HbA1c (%) – 12wk	Continuous	39		8.18968 (SD 1.170944)
HbA1c (%) – 12wk	Continuous	39		8.18968 (SD 1.170944)
Fasting plasma glucose (mmol/l) – 12wk	Continuous	39		9.92 (SD 2.94)
Fasting plasma glucose (mmol/l) – 12wk	Continuous	39		9.92 (SD 2.94)
Body weight:				
BMI (kg/m2) – 12wk	Continuous	39		28.81 (SD 4.45)
BMI (kg/m2) – 12wk	Continuous	39		28.81 (SD 4.45)
Weight (kg) – 12wk	Continuous	39		74.34 (SD 12.81)
Weight (kg) – 12wk	Continuous	39		74.34 (SD 12.81)

Results

		Pioglitazone		
		N	k	mean
Dropouts:				
Total dropouts – 12wk	Dichotomous	55	5	(9.1%)
PP				
Blood glucose:				
HbA1c (%) – 12wk	Mean change	42		-0.722692 (SD 1.30068210650654) a
HbA1c (%) – 12wk	Mean change	42		-0.722692 (SD 1.30068210650654) a
HbA1c (%) – 12wk	Continuous	42		7.36636 (SD 1.619196)
HbA1c (%) – 12wk	Continuous	42		7.36636 (SD 1.619196)
Fasting plasma glucose (mmol/l) – 12wk	Continuous	42		7.64 (SD 1.68)
Fasting plasma glucose (mmol/l) – 12wk	Continuous	42		7.64 (SD 1.68)
Fasting plasma glucose (mmol/l) – 12wk	Mean change	42		-1.76 (SD 2.41378961407189) a
Fasting plasma glucose (mmol/l) – 12wk	Mean change	42		-1.76 (SD 2.41378961407189) a
Body weight:				
BMI (kg/m2) – 12wk	Continuous	42		30.37 (SD 4.71)
BMI (kg/m2) – 12wk	Continuous	42		30.37 (SD 4.71)
BMI (kg/m2) – 12wk	Mean change	42		0.25 (SD 1.5871) a
BMI (kg/m2) – 12wk	Mean change	42		0.25 (SD 1.5871) a
Weight (kg) – 12wk	Continuous	42		77.74 (SD 14.73)
Weight (kg) – 12wk	Mean change	42		0.18 (SD 3.38916) a
Weight (kg) – 12wk	Mean change	42		0.18 (SD 3.38916) a
Weight (kg) – 12wk	Continuous	42		77.74 (SD 14.73)

[a] SD calculated from reported 95% CI

		Metformin		
		N	k	mean
Dropouts:				
Total dropouts – 12wk	Dichotomous	43	2	(4.7%)

	PP				
	Blood glucose:				
	HbA1c (%) – 12wk	Continuous	39		7.36636 (SD 1.41794)
	HbA1c (%) – 12wk	Mean change	39		-0.832468 (SD 1.0201648344) a
	HbA1c (%) – 12wk	Mean change	39		-0.832468 (SD 1.0201648344) a
	HbA1c (%) – 12wk	Continuous	39		7.36636 (SD 1.41794)
	Fasting plasma glucose (mmol/l) – 12wk	Continuous	39		7.78 (SD 1.33)
	Fasting plasma glucose (mmol/l) – 12wk	Continuous	39		7.78 (SD 1.33)
	Fasting plasma glucose (mmol/l) – 12wk	Mean change	39		-2.14 (SD 2.676) a
	Fasting plasma glucose (mmol/l) – 12wk	Mean change	39		-2.14 (SD 2.676) a
	Body weight:				
	BMI (kg/m2) – 12wk	Mean change	39		0.07 (SD 0.876211) a
	BMI (kg/m2) – 12wk	Mean change	39		0.07 (SD 0.876211) a
	BMI (kg/m2) – 12wk	Continuous	39		28.88 (SD 4.36)
	BMI (kg/m2) – 12wk	Continuous	39		28.88 (SD 4.36)
	Weight (kg) – 12wk	Continuous	39		74.49 (SD 12.31)
	Weight (kg) – 12wk	Mean change	39		0.15 (SD 2.262218663) a
	Weight (kg) – 12wk	Mean change	39		0.15 (SD 2.262218663) a
	Weight (kg) – 12wk	Continuous	39		74.49 (SD 12.31)
	[a] SD calculated from reported 95% CI				
	Data were only presented for PP at baseline and follow up				

Table 35: Fang et al. (2014)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** - **Authors' conclusions:** - **Source of funding:** - **Comments:** -
Number and characteristics of patients	**Total number of patients:** 60 **Inclusion criteria:** Chinese adults newly diagnosed with T2DM (within the previous 6 months), naïve to OADs **Exclusion criteria:** -
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** All treatment naive/ no OADs at screening **Details of washout period:** All were OAD naïve people
Lifestyle advice	Received diet and exercise advice (recommended calorie intake on 25-35kcal/kg per day and aerobic activity for 30 minutes 5 times per week)
Follow-up	**Total follow-up (wks):** 15 **Length of titration period (wks):** 3 **Length of maintenance period (wks):** 12 **Frequency of monitoring appointments:** 8 visits over the 15 week period Assessments at baseline and 15 weeks
Arms	**(1) Metformin** N: 20

Treatment duration (wks): 15
Washout period (d): 0
Treatment(s): Metformin (Oral) – fixed-dose
Set dose (mg/d):1500
Frequency of dosing: three times a day
Details of dosing regimen: 500mg 3 times per day taken with meals

(2) Repaglinide

N: 40

Treatment duration (wks): 15
Washout period (d): 0
Treatment(s): repaglinide (Oral) – flexible-dose (dose-adjusted)
Minimum dose (mg/d): 0.5
Maximum dose (mg/d): 6
Frequency of dosing: three times a day
Details of dosing regimen: Taken before meals

Outcomes

Baseline characteristics

		Metformin		
		N	**k**	**mean**
Demographics:				
Age (years)	Continuous	20		49.7 (SD 10)
Sex (n male)	Dichotomous	20	16	(80.0%)
Duration of diabetes (yrs)	Continuous	20		0.4 (SD 0.4)
Blood glucose:				
HbA1c (%) – 15wk	Continuous	20		7.9 (SD 1.6)
HbA1c (%) – 15wk	Continuous	20		7.9 (SD 1.6)
Fasting plasma glucose (mmol/l) – 15wk	Continuous	20		9.1 (SD 2.6)
Fasting plasma glucose (mmol/l) – 15wk	Continuous	20		9.1 (SD 2.6)
Body weight:				
BMI (kg/m2)	Continuous	20		25.1 (SD 3.1)
Weight (kg) – 0wk	Continuous	20		70.84224 (SD 8.74944) a
Weight (kg) – 0wk	Continuous	20		70.84224 (SD 8.74944) a
Weight (kg) – 15wk	Continuous	20		70.7 (SD 11.2)
Weight (kg) – 15wk	Continuous	20		70.7 (SD 11.2)

[a] estimated from BMI assuming mean height of 1.68m

		Repaglinide		
		N	**k**	**mean**
Demographics:				
Age (years)	Continuous	40		46.4 (SD 10.6)
Sex (n male)	Dichotomous	40	21	(52.5%)
Duration of diabetes (yrs)	Continuous	40		0.8 (SD 1.3)
Blood glucose:				
HbA1c (%) – 15wk	Continuous	40		8 (SD 1.5)
HbA1c (%) – 15wk	Continuous	40		8 (SD 1.5)
Fasting plasma glucose (mmol/l) – 15wk	Continuous	40		8.4 (SD 1.9)
Fasting plasma glucose (mmol/l) – 15wk	Continuous	40		8.4 (SD 1.9)
Body weight:				
BMI (kg/m2)	Continuous	40		26.2 (SD 3.5)
Weight (kg) – 0wk	Continuous	40		73.94688 (SD 9.8784) a
Weight (kg) – 0wk	Continuous	40		73.94688 (SD 9.8784) a
Weight (kg) – 15wk	Continuous	40		70.5 (SD 12)
Weight (kg) – 15wk	Continuous	40		70.5 (SD 12)

[a] estimated from BMI assuming mean height of 1.68m

Results

		Metformin		
		N	**k**	**mean**
Blood glucose: HbA1c (%) – 15wk	Mean change	20		-1.6 (SD 1.5)
HbA1c (%) – 15wk	Mean change	20		-1.6 (SD 1.5)
Fasting plasma glucose (mmol/l) – 15wk	Mean change	20		-2.1 (SD 1.7)
Fasting plasma glucose (mmol/l) – 15wk	Mean change	20		-2.1 (SD 1.7)
Body weight: Weight (kg) – 15wk	Mean change	20		-3 (SD 2.4)
Weight (kg) – 15wk	Mean change	20		-3 (SD 2.4)
Hypoglycaemic events: Symptomatic hypoglycaemia – 15wk	Count	2100	0	a
Symptomatic hypoglycaemia – 15wk	Dichotomous	20	0	(0.0%)
Dropouts: Total dropouts – 15wk	Dichotomous	20	0	(0.0%)

[a] (Used in the analysis)

		Repaglinide		
		N	**k**	**mean**
Blood glucose: HbA1c (%) – 15wk	Mean change	40		-1.8 (SD 1.5)
HbA1c (%) – 15wk	Mean change	40		-1.8 (SD 1.5)
Fasting plasma glucose (mmol/l) – 15wk	Mean change	40		-1.7 (SD 1.7)
Fasting plasma glucose (mmol/l) – 15wk	Mean change	40		-1.7 (SD 1.7)
Body weight: Weight (kg) – 15wk	Mean change	40		0 (SD 3.3)
Weight (kg) – 15wk	Mean change	40		0 (SD 3.3)
Hypoglycaemic events: Symptomatic hypoglycaemia – 15wk	Count	4147.5	10	a
Symptomatic hypoglycaemia – 15wk	Dichotomous	40	9	(22.5%)
Dropouts: Total dropouts – 15wk	Dichotomous	40	1	(2.5%)

[a] (Used in the analysis); Patient days estimated assuming dropouts halfway through the study

Table 36: Ferrannini et al. (2013)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** - **Authors' conclusions:** - **Source of funding:** - **Comments:** -
Number and characteristics of patients	**Total number of patients:** 408 **Inclusion criteria:** Adults between 18 and 79 years inclusive, diagnosed with T2DM with BMI no more than 40kg/m2. Patients either did not have any antidiabetic medication at least 10 weeks prior to enrolment or

	were on one antidiabetic treatment (excluding thiazolidinediones, GLP-1 or insulin) at least 10 weeks prior to screening. **Exclusion criteria:** - Pre-randomisation phase: 6 week wash out period: 4 weeks wash out and 2 weeks placebo run-in
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** some on oral hypoglycaemic drugs and/or insulin **Details of washout period:** up to 6 weeks in total Patients previously treated with a stable OAD for at least 10 weeks prior to enrolment: 4 week washout period for plus 2 week open label placebo run in period Patients not using OADs at least 10 weeks prior to enrolment: 2 week open label placebo run in period
Lifestyle advice	Not reported
Follow-up	**Total follow-up (wks):** 18.8 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 12 **Frequency of monitoring appointments:** 7 appointments over 18.8 weeks. Assessments conducted at baseline (after 6 week wash out period), 12 weeks (efficacy) and 4-11 days following end of 12 week treatment period (safety)
Arms	**(1) Metformin** N: 80 Treatment duration (wks): 12 Washout period (d): 42 Comments: Open-label metformin group Treatment(s): Metformin (Oral) – flexible-dose (dose-adjusted) Set dose (mg/d):1000 Mean dose (mg/d): 1567 Frequency of dosing: twice a day Details of dosing regimen: 500mg twice a day with meals for 4 weeks If FBG >6.1mmol/l, dose was increased to 1000mg twice daily or up to maximum tolerated dose Mean final dose 1668mg per day **(2) Placebo** N: 82 Treatment duration (wks): 12 Washout period (d): 42 Treatment(s): Placebo (Oral) Frequency of dosing: once a day Details of dosing regimen: two tablets once a day
Outcomes	**General** Data not extracted from 3 trial arms (empagliflozin 5, 10 and 25mg). Data reported at baseline and follow up for all patients who were treated i.e. full analysis set (defined as all randomised patients receiving at least 1 study drug dose with a baseline HbA1c measurement) with LOCF imputed for missing data.
Baseline characteristics	

		Metformin		
		N	**k**	**mean**
Demographics:				
Age (years) (median)	Continuous	80		58 [rng 34–73]
Sex (n male)	Dichotomous	80	39	(48.8%)
Blood glucose:				
HbA1c (%) – 12wk	Continuous	80		8.1 (SD 0.9)
HbA1c (%) – 12wk	Continuous	80		8.1 (SD 0.9)
Fasting plasma glucose (mmol/l) – 12wk	Continuous	80		9.8 (SD 2.4)
Fasting plasma glucose (mmol/l) – 12wk	Continuous	80		9.8 (SD 2.4)
Body weight:				
BMI (kg/m2) (median)	Continuous	80		28.6 [rng 18.7–40.6]
Weight (kg) – 0wk (median)	Continuous	80		80.72064 [rng 52.77888–114.58944] a
Weight (kg) – 0wk (median)	Continuous	80		80.72064 [rng 52.77888–114.58944] a

Weight (kg) – 12wk (median)	Continuous	80		81.1 [rng 42–126]
Weight (kg) – 12wk (median)	Continuous	80		81.1 [rng 42–126]

[a] estimated from BMI assuming mean height of 1.68m

		Placebo		
		N	k	mean
Demographics:				
Age (years) (median)	Continuous	82		58 [rng 28–80]
Sex (n male)	Dichotomous	82	45	(54.9%)
Blood glucose:				
HbA1c (%) – 12wk	Continuous	82		7.8 (SD 0.8)
HbA1c (%) – 12wk	Continuous	82		7.8 (SD 0.8)
Fasting plasma glucose (mmol/l) – 12wk	Continuous	82		9.5 (SD 2.2)
Fasting plasma glucose (mmol/l) – 12wk	Continuous	82		9.5 (SD 2.2)
Body weight:				
BMI (kg/m2) (median)	Continuous	82		28.8 [rng 20.7–39.6]
Weight (kg) – 0wk (median)	Continuous	82		81.28512 [rng 58.42368–111.76704] a
Weight (kg) – 0wk (median)	Continuous	82		81.28512 [rng 58.42368–111.76704] a
Weight (kg) – 12wk (median)	Continuous	82		82.2 [rng 49–152.3]
Weight (kg) – 12wk (median)	Continuous	82		82.2 [rng 49–152.3]

[a] estimated from BMI assuming mean height of 1.68m

Results

		Metformin		
		N	k	mean
Blood glucose:				
HbA1c (%) – 12wk	Mean change	80		-0.7 (SD 1.00396733599245) a
HbA1c (%) – 12wk	Mean change	80		-0.7 (SD 1.00396733599245) a
Fasting plasma glucose (mmol/l) – 12wk	Mean change	80		-1.66 (SD 2.05356955089364) a
Fasting plasma glucose (mmol/l) – 12wk	Mean change	80		-1.66 (SD 2.05356955089364) a
Body weight:				
Weight (kg) – 12wk	Mean change	80		-1.32 (SD 2.37301370325487) a
Weight (kg) – 12wk	Mean change	80		-1.32 (SD 2.37301370325487) a
Hypoglycaemic events:				
Symptomatic hypoglycaemia – 12wk	Dichotomous	80	1	(1.3%)
Adverse events:				
GI: nausea – 12wk	Dichotomous	80	3	(3.8%)
Dropouts:				
Total dropouts – 12wk	Dichotomous	80	6b	(7.5%)
Dropout due to AEs – 12wk	Dichotomous	80	3b	(3.8%)

[a] SD calculated from reported 95% CI
[b] Data taken from NCT00789035 (clinicaltrials.gov)

		Placebo		
		N	k	mean
Blood glucose:				
HbA1c (%) – 12wk	Mean change	82		0.1 (SD 0.924035871022646) a
HbA1c (%) – 12wk	Mean change	82		0.1 (SD 0.924035871022646) a
Fasting plasma glucose (mmol/l) – 12wk	Mean change	82		0.06 (SD 2.03287891624982) a
Fasting plasma glucose (mmol/l) – 12wk	Mean change	82		0.06 (SD 2.03287891624982) a
Body weight:				
Weight (kg) – 12wk	Mean change	82		-0.75 (SD 2.35629147110775) a
Weight (kg) – 12wk	Mean change	82		-0.75 (SD 2.35629147110775) a

	Hypoglycaemic events: Symptomatic hypoglycaemia – 12wk	Dichotomous	82	1	(1.2%)
	Adverse events: GI: nausea – 12wk	Dichotomous	82	0	(0.0%)
	Dropouts: Total dropouts – 12wk	Dichotomous	82	6b	(7.3%)
	Dropout due to AEs – 12wk	Dichotomous	82	0b	(0.0%)

[a] SD calculated from reported 95% CI
[b] Data taken from NCT00789035 (clinicaltrials.gov)

Table 37: Fischer et al. (1998)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** 7 countries (Austria, Croatia, Germany, Hungary, Italy) **Authors' conclusions:** Acarbose was well tolerated in the dose range of 25 mg tid to 200 mg tid. We could not find a clear relationship between the dose of acarbose and the frequency of gastrointestinal events **Source of funding:** Unclear **Comments:** Double-blind
Number and characteristics of patients	**Total number of patients:** 495 **Inclusion criteria:** patients aged 35-70 years and insufficiently treated with diet alone, Hba1c 6.5-9%, diabetes duration between 6 and 60 months, stable bodyweight and BMI <=35 kg/m2. All were AHA naïve **Exclusion criteria:** Any significant disease or conditions, acute derangement of metabolic control Pre-randomisation phase: There was a 6 week placebo run in pre-treatment period
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** All treatment naive/ no OADs at screening **Details of washout period:** All were AHA naïve
Lifestyle advice	During the screening phase, patients were reinforced with dietary advice by a trained dietitian
Follow-up	**Total follow-up (wks):** 30 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 24 **Frequency of monitoring appointments:** Every 2 weeks for first 10 weeks, and then every 4 weeks
Arms	**(1) Placebo** N: 97 Treatment duration (wks): 24 Washout period (d): 42 Comments: treatment naïve Treatment(s): Placebo (Oral) **(2) Acarbose (25 mg TID)** N: 102 Treatment duration (wks): 24 Washout period (d): 42 Comments: treatment naïve Treatment(s): Acarbose (Oral) – fixed-dose Set dose (mg/d):75 Frequency of dosing: three times a day Details of dosing regimen: Acarbose 25 mg TID **(3) Acarbose (50 mg TID)** N: 99

Treatment duration (wks): 24
Washout period (d): 42
Comments: treatment naïve

Treatment(s): Acarbose (Oral) – fixed-dose
Set dose (mg/d):150
Details of dosing regimen: Acarbose 50 mg TID

(4) Acarbose (100 mg tid)

N: 99

Treatment duration (wks): 24
Washout period (d): 42
Comments: treatment naïve

Treatment(s): Acarbose (Oral) – fixed-dose
Set dose (mg/d):300
Details of dosing regimen: Acarbose 100 mg tid
Dose increased in stepwise fashion, 50mg t.i.d. in first 2 weeks

(5) Acarbose (200 mg tid)

N: 98

Treatment duration (wks): 24
Washout period (d): 42
Comments: treatment naïve

Treatment(s): Acarbose (Oral) – fixed-dose
Set dose (mg/d):600
Frequency of dosing: three times a day
Details of dosing regimen: Acarbose 200 mg TID
Dose increased in stepwise fashion, 100mg t.i.d. in first 2 weeks

Outcomes

Baseline characteristics

		Placebo			Acarbose (25 mg TID)				
		N	k	mean	N	k	mean	Δ	p
Full analysis set (FAS) or efficacy analysis pop									
Demographics: Age (years)	Continuous	81		52.7 (SD 8.7)	86		58.5 (SD 8.4)		
Sex (n male) a	Dichotomous	81	43	(53.1%)	86	46	(53.5%)		
Duration of diabetes (months)	Continuous	81		med: 24	86		med: 26		
Blood glucose: HbA1c (%) – 0wkb	Continuous	81		7.26 (SD 1.09)	86		7.42 (SD 1.09)		
Fasting plasma glucose (mmol/l) – 0wkb	Continuous	81		9.16 (SD 1.23)	86		9.33 (SD 1.24)		

[a] estimated from reported percentages; approximated to nearest integer (percentages only presented in text)
[b] geometric mean/SD

		Placebo			Acarbose (50 mg TID)				
		N	k	mean	N	k	mean	Δ	p
Full analysis set (FAS) or efficacy analysis pop									
Demographics: Age (years)	Continuous	81		52.7 (SD 8.7)	88		55.5 (SD 9.6)		
Sex (n male)	Dichotomous	81	43a	(53.1%)	88	43b	(48.9%)		
Duration of diabetes (months)	Continuous	81		med: 24	88		med: 20		
Blood glucose: HbA1c (%) – 0wkc	Continuous	81		7.26 (SD 1.09)	88		7.52 (SD 1.09)		
Fasting plasma glucose (mmol/l) – 0wkc	Continuous	81		9.16 (SD 1.23)	88		9.33 (SD 1.22)		

[a] estimated from reported percentages; approximated to nearest integer (percentages only presented in text)
[b] estimated from reported percentages; approximated to nearest integer (percentages only presented in text); approximated to nearest integer (percentages only presented in text)
[c] geometric mean/SD

		Placebo			Acarbose (100 mg tid)				
		N	k	mean	N	k	mean	Δ	p
Full analysis set (FAS) or efficacy analysis pop									
Demographics: Age (years)	Continuous	81		52.7 (SD 8.7)	78		56.8 (SD 9.4)		
Sex (n male) a	Dichotomous	81	43	(53.1%)	78	46	(59.0%)		
Duration of diabetes (months)	Continuous	81		med: 24	78		med: 17		
Blood glucose: HbA1c (%) – 0wkb	Continuous	81		7.26 (SD 1.09)	78		7.43 (SD 1.1)		
Fasting plasma glucose (mmol/l) – 0wkb	Continuous	81		9.16 (SD 1.23)	78		9.21 (SD 1.19)		

[a] estimated from reported percentages; approximated to nearest integer (percentages only presented in text)
[b] geometric mean/SD

		Acarbose (25 mg TID)			Acarbose (50 mg TID)				
		N	k	mean	N	k	mean	Δ	p
Full analysis set (FAS) or efficacy analysis pop									
Demographics: Age (years)	Continuous	86		58.5 (SD 8.4)	88		55.5 (SD 9.6)		
Sex (n male)	Dichotomous	86	46a	(53.5%)	88	43b	(48.9%)		
Duration of diabetes (months)	Continuous	86		med: 26	88		med: 20		
Blood glucose: HbA1c (%) – 0wkc	Continuous	86		7.42 (SD 1.09)	88		7.52 (SD 1.09)		
Fasting plasma glucose (mmol/l) – 0wkc	Continuous	86		9.33 (SD 1.24)	88		9.33 (SD 1.22)		

[a] estimated from reported percentages; approximated to nearest integer (percentages only presented in text)
[b] estimated from reported percentages; approximated to nearest integer (percentages only presented in text); approximated to nearest integer (percentages only presented in text)
[c] geometric mean/SD

		Acarbose (25 mg TID)			Acarbose (100 mg tid)				
		N	k	mean	N	k	mean	Δ	p
Full analysis set (FAS) or efficacy analysis pop									
Demographics: Age (years)	Continuous	86		58.5 (SD 8.4)	78		56.8 (SD 9.4)		
Sex (n male) a	Dichotomous	86	46	(53.5%)	78	46	(59.0%)		
Duration of diabetes (months)	Continuous	86		med: 26	78		med: 17		
Blood glucose: HbA1c (%) – 0wkb	Continuous	86		7.42 (SD 1.09)	78		7.43 (SD 1.1)		
Fasting plasma glucose (mmol/l) – 0wkb	Continuous	86		9.33 (SD 1.24)	78		9.21 (SD 1.19)		

[a] estimated from reported percentages; approximated to nearest integer (percentages only presented in text)
[b] geometric mean/SD

		Acarbose (25 mg TID)			Acarbose (200 mg tid)				
		N	k	mean	N	k	mean	Δ	p

Full analysis set (FAS) or efficacy analysis pop									
Demographics: Age (years)	Continuous	86		58.5 (SD 8.4)	87		59.4 (SD 8.6)		
Sex (n male) a	Dichotomous	86	46	(53.5%)	87	44	(50.6%)		
Duration of diabetes (months)	Continuous	86		med: 26	87		med: 21		
Blood glucose: HbA1c (%) – 0wkb	Continuous	86		7.42 (SD 1.09)	87		7.51 (SD 1.1)		
Fasting plasma glucose (mmol/l) – 0wkb	Continuous	86		9.33 (SD 1.24)	87		9.27 (SD 1.23)		

[a] estimated from reported percentages; approximated to nearest integer (percentages only presented in text)
[b] geometric mean/SD

		Acarbose (50 mg TID)			Acarbose (100 mg tid)				
		N	k	mean	N	k	mean	Δ	p
Full analysis set (FAS) or efficacy analysis pop									
Demographics: Age (years)	Continuous	88		55.5 (SD 9.6)	78		56.8 (SD 9.4)		
Sex (n male)	Dichotomous	88	43a	(48.9%)	78	46b	(59.0%)		
Duration of diabetes (months)	Continuous	88		med: 20	78		med: 17		
Blood glucose: HbA1c (%) – 0wkc	Continuous	88		7.52 (SD 1.09)	78		7.43 (SD 1.1)		
Fasting plasma glucose (mmol/l) – 0wkc	Continuous	88		9.33 (SD 1.22)	78		9.21 (SD 1.19)		

[a] estimated from reported percentages; approximated to nearest integer (percentages only presented in text); approximated to nearest integer (percentages only presented in text)
[b] estimated from reported percentages; approximated to nearest integer (percentages only presented in text)
[c] geometric mean/SD

		Acarbose (100 mg tid)			Acarbose (200 mg tid)				
		N	k	mean	N	k	mean	Δ	p
Full analysis set (FAS) or efficacy analysis pop									
Demographics: Age (years)	Continuous	78		56.8 (SD 9.4)	87		59.4 (SD 8.6)		
Sex (n male) a	Dichotomous	78	46	(59.0%)	87	44	(50.6%)		
Duration of diabetes (months)	Continuous	78		med: 17	87		med: 21		
Blood glucose: HbA1c (%) – 0wkb	Continuous	78		7.43 (SD 1.1)	87		7.51 (SD 1.1)		
Fasting plasma glucose (mmol/l) – 0wkb	Continuous	78		9.21 (SD 1.19)	87		9.27 (SD 1.23)		

[a] estimated from reported percentages; approximated to nearest integer (percentages only presented in text)
[b] geometric mean/SD

Results

		Placebo			Acarbose (25 mg TID)				
		N	k	mean	N	k	mean	Δ	p
Hypoglycaemic events: All hypoglycaemic events (no patients) – 24wk	Dichotomous	81	0	(0.0%)	86	0	(0.0%)		
Dropouts: Total dropouts – 24wk	Dichotomous	97	11	(11.3%)	102	10	(9.8%)		
Dropout due to AEs – 24wk	Dichotomous	97	0	(0.0%)	102	1	(1.0%)		

Full analysis set (FAS) or efficacy analysis pop									
Blood glucose: HbA1c (%) – 12wk[a]	Continuous	81		7.64 (SD 1.18)	86		7.21 (SD 1.17)		
HbA1c (%) – 24wk[a]	Continuous	81		7.83 (SD 1.21)	86		7.37 (SD 1.17)		
Fasting plasma glucose (mmol/l) – 24wk[b]	Percentage change from baseline	81		-0.4	86		-4.3		
Body weight: Weight (kg) – 24wk[c]	Mean change	81		-0.3	86		-0.5		

[a] geometric mean and SD
[b] error bars not reported
[c] SD not reported

		Placebo			Acarbose (50 mg TID)			Δ	p
		N	k	mean	N	k	mean		
Hypoglycaemic events: All hypoglycaemic events (no patients) – 24wk	Dichotomous	81	0	(0.0%)	88	0	(0.0%)		
Dropouts: Total dropouts – 24wk	Dichotomous	97	11	(11.3%)	99	5	(5.1%)		
Dropout due to AEs – 24wk	Dichotomous	97	0	(0.0%)	99	1	(1.0%)		
Full analysis set (FAS) or efficacy analysis pop									
Blood glucose: HbA1c (%) – 12wk[a]	Continuous	81		7.64 (SD 1.18)	88		7.02 (SD 1.17)		
HbA1c (%) – 24wk[a]	Continuous	81		7.83 (SD 1.21)	88		7.08 (SD 1.18)		
Fasting plasma glucose (mmol/l) – 24wk[b]	Percentage change from baseline	81		-0.4	88		-11.8		
Body weight: Weight (kg) – 24wk[c]	Mean change	81		-0.3	88		-0.4		

[a] geometric mean and SD
[b] error bars not reported
[c] SD not reported

		Placebo			Acarbose (100 mg tid)			Δ	p
		N	k	mean	N	k	mean		
Hypoglycaemic events: All hypoglycaemic events (no patients) – 24wk	Dichotomous	81	0	(0.0%)	78	0	(0.0%)		
Dropouts: Total dropouts – 24wk	Dichotomous	97	11	(11.3%)	99	11	(11.1%)		
Dropout due to AEs – 24wk	Dichotomous	97	0	(0.0%)	99	6	(6.1%)		
Full analysis set (FAS) or efficacy analysis pop									
Blood glucose: HbA1c (%) – 12wk[a]	Continuous	81		7.64 (SD 1.18)	78		6.95 (SD 1.19)		
HbA1c (%) – 24wk[a]	Continuous	81		7.83 (SD 1.21)	78		6.98 (SD 1.2)		
Fasting plasma glucose (mmol/l) – 24wk[b]	Percentage change from baseline	81		-0.4	78		-15		
Body weight: Weight (kg) – 24wk[c]	Mean change	81		-0.3	78		-0.7		

[a] geometric mean and SD
[b] error bars not reported
[c] SD not reported

		Acarbose (25 mg TID)			Acarbose (50 mg TID)			Δ	p
		N	k	mean	N	k	mean		
Hypoglycaemic events: All hypoglycaemic events (no patients) – 24wk	Dichotomous	86	0	(0.0%)	88	0	(0.0%)		
Dropouts: Total dropouts – 24wk	Dichotomous	102	10	(9.8%)	99	5	(5.1%)		
Dropout due to AEs – 24wk	Dichotomous	102	1	(1.0%)	99	1	(1.0%)		
Full analysis set (FAS) or efficacy analysis pop Blood glucose: HbA1c (%) – 12wka	Continuous	86		7.21 (SD 1.17)	88		7.02 (SD 1.17)		
HbA1c (%) – 24wka	Continuous	86		7.37 (SD 1.17)	88		7.08 (SD 1.18)		
Fasting plasma glucose (mmol/l) – 24wkb	Percentage change from baseline	86		-4.3	88		-11.8		
Body weight: Weight (kg) – 24wkc	Mean change	86		-0.5	88		-0.4		

[a] geometric mean and SD
[b] error bars not reported
[c] SD not reported

		Acarbose (25 mg TID)			Acarbose (100 mg tid)			Δ	p
		N	k	mean	N	k	mean		
Hypoglycaemic events: All hypoglycaemic events (no patients) – 24wk	Dichotomous	86	0	(0.0%)	78	0	(0.0%)		
Dropouts: Total dropouts – 24wk	Dichotomous	102	10	(9.8%)	99	11	(11.1%)		
Dropout due to AEs – 24wk	Dichotomous	102	1	(1.0%)	99	6	(6.1%)		
Full analysis set (FAS) or efficacy analysis pop Blood glucose: HbA1c (%) – 12wka	Continuous	86		7.21 (SD 1.17)	78		6.95 (SD 1.19)		
HbA1c (%) – 24wka	Continuous	86		7.37 (SD 1.17)	78		6.98 (SD 1.2)		
Fasting plasma glucose (mmol/l) – 24wkb	Percentage change from baseline	86		-4.3	78		-15		
Body weight: Weight (kg) – 24wkc	Mean change	86		-0.5	78		-0.7		

[a] geometric mean and SD
[b] error bars not reported
[c] SD not reported

		Acarbose (25 mg TID)			Acarbose (200 mg tid)			Δ	p
		N	k	mean	N	k	mean		
Hypoglycaemic events: All hypoglycaemic events (no patients) – 24wk	Dichotomous	86	0	(0.0%)	87	0	(0.0%)		
Dropouts: Total dropouts – 24wk	Dichotomous	102	10	(9.8%)	98	6	(6.1%)		
Dropout due to AEs – 24wk	Dichotomous	102	1	(1.0%)	98	3	(3.1%)		

Full analysis set (FAS) or efficacy analysis pop								
Blood glucose: HbA1c (%) – 12wka	Continuous	86		7.21 (SD 1.17)	87		6.85 (SD 1.19)	
HbA1c (%) – 24wka	Continuous	86		7.37 (SD 1.17)	87		6.79 (SD 1.19)	
Fasting plasma glucose (mmol/l) – 24wkb	Percentage change from baseline	86		-4.3	87		-7.5	
Body weight: Weight (kg) – 24wkc	Mean change	86		-0.5	87		-0.8	

[a] geometric mean and SD
[b] error bars not reported
[c] SD not reported

		Acarbose (50 mg TID)			Acarbose (100 mg tid)				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Hypoglycaemic events: All hypoglycaemic events (no patients) – 24wk	Dichotomous	88	0	(0.0%)	78	0	(0.0%)		
Dropouts: Total dropouts – 24wk	Dichotomous	99	5	(5.1%)	99	11	(11.1%)		
Dropout due to AEs – 24wk	Dichotomous	99	1	(1.0%)	99	6	(6.1%)		
Full analysis set (FAS) or efficacy analysis pop									
Blood glucose: HbA1c (%) – 12wka	Continuous	88		7.02 (SD 1.17)	78		6.95 (SD 1.19)		
HbA1c (%) – 24wka	Continuous	88		7.08 (SD 1.18)	78		6.98 (SD 1.2)		
Fasting plasma glucose (mmol/l) – 24wkb	Percentage change from baseline	88		-11.8	78		-15		
Body weight: Weight (kg) – 24wkc	Mean change	88		-0.4	78		-0.7		

[a] geometric mean and SD
[b] error bars not reported
[c] SD not reported

		Acarbose (100 mg tid)			Acarbose (200 mg tid)				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Hypoglycaemic events: All hypoglycaemic events (no patients) – 24wk	Dichotomous	78	0	(0.0%)	87	0	(0.0%)		
Dropouts: Total dropouts – 24wk	Dichotomous	99	11	(11.1%)	98	6	(6.1%)		
Dropout due to AEs – 24wk	Dichotomous	99	6	(6.1%)	98	3	(3.1%)		
Full analysis set (FAS) or efficacy analysis pop									
Blood glucose: HbA1c (%) – 12wka	Continuous	78		6.95 (SD 1.19)	87		6.85 (SD 1.19)		
HbA1c (%) – 24wka	Continuous	78		6.98 (SD 1.2)	87		6.79 (SD 1.19)		
Fasting plasma glucose (mmol/l) – 24wkb	Percentage change from baseline	78		-15	87		-7.5		
Body weight: Weight (kg) – 24wkc	Mean change	78		-0.7	87		-0.8		

[a] geometric mean and SD
[b] error bars not reported
[c] SD not reported

	Outcomes reported in cochrane not used (results not found in full paper)

Table 38: Foley & (2009)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** 16 countries including Europe, Latin America and South Africa **Authors' conclusions:** Although the hypothesis of noninferiority to gliclazide was not bourne out statistically, the reductions in Hba1c were similar over a two year period and vildagliptin had significant benefits in terms of less weight gain and less hypoglycaemia **Source of funding:** Author from Novartis **Comments:** Multicenter, double-blind, randomised, active controlled study
Number and characteristics of patients	**Total number of patients:** 1092 **Inclusion criteria:** Male and female patients aged >=18 years with type 2 diabetes, BMI 22-45 kg/m2, Hba1c 7.5-11% (on no pharamcological therapy in previous 12 weeks) and FPG <15 mmol/l. Patients who had taken no OAD for at least 12 weeks prioir to screening and no OAD for >3 consecutive months at any time in the past were considered to be representative of a drug naïve population **Exclusion criteria:** Patients who were pregnant or lactating, had a history of type 1 diabetes, Pancreatic injury, secondary forms of diabetes, symptomatic autonomic neuropathy, acute infections, CHF or ECG abnormalities, cirrhosis or chronic active hepatitis were excluded. Pre-randomisation phase: 12 week titration is assumed to form part of the maintenance period
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** some on oral hypoglycaemic drugs and/or insulin **Details of washout period:** Drug naïve defined as not on OAD for at least 12 weeks prior to screening and no history of OAD for 3 consecutive months
Lifestyle advice	No details reported
Follow-up	**Total follow-up (wks):** 104 **Length of titration period (wks):** 12 **Length of maintenance period (wks):** 104 **Frequency of monitoring appointments:** -
Arms	**(1) Vildagliptin (50 mg bid)** N: 546 Treatment duration (wks): 104 Washout period (d): 0 Comments: Drug naïve defined as not on OAD for at least 12 weeks prior to screening and no history of OAD for 3 consecutive months Treatment(s): Vildagliptin (Oral) – fixed-dose Set dose (mg/d):100 Frequency of dosing: twice a day Details of dosing regimen: Vildagliptin 50 mg bid. There were no dose adjustments with vildagliptin at any time. **(2) Gliclazide** N: 546 Treatment duration (wks): 104 Washout period (d): 0 Comments: Drug naïve defined as not on OAD for at least 12 weeks prior to screening and no history of OAD for 3 consecutive months Treatment(s): Sulfonylurea (Oral) – flexible-dose (dose-adjusted) Mean dose (mg/d): 209 Minimum dose (mg/d): 80 Maximum dose (mg/d): 320 Details of dosing regimen: Patients received 80 mg gliclazide at baseline and were titrated to the next dose level of 160 mg after 4 weeks, 240 mg after 8 weeks and 320 mg after 12 weeks if FPG >7 mmol/l and titration was not contraindicated in the investigators opinion

due to the risk of hypoglycaemia. The dose could be adjusted downwards to no less than 80 mg at any time if there were three grade 1 hypoglycaemic events per week. Metformin could be prescribed as rescue medication in addition to blinded study medication according to clinical judgement at or after week 24 for patients who had reached gilclazide 320 mg daily or placebo and had unsatisfactory therapeutic effect as defined by confirmed FPG>13.3 mmol/l or symptoms of worsening hyperglycaemia or these patients were discontinued to received treatment.

Outcomes

General

137/546 patients (25.1%) from the vildagliptin group and 144/546 (26.4%) in the gliclazide group discontinued from the study.

162 patients in the vildagliptin group and 113 patients in gliclazide group received rescue medication.

Outcomes not extracted in this evidemce table include proinsulin, insulin and proinsulin/insulin ratio.

Efficacy analyses were conducted in PP population (unclear how many patients in each group).The randomised population consists of all patients as randomised and was utilised for safety assessments. The ITT population comprised all patients with baseline value, who received at least one dose of trial medication, and had at least one post baseline assessment. The per protocol population is a subset of the ITT population which excluded major protocol violations (1. treatment for at least 96 weeks with no rescue medication, no protocol deviation and a valid assessment within 7 days of the last dose of study drug; 2. completed at least 24 weeks of treatment with no rescue medication and started rescue medication at or after week 24 with a valid Hba1c measurement within 7 days and no major protocol violations before rescue therapy; 3. 24 weeks of treatment without rescue medication, who discontinued with a valid Hba1c assessment and no major protocol violations before rescue therapy.)

Efficacy assessments while on rescue medication were not considered.

Safety population included all randomised patients receiving at least one dose of the study drug. These included individuals who received rescue medication and therefore data were not extracted for these outcomes.

Hypoglycaemic events

Major/severe hypoglycaemic event (Grade 2 hypoglycaemia was defined as requiring the assistance of another party)

symptomatic (confirmed) (Grade 1 hypoglycaemia was defined as symptoms suggestive of low blood glucose confirmed by self-monitored blood glucose value <3.1 mmol/l and does not require assistance from another party)

Baseline characteristics

		Vildagliptin (50 mg bid)			Gliclazide				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	546		55.2 (SD 10.6)	546		54.3 (SD 10.4)		
Sex (n male)	Dichotomous	546	321	(58.8%)	546	288	(52.7%)		
Duration of diabetes (yrs)	Continuous	546		2.4 (SD 4.3)	546		1.9 (SD 3.1)		
Ethnicity-White	Dichotomous	546	405	(74.2%)	546	401	(73.4%)		
Ethnicity-Hispanic	Dichotomous	546	82	(15.0%)	546	82	(15.0%)		
Ethnicity-Other	Dichotomous	546	59	(10.8%)	546	63	(11.5%)		
Blood glucose: HbA1c (%) – 0wk	Continuous	546		8.6 (SD 1)	546		8.69 (SD 1.1)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	546		10.8 (SD 2.9)	546		10.8 (SD 2.9)		
Body weight: BMI (kg/m2)	Continuous	546		30.6 (SD 5)	546		30.8 (SD 5.5)		
Weight (kg) – 0wk	Continuous	546		84.2 (SD 16.3)	546		84.3 (SD 17.6)		
Waist circumference (cms)	Continuous	546		101.9 (SD 11.5)	546		101.3 (SD 12.6)		
PP									
Blood glucose: HbA1c (%) – 4wk[a]	Continuous	409		8.525 (SD 1.01)	402		8.7 (SD 1)		

[a] Extracted from graph; SD calculated from SE; assumed PP are completors from trial flow chart

Results

	Vildagliptin (50 mg bid)	Gliclazide	Δ	p

		N	k	mean	N	k	mean		
PP									
Blood glucose: HbA1c (%) – 12wka	Continuous	409		7.4 (SD 1.01)	402		7.225 (SD 1.34)		
HbA1c (%) – 24wka	Continuous	409		7.35 (SD 1.35)	402		7.075 (SD 1.34)		
HbA1c (%) – 52wka	Continuous	409		7.325 (SD 1.68)	402		7.21 (SD 2)		
HbA1c (%) – 104wka	Continuous	409		7.825 (SD 2.02)	402		7.81 (SD 2)		
HbA1c (%) – 104wk	Mean change	546			546			MD=0.130 (CI: -0.060, 0.320)	NSb
Fasting plasma glucose (mmol/l) – 104wkc	Mean change	546		-0.2 (SD 4.04)	546		-0.7 (SD 4.01)	MD=0.500	<0.025b
Fasting plasma glucose (mmol/l) – 104wkc	Mean change	409		-0.2 (SD 4.04)	402		-0.7 (SD 4.01)	MD=0.500	<0.025b
Body weight: Weight (kg) – 104wkd	Mean change	546		0.8 (SD 4.04)	546		1.6 (SD 4.01)		<0.01b
Weight (kg) – 104wkd	Mean change	409		0.8 (SD 4.04)	402		1.6 (SD 4.01)		<0.01b
Baseline Hba1c <=8%									
Blood glucose: HbA1c (%) – 104wkb	Continuous	0		0 (SD 0)	0		0 (SD 0)		
Hba1c>9.0%									
Blood glucose: HbA1c (%) – 104wkb	Continuous	0		-0.93 (SD 0)	0		-1.38 (SD 0)		

[a] Extracted from graph; SD calculated from SE; assumed PP are completors from trial flow chart
[b] unclear denominator
[c] assumed SE reported, assumed PP are completors from trial flow chart
[d] assumed PP are completors from trial flow chart

Hba1c was analysed using ANCOVA model with treatment and pooled centre as classification varaibles and baseline Hba1c as the covariate. P-values for between group differences for adverse events were not reported

Table 39: Fonseca et al. (2013)

General

Phase:
☑ monotherapy
☐ dual therapy
☐ triple therapy
☐ insulin monotherapy
☐ insulin+oral

Parallel / crossover: Parallel

Country: -

Authors' conclusions: -

Source of funding: -

Comments: -

Number and characteristics of patients

Total number of patients: 138

Inclusion criteria: Adults (18 years and over) diagnosed with T2DM for at least 6 months, HbA1c between 7 and 9.5% and BMI between 20 and 45kg/m2.

Patients were either AHA naïve or receiving up to 2 OADs (with <50% of the maximum dose for each component)

Exclusion criteria: -

Pre-randomisation phase: 8 week wash out period: 6 week wash out period (for people on previous OADs) and 2 week single blind placebo run in (for all patients)

Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** some on oral hypoglycaemic drugs and/or insulin **Details of washout period:** 8 week wash out period: 6 week wash out period (for people on previous OADs) and 2 week single blind placebo run in (for all patients)
Lifestyle advice	All patients were on a stable exercise and diet programme
Follow-up	**Total follow-up (wks):** 20 **Length of titration period (wks):** - **Length of maintenance period (wks):** 12 **Frequency of monitoring appointments:** Assessments undertaken at baseline (following 2 week single blind placebo run in), Week 1, 2, 4, 8 and 12
Arms	**(1) Metformin** N: 69 Treatment duration (wks): 12 Washout period (d): 56 Comments: 29/69 (42%) with completely treatment naïve Metformin started at 1000mg/day and increased to 1500mg/day after 2 weeks Treatment(s): Metformin (Oral) – flexible-dose (dose-adjusted) Minimum dose (mg/d): 1000 Maximum dose (mg/d): 1500 Details of dosing regimen: Starting dose of 1000mg/d, increased to 1500mg/d after 2 weeks **(2) Placebo** N: 69 Treatment duration (wks): 12 Washout period (d): 56 Comments: 29/69 (42%) with completely treatment naïve Treatment(s): Placebo (Oral)
Outcomes	**General** Data not reported for 4 trial arms receiving ipragliflozin at 12.5, 50, 150 and 300mg. Total dropouts were not explicitly stated per group and therefore not extracted.

Baseline characteristics

		Metformin		
		N	**k**	**mean**
Demographics:				
Age (years)	Continuous	69		53.1 (SD 11.7)
Sex (n male)	Dichotomous	69	40	(58.0%)
Duration of diabetes (yrs)	Continuous	69		4.13 (SD 4.71)
Blood glucose:				
HbA1c (%) – 12wk	Continuous	69		8.03 (SD 0.9)
HbA1c (%) – 12wk	Continuous	69		8.03 (SD 0.9)
Fasting plasma glucose (mmol/l) – 12wk	Continuous	69		9.42 (SD 2.78)
Fasting plasma glucose (mmol/l) – 12wk	Continuous	69		9.42 (SD 2.78)
Body weight:				
BMI (kg/m2)	Continuous	69		29.8 (SD 5.5)
Weight (kg) – 0wk	Continuous	69		84.10752 (SD 15.5232) a
Weight (kg) – 0wk	Continuous	69		84.10752 (SD 15.5232) a
Weight (kg) – 12wk	Continuous	69		84.1 (SD 21.8)
Weight (kg) – 12wk	Continuous	69		84.1 (SD 21.8)
Previous blood glucose lowering drugs:				
Diet alone (i.e. drug naïve)	Dichotomous	69	29	(42.0%)

[a] estimated from BMI assuming mean height of 1.68m

	Placebo		
	N	**k**	**mean**

Demographics:				
Age (years)	Continuous	69		53.4 (SD 9.7)
Sex (n male)	Dichotomous	69	32	(46.4%)
Duration of diabetes (yrs)	Continuous	69		4.64 (SD 5.93)
Blood glucose:				
HbA1c (%) – 12wk	Continuous	69		7.84 (SD 0.78)
HbA1c (%) – 12wk	Continuous	69		7.84 (SD 0.78)
Fasting plasma glucose (mmol/l) – 12wk	Continuous	69		9.03 (SD 2.49)
Fasting plasma glucose (mmol/l) – 12wk	Continuous	69		9.03 (SD 2.49)
Body weight:				
BMI (kg/m2)	Continuous	69		30.9 (SD 5.5)
Weight (kg) – 0wk	Continuous	69		87.21216 (SD 15.5232) a
Weight (kg) – 0wk	Continuous	69		87.21216 (SD 15.5232) a
Weight (kg) – 12wk	Continuous	69		81.8 (SD 17.6)
Weight (kg) – 12wk	Continuous	69		81.8 (SD 17.6)
Previous blood glucose lowering drugs:				
Diet alone (i.e. drug naïve)	Dichotomous	69	29	(42.0%)

[a] estimated from BMI assuming mean height of 1.68m

Results

		Metformin		
		N	**k**	**mean**
Blood glucose:				
HbA1c (%) – 12wk	Mean change	69		-0.42 (SD 0.825) a
HbA1c (%) – 12wk	Mean change	69		-0.42 (SD 0.825) a
Body weight:				
Weight (kg) – 12wk	Mean change	69		-0.8 (SD 2.4) a
Weight (kg) – 12wk	Mean change	69		-0.8 (SD 2.4) a
Hypoglycaemic events:				
All hypoglycaemic events (no events) – 12wk	Dichotomous	69	0	(0.0%)
Dropouts:				
Dropout due to AEs – 12wk	Dichotomous	69	1b	(1.4%)

[a] Data extracted from graph
[b] Data only represent dropouts due to drug related adverse events

		Placebo		
		N	**k**	**mean**
Blood glucose:				
HbA1c (%) – 12wk	Mean change	69		0.26 (SD 0.8) a
HbA1c (%) – 12wk	Mean change	69		0.26 (SD 0.8) a
Body weight:				
Weight (kg) – 12wk	Mean change	69		-0.9 (SD 2.05) a
Weight (kg) – 12wk	Mean change	69		-0.9 (SD 2.05) a
Hypoglycaemic events:				
All hypoglycaemic events (no events) – 12wk	Dichotomous	69	0	(0.0%)
Dropouts:				
Dropout due to AEs – 12wk	Dichotomous	69	1b	(1.4%)

[a] Data extracted from graph
[b] Data only represent dropouts due to drug related adverse events

Table 40: Formoso et al. (2008)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** Italy **Authors' conclusions:** The data suggest that metformin could improve oxidative stress, preserve antioxidant function and restrain platelet activation in type 2 diabetes **Source of funding:** supported in part by Italian Government grants. This research was also supported by ECFP6 funding **Comments:** No details of randomisation or allocation concealment. This was an open label trial.
Number and characteristics of patients	**Total number of patients:** 26 **Inclusion criteria:** newly diagnosed (diagnosis of diabetes in the prior 6 months) with type 2 diabetes, patients were recruited from Pescara Town Hospital University Diabetes Clinic. All patients were non-smokers and normotensive. States participants are OAD naïve **Exclusion criteria:** patients did not present with any alteration of urinary albumin excretion, lipid profile or function sof any major organ or system Pre-randomisation phase: assumed titration of drug occurred during maintenance period
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** All treatment naive/ no OADs at screening **Details of washout period:** States participants are OAD naïve, newly diagnosed
Lifestyle advice	All patients were instructed to follow a moderately hypocaloric diet (-20% of estimated daily energy requirement)
Follow-up	**Total follow-up (wks):** 12 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 12 **Frequency of monitoring appointments:** Patients were seen in the clinic every 2 weeks during the first month of treatment and monthly thereafter
Arms	**(1) Metformin** N: 13 Treatment duration (wks): 12 Washout period (d): 0 Treatment(s): Metformin (Oral) – flexible-dose (dose-adjusted) Minimum dose (mg/d): 850 Maximum dose (mg/d): 2550 Details of dosing regimen: Metformin was started at the dose of 850 mg/day. Drugs were uptitrated as needed on the basis of home-recorded blood glucose profiles and Hba1c levels, so as to achieve good glycaemic control (fasting plasma glucose <7 mmol/l and/or Hba1c <=7%) up to a maximum of 2550 mg/day for metformin. **(2) Gliclazide** N: 13 Treatment duration (wks): 12 Washout period (d): 0 Treatment(s): Sulfonylurea (Oral) – flexible-dose (dose-adjusted) Minimum dose (mg/d): 80 Maximum dose (mg/d): 240 Details of dosing regimen: gliclazide was started at 80 mg/day. Drugs were uptitrated as needed on the basis of home-recorded blood glucose profiles and Hba1c levels, so as to achieve good glycaemic control (fasting plasma glucose <7 mmol/l and/or Hba1c <=7%) up to a maximum of 240 mg/day for gliclazide.
Outcomes	**General** Outcomes not extracted in this evidence table include plasma vitamin A and E, urinary 8-iso-PGF, urinary 11-dehydro-TXB2 and insulin resistance Assumed no drop-outs as not reported and analysis conducted on all patients No details of ITT analysis reported
Baseline characteristics	

	Metformin	Gliclazide	Δ	p

			N	k	mean	N	k	mean		
Demographics: Age (years)		Continuous	13		58.8 (SD 1.32)	13		57.2 (SD 1.56)		
Sex (n male)		Dichotomous	13	6	(46.2%)	13	7	(53.8%)		
Blood glucose: HbA1c (%) – 0wka		Continuous	13		8.6 (SD 0.04)	13		8 (SD 0.03)		
Fasting plasma glucose (mmol/l) – 0wk		Continuous	13		8.8 (SD 0.7)	13		9 (SD 0.6)		
Body weight: BMI (kg/m2) – 0wk		Continuous	13		33.4 (SD 1.22)	13		30.9 (SD 1.05)		
Waist circumference (cms) – 0wk		Continuous	13		102 (SD 1.24)	13		100.8 (SD 2.2)		
Blood pressure: Systolic blood pressure (mmHg) – 0wk		Continuous	13		130 (SD 5)	13		125 (SD 6)		
Diastolic blood pressure (mmHg) – 0wk		Continuous	13		80 (SD 3)	13		80 (SD 4)		
Lipids: Total cholesterol (mmol/l) – 0wk		Continuous	13		4.5 (SD 0.2)	13		4.8 (SD 0.2)		
HDL cholesterol (mmol/l) – 0wk		Continuous	13		1 (SD 0.09)	13		1.1 (SD 0.04)		
Triglycerides (mmol/l) – 0wk		Continuous	13		1.4 (SD 0.1)	13		1.4 (SD 0.1)		
LDL cholesterol (mmol/l) – 0wk		Continuous	13		2.8 (SD 0.2)	13		3 (SD 0.2)		

[a] Reported as SD

Results

		Metformin			Gliclazide				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 12wka	Continuous	13		6.4 (SD 0.004)	13		6.6 (SD 0.003)		NS
Fasting plasma glucose (mmol/l) – 12wk	Continuous	13		7.1 (SD 0.5)	13		7 (SD 0.5)		NS
Body weight: BMI (kg/m2) – 12wk	Continuous	13		31.9 (SD 1.36)	13		31 (SD 1.08)		NS
Waist circumference (cms) – 12wk	Continuous	13		99.3 (SD 1.45)	13		101.4 (SD 2.8)		NS
Blood pressure: Systolic blood pressure (mmHg) – 12wk	Continuous	13		130 (SD 7)	13		125 (SD 7)		NS
Diastolic blood pressure (mmHg) – 12wk	Continuous	13		80 (SD 6)	13		80 (SD 3)		NS
Lipids: Total cholesterol (mmol/l) – 12wk	Continuous	13		4.6 (SD 0.1)	13		4.6 (SD 0.2)		NS
HDL cholesterol (mmol/l) – 12wk	Continuous	13		1 (SD 0.08)	13		1 (SD 0.07)		NS
Triglycerides (mmol/l) – 12wk	Continuous	13		1.5 (SD 0.1)	13		1.3 (SD 0.1)		NS
LDL cholesterol (mmol/l) – 12wk	Continuous	13		2.9 (SD 0.1)	13		3 (SD 0.2)		NS

[a] Reported as SD

Changes in variables of interest after therapy within treatment groups were analysed by Student's paired t-test.

Table 41: Gao et al. (2008)

General

Phase:
☑ monotherapy
☐ dual therapy
☐ triple therapy

	☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** China **Authors' conclusions:** The effects of once daily extended release metformin (MXR) on chronic glycaemia, BMI, lipid profiles, insulin resistance and islet function are comparable with that of thrice daily immediate release metformin (MIR) in an oriental population **Source of funding:** supported by grants from the National 973 Program of China, the Natural Science Foundation of Beijing and the National natural Science Foundation of China. The study received partial financial support from Beijing Wanhui Double-Crane Pharmaceutical Co **Comments:** randomised, open label, active controlled trial
Number and characteristics of patients	**Total number of patients:** 150 **Inclusion criteria:** patients with type 2 diabetes in outpatients clinics were enrolled in this study. Inclusion criteria were 30-70 years of age, BMI 19-35 kg/m2, fasting plasma glucose <=13 mmol/l, Hba1c <=9.5% and treatment with diet alone or monotherapy with immediate release metformin (MIR) or alpha-glucosidase inhibitor. **Exclusion criteria:** Patents were required to be free of diabetic symptoms, diabetic ketoacidosis, and non-ketotic hyperosmolar coma, renal dysfunction, hepatic dysfunction and severe heart disease. In addition, patients receiving insulin therapy, sulfonylureas, glinides or thiazolidinediones and pregnant or breast-feeding women were also excluded. Patients were required to achieve <=1.67 mmol/l in the change of fasting plasma glucose within 2 consecutive weeks or were not eligible after the run-in period for randomisation. After the initial 2 weeks of therapy with either MXR or MIR, the patients withdrew from the study if FPG were >13.0 or <3.5 mmol/l Pre-randomisation phase: During 2 weeks of run-in period, all patients received MIR (500 mg thrice daily) after each meal and the previous antihyperglycaemic, if any, was discontinued.
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** some on oral hypoglycaemic drugs and/or insulin **Details of washout period:** see baseline characteristics for details. There was a 2 week run-in period where previous antihyperglycaemic agents were discontinued.
Lifestyle advice	Physical exercise and diet control were unchanged during the study period in both groups
Follow-up	**Total follow-up (wks):** 14 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 12 **Frequency of monitoring appointments:** No details reported
Arms	**(1) Metformin extended release (MXR)** N: 75 Treatment duration (wks): 12 Washout period (d): 14 Comments: 2 week run-in period where patients discontinue previous OHAs and start metformin immediate release Treatment(s): Metformin (modified release) (Oral) – fixed-dose Set dose (mg/d):1500 Frequency of dosing: once a day Compliance: the tablets left in blisters and boxes were counted and compliance was defined as the proportion of tablets taken. The total percentage of compliance was 97.2% in the MXR group Details of dosing regimen: 1500 mg given once daily after dinner **(2) Metformin immediate release (MIR)** N: 75 Treatment duration (wks): 12 Washout period (d): 14 Comments: 2 week run-in period where patients discontinue previous OHAs and start metformin immediate release Treatment(s): Metformin (Oral) – fixed-dose Set dose (mg/d):1500 Frequency of dosing: three times a day Compliance: the tablets left in blisters and boxes were counted and compliance was defined as the proportion of tablets taken. The total percentage of compliance was 93.8% in the MIR group Details of dosing regimen: continued with 500 mg given thrice daily after meals.
Outcomes	**General** 6 (8%) patients in the MXR and 4 (5%) in the MIR groups discontinued the study Outcomes not extracted in this evidence table include area under the curve (AUC) of plasma glucose and insulin, fasting and post-prandial insulin levels and measures of insulin resistance

	ITT analysis not reported

Baseline characteristics

		Metformin extended release (MXR)			Metformin immediate release (MIR)				
		N	k	mean	N	k	mean	Δ	p
Demographics:									
Age (years)	Continuous	75		55.7 (SD 8.8)	75		53.5 (SD 8.1)		
Sex (n male)	Dichotomous	75	38	(50.7%)	75	37	(49.3%)		
Duration of diabetes (yrs)	Continuous	75		3.2 (SD 2.7)	75		3.8 (SD 3.3)		
Blood glucose:									
HbA1c (%) – 0wk	Continuous	69		6.5 (SD 1.1)	71		6.4 (SD 0.9)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	69		6.8 (SD 1.3)	71		6.9 (SD 1.4)		
2-h post prandial glucose (mmol/l) – 0wk	Continuous	69		10.1 (SD 3.1)	71		10 (SD 2.8)		
Body weight:									
BMI (kg/m2) – 0wk	Continuous	69		26.4 (SD 3.2)	71		26.4 (SD 2.8)		
Blood pressure:									
Systolic blood pressure (mmHg)	Continuous	75		125.1 (SD 14.5)	75		122.7 (SD 13.7)		
Diastolic blood pressure (mmHg)	Continuous	75		78.6 (SD 8.8)	75		78.7 (SD 8.9)		
Lipids:									
Total cholesterol (mmol/l) – 0wk	Continuous	69		5.1 (SD 0.9)	71		5 (SD 0.8)		
HDL cholesterol (mmol/l) – 0wk	Continuous	69		1.4 (SD 0.5)	71		1.5 (SD 0.8)		
Triglycerides (mmol/l) – 0wk	Continuous	69		1.9 (SD 1.4)	71		2 (SD 1.2)		
LDL cholesterol (mmol/l) – 0wk	Continuous	69		3.1 (SD 0.8)	71		3 (SD 0.7)		
Previous blood glucose lowering drugs:									
Diet alone (i.e. drug naïve)	Dichotomous	75	22	(29.3%)	75	16	(21.3%)		
Metformin	Dichotomous	75	41	(54.7%)	75	52	(69.3%)		
Acarbose	Dichotomous	75	12	(16.0%)	75	7	(9.3%)		
Other medication:									
ACE inhibitor/ARB	Dichotomous	75	9	(12.0%)	75	10	(13.3%)		
Calcilm channel blocker	Dichotomous	75	5	(6.7%)	75	10	(13.3%)		
Other hypertension treatment	Dichotomous	75	20	(26.7%)	75	16	(21.3%)		

Results

		Metformin extended release (MXR)			Metformin immediate release (MIR)				
		N	k	mean	N	k	mean	Δ	p
Blood glucose:									
HbA1c (%) – 12wk	Continuous	69		6.2 (SD 0.8)	71		6.1 (SD 0.8)		0.73
Fasting plasma glucose (mmol/l) – 12wk	Continuous	69		7 (SD 1.3)	71		6.7 (SD 1.1)		<0.01
2-h post prandial glucose (mmol/l) – 12wk	Continuous	69		11 (SD 3.1)	71		9.7 (SD 2.6)		0.002
Body weight:									
BMI (kg/m2) – 12wk	Continuous	69		25.9 (SD 3)	71		25.9 (SD 2.7)		>0.05
Adverse events:									
GI: nausea – 12wk	Dichotomous	69	0	(0.0%)	71	1	(1.4%)		NR
Dizziness – 12wk	Dichotomous	69	3	(4.3%)	71	0	(0.0%)		NR
Flatulence – 12wk	Dichotomous	69	1	(1.4%)	71	1	(1.4%)		NR

	Gastrointestinal disorders (any) – 12wk	Dichotomous	69	3	(4.3%)	71	8	(11.3%)		0.12
	GI: diarrhoea – 12wk	Dichotomous	69	0	(0.0%)	71	4	(5.6%)		NR
	GI: abdominal pain – 12wk	Dichotomous	69	2	(2.9%)	71	2	(2.8%)		NR
	Dropouts:									
	Drop out due to unsatisfactory effect – 12wk	Dichotomous	75	1	(1.3%)	75	2	(2.7%)		NR
	Lipids:									
	Total cholesterol (mmol/l) – 12wk	Continuous	75			75				>0.05
	Total cholesterol (mmol/l) – 12wk	Mean change	69		5.2 (SD 1.2)	71		5 (SD 0.8)		
	HDL cholesterol (mmol/l) – 12wk	Continuous	75			75				>0.05
	HDL cholesterol (mmol/l) – 12wk	Mean change	69		1.4 (SD 0.4)	71		1.4 (SD 0.3)		
	Triglycerides (mmol/l) – 12wk	Continuous	75			75				>0.05
	Triglycerides (mmol/l) – 12wk	Mean change	69		2.1 (SD 1.6)	71		1.9 (SD 1.5)		
	LDL cholesterol (mmol/l) – 12wk	Mean change	69		3 (SD 0.9)	71		3 (SD 0.7)		
	LDL cholesterol (mmol/l) – 12wk	Continuous	75			75				>0.05
	Compliance:									
	Compliance – 12wk	Dichotomous	69	67	(97.1%)	71	67a	(94.4%)		NR

[a] approximated to nearest integer (percentages only presented in text)

	Two tailed paired Student's t-test or Wilcoxon signed-rank test was applied for paired comparisons within groups. Please note that baseline values for BMI, Hba1c, FPG, PPG and all lipid measures were extracted from the baseline period in the analysis (which may have differed slightly to the end of run-in characteristics which are reported as baseline data) and denominators have been amended accordingly. ANOVA or Mann-Whitney test was used to compare values between groups. Statistical comparisons of frequency between groups was tested using Pearsons chi-squared test

Table 42: Genovese et al. (2013)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** - **Authors' conclusions:** - **Source of funding:** - **Comments:** -
Number and characteristics of patients	**Total number of patients:** 58 **Inclusion criteria:** Adults (35 to 75 years) with T2DM, HbA1c <=9%, no antihyperglycaemic medication in previous 3 months **Exclusion criteria:** - Pre-randomisation phase: up to 1 week run in period
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** some on oral hypoglycaemic drugs and/or insulin **Details of washout period:** up to 1 week run-in period Patients were excluded if they had antihyperglycaemic medication within 3 months of study enrolment Not clearly stated whether patients were on previous medication

Lifestyle advice	Not reported
Follow-up	**Total follow-up (wks):** 17 **Length of titration period (wks):** - **Length of maintenance period (wks):** 16 **Frequency of monitoring appointments:** 5 visits at start and end of run in period, and at weeks 4, 8 and 16.
Arms	**(1) Metformin** N: 29 Treatment duration (wks): 16 Washout period (d): 0 Comments: Metformin dose = 850mg/day uptitrated to 850mg/day twice or three times a day depending on glycaemic response Treatment(s): Metformin (Oral) – flexible-dose (dose-adjusted) Minimum dose (mg/d): 850 Maximum dose (mg/d): 2550 Details of dosing regimen: Starting dose = 850mg/day uptitrated to 850mg/day twice or three times a day depending on glycaemic response **(2) Pioglitazone** N: 29 Treatment duration (wks): 16 Washout period (d): 0 Comments: Pioglitazone dose = 30mg/day uptitrated to 45mg/day depending on glycaemic response Treatment(s): Pioglitazone (Oral) – flexible-dose (dose-adjusted) Minimum dose (mg/d): 30 Maximum dose (mg/d): 45 Frequency of dosing: once a day Details of dosing regimen: Starting dose = 30mg/day uptitrated to 45mg/day depending on glycaemic response
Outcomes	

Baseline characteristics

		Metformin		
		N	**k**	**mean**
Demographics:				
Age (years)	Continuous	29		56.4 (SD 7.9)
Sex (n male)	Dichotomous	29	19	(65.5%)
Duration of diabetes (yrs)	Continuous	29		3.9 (SD 2.2)
Blood glucose:				
HbA1c (%) – 16wk	Continuous	29		6.8 (SD 0.7)
HbA1c (%) – 16wk	Continuous	29		6.8 (SD 0.7)
Fasting plasma glucose (mg/dl) – 16wk	Continuous	29		146 (SD 46)
Fasting plasma glucose (mg/dl) – 16wk	Continuous	29		146 (SD 46)
Body weight:				
BMI (kg/m2)	Continuous	29		31.7 (SD 3.6)
Weight (kg)	Continuous	29		87.8 (SD 11.5)
ITT				
Blood glucose:				
HbA1c (%) – 16wk	Continuous	26		6.7 (SD 0.7)
HbA1c (%) – 16wk	Continuous	26		6.7 (SD 0.7)
Fasting plasma glucose (mg/dl) – 16wk	Continuous	26		144 (SD 47)
Fasting plasma glucose (mg/dl) – 16wk	Continuous	26		144 (SD 47)

		Pioglitazone		
		N	**k**	**mean**
Demographics:				
Age (years)	Continuous	29		59.1 (SD 6.8)

Sex (n male)	Dichotomous	29	14	(48.3%)
Duration of diabetes (yrs)	Continuous	29		4.4 (SD 3.2)
Blood glucose:				
HbA1c (%) – 16wk	Continuous	29		6.9 (SD 0.8)
HbA1c (%) – 16wk	Continuous	29		6.9 (SD 0.8)
Fasting plasma glucose (mg/dl) – 16wk	Continuous	29		152 (SD 38)
Fasting plasma glucose (mg/dl) – 16wk	Continuous	29		152 (SD 38)
Body weight:				
BMI (kg/m2)	Continuous	29		31.1 (SD 3.2)
Weight (kg)	Continuous	29		84.1 (SD 12.5)
ITT				
Blood glucose:				
HbA1c (%) – 16wk	Continuous	24		6.9 (SD 0.9)
HbA1c (%) – 16wk	Continuous	24		6.9 (SD 0.9)
Fasting plasma glucose (mg/dl) – 16wk	Continuous	24		153 (SD 40)
Fasting plasma glucose (mg/dl) – 16wk	Continuous	24		153 (SD 40)

Results

		Metformin		
		N	**k**	**mean**
Hypoglycaemic events:				
All hypoglycaemic events (no events) – 16wk	Count	3080	0	a
Dropouts:				
Total dropouts – 16wk	Dichotomous	29	3	(10.3%)
Dropout due to AEs – 16wk	Dichotomous	29	2	(6.9%)
ITT				
Blood glucose:				
HbA1c (%) – 16wk	Continuous	26		6.5 (SD 0.7)
HbA1c (%) – 16wk	Continuous	26		6.5 (SD 0.7)
Fasting plasma glucose (mg/dl) – 16wk	Continuous	26		135 (SD 48)
Fasting plasma glucose (mg/dl) – 16wk	Continuous	26		135 (SD 48)

[a] Patient days estimated assuming dropouts occurred halfway through the study

		Pioglitazone		
		N	**k**	**mean**
Hypoglycaemic events:				
All hypoglycaemic events (no events) – 16wk	Count	2968	4	a
Dropouts:				
Total dropouts – 16wk	Dichotomous	29	5	(17.2%)
Dropout due to AEs – 16wk	Dichotomous	29	4	(13.8%)
ITT				
Blood glucose:				
HbA1c (%) – 16wk	Continuous	24		6.5 (SD 0.8)
HbA1c (%) – 16wk	Continuous	24		6.5 (SD 0.8)
Fasting plasma glucose (mg/dl) – 16wk	Continuous	24		126 (SD 25)
Fasting plasma glucose (mg/dl) – 16wk	Continuous	24		126 (SD 25)

[a] Patient days estimated assuming dropouts occurred halfway through the study

Table 43: Goke (2002)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** Germany **Authors' conclusions:** six months of pioglitazone treatment decreased insulin resistance and improved glycaemic control to a significantly greater extent than acarbose treatment. Pioglitazone was also associated with a significantly improved lipid profile, suggesting a reduction in risk of coronary heart disease **Source of funding:** funded by Takeda Pharma (principle investigator was a member of the advisory board for Takeda) **Comments:** randomised, parallel group, open-label trial. Randomisation was computerised and telephone based, the method was stratified for gender, two BMI class and study centre in blocks of 4
Number and characteristics of patients	**Total number of patients:** 265 **Inclusion criteria:** patients were either newly diagnosed with type 2 diabetes or had previous treatment with oral antihyperglycaemics, but in this case patients had to stop the administration of oral agents at least 2 months prior to starting the study. Patients had diabetes that was not well controlled with Hba1c levels between 7.5 and 11.5% and fasting blood glucose levels >= 140 mg/dl and they had a BMI between 25 and 43 kg/m2. **Exclusion criteria:** patients were not included if they were insulin dependent, required other specific antidiabetic drugs, had a history of ketoacidosis, had any disease causing malabsorption or digestive problems, had a history of heart disease, hematological disease or HIV infection or had evidence of liver, kidney or bone marrow impairment. Patients were discontinued from the study if Hba1c levels were >11.5% or FBG >250 mg/dl for more than 3 months, if clinical complications of diabetes occurred or if adverse events including clinically relevant changes in laboratory parameters occurred. Pre-randomisation phase: all patients underwent a 1 week run-in period with dietary advice. There was a 3 week titration period for acarbose (this was assumed to be part of the 26 week maintenance period).
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** some on oral hypoglycaemic drugs and/or insulin **Details of washout period:** patients were either newly diagnosed with type 2 diabetes or had previous treatment with oral antihyperglycaemics, but in this case patients had to stop the administration of oral agents at least 2 months prior to starting the study. In addition patients had a 1 week run in period where they were given diet therapy
Lifestyle advice	During the 1 week run-in patients had to follow a disease and body weight-oriented dietary regimen. The aim of the individualised dietary advice was the supply of appropraite calories and nutrients as well as body weight reduction in those with obesity. Patients were asked to continue with the recommneded diet and to maintain other aspects of their lifestyle throughout the remainder of the study.
Follow-up	**Total follow-up (wks):** 27 **Length of titration period (wks):** 3 **Length of maintenance period (wks):** 26 **Frequency of monitoring appointments:** patients attended clinic visits at 4 weekly intervals during the study.
Arms	**(1) Pioglitazone** N: 129 Treatment duration (wks): 26 Washout period (d): 7 Comments: OADs were stopped at least 2 months before starting the study Treatment(s): Pioglitazone (Oral) – fixed-dose Set dose (mg/d):45 Frequency of dosing: once a day Compliance: compliance was determined by investigators from return of empty blister packs or unused tablets Details of dosing regimen: pioglitazone was administered orally once daily, before or after breakfast, at a dose of 45 mg/day **(2) Acarbose** N: 136 Treatment duration (wks): 26 Washout period (d): 7 Comments: OADs were stopped at least 2 months before starting the study Treatment(s): Acarbose (Oral) – forced titration Minimum dose (mg/d): 50 Maximum dose (mg/d): 300

	Frequency of dosing: three times a day Compliance: compliance was determined by investigators from return of empty blister packs or unused tablets Details of dosing regimen: Patients assigned to acarbose started with 50 mg once daily for tolerability reasons and were titrated over a period of 3 weeks up to 300 mg/day administered orally as 3 equal doses with main meals
Outcomes	**General** At the end of 26 week study, patients receiving pioglitazone could continue with the same treatment while those receiving acarbose could start taking pioglitazone in addition to acarbose for a further 38 week extension period (data not extracted in this evidence table). Other outcomes not extracted in this evidence table include fasting insulin, HOMA insulin resistance, c-peptides and VLDL-cholesterol Statistical analyses were carried out on an ITT basis that included all patients who took at least one dose of study medication and used last observation carried forward where evaluations were missing. For Hba1c a per protocol analysis was also evaluated. This did not include patients who discontinued therapy or who had major protocol violations. 19 (14.7%) patients in the pioglitazone group and 39 (28.7%) in the acarbose group discontinued the study.

Baseline characteristics

		Pioglitazone			Acarbose				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	129		58.9 (SD 9.1)	136		58.8 (SD 9.1)		
Sex (n male)	Dichotomous	129	69	(53.5%)	136	74	(54.4%)		
Duration of diabetes (months)	Continuous	129		57 (SD 55.4)	136		59.1 (SD 50.3)		
Body weight: BMI (kg/m2)	Continuous	129		30.9 (SD 5.3)	136		30.8 (SD 4.4)		
Weight (kg) – 0wka	Continuous	129		87.21216 (SD 15)	136		86.92992 (SD 12.4)		
Blood pressure: Systolic blood pressure (mmHg) – 0wk	Continuous	129		145.2 (SD 19)	136		141.5 (SD 18.8)		
Diastolic blood pressure (mmHg) – 0wk	Continuous	129		84.8 (SD 10.6)	136		84.4 (SD 11.2)		
Previous blood glucose lowering drugs: Oral antidiabetic medication	Dichotomous	129	60	(46.5%)	136	65	(47.8%)		
ITT Blood glucose: HbA1c (%) – 0wk	Continuous	129		8.98 (SD 1.2)	136		9.03 (SD 1.32)		
PP Blood glucose: HbA1c (%) – 0wk	Continuous	75		8.94 (SD 1.09)	55		8.64 (SD 1.06)		
Pre-study diet alone (i.e. drug naive) Blood glucose: HbA1c (%) – 0wk	Continuous	69		8.99 (SD 1.16)	70		8.85 (SD 1.22)		
Pre-study oral antidiabetics (i.e. not drug naive) Blood glucose: HbA1c (%) – 0wk	Continuous	60		8.98 (SD 1.26)	65		9.23 (SD 1.4)		

[a] estimated from BMI assuming mean height of 1.68m

Results

		Pioglitazone			Acarbose				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 26wka	Mean change	129		-1.18	136		-0.5		

ITT										
Blood glucose: HbA1c (%) – 26wk	Mean change	129			136					<0.001
HbA1c (%) – 26wk	Continuous	129		7.82 (SD 1.95)	136		8.55 (SD 1.96)			
HbA1c <= 6.5% – 26wk	Dichotomous	129	40	(31.0%)	136	18b	(13.2%)			<0.001
Hba1c <=7%, Hba1c decrease >=0.6% or decrease FPG >=30mg/dl – 26wkb	Dichotomous	129	104	(80.6%)	136	78	(57.4%)			<0.001
Fasting plasma glucose (mmol/l) – 26wk	Mean change	129		-3.130755 (SD 4.08)	136		-1.25097 (SD 3.66)			<0.001
Body weight: Weight (kg) – 26wk	Mean change	129		1.23 (SD 5.42)	136		-2.09 (SD 3.58)			<0.001
Adverse events: Any serious adverse event(s) – 26wk	Dichotomous	129	0	(0.0%)	136	0	(0.0%)			
Study drug-related adverse event – 26wk	Dichotomous	129	13	(10.1%)	136	54c	(39.7%)			
Dropouts: Total dropouts – 26wk	Dichotomous	129	19	(14.7%)	136	39	(28.7%)			
Dropout due to AEs – 26wk	Dichotomous	129	1	(0.8%)	136	5	(3.7%)			
Blood pressure: Systolic blood pressure (mmHg) – 26wk	Mean change	129		-5.6 (SD 17.7)	136		0.4 (SD 18.4)			<0.001
Diastolic blood pressure (mmHg) – 26wk	Mean change	129		-3 (SD 11.3)	136		-1.2 (SD 11.4)			0.078
Lipids: Total cholesterol (mmol/l) – 26wk	Mean change	129		-0.0858552 (SD 0.828)	136		-0.0235326 (SD 0.703)			0.403
HDL cholesterol (mmol/l) – 26wk	Mean change	129		0.201708 (SD 0.264)	136		-0.020688 (SD 0.623)			<0.001
Triglycerides (mmol/l) – 26wk	Mean change	129		-0.802719 (SD 2.08)	136		-0.430149 (SD 1.93)			0.001
LDL cholesterol (mmol/l) – 26wk	Mean change	129		0.01293 (SD 0.794)	136		0.1179216 (SD 0.714)			0.124
PP										
Blood glucose: HbA1c (%) – 26wk	Continuous	75		6.93 (SD 1.16)	55		7.43 (SD 1.37)			
HbA1c (%) – 26wka	Mean change	75		-2.3	55		-1.21			<0.001
Pre-study diet alone (i.e. drug naive)										
Blood glucose: HbA1c (%) – 26wk	Continuous	69		7.27 (SD 1.75)	70		7.94 (SD 1.85)			
HbA1c (%) – 26wka	Mean change	69		-1.72	70		-0.98			<0.001
Pre-study oral antidiabetics (i.e. not drug naive)										
Blood glucose: HbA1c (%) – 26wka	Mean change	60		-0.52	65		-0.02			0.009
HbA1c (%) – 26wk	Continuous	60		8.46 (SD 1.99)	65		9.21 (SD 1.88)			

[a] estimated from graph; SE not reported
[b] approximated to nearest integer (percentages only presented in text)
[c] mainly abdominal distension/flatulence

Differences between the two treatment groups were determined using Wilcoxon rank sum tests for parallel groups (one-sided). Between group comparison p-values were not reported for adverse events

Table 44: Goke et al. (2008)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** see Schweizer (2007) **Authors' conclusions:** Both vildagliptin and metformin monotherapy provided clinically meaningful decreases in Hba1c over 2 years in drug naïve patients with type 2 diabetes. Vildagliptin was weight neutral, while weight loss was observed with metformin. However, metformin was associated with significantly worse gastrointestinal tolerability **Source of funding:** see Schweizer (2007) **Comments:** -
Number and characteristics of patients	**Total number of patients:** 463 **Inclusion criteria:** Patients who completed the core phase (see Schweizer 2007) and agreed to participate in the extension **Exclusion criteria:** see Schweizer (2007) Pre-randomisation phase: see Schweizer (2007)
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** All treatment naive/ no OADs at screening **Details of washout period:** N/A
Lifestyle advice	see Schweizer (2007)
Follow-up	**Total follow-up (wks):** 104 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 104 **Frequency of monitoring appointments:** Patients attended four additional visits at weeks 64, 76, 88 and 104
Arms	**(1) Vildagliptin** N: 305 Treatment duration (wks): 104 Washout period (d): 0 Treatment(s): Vildagliptin (Oral) – fixed-dose Set dose (mg/d):100 Frequency of dosing: variable Details of dosing regimen: dose was given as equally divided doses. Pioglitazone was added to the blinded study drug from the first visit of the extension as rescue medication for patients with confirmed FPG>10 mmol/l according to the investigators clinical judegement and prescribing guidelines. **(2) Metformin** N: 158 Treatment duration (wks): 104 Washout period (d): 0 Treatment(s): Metformin (Oral) – fixed-dose Set dose (mg/d):2000 Frequency of dosing: variable Details of dosing regimen: dose was given as equally divided doses. Rescue therapy as vildagliptin group.
Outcomes	**General** The extension ITT comprised all patients who received at least one dose of extension trial medication and had at least one Hba1c measurement during an extension visit. The primray efficacy variable was obtained from ANCOVA with treatment and pooled centre as classification variables and baseline Hba1c as covariate. The endpoint was the last available post week 52 assessment obtained before or at the start of rescue medication or up to the last scheduled visit for those not on rescue medication. The extension safety population consisted of all patients who received at leat one dose of extension study drug and had at least one post-week 52 safety assessment. Events that occurred after the start of rescue medication were not included in the primary analysis of safety.

Baseline characteristics	
Results	
	Assumed mean change values report SE rather than SD although paper reports SD

Table 45: Goldstein et al. (2007)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** Includes Australia, South America, Europe, South Africa, USA **Authors' conclusions:** The initial combination of sitagliptin and metformin provided substantial and additive glycemic improvement and was generally well tolerated in patients with type 2 diabetes. **Source of funding:** Funded by Merck and company **Comments:** This was a multinational, randomised, double-blind, placebo-controlled study
Number and characteristics of patients	**Total number of patients:** 1091 **Inclusion criteria:** Patients with type 2 diabetes, 18–78 years of age, who were either on or not on an OHA at the screening visit were eligible to participate. **Exclusion criteria:** Those with type 1 diabetes, unstable cardiac disease, significant renal impairment), or elevated (more than twofold the upper limit of normal) alanine aminotransferase or aspartate aminotransferase were excluded. Patients who met nonglycemic eligibility criteria but who had an A1C >11% or a fasting glucose value >280 mg/dl after the run-in period were not eligible for randomisation. Pre-randomisation phase: At screening, patients with an A1C of 7.5– 11% and not on an OHA for >=8 weeks were eligible to directly enter a 2-week, single-blind, placebo run-in period. Patients with A1C >11% and not on an OHA entered a diet and exercise run-in period of up to 6 weeks; and patients on an OHA with an A1C of 7–10.5% had the agent(s) discontinued and entered a wash-off period of 6–10 weeks (8–12 weeks for those on thiazolidinediones). After the wash-off/run-in period, patients with an A1C of 7.5–11% entered a 2-week, single-blind, placebo run-in period. All patients with adequate compliance (>=75% as assessed by tablet counts) during the placebo run-in period had baseline assessments and were randomised
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** some on oral hypoglycaemic drugs and/or insulin **Details of washout period:** Inclusion criterion that patients not be on AHA at least 8 weeks prior to enrollment Variable placebo run in period depending on previous AHA: ranged from 2 to 14 weeks (thiazolidinediones)
Lifestyle advice	Patients received counseling on diet and exercise consistent with American Diabetes Association recommendations throughout the study
Follow-up	**Total follow-up (wks):** 38 **Length of titration period (wks):** 4 **Length of maintenance period (wks):** 24 **Frequency of monitoring appointments:** Includes up to 14 week wash out/placebo run in period and 24 week treatment
Arms	**(1) Sitagliptin (100mg qd)** N: 179 Treatment duration (wks): 24 Washout period (d): 98 Comments: Max of 14 week washout/placebo run in period (for thiazolidinedione) Treatment(s): Sitagliptin (Oral) – fixed-dose Set dose (mg/d):100 Frequency of dosing: once a day Details of dosing regimen: Doses of study medication were administered before the morning and evening meals. Patients randomised to the sitagliptin 100 mg q.d. treatment group were administered two 50-mg tablets once daily before the morning meal. During the active treatment period, patients not meeting progressively stricter glycemic goals were

	provided glycemic rescue therapy (glibenclamide) until study completion. The glycemic rescue criteria were fasting plasma glucose (FPG) >270 mg/dl between randomisation (day 1) and week 6, FPG >240 mg/dl after weeks 6–12, and FPG >200 mg/dl after weeks 12–24. Study investigators were responsible for titration of the sulfonylurea rescue medication **(2) Metformin (500 mg bid)** N: 182 Treatment duration (wks): 24 Washout period (d): 98 Comments: Max of 14 week washout/placebo run in period (for thiazolidinedione) Treatment(s): Metformin (Oral) – forced titration Set dose (mg/d):1000 Frequency of dosing: twice a day Details of dosing regimen: 500 mg bid. To reduce gastrointestinal intolerance associated with metformin, a brief period of uptitration was implemented. For patients randomised to receive metformin monotherapy (500 or 1,000 mg b.i.d.), therapy was started at metformin 500 mg q.d. and increased in a blinded manner by increments of 500 mg per week to achieve a stable dose of either metformin 500 or 1,000 mg b.i.d. During the active treatment period, patients not meeting progressively stricter glycemic goals were provided glycemic rescue therapy (glibenclamide) until study completion. The glycemic rescue criteria were fasting plasma glucose (FPG) >270 mg/dl between randomisation (day 1) and week 6, FPG >240 mg/dl after weeks 6–12, and FPG >200 mg/dl after weeks 12–24. Study investigators were responsible for titration of the sulfonylurea rescue medication **(3) Metformin (1000 mg bid)** N: 182 Treatment duration (wks): 24 Washout period (d): 98 Comments: Max of 14 week washout/placebo run in period (for thiazolidinedione) Treatment(s): Metformin (Oral) – forced titration Set dose (mg/d):2000 Frequency of dosing: twice a day Details of dosing regimen: 1000 mg given bid. To reduce gastrointestinal intolerance associated with metformin, a brief period of uptitration was implemented. For patients randomised to receive metformin monotherapy (500 or 1,000 mg b.i.d.), therapy was started at metformin 500 mg q.d. and increased in a blinded manner by increments of 500 mg per week to achieve a stable dose of either metformin 500 or 1,000 mg b.i.d. During the active treatment period, patients not meeting progressively stricter glycemic goals were provided glycemic rescue therapy (glibenclamide) until study completion. The glycemic rescue criteria were fasting plasma glucose (FPG) >270 mg/dl between randomisation (day 1) and week 6, FPG >240 mg/dl after weeks 6–12, and FPG >200 mg/dl after weeks 12–24. Study investigators were responsible for titration of the sulfonylurea rescue medication **(4) Placebo** N: 176 Treatment duration (wks): 24 Washout period (d): 98 Comments: Max of 14 week washout/placebo run in period (for thiazolidinedione) Treatment(s): Placebo (Oral) Details of dosing regimen: During the active treatment period, patients not meeting progressively stricter glycemic goals were provided glycemic rescue therapy (glibenclamide) until study completion. The glycemic rescue criteria were fasting plasma glucose (FPG) >270 mg/dl between randomisation (day 1) and week 6, FPG >240 mg/dl after weeks 6–12, and FPG >200 mg/dl after weeks 12–24. Study investigators were responsible for titration of the sulfonylurea rescue medication
Outcomes	**General** Data was not extracted from the open label cohort. Outcomes not extracted include fasting proinsulin, measures of insulin resistance, insulin, c-peptide, insulin AUC/glucose AUC ratios. Data not extracted from 2 trial arms (combination groups as they are dose comparisons which are outside the scope of this review). 49/176 (28%) in placebo group, 37/179 (21%) in sitagliptin 100 mg, 29/182 (16%) in metformin 500 mg bid, 26/182 (14%) metformin 1000 mg bid discontinued the study Efficacy analyses were based on the allpatients- treated (APT) population, consisting of all randomised patients who received at least one dose of study treatment and who had both a baseline and at least one postbaseline measurement. Safety and tolerability were assessed in patients who received at least one dose of study medication by review of safety parameters. Missing data were handled using the last-observation-carriedforward method. To avoid the confounding influence of glycemic rescue therapy on efficacy comparisons, efficacy data collected after initiation of rescue therapy were treated as missing. In addition, data on body weight change, hypoglycaemia incidence and GI adverse events excluded data obtained after rescue therapy initiation. 57/176 in placebo, 38/179 in sitagliptin 100mg, 31/182 in metformin 500 mg bid and 21/182 in metformin

1000 mg bid required rescue medication

Following the initial 24 week study, participants not on rescue medication continued on a 30 week extension study (data at 54 weeks) and subsequently a 50 week extension study (data at 104 weeks). Participants in the placebo group were switched to metformin in the extension study at 24 weeks, therefore data were not extracted for this group at subsequent time points.

Baseline characteristics

		Sitagliptin (100mg qd)			Metformin (500 mg bid)				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	179		53.3 (SD 10.2)	182		53.4 (SD 10.2)		
Sex (n male)	Dichotomous	179	93	(52.0%)	182	89	(48.9%)		
Duration of diabetes (yrs)	Continuous	179		4.4 (SD 4.6)	182		4.5 (SD 3.9)		
Ethnicity-White	Dichotomous	179	93	(52.0%)	182	87	(47.8%)		
Ethnicity-Black	Dichotomous	179	11	(6.1%)	182	12	(6.6%)		
Ethnicity-Asian	Dichotomous	179	6	(3.4%)	182	14	(7.7%)		
Ethnicity-Hispanic	Dichotomous	179	52	(29.1%)	182	55	(30.2%)		
Ethnicity-Other	Dichotomous	179	17	(9.5%)	182	14	(7.7%)		
Blood glucose: HbA1c (%) – 0wk	Continuous	179		8.9 (SD 1)	182		8.9 (SD 1)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	179		11.1888 (SD 2.74)	182		11.37195 (SD 2.8)		
Body weight: BMI (kg/m2)	Continuous	179		31.2 (SD 5.9)	182		32.1 (SD 6.8)		
Weight (kg) – 0wka	Continuous	179		88.05888 (SD 16.7)	182		90.59904 (SD 19.2)		
Previous blood glucose lowering drugs: Diet alone (i.e. drug naïve)	Dichotomous	179	91	(50.8%)	182	91	(50.0%)		
Oral antidiabetic medication	Dichotomous	179	88	(49.2%)	182	91	(50.0%)		
2-year follow-up (reported in Williams-Herman et al. 2010) - Full analysis set (FAS) or efficacy analysis pop Demographics: Age (years)	Continuous	52		54.1 (SD 9.1)	65		55.9 (SD 8.9)		
Sex (n male)	Dichotomous	52	30	(57.7%)	65	30	(46.2%)		
Duration of diabetes (yrs)	Continuous	52		3.7 (SD 4.9)	65		4 (SD 3.9)		
Blood glucose: HbA1c (%) – 0wk	Continuous	52		8.5 (SD 0.9)	65		8.6 (SD 0.9)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	52		9.89565 (SD 2.05)	65		10.0122 (SD 2.26)		
Body weight: BMI (kg/m2)	Continuous	52		30.3 (SD 5.5)	65		32.2 (SD 6.9)		
Weight (kg) – 0wka	Continuous	52		85.51872 (SD 15.5)	65		90.88128 (SD 19.5)		
Lipids: Total cholesterol (mmol/l) – 0wk	Continuous	47		4.923744 (SD 1.06)	59		4.962534 (SD 1.19)		
HDL cholesterol (mmol/l) – 0wk	Continuous	45		1.070604 (SD 0.197)	59		1.101636 (SD 0.222)		
Triglycerides (mmol/l) – 0wk	Continuous	47		med: 1.71608 (SD 0.546)	59		med: 2.13381 (SD 1.07)		

LDL cholesterol (mmol/l) – 0wk	Continuous	45		2.968728 (SD 0.869)	59		2.774778 (SD 0.773)		
1-year follow up APT (reported in Ref 869)									
Demographics:									
Age (years)	Continuous	106		53.5 (SD 9.1)	122		53.7 (SD 9.9)		
Sex (n male)	Dichotomous	106	55	(51.9%)	122	58	(47.5%)		
Duration of diabetes (yrs)	Continuous	106		3.9 (SD 4.6)	122		4.1 (SD 3.8)		
Blood glucose:									
HbA1c (%) – 6wk	Continuous	106		8.7 (SD 1)	122		8.7 (SD 1)		
Fasting plasma glucose (mg/dl) – 3wk	Continuous	106		183 (SD 39)	122		189 (SD 41)		
Body weight:									
BMI (kg/m2)	Continuous	106		31 (SD 6)	122		32 (SD 7)		
Weight (kg) – 0wka	Continuous	106		87.4944 (SD 16.9)	122		90.3168 (SD 19.8)		

[a] estimated from BMI assuming mean height of 1.68m

		Sitagliptin (100mg qd)			Metformin (1000 mg bid)			Δ	p
		N	k	mean	N	k	mean		
Demographics:									
Age (years)	Continuous	179		53.3 (SD 10.2)	182		53.2 (SD 9.6)		
Sex (n male)	Dichotomous	179	93	(52.0%)	182	82	(45.1%)		
Duration of diabetes (yrs)	Continuous	179		4.4 (SD 4.6)	182		4.4 (SD 4.4)		
Ethnicity-White	Dichotomous	179	93	(52.0%)	182	106	(58.2%)		
Ethnicity-Black	Dichotomous	179	11	(6.1%)	182	9	(4.9%)		
Ethnicity-Asian	Dichotomous	179	6	(3.4%)	182	10	(5.5%)		
Ethnicity-Hispanic	Dichotomous	179	52	(29.1%)	182	39	(21.4%)		
Ethnicity-Other	Dichotomous	179	17	(9.5%)	182	18	(9.9%)		
Blood glucose:									
HbA1c (%) – 0wk	Continuous	179		8.9 (SD 1)	182		8.7 (SD 0.9)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	179		11.1888 (SD 2.74)	182		10.989 (SD 2.63)		
Body weight:									
BMI (kg/m2)	Continuous	179		31.2 (SD 5.9)	182		32.2 (SD 7.1)		
Weight (kg) – 0wka	Continuous	179		88.05888 (SD 16.7)	182		90.88128 (SD 20)		
Previous blood glucose lowering drugs:									
Diet alone (i.e. drug naïve)	Dichotomous	179	91	(50.8%)	182	90	(49.5%)		
Oral antidiabetic medication	Dichotomous	179	88	(49.2%)	182	92	(50.5%)		
2-year follow-up (reported in Williams-Herman et al. 2010) - Full analysis set (FAS) or efficacy analysis pop									
Demographics:									
Age (years)	Continuous	52		54.1 (SD 9.1)	88		54.3 (SD 9.9)		
Sex (n male)	Dichotomous	52	30	(57.7%)	88	39	(44.3%)		
Duration of diabetes (yrs)	Continuous	52		3.7 (SD 4.9)	88		3.9 (SD 4)		
Blood glucose:									
HbA1c (%) – 0wk	Continuous	52		8.5 (SD 0.9)	88		8.5 (SD 0.8)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	52		9.89565 (SD 2.05)	88		10.30635 (SD 2.5)		

Body weight: BMI (kg/m2)	Continuous	52		30.3 (SD 5.5)	88		31.9 (SD 7.1)		
Weight (kg) – 0wka	Continuous	52		85.51872 (SD 15.5)	88		90.03456 (SD 20)		
Lipids: Total cholesterol (mmol/l) – 0wk	Continuous	47		4.923744 (SD 1.06)	83		4.877196 (SD 1.09)		
HDL cholesterol (mmol/l) – 0wk	Continuous	45		1.070604 (SD 0.197)	83		1.158528 (SD 0.287)		
Triglycerides (mmol/l) – 0wk	Continuous	47		med: 1.71608 (SD 0.546)	83		med: 1.70479 (SD 1.2)		
LDL cholesterol (mmol/l) – 0wk	Continuous	45		2.968728 (SD 0.869)	82		2.743746 (SD 0.918)		
1-year follow up APT (reported in Ref 869) Demographics: Age (years)	Continuous	106		53.5 (SD 9.1)	137		54.2 (SD 9.5)		
Sex (n male)	Dichotomous	106	55	(51.9%)	137	62	(45.3%)		
Duration of diabetes (yrs)	Continuous	106		3.9 (SD 4.6)	137		4.1 (SD 4)		
Blood glucose: HbA1c (%) – 6wk	Continuous	106		8.7 (SD 1)	137		8.5 (SD 0.8)		
Fasting plasma glucose (mg/dl) – 3wk	Continuous	106		183 (SD 39)	137		188 (SD 43)		
Body weight: BMI (kg/m2)	Continuous	106		31 (SD 6)	137		32 (SD 7)		
Weight (kg) – 0wka	Continuous	106		87.4944 (SD 16.9)	137		90.3168 (SD 19.8)		

[a] estimated from BMI assuming mean height of 1.68m

		Sitagliptin (100mg qd)			Placebo				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	179		53.3 (SD 10.2)	176		53.6 (SD 10)		
Sex (n male)	Dichotomous	179	93	(52.0%)	176	93	(52.8%)		
Duration of diabetes (yrs)	Continuous	179		4.4 (SD 4.6)	176		4.6 (SD 4.9)		
Ethnicity-White	Dichotomous	179	93	(52.0%)	176	81	(46.0%)		
Ethnicity-Black	Dichotomous	179	11	(6.1%)	176	17	(9.7%)		
Ethnicity-Asian	Dichotomous	179	6	(3.4%)	176	12	(6.8%)		
Ethnicity-Hispanic	Dichotomous	179	52	(29.1%)	176	47	(26.7%)		
Ethnicity-Other	Dichotomous	179	17	(9.5%)	176	19	(10.8%)		
Blood glucose: HbA1c (%) – 0wk	Continuous	179		8.9 (SD 1)	176		8.7 (SD 1)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	179		11.1888 (SD 2.74)	176		10.9335 (SD 2.61)		
Body weight: BMI (kg/m2)	Continuous	179		31.2 (SD 5.9)	176		32.5 (SD 6.7)		
Weight (kg) – 0wka	Continuous	179		88.05888 (SD 16.7)	176		91.728 (SD 18.9)		
Previous blood glucose lowering drugs: Diet alone (i.e. drug naïve)	Dichotomous	179	91	(50.8%)	176	88	(50.0%)		
Oral antidiabetic medication	Dichotomous	179	88	(49.2%)	176	88	(50.0%)		

[a] estimated from BMI assuming mean height of 1.68m

		Metformin (500 mg bid)			Metformin (1000 mg bid)				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	182		53.4 (SD 10.2)	182		53.2 (SD 9.6)		
Sex (n male)	Dichotomous	182	89	(48.9%)	182	82	(45.1%)		
Duration of diabetes (yrs)	Continuous	182		4.5 (SD 3.9)	182		4.4 (SD 4.4)		
Ethnicity-White	Dichotomous	182	87	(47.8%)	182	106	(58.2%)		
Ethnicity-Black	Dichotomous	182	12	(6.6%)	182	9	(4.9%)		
Ethnicity-Asian	Dichotomous	182	14	(7.7%)	182	10	(5.5%)		
Ethnicity-Hispanic	Dichotomous	182	55	(30.2%)	182	39	(21.4%)		
Ethnicity-Other	Dichotomous	182	14	(7.7%)	182	18	(9.9%)		
Blood glucose: HbA1c (%) – 0wk	Continuous	182		8.9 (SD 1)	182		8.7 (SD 0.9)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	182		11.37195 (SD 2.8)	182		10.989 (SD 2.63)		
Body weight: BMI (kg/m2)	Continuous	182		32.1 (SD 6.8)	182		32.2 (SD 7.1)		
Weight (kg) – 0wka	Continuous	182		90.59904 (SD 19.2)	182		90.88128 (SD 20)		
Previous blood glucose lowering drugs: Diet alone (i.e. drug naïve)	Dichotomous	182	91	(50.0%)	182	90	(49.5%)		
Oral antidiabetic medication	Dichotomous	182	91	(50.0%)	182	92	(50.5%)		
2-year follow-up (reported in Williams-Herman et al. 2010) - Full analysis set (FAS) or efficacy analysis pop Demographics: Age (years)	Continuous	65		55.9 (SD 8.9)	88		54.3 (SD 9.9)		
Sex (n male)	Dichotomous	65	30	(46.2%)	88	39	(44.3%)		
Duration of diabetes (yrs)	Continuous	65		4 (SD 3.9)	88		3.9 (SD 4)		
Blood glucose: HbA1c (%) – 0wk	Continuous	65		8.6 (SD 0.9)	88		8.5 (SD 0.8)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	65		10.0122 (SD 2.26)	88		10.30635 (SD 2.5)		
Body weight: BMI (kg/m2)	Continuous	65		32.2 (SD 6.9)	88		31.9 (SD 7.1)		
Weight (kg) – 0wka	Continuous	65		90.88128 (SD 19.5)	88		90.03456 (SD 20)		
Lipids: Total cholesterol (mmol/l) – 0wk	Continuous	59		4.962534 (SD 1.19)	83		4.877196 (SD 1.09)		
HDL cholesterol (mmol/l) – 0wk	Continuous	59		1.101636 (SD 0.222)	83		1.158528 (SD 0.287)		
Triglycerides (mmol/l) – 0wk	Continuous	59		med: 2.13381 (SD 1.07)	83		med: 1.70479 (SD 1.2)		
LDL cholesterol (mmol/l) – 0wk	Continuous	59		2.774778 (SD 0.773)	82		2.743746 (SD 0.918)		

1-year follow up APT (reported in Ref 869)									
Demographics: Age (years)	Continuous	122		53.7 (SD 9.9)	137		54.2 (SD 9.5)		
Sex (n male)	Dichotomous	122	58	(47.5%)	137	62	(45.3%)		
Duration of diabetes (yrs)	Continuous	122		4.1 (SD 3.8)	137		4.1 (SD 4)		
Blood glucose: HbA1c (%) – 6wk	Continuous	122		8.7 (SD 1)	137		8.5 (SD 0.8)		
Fasting plasma glucose (mg/dl) – 3wk	Continuous	122		189 (SD 41)	137		188 (SD 43)		
Body weight: BMI (kg/m2)	Continuous	122		32 (SD 7)	137		32 (SD 7)		
Weight (kg) – 0wka	Continuous	122		90.3168 (SD 19.8)	137		90.3168 (SD 19.8)		

[a] estimated from BMI assuming mean height of 1.68m

		Metformin (500 mg bid)			Placebo				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	182		53.4 (SD 10.2)	176		53.6 (SD 10)		
Sex (n male)	Dichotomous	182	89	(48.9%)	176	93	(52.8%)		
Duration of diabetes (yrs)	Continuous	182		4.5 (SD 3.9)	176		4.6 (SD 4.9)		
Ethnicity-White	Dichotomous	182	87	(47.8%)	176	81	(46.0%)		
Ethnicity-Black	Dichotomous	182	12	(6.6%)	176	17	(9.7%)		
Ethnicity-Asian	Dichotomous	182	14	(7.7%)	176	12	(6.8%)		
Ethnicity-Hispanic	Dichotomous	182	55	(30.2%)	176	47	(26.7%)		
Ethnicity-Other	Dichotomous	182	14	(7.7%)	176	19	(10.8%)		
Blood glucose: HbA1c (%) – 0wk	Continuous	182		8.9 (SD 1)	176		8.7 (SD 1)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	182		11.37195 (SD 2.8)	176		10.9335 (SD 2.61)		
Body weight: BMI (kg/m2)	Continuous	182		32.1 (SD 6.8)	176		32.5 (SD 6.7)		
Weight (kg) – 0wka	Continuous	182		90.59904 (SD 19.2)	176		91.728 (SD 18.9)		
Previous blood glucose lowering drugs: Diet alone (i.e. drug naïve)	Dichotomous	182	91	(50.0%)	176	88	(50.0%)		
Oral antidiabetic medication	Dichotomous	182	91	(50.0%)	176	88	(50.0%)		

[a] estimated from BMI assuming mean height of 1.68m

		Metformin (1000 mg bid)			Placebo				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	182		53.2 (SD 9.6)	176		53.6 (SD 10)		
Sex (n male)	Dichotomous	182	82	(45.1%)	176	93	(52.8%)		
Duration of diabetes (yrs)	Continuous	182		4.4 (SD 4.4)	176		4.6 (SD 4.9)		
Ethnicity-White	Dichotomous	182	106	(58.2%)	176	81	(46.0%)		
Ethnicity-Black	Dichotomous	182	9	(4.9%)	176	17	(9.7%)		
Ethnicity-Asian	Dichotomous	182	10	(5.5%)	176	12	(6.8%)		
Ethnicity-Hispanic	Dichotomous	182	39	(21.4%)	176	47	(26.7%)		
Ethnicity-Other	Dichotomous	182	18	(9.9%)	176	19	(10.8%)		

Blood glucose: HbA1c (%) – 0wk	Continuous	182		8.7 (SD 0.9)	176		8.7 (SD 1)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	182		10.989 (SD 2.63)	176		10.9335 (SD 2.61)		
Body weight: BMI (kg/m2)	Continuous	182		32.2 (SD 7.1)	176		32.5 (SD 6.7)		
Weight (kg) – 0wka	Continuous	182		90.88128 (SD 20)	176		91.728 (SD 18.9)		
Previous blood glucose lowering drugs: Diet alone (i.e. drug naïve)	Dichotomous	182	90	(49.5%)	176	88	(50.0%)		
Oral antidiabetic medication	Dichotomous	182	92	(50.5%)	176	88	(50.0%)		

[a] estimated from BMI assuming mean height of 1.68m

Results

		Sitagliptin (100mg qd)			Metformin (500 mg bid)				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 12wka	Continuous	175		8.2 (SD 0.661)	178		8.07 (SD 0.667)		
HbA1c (%) – 24wk	Continuous	175		8.18 (SD 1.45)	178		8.04 (SD 1.36)		
HbA1c (%) – 24wkb	Mean change	175		-0.66 (SD 1.16)	178		-0.82 (SD 1.1)		
HbA1c < 7% or <=7% – 24wk	Dichotomous	175	35	(20.0%)	178	41	(23.0%)		
Hba1c <6.5% – 24wk	Dichotomous	175	18	(10.3%)	178	16	(9.0%)		
Fasting plasma glucose (mmol/l) – 12wkc	Mean change	178		-1.11012 (SD 1.48)	179		-1.554168 (SD 1.49)		
Fasting plasma glucose (mmol/l) – 12wk	Continuous	178		10.1798004 (SD 3.04)	179		9.7579548 (SD 3.11)		
Fasting plasma glucose (mmol/l) – 24wk	Mean change	178		-0.97125 (SD 2.5)	179		-1.51515 (SD 2.56)		
2-h post prandial glucose (mmol/l) – 24wk	Mean change	136		-2.88045 (SD 3.43)	141		-2.9637 (SD 3.43)		
Hypoglycaemic events: All hypoglycaemic events (no patients) – 24wk	Dichotomous	179	1	(0.6%)	182	1	(0.5%)		
Adverse events: GI: nausea – 24wk	Dichotomous	179	2	(1.1%)	182	5	(2.7%)		
Any adverse event(s) – 24wk	Dichotomous	179	96	(53.6%)	182	101	(55.5%)		
Any serious adverse event(s) – 24wk	Dichotomous	179	9	(5.0%)	182	4	(2.2%)		
Serious AE drug related – 24wk	Dichotomous	179	0	(0.0%)	182	0	(0.0%)		
Study drug-related adverse event – 24wk	Dichotomous	179	12	(6.7%)	182	21	(11.5%)		
Death – 24wk	Dichotomous	179	0	(0.0%)	182	0	(0.0%)		
Gastrointestinal disorders (any) – 24wk	Dichotomous	179	27	(15.1%)	182	29	(15.9%)		
GI: diarrhoea – 24wk	Dichotomous	179	5	(2.8%)	182	9	(4.9%)		
GI: vomiting – 24wk	Dichotomous	179	0	(0.0%)	182	0	(0.0%)		
GI: abdominal pain – 24wk	Dichotomous	179	6	(3.4%)	182	5	(2.7%)		
Dropouts: Total dropouts – 24wk	Dichotomous	179	37	(20.7%)	182	29	(15.9%)		
Dropout due to AEs – 24wk	Dichotomous	179	8	(4.5%)	182	4	(2.2%)		
drop out due to drug related AE – 24wk	Dichotomous	179	0	(0.0%)	182	2	(1.1%)		
drop out due to SAE – 24wk	Dichotomous	179	4	(2.2%)	182	2	(1.1%)		
drop out due to drug related SAE – 24wk	Dichotomous	179	0	(0.0%)	182	0	(0.0%)		

dropout due to laboratory AE – 24wk	Dichotomous	179	2	(1.1%)	182	0	(0.0%)		
Drop out due to unsatisfactory effect – 24wk	Dichotomous	179	3	(1.7%)	182	5	(2.7%)		
Other medication:									
Taking rescue medication – 24wk	Dichotomous	179	38	(21.2%)	182	31	(17.0%)		
2-year follow-up (reported in Williams-Herman et al. 2010)									
Dropouts:									
Total dropouts – 24wk	Dichotomous	179	114	(63.7%)	182	102	(56.0%)		
Drop out due to unsatisfactory effect – 104wk	Dichotomous	179	37	(20.7%)	182	29	(15.9%)		
2-year follow-up (reported in Williams-Herman et al. 2010) - Safety population									
Hypoglycaemic events:									
All hypoglycaemic events (no patients) – 104wk	Dichotomous	179	2	(1.1%)	182	3	(1.6%)		
Adverse events:									
GI: nausea – 104wk	Dichotomous	179	2	(1.1%)	182	6	(3.3%)		
Any adverse event(s) – 104wk	Dichotomous	179	108	(60.3%)	182	117	(64.3%)		
Any serious adverse event(s) – 104wk	Dichotomous	179	13	(7.3%)	182	7	(3.8%)		
Serious AE drug related – 104wk	Dichotomous	179	0	(0.0%)	182	0	(0.0%)		
Study drug-related adverse event – 104wk	Dichotomous	179	17	(9.5%)	182	27	(14.8%)		
Death – 104wk	Dichotomous	179	0	(0.0%)	182	1	(0.5%)		
Gastrointestinal disorders (any) – 104wk	Dichotomous	179	37	(20.7%)	182	38	(20.9%)		
GI: diarrhoea – 104wk	Dichotomous	179	8	(4.5%)	182	14	(7.7%)		
GI: vomiting – 104wk	Dichotomous	179	1	(0.6%)	182	0	(0.0%)		
GI: abdominal pain – 104wk	Dichotomous	179	9	(5.0%)	182	7	(3.8%)		
Dropouts:									
Dropout due to AEs – 104wk	Dichotomous	179	14	(7.8%)	182	12	(6.6%)		
drop out due to drug related AE – 104wk	Dichotomous	179	0	(0.0%)	182	2	(1.1%)		
drop out due to SAE – 104wk	Dichotomous	179	4	(2.2%)	182	5	(2.7%)		
drop out due to drug related SAE – 104wk	Dichotomous	179	0	(0.0%)	182	0	(0.0%)		
2-year follow-up (reported in Williams-Herman et al. 2010) - Baseline Hba1c <8%									
Blood glucose:									
HbA1c (%) – 104wkc	Mean change	17		-0.46 (SD 0.618)	20		-0.41 (SD 0.447)		
2-year follow-up (reported in Williams-Herman et al. 2010) - baseline Hba1c >=8 to <9%									
Blood glucose:									
HbA1c (%) – 104wkc	Mean change	19		-0.99 (SD 0.872)	24		-1.05 (SD 0.931)		
2-year follow-up (reported in Williams-Herman et al. 2010) - baseline Hba1c >=9%									
Blood glucose:									
HbA1c (%) – 104wkc	Mean change	14		-2.2 (SD 0.673)	20		-1.84 (SD 0.805)		
2-year follow-up (reported in Williams-Herman et al. 2010) - Full analysis set (FAS) or efficacy analysis pop									
Blood glucose:									
HbA1c (%) – 104wk	Continuous	50		7.4 (SD 0.7)	64		7.5 (SD 0.7)		
HbA1c (%) – 104wkb	Mean change	50		-1.2 (SD 0.722)	64		-1.1 (SD 0.816)		

HbA1c < 7% or <=7% – 104wk	Dichotomous	50	16	(32.0%)	64	18	(28.1%)		
Fasting plasma glucose (mg/dl) – 104wk	Continuous	50		156 (SD 36.4)	64		141.3 (SD 30.3)		
Fasting plasma glucose (mg/dl) – 104wkb	Mean change	50		-26.8 (SD 33.9)	64		-41.4 (SD 34.3)		
Body weight:									
Weight (kg) – 104wkb	Mean change	50		0.5 (SD 4.33)	59		-0.8 (SD 4.31)		
Lipids:									
Total cholesterol (mmol/l) – 104wk	Percentage change from baseline	47		0.015516 (SD 0.457)	59		-0.031032 (SD 0.457)		
Total cholesterol (mmol/l) – 104wk	Continuous	47		4.93926 (SD 1.19)	59		4.804788 (SD 0.954)		
HDL cholesterol (mmol/l) – 104wk	Percentage change from baseline	45		0.16809 (SD 0.478)	59		0.201708 (SD 0.476)		
HDL cholesterol (mmol/l) – 104wk	Continuous	45		1.143012 (SD 0.253)	59		1.18956 (SD 0.287)		
Triglycerides (mmol/l) – 104wk	Percentage change from baseline	47	d	med: 0.012419	59	e	med: 0.029354		
Triglycerides (mmol/l) – 104wk	Continuous	47		med: 1.74995 (SD 0.82)	59		med: 2.00962 (SD 1.13)		
LDL cholesterol (mmol/l) – 104wk	Percentage change from baseline	45		-0.054306 (SD 0.805)	59		-0.124128 (SD 0.811)		
LDL cholesterol (mmol/l) – 104wk	Continuous	45		2.823912 (SD 0.954)	59		2.622204 (SD 0.809)		
1-year follow up (reported in Ref 869)									
Dropouts:									
Total dropouts – 54wk	Dichotomous	179	57	(31.8%)	182	56	(30.8%)		
Dropout due to AEs – 54wk	Dichotomous	179	12	(6.7%)	182	9	(4.9%)		
1-year follow up APT (reported in Ref 869)									
Blood glucose:									
HbA1c (%) – 54wk	Continuous	106		7.8 (SD 1.2)	117		7.7 (SD 0.9)		
HbA1c (%) – 54wkb	Mean change	106		-0.8 (SD 1.05)	117		-1 (SD 1.1)		
Fasting plasma glucose (mg/dl) – 54wkb	Mean change	106		-16 (SD 37.8)	117		-29 (SD 38.1)		
Fasting plasma glucose (mg/dl) – 54wk	Continuous	106		171.2 (SD 44.2)	117		159.8 (SD 40.9)		
Hypoglycaemic events:									
All hypoglycaemic events (no patients) – 54wk	Dichotomous	179	2	(1.1%)	182	2	(1.1%)		
Adverse events:									
GI: nausea – 54wk	Dichotomous	179	2	(1.1%)	182	6	(3.3%)		

[a] estimated from graph; least square means, SD calculated from SE
[b] SD calculated from reported 95% CI
[c] estimated from graph
[d] 95% CI -14.3 to 16.5
[e] 95% CI -7.4 to 12.7

		Sitagliptin (100mg qd)			Metformin (1000 mg bid)				
		N	k	mean	N	k	mean	Δ	p
Blood glucose:									
HbA1c (%) – 12wka	Continuous	175		8.2 (SD 0.661)	177		7.85 (SD 0.665)		

HbA1c (%) – 24wkb	Mean change	175		-0.66 (SD 1.16)	177		-1.13 (SD 1.1)		
HbA1c (%) – 24wk	Continuous	175		8.18 (SD 1.45)	177		7.58 (SD 1.27)		
HbA1c < 7% or <=7% – 24wk	Dichotomous	175	35	(20.0%)	177	68	(38.4%)		
Hba1c <6.5% – 24wk	Dichotomous	175	18	(10.3%)	177	36	(20.3%)		
Fasting plasma glucose (mmol/l) – 12wkc	Mean change	178		-1.11012 (SD 1.48)	179		-1.720686 (SD 1.49)		
Fasting plasma glucose (mmol/l) – 12wk	Continuous	178		10.1798004 (SD 3.04)	179		9.380514 (SD 3.6)		
Fasting plasma glucose (mmol/l) – 24wk	Mean change	178		-0.97125 (SD 2.5)	179		-1.62615 (SD 2.52)		
2-h post prandial glucose (mmol/l) – 24wk	Mean change	136		-2.88045 (SD 3.43)	138		-4.329 (SD 3.43)		
Hypoglycaemic events:									
All hypoglycaemic events (no patients) – 24wk	Dichotomous	179	1	(0.6%)	182	2	(1.1%)		
Adverse events:									
GI: nausea – 24wk	Dichotomous	179	2	(1.1%)	182	15	(8.2%)		
Any adverse event(s) – 24wk	Dichotomous	179	96	(53.6%)	182	113	(62.1%)		
Any serious adverse event(s) – 24wk	Dichotomous	179	9	(5.0%)	182	2	(1.1%)		
Serious AE drug related – 24wk	Dichotomous	179	0	(0.0%)	182	0	(0.0%)		
Study drug-related adverse event – 24wk	Dichotomous	179	12	(6.7%)	182	30	(16.5%)		
Death – 24wk	Dichotomous	179	0	(0.0%)	182	0	(0.0%)		
Gastrointestinal disorders (any) – 24wk	Dichotomous	179	27	(15.1%)	182	46	(25.3%)		
GI: diarrhoea – 24wk	Dichotomous	179	5	(2.8%)	182	19	(10.4%)		
GI: vomiting – 24wk	Dichotomous	179	0	(0.0%)	182	2	(1.1%)		
GI: abdominal pain – 24wk	Dichotomous	179	6	(3.4%)	182	9	(4.9%)		
Dropouts:									
Total dropouts – 24wk	Dichotomous	179	37	(20.7%)	182	26	(14.3%)		
Dropout due to AEs – 24wk	Dichotomous	179	8	(4.5%)	182	5	(2.7%)		
drop out due to drug related AE – 24wk	Dichotomous	179	0	(0.0%)	182	5	(2.7%)		
drop out due to SAE – 24wk	Dichotomous	179	4	(2.2%)	182	0	(0.0%)		
drop out due to drug related SAE – 24wk	Dichotomous	179	0	(0.0%)	182	0	(0.0%)		
dropout due to laboratory AE – 24wk	Dichotomous	179	2	(1.1%)	182	0	(0.0%)		
Drop out due to unsatisfactory effect – 24wk	Dichotomous	179	3	(1.7%)	182	3	(1.6%)		
Other medication:									
Taking rescue medication – 24wk	Dichotomous	179	38	(21.2%)	182	21	(11.5%)		
2-year follow-up (reported in Williams-Herman et al. 2010)									
Dropouts:									
Total dropouts – 24wk	Dichotomous	179	114	(63.7%)	182	87	(47.8%)		
Drop out due to unsatisfactory effect – 104wk	Dichotomous	179	37	(20.7%)	182	20	(11.0%)		
2-year follow-up (reported in Williams-Herman et al. 2010) - Safety population									
Hypoglycaemic events:									
All hypoglycaemic events (no patients) – 104wk	Dichotomous	179	2	(1.1%)	182	4	(2.2%)		
Adverse events:									
GI: nausea – 104wk	Dichotomous	179	2	(1.1%)	182	19	(10.4%)		

Any adverse event(s) – 104wk	Dichotomous	179	108	(60.3%)	182	135	(74.2%)		
Any serious adverse event(s) – 104wk	Dichotomous	179	13	(7.3%)	182	9	(4.9%)		
Serious AE drug related – 104wk	Dichotomous	179	0	(0.0%)	182	0	(0.0%)		
Study drug-related adverse event – 104wk	Dichotomous	179	17	(9.5%)	182	35	(19.2%)		
Death – 104wk	Dichotomous	179	0	(0.0%)	182	0	(0.0%)		
Gastrointestinal disorders (any) – 104wk	Dichotomous	179	37	(20.7%)	182	60	(33.0%)		
GI: diarrhoea – 104wk	Dichotomous	179	8	(4.5%)	182	23	(12.6%)		
GI: vomiting – 104wk	Dichotomous	179	1	(0.6%)	182	8	(4.4%)		
GI: abdominal pain – 104wk	Dichotomous	179	9	(5.0%)	182	12	(6.6%)		
Dropouts:									
Dropout due to AEs – 104wk	Dichotomous	179	14	(7.8%)	182	13	(7.1%)		
drop out due to drug related AE – 104wk	Dichotomous	179	0	(0.0%)	182	5	(2.7%)		
drop out due to SAE – 104wk	Dichotomous	179	4	(2.2%)	182	1	(0.5%)		
drop out due to drug related SAE – 104wk	Dichotomous	179	0	(0.0%)	182	0	(0.0%)		
2-year follow-up (reported in Williams-Herman et al. 2010) - Baseline Hba1c <8%									
Blood glucose:									
HbA1c (%) – 104wkc	Mean change	17		-0.46 (SD 0.618)	27		-0.8 (SD 0.52)		
2-year follow-up (reported in Williams-Herman et al. 2010) - baseline Hba1c >=8 to <9%									
Blood glucose:									
HbA1c (%) – 104wkc	Mean change	19		-0.99 (SD 0.872)	34		-1.05 (SD 1.11)		
2-year follow-up (reported in Williams-Herman et al. 2010) - baseline Hba1c >=9%									
Blood glucose:									
HbA1c (%) – 104wkc	Mean change	14		-2.2 (SD 0.673)	26		-2.02 (SD 0.918)		
2-year follow-up (reported in Williams-Herman et al. 2010) - Full analysis set (FAS) or efficacy analysis pop									
Blood glucose:									
HbA1c (%) – 104wkb	Mean change	50		-1.2 (SD 0.722)	87		-1.3 (SD 0.952)		
HbA1c (%) – 104wk	Continuous	50		7.4 (SD 0.7)	87		7.2 (SD 0.9)		
HbA1c < 7% or <=7% – 104wk	Dichotomous	50	16	(32.0%)	87	39d	(44.8%)		
Fasting plasma glucose (mg/dl) – 104wkb	Mean change	50		-26.8 (SD 33.9)	87		-43.2 (SD 33.8)		
Fasting plasma glucose (mg/dl) – 104wk	Continuous	50		156 (SD 36.4)	87		140.4 (SD 40)		
Lipids:									
Total cholesterol (mmol/l) – 104wk	Percentage change from baseline	47		0.015516 (SD 0.457)	83		0.015516 (SD 0.446)		
Total cholesterol (mmol/l) – 104wk	Continuous	47		4.93926 (SD 1.19)	83		4.86168 (SD 1.19)		
HDL cholesterol (mmol/l) – 104wk	Percentage change from baseline	45		0.16809 (SD 0.478)	83		0.243084 (SD 0.469)		
HDL cholesterol (mmol/l) – 104wk	Continuous	45		1.143012 (SD 0.253)	83		1.249038 (SD 0.321)		
Triglycerides (mmol/l) – 104wk	Percentage change from baseline	47	e	med: 0.012419	83	f	med: -0.029354		

Triglycerides (mmol/l) – 104wk	Continuous	47		med: 1.74995 (SD 0.82)	83		med: 1.90801 (SD 1.3)		
LDL cholesterol (mmol/l) – 104wk	Percentage change from baseline	45		-0.054306 (SD 0.805)	82		0.02586 (SD 0.812)		
LDL cholesterol (mmol/l) – 104wk	Continuous	45		2.823912 (SD 0.954)	82		2.645478 (SD 0.962)		
1-year follow up (reported in Ref 869)									
Dropouts:									
Total dropouts – 54wk	Dichotomous	179	57	(31.8%)	182	46	(25.3%)		
Dropout due to AEs – 54wk	Dichotomous	179	12	(6.7%)	182	11	(6.0%)		
1-year follow up APT (reported in Ref 869)									
Blood glucose:									
HbA1c (%) – 54wk	Continuous	106		7.8 (SD 1.2)	134		7.3 (SD 1)		
HbA1c (%) – 54wkb	Mean change	106		-0.8 (SD 1.05)	134		-1.3 (SD 1.18)		
Fasting plasma glucose (mg/dl) – 54wkb	Mean change	106		-16 (SD 37.8)	134		-39.6 (SD 37.8)		
Fasting plasma glucose (mg/dl) – 54wk	Continuous	106		171.2 (SD 44.2)	134		148.9 (SD 40.5)		
Hypoglycaemic events:									
All hypoglycaemic events (no patients) – 54wk	Dichotomous	179	2	(1.1%)	182	2	(1.1%)		
Adverse events:									
GI: nausea – 54wk	Dichotomous	179	2	(1.1%)	182	18	(9.9%)		

[a] estimated from graph; least square means, SD calculated from SE
[b] SD calculated from reported 95% CI
[c] estimated from graph
[d] approximated to nearest integer (percentages only presented in text)
[e] 95% CI -14.3 to 16.5
[f] 95% CI -13.7 to 8.4

		Sitagliptin (100mg qd)			Placebo				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Blood glucose:									
HbA1c (%) – 12wka	Continuous	175		8.2 (SD 0.661)	165		8.95 (SD 0.771)		
HbA1c (%) – 24wk	Continuous	175		8.18 (SD 1.45)	165		8.88 (SD 1.47)		
HbA1c (%) – 24wkb	Mean change	175		-0.66 (SD 1.16)	165		0.17 (SD 1.15)	MD=-0.830 (CI: -1.060, -0.600)	<=0.001
HbA1c < 7% or <=7% – 24wk	Dichotomous	175	35	(20.0%)	165	15	(9.1%)		<0.001
Hba1c <6.5% – 24wk	Dichotomous	175	18	(10.3%)	165	4	(2.4%)		<=0.005
Fasting plasma glucose (mmol/l) – 12wk	Continuous	178		10.1798004 (SD 3.04)	169		11.3010216 (SD 3.39)		
Fasting plasma glucose (mmol/l) – 12wkc	Mean change	178		-1.11012 (SD 1.48)	169		0.333036 (SD 1.8)		
Fasting plasma glucose (mmol/l) – 24wk	Mean change	178		-0.97125 (SD 2.5)	169		0.3219 (SD 2.55)	MD=-1.293 (CI: -1.820, -0.766)	<=0.001

2-h post prandial glucose (mmol/l) – 24wk	Mean change	136		-2.88045 (SD 3.43)	129		0.01665 (SD 3.44)	MD=-2.897 (CI: -3.724, -2.070)	<=0.001
Hypoglycaemic events: All hypoglycaemic events (no patients) – 24wk	Dichotomous	179	1	(0.6%)	176	1	(0.6%)		
Adverse events: GI: nausea – 24wk	Dichotomous	179	2	(1.1%)	176	2	(1.1%)		
Any adverse event(s) – 24wk	Dichotomous	179	96	(53.6%)	176	89	(50.6%)		
Any serious adverse event(s) – 24wk	Dichotomous	179	9	(5.0%)	176	10	(5.7%)		
Serious AE drug related – 24wk	Dichotomous	179	0	(0.0%)	176	1	(0.6%)		
Study drug-related adverse event – 24wk	Dichotomous	179	12	(6.7%)	176	17	(9.7%)		
Death – 24wk	Dichotomous	179	0	(0.0%)	176	1	(0.6%)		
Gastrointestinal disorders (any) – 24wk	Dichotomous	179	27	(15.1%)	176	19	(10.8%)		
GI: diarrhoea – 24wk	Dichotomous	179	5	(2.8%)	176	7	(4.0%)		
GI: vomiting – 24wk	Dichotomous	179	0	(0.0%)	176	1	(0.6%)		
GI: abdominal pain – 24wk	Dichotomous	179	6	(3.4%)	176	4	(2.3%)		
Dropouts: Total dropouts – 24wk	Dichotomous	179	37	(20.7%)	176	49	(27.8%)		
Dropout due to AEs – 24wk	Dichotomous	179	8	(4.5%)	176	9	(5.1%)		
drop out due to drug related AE – 24wk	Dichotomous	179	0	(0.0%)	176	2	(1.1%)		
drop out due to SAE – 24wk	Dichotomous	179	4	(2.2%)	176	5	(2.8%)		
drop out due to drug related SAE – 24wk	Dichotomous	179	0	(0.0%)	176	1	(0.6%)		
dropout due to laboratory AE – 24wk	Dichotomous	179	2	(1.1%)	176	2	(1.1%)		
Drop out due to unsatisfactory effect – 24wk	Dichotomous	179	3	(1.7%)	176	12	(6.8%)		
Other medication: Taking rescue medication – 24wk	Dichotomous	179	38	(21.2%)	176	57	(32.4%)		

[a] estimated from graph; least square means, SD calculated from SE
[b] SD calculated from reported 95% CI
[c] estimated from graph

		Metformin (500 mg bid)			Metformin (1000 mg bid)				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 12wka	Continuous	178		8.07 (SD 0.667)	177		7.85 (SD 0.665)		
HbA1c (%) – 24wkb	Mean change	178		-0.82 (SD 1.1)	177		-1.13 (SD 1.1)		
HbA1c (%) – 24wk	Continuous	178		8.04 (SD 1.36)	177		7.58 (SD 1.27)		
HbA1c < 7% or <=7% – 24wk	Dichotomous	178	41	(23.0%)	177	68	(38.4%)		
Hba1c <6.5% – 24wk	Dichotomous	178	16	(9.0%)	177	36	(20.3%)		

Fasting plasma glucose (mmol/l) – 12wkc	Mean change	179		-1.554168 (SD 1.49)	179		-1.720686 (SD 1.49)		
Fasting plasma glucose (mmol/l) – 12wk	Continuous	179		9.7579548 (SD 3.11)	179		9.380514 (SD 3.6)		
Fasting plasma glucose (mmol/l) – 24wk	Mean change	179		-1.51515 (SD 2.56)	179		-1.62615 (SD 2.52)		
2-h post prandial glucose (mmol/l) – 24wk	Mean change	141		-2.9637 (SD 3.43)	138		-4.329 (SD 3.43)		
Hypoglycaemic events:									
All hypoglycaemic events (no patients) – 24wk	Dichotomous	182	1	(0.5%)	182	2	(1.1%)		
Adverse events:									
GI: nausea – 24wk	Dichotomous	182	5	(2.7%)	182	15	(8.2%)		
Any adverse event(s) – 24wk	Dichotomous	182	101	(55.5%)	182	113	(62.1%)		
Any serious adverse event(s) – 24wk	Dichotomous	182	4	(2.2%)	182	2	(1.1%)		
Serious AE drug related – 24wk	Dichotomous	182	0	(0.0%)	182	0	(0.0%)		
Study drug-related adverse event – 24wk	Dichotomous	182	21	(11.5%)	182	30	(16.5%)		
Death – 24wk	Dichotomous	182	0	(0.0%)	182	0	(0.0%)		
Gastrointestinal disorders (any) – 24wk	Dichotomous	182	29	(15.9%)	182	46	(25.3%)		
GI: diarrhoea – 24wk	Dichotomous	182	9	(4.9%)	182	19	(10.4%)		
GI: vomiting – 24wk	Dichotomous	182	0	(0.0%)	182	2	(1.1%)		
GI: abdominal pain – 24wk	Dichotomous	182	5	(2.7%)	182	9	(4.9%)		
Dropouts:									
Total dropouts – 24wk	Dichotomous	182	29	(15.9%)	182	26	(14.3%)		
Dropout due to AEs – 24wk	Dichotomous	182	4	(2.2%)	182	5	(2.7%)		
drop out due to drug related AE – 24wk	Dichotomous	182	2	(1.1%)	182	5	(2.7%)		
drop out due to SAE – 24wk	Dichotomous	182	2	(1.1%)	182	0	(0.0%)		
drop out due to drug related SAE – 24wk	Dichotomous	182	0	(0.0%)	182	0	(0.0%)		
dropout due to laboratory AE – 24wk	Dichotomous	182	0	(0.0%)	182	0	(0.0%)		
Drop out due to unsatisfactory effect – 24wk	Dichotomous	182	5	(2.7%)	182	3	(1.6%)		
Other medication:									
Taking rescue medication – 24wk	Dichotomous	182	31	(17.0%)	182	21	(11.5%)		
2-year follow-up (reported in Williams-Herman et al. 2010)									
Dropouts:									
Total dropouts – 24wk	Dichotomous	182	102	(56.0%)	182	87	(47.8%)		
Drop out due to unsatisfactory effect – 104wk	Dichotomous	182	29	(15.9%)	182	20	(11.0%)		
2-year follow-up (reported in Williams-Herman et al. 2010) - Safety population									
Hypoglycaemic events:									
All hypoglycaemic events (no patients) – 104wk	Dichotomous	182	3	(1.6%)	182	4	(2.2%)		
Adverse events:									
GI: nausea – 104wk	Dichotomous	182	6	(3.3%)	182	19	(10.4%)		
Any adverse event(s) – 104wk	Dichotomous	182	117	(64.3%)	182	135	(74.2%)		
Any serious adverse event(s) – 104wk	Dichotomous	182	7	(3.8%)	182	9	(4.9%)		
Serious AE drug related – 104wk	Dichotomous	182	0	(0.0%)	182	0	(0.0%)		
Study drug-related adverse event – 104wk	Dichotomous	182	27	(14.8%)	182	35	(19.2%)		

Death – 104wk	Dichotomous	182	1	(0.5%)	182	0	(0.0%)			
Gastrointestinal disorders (any) – 104wk	Dichotomous	182	38	(20.9%)	182	60	(33.0%)			
GI: diarrhoea – 104wk	Dichotomous	182	14	(7.7%)	182	23	(12.6%)			
GI: vomiting – 104wk	Dichotomous	182	0	(0.0%)	182	8	(4.4%)			
GI: abdominal pain – 104wk	Dichotomous	182	7	(3.8%)	182	12	(6.6%)			
Dropouts:										
Dropout due to AEs – 104wk	Dichotomous	182	12	(6.6%)	182	13	(7.1%)			
drop out due to drug related AE – 104wk	Dichotomous	182	2	(1.1%)	182	5	(2.7%)			
drop out due to SAE – 104wk	Dichotomous	182	5	(2.7%)	182	1	(0.5%)			
drop out due to drug related SAE – 104wk	Dichotomous	182	0	(0.0%)	182	0	(0.0%)			
2-year follow-up (reported in Williams-Herman et al. 2010) - Baseline Hba1c <8%										
Blood glucose:										
HbA1c (%) – 104wkc	Mean change	20		-0.41 (SD 0.447)	27		-0.8 (SD 0.52)			
2-year follow-up (reported in Williams-Herman et al. 2010) - baseline Hba1c >=8 to <9%										
Blood glucose:										
HbA1c (%) – 104wkc	Mean change	24		-1.05 (SD 0.931)	34		-1.05 (SD 1.11)			
2-year follow-up (reported in Williams-Herman et al. 2010) - baseline Hba1c >=9%										
Blood glucose:										
HbA1c (%) – 104wkc	Mean change	20		-1.84 (SD 0.805)	26		-2.02 (SD 0.918)			
2-year follow-up (reported in Williams-Herman et al. 2010) - Full analysis set (FAS) or efficacy analysis pop										
Blood glucose:										
HbA1c (%) – 104wkb	Mean change	64		-1.1 (SD 0.816)	87		-1.3 (SD 0.952)			
HbA1c (%) – 104wk	Continuous	64		7.5 (SD 0.7)	87		7.2 (SD 0.9)			
HbA1c < 7% or <=7% – 104wk	Dichotomous	64	18	(28.1%)	87	39d	(44.8%)			
Fasting plasma glucose (mg/dl) – 104wkb	Mean change	64		-41.4 (SD 34.3)	87		-43.2 (SD 33.8)			
Fasting plasma glucose (mg/dl) – 104wk	Continuous	64		141.3 (SD 30.3)	87		140.4 (SD 40)			
Lipids:										
Total cholesterol (mmol/l) – 104wk	Percentage change from baseline	59		-0.031032 (SD 0.457)	83		0.015516 (SD 0.446)			
Total cholesterol (mmol/l) – 104wk	Continuous	59		4.804788 (SD 0.954)	83		4.86168 (SD 1.19)			
HDL cholesterol (mmol/l) – 104wk	Percentage change from baseline	59		0.201708 (SD 0.476)	83		0.243084 (SD 0.469)			
HDL cholesterol (mmol/l) – 104wk	Continuous	59		1.18956 (SD 0.287)	83		1.249038 (SD 0.321)			
Triglycerides (mmol/l) – 104wk	Percentage change from baseline	59	e	med: 0.029354	83	f	med: -0.029354			
Triglycerides (mmol/l) – 104wk	Continuous	59		med: 2.00962 (SD 1.13)	83		med: 1.90801 (SD 1.3)			
LDL cholesterol (mmol/l) – 104wk	Percentage change from baseline	59		-0.124128 (SD 0.811)	82		0.02586 (SD 0.812)			

LDL cholesterol (mmol/l) – 104wk	Continuous	59		2.622204 (SD 0.809)	82		2.645478 (SD 0.962)		
1-year follow up (reported in Ref 869)									
Dropouts:									
Total dropouts – 54wk	Dichotomous	182	56	(30.8%)	182	46	(25.3%)		
Dropout due to AEs – 54wk	Dichotomous	182	9	(4.9%)	182	11	(6.0%)		
1-year follow up APT (reported in Ref 869)									
Blood glucose:									
HbA1c (%) – 54wk	Continuous	117		7.7 (SD 0.9)	134		7.3 (SD 1)		
HbA1c (%) – 54wkb	Mean change	117		-1 (SD 1.1)	134		-1.3 (SD 1.18)		
Fasting plasma glucose (mg/dl) – 54wkb	Mean change	117		-29 (SD 38.1)	134		-39.6 (SD 37.8)		
Fasting plasma glucose (mg/dl) – 54wk	Continuous	117		159.8 (SD 40.9)	134		148.9 (SD 40.5)		
Hypoglycaemic events:									
All hypoglycaemic events (no patients) – 54wk	Dichotomous	182	2	(1.1%)	182	2	(1.1%)		
Adverse events:									
GI: nausea – 54wk	Dichotomous	182	6	(3.3%)	182	18	(9.9%)		

[a] estimated from graph; least square means, SD calculated from SE
[b] SD calculated from reported 95% CI
[c] estimated from graph
[d] approximated to nearest integer (percentages only presented in text)
[e] 95% CI -7.4 to 12.7
[f] 95% CI -13.7 to 8.4

		Metformin (500 mg bid)			Placebo				
		N	k	mean	N	k	mean	Δ	p
Blood glucose:									
HbA1c (%) – 12wka	Continuous	178		8.07 (SD 0.667)	165		8.95 (SD 0.771)		
HbA1c (%) – 24wk	Continuous	178		8.04 (SD 1.36)	165		8.88 (SD 1.47)		
HbA1c (%) – 24wkb	Mean change	178		-0.82 (SD 1.1)	165		0.17 (SD 1.15)	MD=-0.990 (CI: -1.220, -0.760)	<=0.001
HbA1c < 7% or <=7% – 24wk	Dichotomous	178	41	(23.0%)	165	15	(9.1%)		<0.001
Hba1c <6.5% – 24wk	Dichotomous	178	16	(9.0%)	165	4	(2.4%)		<=0.005
Fasting plasma glucose (mmol/l) – 12wk	Continuous	179		9.7579548 (SD 3.11)	169		11.3010216 (SD 3.39)		
Fasting plasma glucose (mmol/l) – 12wkc	Mean change	179		-1.554168 (SD 1.49)	169		0.333036 (SD 1.8)		
Fasting plasma glucose (mmol/l) – 24wk	Mean change	179		-1.51515 (SD 2.56)	169		0.3219 (SD 2.55)	MD=-1.837 (CI: -2.370, -1.304)	<=0.001
2-h post prandial glucose (mmol/l) – 24wk	Mean change	141		-2.9637 (SD 3.43)	129		0.01665 (SD 3.44)	MD=-2.980 (CI: -3.802, -2.159)	<=0.001
Hypoglycaemic events:									
All hypoglycaemic events (no patients) – 24wk	Dichotomous	182	1	(0.5%)	176	1	(0.6%)		

Adverse events:									
GI: nausea – 24wk	Dichotomous	182	5	(2.7%)	176	2	(1.1%)		
Any adverse event(s) – 24wk	Dichotomous	182	101	(55.5%)	176	89	(50.6%)		
Any serious adverse event(s) – 24wk	Dichotomous	182	4	(2.2%)	176	10	(5.7%)		
Serious AE drug related – 24wk	Dichotomous	182	0	(0.0%)	176	1	(0.6%)		
Study drug-related adverse event – 24wk	Dichotomous	182	21	(11.5%)	176	17	(9.7%)		
Death – 24wk	Dichotomous	182	0	(0.0%)	176	1	(0.6%)		
Gastrointestinal disorders (any) – 24wk	Dichotomous	182	29	(15.9%)	176	19	(10.8%)		
GI: diarrhoea – 24wk	Dichotomous	182	9	(4.9%)	176	7	(4.0%)		
GI: vomiting – 24wk	Dichotomous	182	0	(0.0%)	176	1	(0.6%)		
GI: abdominal pain – 24wk	Dichotomous	182	5	(2.7%)	176	4	(2.3%)		
Dropouts:									
Total dropouts – 24wk	Dichotomous	182	29	(15.9%)	176	49	(27.8%)		
Dropout due to AEs – 24wk	Dichotomous	182	4	(2.2%)	176	9	(5.1%)		
drop out due to drug related AE – 24wk	Dichotomous	182	2	(1.1%)	176	2	(1.1%)		
drop out due to SAE – 24wk	Dichotomous	182	2	(1.1%)	176	5	(2.8%)		
drop out due to drug related SAE – 24wk	Dichotomous	182	0	(0.0%)	176	1	(0.6%)		
dropout due to laboratory AE – 24wk	Dichotomous	182	0	(0.0%)	176	2	(1.1%)		
Drop out due to unsatisfactory effect – 24wk	Dichotomous	182	5	(2.7%)	176	12	(6.8%)		
Other medication:									
Taking rescue medication – 24wk	Dichotomous	182	31	(17.0%)	176	57	(32.4%)		

[a] estimated from graph; least square means, SD calculated from SE
[b] SD calculated from reported 95% CI
[c] estimated from graph

		Metformin (1000 mg bid)			Placebo				
		N	k	mean	N	k	mean	Δ	p
Blood glucose:									
HbA1c (%) – 12wka	Continuous	177		7.85 (SD 0.665)	165		8.95 (SD 0.771)		
HbA1c (%) – 24wk	Continuous	177		7.58 (SD 1.27)	165		8.88 (SD 1.47)		
HbA1c (%) – 24wkb	Mean change	177		-1.13 (SD 1.1)	165		0.17 (SD 1.15)	MD=-1.300 (CI: -1.530, -1.070)	<=0.001
HbA1c < 7% or <=7% – 24wk	Dichotomous	177	68	(38.4%)	165	15	(9.1%)		<0.001
Hba1c <6.5% – 24wk	Dichotomous	177	36	(20.3%)	165	4	(2.4%)		<=0.005
Fasting plasma glucose (mmol/l) – 12wk	Continuous	179		9.380514 (SD 3.6)	169		11.3010216 (SD 3.39)		
Fasting plasma glucose (mmol/l) – 12wkc	Mean change	179		-1.720686 (SD 1.49)	169		0.333036 (SD 1.8)		

Fasting plasma glucose (mmol/l) – 24wk	Mean change	179		-1.62615 (SD 2.52)	169		0.3219 (SD 2.55)	MD=-1.948 (CI: -2.475, -1.421)	<=0.001
2-h post prandial glucose (mmol/l) – 24wk	Mean change	138		-4.329 (SD 3.43)	129		0.01665 (SD 3.44)	MD=-4.346 (CI: -5.167, -3.524)	<=0.001
Hypoglycaemic events:									
All hypoglycaemic events (no patients) – 24wk	Dichotomous	182	2	(1.1%)	176	1	(0.6%)		
Adverse events:									
GI: nausea – 24wk	Dichotomous	182	15	(8.2%)	176	2	(1.1%)		
Any adverse event(s) – 24wk	Dichotomous	182	113	(62.1%)	176	89	(50.6%)		
Any serious adverse event(s) – 24wk	Dichotomous	182	2	(1.1%)	176	10	(5.7%)		
Serious AE drug related – 24wk	Dichotomous	182	0	(0.0%)	176	1	(0.6%)		
Study drug-related adverse event – 24wk	Dichotomous	182	30	(16.5%)	176	17	(9.7%)		
Death – 24wk	Dichotomous	182	0	(0.0%)	176	1	(0.6%)		
Gastrointestinal disorders (any) – 24wk	Dichotomous	182	46	(25.3%)	176	19	(10.8%)		
GI: diarrhoea – 24wk	Dichotomous	182	19	(10.4%)	176	7	(4.0%)		
GI: vomiting – 24wk	Dichotomous	182	2	(1.1%)	176	1	(0.6%)		
GI: abdominal pain – 24wk	Dichotomous	182	9	(4.9%)	176	4	(2.3%)		
Dropouts:									
Total dropouts – 24wk	Dichotomous	182	26	(14.3%)	176	49	(27.8%)		
Dropout due to AEs – 24wk	Dichotomous	182	5	(2.7%)	176	9	(5.1%)		
drop out due to drug related AE – 24wk	Dichotomous	182	5	(2.7%)	176	2	(1.1%)		
drop out due to SAE – 24wk	Dichotomous	182	0	(0.0%)	176	5	(2.8%)		
drop out due to drug related SAE – 24wk	Dichotomous	182	0	(0.0%)	176	1	(0.6%)		
dropout due to laboratory AE – 24wk	Dichotomous	182	0	(0.0%)	176	2	(1.1%)		
Drop out due to unsatisfactory effect – 24wk	Dichotomous	182	3	(1.6%)	176	12	(6.8%)		
Other medication:									
Taking rescue medication – 24wk	Dichotomous	182	21	(11.5%)	176	57	(32.4%)		

[a] estimated from graph; least square means, SD calculated from SE
[b] SD calculated from reported 95% CI
[c] estimated from graph

The primary analyses focused on the efficacy response to the coadministration of sitagliptin and metformin compared with placebo and the respective monotherapies. An ANCOVA model compared treatment groups for continuous efficacy parameters, focusing on change from baseline at week 24 with baseline values and prior OHA status as covariates. The between-group differences for efficacy end points were assessed by testing the difference in the least-squares mean change (or percent change) from baseline at week 24. The proportion of patients achieving A1C <7 or <6.5% was compared

among groups using a logistic regression analysis. P-values for between group comparisons for adverse events were not reported

Table 46: H+¤llsten et al. (2002)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** Finland **Authors' conclusions:** Results suggest that rosiglitazone improves synergic action of insulin and exercise **Source of funding:** Academy of Finland, Novo Nordisk Foundation, Finish Diabetes Research Society, GlaxoSmithKline **Comments:** -
Number and characteristics of patients	**Total number of patients:** 45 **Inclusion criteria:** patients newly diagnosed with type 2 diabetes (without diabetic complications), only diet-treated, AHA naïve **Exclusion criteria:** patients were excluded if FBG <6.1 mmol/l or >11.0 mmol/l, BP was >160/100 mmHg , previous or present abnormal hepatic or renal function, use of antidiabetic medication, or corticosteroid treatment Pre-randomisation phase: There was a 4 week runin period with written diet instructions
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** All treatment naive/ no OADs at screening **Details of washout period:** All were AHA naïve
Lifestyle advice	written diet instructions were given as part of the run-in period
Follow-up	**Total follow-up (wks):** 26 **Length of titration period (wks):** 2 **Length of maintenance period (wks):** 26 **Frequency of monitoring appointments:** -
Arms	**(1) Placebo** N: 14 Treatment duration (wks): - Washout period (d): - Treatment(s): Placebo (Oral) **(2) Metformin** N: 16 Treatment duration (wks): - Washout period (d): - Treatment(s): Metformin (Oral) – fixed-dose Set dose (mg/d):2000 Details of dosing regimen: 1 g bid. Metformin was given 500 mg bid for 2 weeks then 1 g bid thereafter.
Outcomes	
Baseline characteristics	

		Placebo			Metformin				
		N	k	mean	N	k	mean	Δ	p
PP									
Demographics: Age (years) a	Continuous	14		57.7 (SD 7.11)	13		57.8 (SD 7.93)		
Sex (n male)	Dichotomous	14	10	(71.4%)	13	8	(61.5%)		
Blood glucose: HbA1c (%) – 0wka	Continuous	14		6.3 (SD 0.374)	13		6.9 (SD 0.721)		
Fasting plasma glucose (mmol/l) – 0wka	Continuous	14		7.2 (SD 1.12)	13		8 (SD 1.8)		
Body weight: BMI (kg/m2) a	Continuous	14		30.3 (SD 4.49)	13		29.9 (SD 3.97)		
Weight (kg) – 0wka	Continuous	14		88.3 (SD 9.35)	13		88.8 (SD 10.8)		

Blood pressure: Systolic blood pressure (mmHg) – 0wk	Continuous	14		147.2 (SD 12)	13		145 (SD 14.8)		
Diastolic blood pressure (mmHg) – 0wk	Continuous	14		85.1 (SD 8.61)	13		91.4 (SD 9.01)		

[a] SD calculated from reported SE

Results

		Placebo			Metformin				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Dropouts: Total dropouts – 26wk	Dichotomous	14	0	(0.0%)	16	3	(18.8%)		
Dropout due to AEs – 26wk	Dichotomous	14	0	(0.0%)	16	1	(6.3%)		
PP									
Blood glucose: HbA1c (%) – 26wka	Continuous	14		6.1 (SD 0.37)	13		6.2 (SD 0.72)		
Fasting plasma glucose (mmol/l) – 26wka	Continuous	14		7.2 (SD 1.12)	13		6.8 (SD 1.08)		
Body weight: Weight (kg) – 26wka	Continuous	14		88.4 (SD 9.35)	13		86.8 (SD 10.4)		
Blood pressure: Systolic blood pressure (mmHg) – 26wk	Continuous	14		144.4 (SD 14.2)	13		141.8 (SD 14.4)		
Diastolic blood pressure (mmHg) – 26wk	Continuous	14		85.4 (SD 8.97)	13		85.5 (SD 9.37)		

[a] SD calculated from reported SE

Table 47: Haak et al. (2012)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** 14 countries **Authors' conclusions:** Initial combination therapy with linagliptin plus metformin was superior to metformin monotherapy in improving glycaemic control, with a similar safety and tolerability profile, no weight gain and a low risk of hypoglycaemia **Source of funding:** Boehringer Ingelheim is the study sponsor **Comments:** Multicentre, double blind, randomised, placebo controlled, international, phase 3 clinical trial
Number and characteristics of patients	**Total number of patients:** 791 **Inclusion criteria:** 18-80 years of age, with a diagnosis of type 2 diabetes and BMI <=40 kg/m2. Patients were either treatment naïve or had been treated with not more than one OAD (unchanged from 10 weeks prior to enrolment). At initial screening Hba1c had to be >=7% to <=10.5% for patients undergoing washout of previous drug therapy and Hba1c >=7.5 to <11% for treatment naïve patients, treatment at the start of the placebo run-in period had to be >=7.5% to <11%. **Exclusion criteria:** Patients were excluded if they had received previous treatment with rosiglitazone, pioglitazone, GLP-1 analogue, insulin or anti-obesity drugin the previous 3 months, were receiving treatment with systemic steroids or had a change in the dosage of thyroid in the previous 6 weeks, had undergone gastric bypass, had experienced MI or TIA in the previous 6 months, had unstable or acute congestive heart failure, had renal or hepatic dysfunction, known hypersensitivity or allergy to linagliptin, metformin or placebo, had a history of alcohol or drug abuse in the previous 3 months, had acute or chronic metabolic acidosis, women who were pre-menopausal, nursing or pregnant. Pre-randomisation phase: There was a 4 week drug washout period (for those pretreated with one OAD) followed by a 2 week placebo run-in period before double-blind treatment.

Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** some on oral hypoglycaemic drugs and/or insulin **Details of washout period:** 4 week drug washout period (for those pretreated with one OAD) followed by a 2 week placebo run-in period
Lifestyle advice	No details reported
Follow-up	**Total follow-up (wks):** 30 **Length of titration period (wks):** 2 **Length of maintenance period (wks):** 24 **Frequency of monitoring appointments:** 4 week wash out period, 2 week placebo run in and 24 week treatment. Only those receiving metformin 1000mg bid underwent a 2 week forced titration period. A total of 9 study visits were scheduled screening, start of placebo run-in, weeks 0, 2, 6, 12, 18 and 24 and at week 25 follow-up
Arms	**(1) Linagliptin (5 mg qd)** N: 142 Treatment duration (wks): - Washout period (d): - Treatment(s): Linagliptin (Oral) – fixed-dose Set dose (mg/d):5 Frequency of dosing: once a day Details of dosing regimen: The use of rescue therapy (with sulfonylureas, thiazolidinediones or insulin) was permitted during the randomised treatment period (weeks 0-24) and was administered only if a patients had FPG confirmed by a second glucose determination, performed on a different day. The following criteria for hyperglycaemia had to be met: during visits 3-6 the patient had a FPG>13.3 mmol/l or randomly determined glucose level >22.2 mmol/l; alternatively during visits 6-8 patient had a FPG>11.1 mmol/l or a random blood glucose >22.2 mmol/l. Patients meeting these criteria were discontinued for lack of efficacy. **(2) Metformin (500 mg bid)** N: 144 Treatment duration (wks): - Washout period (d): - Treatment(s): Metformin (Oral) – fixed-dose Set dose (mg/d):1000 Frequency of dosing: twice a day **(3) Metformin (1000 mg bid)** N: 147 Treatment duration (wks): - Washout period (d): - Treatment(s): Metformin (Oral) – forced titration Set dose (mg/d):2000 Frequency of dosing: twice a day Details of dosing regimen: Patients randomised to an arm containing metformin 1000 mg underwent a forced titration phase of 2 weeks during which the metformin dose was increased gradually from 500 to 1000 mg bid **(4) Placebo** N: 72 Treatment duration (wks): - Washout period (d): - Treatment(s): Placebo (Oral)
Outcomes	**General** Data from the open-label arm contained patients with a baseline Hba1c >11% who were not eligible for randomisation, therefore these have not been extracted in this evidence table. Data have also not been extracted from 2 trial arms (dual therapy with linagliptin plus metformin in which metformin dose comparisons were undertaken - outside scope of review). The primary analysis was conducted in the full analysis set which included randomised patients who had received at least one dose of study medication and had Hba1c measured at baseline and at least once during treatment. A LOCF approach was used to replace missing data and values obtained after rescue therapy was initiated were not used in the LOCF and observed case analyses. 21/142 (14.8%) patients in the linagliptin group, 17/144 (11.8%) in metformin 500 mg bid group, 21/147 (14.3%) in metformin 1000 mg bid and 18/72 (25%) in placebo group discontinued from the study
Baseline characteristics	

	Linagliptin (5 mg qd)	Metformin (500 mg bid)	Δ	p

		N	k	mean	N	k	mean		
Demographics: Age (years)	Continuous	142		56.2 (SD 10.8)	144		52.9 (SD 10.4)		
Sex (n male)	Dichotomous	142	80	(56.3%)	144	82	(56.9%)		
Ethnicity-White	Dichotomous	142	97	(68.3%)	144	93	(64.6%)		
Ethnicity-Black	Dichotomous	142	0	(0.0%)	144	0	(0.0%)		
Ethnicity-Asian	Dichotomous	142	45	(31.7%)	144	51	(35.4%)		
Body weight: BMI (kg/m2)	Continuous	142		29 (SD 4.7)	144		28.9 (SD 4.8)		
Weight (kg) – 0wk	Continuous	142		79.1 (SD 17.3)	144		79.9 (SD 18.4)		
Full analysis set (FAS) or efficacy analysis pop Blood glucose: HbA1c (%) – 0wk	Continuous	135		8.7 (SD 1)	141		8.7 (SD 0.9)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	135		10.8 (SD 2.8)	141		10.6 (SD 2.6)		
Previous blood glucose lowering drugs: Diet alone (i.e. drug naïve)	Dichotomous	135	61	(45.2%)	141	69	(48.9%)		

		Linagliptin (5 mg qd)			Metformin (1000 mg bid)			Δ	p
		N	k	mean	N	k	mean		
Demographics: Age (years)	Continuous	142		56.2 (SD 10.8)	147		55.2 (SD 10.6)		
Sex (n male)	Dichotomous	142	80	(56.3%)	147	78	(53.1%)		
Ethnicity-White	Dichotomous	142	97	(68.3%)	147	95	(64.6%)		
Ethnicity-Black	Dichotomous	142	0	(0.0%)	147	2	(1.4%)		
Ethnicity-Asian	Dichotomous	142	45	(31.7%)	147	50	(34.0%)		
Body weight: BMI (kg/m2)	Continuous	142		29 (SD 4.7)	147		29.5 (SD 5.3)		
Weight (kg) – 0wk	Continuous	142		79.1 (SD 17.3)	147		80 (SD 18.5)		
Full analysis set (FAS) or efficacy analysis pop Blood glucose: HbA1c (%) – 0wk	Continuous	135		8.7 (SD 1)	138		8.5 (SD 0.9)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	135		10.8 (SD 2.8)	138		10.7 (SD 2.9)		
Previous blood glucose lowering drugs: Diet alone (i.e. drug naïve)	Dichotomous	135	61	(45.2%)	138	67	(48.6%)		

		Linagliptin (5 mg qd)			Placebo			Δ	p
		N	k	mean	N	k	mean		
Demographics: Age (years)	Continuous	142		56.2 (SD 10.8)	72		55.7 (SD 11)		
Sex (n male)	Dichotomous	142	80	(56.3%)	72	36	(50.0%)		
Ethnicity-White	Dichotomous	142	97	(68.3%)	72	46	(63.9%)		
Ethnicity-Black	Dichotomous	142	0	(0.0%)	72	0	(0.0%)		
Ethnicity-Asian	Dichotomous	142	45	(31.7%)	72	26	(36.1%)		

Body weight: BMI (kg/m2)	Continuous	142		29 (SD 4.7)	72		28.6 (SD 5.2)		
Weight (kg) – 0wk	Continuous	142		79.1 (SD 17.3)	72		76.8 (SD 17.5)		
Full analysis set (FAS) or efficacy analysis pop Blood glucose: HbA1c (%) – 0wk	Continuous	135		8.7 (SD 1)	65		8.7 (SD 1)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	135		10.8 (SD 2.8)	65		11.3 (SD 2.8)		
Previous blood glucose lowering drugs: Diet alone (i.e. drug naïve)	Dichotomous	135	61	(45.2%)	65	32	(49.2%)		

		Metformin (500 mg bid)			Metformin (1000 mg bid)				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	144		52.9 (SD 10.4)	147		55.2 (SD 10.6)		
Sex (n male)	Dichotomous	144	82	(56.9%)	147	78	(53.1%)		
Ethnicity-White	Dichotomous	144	93	(64.6%)	147	95	(64.6%)		
Ethnicity-Black	Dichotomous	144	0	(0.0%)	147	2	(1.4%)		
Ethnicity-Asian	Dichotomous	144	51	(35.4%)	147	50	(34.0%)		
Body weight: BMI (kg/m2)	Continuous	144		28.9 (SD 4.8)	147		29.5 (SD 5.3)		
Weight (kg) – 0wk	Continuous	144		79.9 (SD 18.4)	147		80 (SD 18.5)		
Full analysis set (FAS) or efficacy analysis pop Blood glucose: HbA1c (%) – 0wk	Continuous	141		8.7 (SD 0.9)	138		8.5 (SD 0.9)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	141		10.6 (SD 2.6)	138		10.7 (SD 2.9)		
Previous blood glucose lowering drugs: Diet alone (i.e. drug naïve)	Dichotomous	141	69	(48.9%)	138	67	(48.6%)		

		Metformin (500 mg bid)			Placebo				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	144		52.9 (SD 10.4)	72		55.7 (SD 11)		
Sex (n male)	Dichotomous	144	82	(56.9%)	72	36	(50.0%)		
Ethnicity-White	Dichotomous	144	93	(64.6%)	72	46	(63.9%)		
Ethnicity-Black	Dichotomous	144	0	(0.0%)	72	0	(0.0%)		
Ethnicity-Asian	Dichotomous	144	51	(35.4%)	72	26	(36.1%)		
Body weight: BMI (kg/m2)	Continuous	144		28.9 (SD 4.8)	72		28.6 (SD 5.2)		
Weight (kg) – 0wk	Continuous	144		79.9 (SD 18.4)	72		76.8 (SD 17.5)		
Full analysis set (FAS) or efficacy analysis pop Blood glucose: HbA1c (%) – 0wk	Continuous	141		8.7 (SD 0.9)	65		8.7 (SD 1)		

Fasting plasma glucose (mmol/l) – 0wk	Continuous	141		10.6 (SD 2.6)	65		11.3 (SD 2.8)		
Previous blood glucose lowering drugs: Diet alone (i.e. drug naïve)	Dichotomous	141	69	(48.9%)	65	32	(49.2%)		

		Metformin (1000 mg bid)			Placebo				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	147		55.2 (SD 10.6)	72		55.7 (SD 11)		
Sex (n male)	Dichotomous	147	78	(53.1%)	72	36	(50.0%)		
Ethnicity-White	Dichotomous	147	95	(64.6%)	72	46	(63.9%)		
Ethnicity-Black	Dichotomous	147	2	(1.4%)	72	0	(0.0%)		
Ethnicity-Asian	Dichotomous	147	50	(34.0%)	72	26	(36.1%)		
Body weight: BMI (kg/m2)	Continuous	147		29.5 (SD 5.3)	72		28.6 (SD 5.2)		
Weight (kg) – 0wk	Continuous	147		80 (SD 18.5)	72		76.8 (SD 17.5)		
Full analysis set (FAS) or efficacy analysis pop Blood glucose: HbA1c (%) – 0wk	Continuous	138		8.5 (SD 0.9)	65		8.7 (SD 1)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	138		10.7 (SD 2.9)	65		11.3 (SD 2.8)		
Previous blood glucose lowering drugs: Diet alone (i.e. drug naïve)	Dichotomous	138	67	(48.6%)	65	32	(49.2%)		

Results

		Linagliptin (5 mg qd)			Metformin (500 mg bid)				
		N	k	mean	N	k	mean	Δ	p
Hypoglycaemic events: All hypoglycaemic events (no patients) – 24wk	Dichotomous	142	0	(0.0%)	144	2	(1.4%)		
Major/severe hypoglycaemic event – 24wk	Dichotomous	142	0	(0.0%)	144	0	(0.0%)		
Adverse events: GI: nausea – 24wk	Dichotomous	142	1	(0.7%)	144	0	(0.0%)		
Any adverse event(s) – 24wk	Dichotomous	142	80	(56.3%)	144	75	(52.1%)		
Study drug-related adverse event – 24wk	Dichotomous	142	15	(10.6%)	144	14	(9.7%)		
Gastrointestinal disorders (any) – 24wk	Dichotomous	142	17	(12.0%)	144	14	(9.7%)		
GI: diarrhoea – 24wk	Dichotomous	142	5	(3.5%)	144	3	(2.1%)		
GI: vomiting – 24wk	Dichotomous	142	2	(1.4%)	144	0	(0.0%)		
GI: gastritis – 24wk	Dichotomous	142	1	(0.7%)	144	1	(0.7%)		
GI: gatroenteritis – 24wk	Dichotomous	142	3	(2.1%)	144	2	(1.4%)		
GI: constipation – 24wk	Dichotomous	142	2	(1.4%)	144	3	(2.1%)		
Headache – 24wk	Dichotomous	142	6	(4.2%)	144	7	(4.9%)		
Infection (upper airway or other common) – 24wk	Dichotomous	142	1	(0.7%)	144	6	(4.2%)		
Nasopharyngitis – 24wk	Dichotomous	142	8	(5.6%)	144	4	(2.8%)		
paresthesia – 24wk	Dichotomous	142	1	(0.7%)	144	3	(2.1%)		
Temperature/influenza – 24wk	Dichotomous	142	6	(4.2%)	144	7	(4.9%)		

UTI – 24wk	Dichotomous	142	2	(1.4%)	144	4	(2.8%)		
Study drug exposure – 24wk	Continuous	142		158.4	144		a		
Dropouts:									
Total dropouts – 24wk	Dichotomous	142	21	(14.8%)	144	17	(11.8%)		
Dropout due to AEs – 24wk	Dichotomous	142	6	(4.2%)	144	4	(2.8%)		
drop out due to SAE – 24wk	Dichotomous	142	3	(2.1%)	144	3	(2.1%)		
Drop out due to unsatisfactory effect – 24wk	Dichotomous	142	3	(2.1%)	144	4	(2.8%)		
Other medication:									
Taking rescue medication – 24wkb	Dichotomous	142	16	(11.3%)	144	19	(13.2%)		
Full analysis set (FAS) or efficacy analysis pop									
Blood glucose:									
HbA1c (%) – 24wkc	Continuous	135		8.2 (SD 1.16)	141		8 (SD 1.19)		
HbA1c (%) – 24wkc	Mean change	135		-0.5 (SD 1.16)	141		-0.6 (SD 1.19)		
Fasting plasma glucose (mmol/l) – 24wkc	Mean change	134		-0.5 (SD 2.32)	136		-0.9 (SD 2.33)		
Fasting plasma glucose (mmol/l) – 24wkc	Continuous	134		10.3 (SD 2.32)	136		9.9 (SD 2.33)		
Body weight:									
Weight (kg) – 24wkd	Continuous	112		0.2 (SD 3.17)	117		-0.7 (SD 3.24)		
Pre-study diet alone (i.e. drug naive)									
Blood glucose:									
HbA1c (%) – 12wke	Mean change	61		-0.65 (SD 0.703)	69		-1.05 (SD 0.581)		
HbA1c (%) – 24wke	Mean change	61		-0.7 (SD 0.547)	69		-1.1 (SD 0.581)		
Pre-study oral antidiabetics (i.e. not drug naive)									
Blood glucose:									
HbA1c (%) – 12wke	Mean change	74		-0.2 (SD 0.602)	72		-0.2 (SD 0.594)		
HbA1c (%) – 24wke	Mean change	74		-0.25 (SD 0.43)	72		-0.25 (SD 0.424)		
Baseline Hba1c <8.5%									
Blood glucose:									
HbA1c (%) – 24wkf	Continuous	66		-0.4 (SD 0.894)	68		-0.75 (SD 0.99)		
Baseline Hba1c <=8.5% and <11%									
Blood glucose:									
HbA1c (%) – 24wkf	Continuous	69		-0.8 (SD 0.997)	73		-0.78 (SD 1.03)		

[a] 160 days in metformin monotherapy group
[b] approximated to nearest integer (percentages only presented in text)
[c] SD calculated from reported SE
[d] from online supplement; SD calculated from reported SE
[e] Full analysis set, extracted from graph
[f] estimated from graph

		Linagliptin (5 mg qd)			Metformin (1000 mg bid)				
		N	k	mean	N	k	mean	Δ	p
Hypoglycaemic events:									
All hypoglycaemic events (no patients) – 24wk	Dichotomous	142	0	(0.0%)	147	5	(3.4%)		
Major/severe hypoglycaemic event – 24wk	Dichotomous	142	0	(0.0%)	147	1	(0.7%)		
Adverse events:									
GI: nausea – 24wk	Dichotomous	142	1	(0.7%)	147	5	(3.4%)		
Any adverse event(s) – 24wk	Dichotomous	142	80	(56.3%)	147	74	(50.3%)		
Study drug-related adverse event – 24wk	Dichotomous	142	15	(10.6%)	147	13	(8.8%)		

Gastrointestinal disorders (any) – 24wk	Dichotomous	142	17	(12.0%)	147	23	(15.6%)		
GI: diarrhoea – 24wk	Dichotomous	142	5	(3.5%)	147	8	(5.4%)		
GI: vomiting – 24wk	Dichotomous	142	2	(1.4%)	147	1	(0.7%)		
GI: gastritis – 24wk	Dichotomous	142	1	(0.7%)	147	0	(0.0%)		
GI: gatroenteritis – 24wk	Dichotomous	142	3	(2.1%)	147	1	(0.7%)		
GI: constipation – 24wk	Dichotomous	142	2	(1.4%)	147	0	(0.0%)		
Headache – 24wk	Dichotomous	142	6	(4.2%)	147	3	(2.0%)		
Infection (upper airway or other common) – 24wk	Dichotomous	142	1	(0.7%)	147	0	(0.0%)		
Nasopharyngitis – 24wk	Dichotomous	142	8	(5.6%)	147	4	(2.7%)		
paresthesia – 24wk	Dichotomous	142	1	(0.7%)	147	1	(0.7%)		
Temperature/influenza – 24wk	Dichotomous	142	6	(4.2%)	147	5	(3.4%)		
UTI – 24wk	Dichotomous	142	2	(1.4%)	147	3	(2.0%)		
Study drug exposure – 24wk	Continuous	142		158.4	147		a		
Dropouts:									
Total dropouts – 24wk	Dichotomous	142	21	(14.8%)	147	21	(14.3%)		
Dropout due to AEs – 24wk	Dichotomous	142	6	(4.2%)	147	6	(4.1%)		
drop out due to SAE – 24wk	Dichotomous	142	3	(2.1%)	147	6	(4.1%)		
Drop out due to unsatisfactory effect – 24wk	Dichotomous	142	3	(2.1%)	147	2	(1.4%)		
Other medication:									
Taking rescue medication – 24wkb	Dichotomous	142	16	(11.3%)	147	12	(8.2%)		
Full analysis set (FAS) or efficacy analysis pop									
Blood glucose:									
HbA1c (%) – 24wkc	Continuous	135		8.2 (SD 1.16)	138		7.6 (SD 1.17)		
HbA1c (%) – 24wkc	Mean change	135		-0.5 (SD 1.16)	138		-1.1 (SD 1.17)		
Fasting plasma glucose (mmol/l) – 24wkc	Mean change	134		-0.5 (SD 2.32)	132		-1.8 (SD 2.3)		
Fasting plasma glucose (mmol/l) – 24wkc	Continuous	134		10.3 (SD 2.32)	132		9 (SD 2.3)		
Body weight:									
Weight (kg) – 24wkd	Continuous	112		0.2 (SD 3.17)	122		-0.5 (SD 3.31)		
Pre-study diet alone (i.e. drug naive)									
Blood glucose:									
HbA1c (%) – 12wke	Mean change	61		-0.65 (SD 0.703)	67		-1.28 (SD 0.573)		
HbA1c (%) – 24wke	Mean change	61		-0.7 (SD 0.547)	67		-1.45 (SD 0.819)		
Pre-study oral antidiabetics (i.e. not drug naive)									
Blood glucose:									
HbA1c (%) – 12wke	Mean change	74		-0.2 (SD 0.602)	71		-0.65 (SD 0.506)		
HbA1c (%) – 24wke	Mean change	74		-0.25 (SD 0.43)	71		-0.79 (SD 0.421)		
Baseline Hba1c <8.5%									
Blood glucose:									
HbA1c (%) – 24wkf	Continuous	66		-0.4 (SD 0.894)	74		-1 (SD 1.03)		
Baseline Hba1c <=8.5% and <11%									
Blood glucose:									
HbA1c (%) – 24wkf	Continuous	69		-0.8 (SD 0.997)	64		-1.39 (SD 1.04)		

[a] 160 days in metformin monotherapy group
[b] approximated to nearest integer (percentages only presented in text)
[c] SD calculated from reported SE
[d] from online supplement; SD calculated from reported SE
[e] Full analysis set, extracted from graph
[f] estimated from graph

		Linagliptin (5 mg qd)			Placebo				
		N	k	mean	N	k	mean	Δ	p
Hypoglycaemic events: All hypoglycaemic events (no patients) – 24wk	Dichotomous	142	0	(0.0%)	72	1	(1.4%)		
Major/severe hypoglycaemic event – 24wk	Dichotomous	142	0	(0.0%)	72	0	(0.0%)		
Adverse events: GI: nausea – 24wk	Dichotomous	142	1	(0.7%)	72	0	(0.0%)		
Any adverse event(s) – 24wk	Dichotomous	142	80	(56.3%)	72	39	(54.2%)		
Study drug-related adverse event – 24wk	Dichotomous	142	15	(10.6%)	72	10	(13.9%)		
Gastrointestinal disorders (any) – 24wk	Dichotomous	142	17	(12.0%)	72	10	(13.9%)		
GI: diarrhoea – 24wk	Dichotomous	142	5	(3.5%)	72	2	(2.8%)		
GI: vomiting – 24wk	Dichotomous	142	2	(1.4%)	72	1	(1.4%)		
GI: gastritis – 24wk	Dichotomous	142	1	(0.7%)	72	2	(2.8%)		
GI: gatroenteritis – 24wk	Dichotomous	142	3	(2.1%)	72	1	(1.4%)		
GI: constipation – 24wk	Dichotomous	142	2	(1.4%)	72	1	(1.4%)		
Headache – 24wk	Dichotomous	142	6	(4.2%)	72	1	(1.4%)		
Infection (upper airway or other common) – 24wk	Dichotomous	142	1	(0.7%)	72	2	(2.8%)		
Nasopharyngitis – 24wk	Dichotomous	142	8	(5.6%)	72	1	(1.4%)		
paresthesia – 24wk	Dichotomous	142	1	(0.7%)	72	1	(1.4%)		
Temperature/influenza – 24wk	Dichotomous	142	6	(4.2%)	72	3	(4.2%)		
UTI – 24wk	Dichotomous	142	2	(1.4%)	72	2	(2.8%)		
Study drug exposure – 24wk	Continuous	142		158.4	72		a		
Dropouts: Total dropouts – 24wk	Dichotomous	142	21	(14.8%)	72	18	(25.0%)		
Dropout due to AEs – 24wk	Dichotomous	142	6	(4.2%)	72	3	(4.2%)		
drop out due to SAE – 24wk	Dichotomous	142	3	(2.1%)	72	1	(1.4%)		
Drop out due to unsatisfactory effect – 24wk	Dichotomous	142	3	(2.1%)	72	6	(8.3%)		
Other medication: Taking rescue medication – 24wk	Dichotomous	142	16b		72	a			
Full analysis set (FAS) or efficacy analysis pop Blood glucose: HbA1c (%) – 24wkc	Mean change	135		-0.5 (SD 1.16)	65		0.1 (SD 0.806)	MD=-0.600 (CI: -0.796, -0.404)	<0.0001
HbA1c (%) – 24wkc	Continuous	135		8.2 (SD 1.16)	65		8.8 (SD 0.806)		
Fasting plasma glucose (mmol/l) – 24wkc	Mean change	134		-0.5 (SD 2.32)	61		0.6 (SD 2.34)	MD=-1.000 (CI: -1.784, -0.216)	0.0033
Fasting plasma glucose (mmol/l) – 24wkc	Continuous	134		10.3 (SD 2.32)	61		11.4 (SD 2.34)		
Body weight: Weight (kg) – 24wkd	Continuous	112		0.2 (SD 3.17)	43		-0.7 (SD 2.62)		

Weight (kg) – 24wkd	Continuous	142		0.2 (SD 3.17)	72		-0.7 (SD 2.62)		
Pre-study diet alone (i.e. drug naive)									
Blood glucose:									
HbA1c (%) – 12wke	Mean change	61		-0.65 (SD 0.703)	32		-0.15 (SD 0.622)		
HbA1c (%) – 24wke	Mean change	61		-0.7 (SD 0.547)	32		-0.23 (SD 0.679)		
Pre-study oral antidiabetics (i.e. not drug naive)									
Blood glucose:									
HbA1c (%) – 12wke	Mean change	74		-0.2 (SD 0.602)	33		0.45 (SD 0.574)		
HbA1c (%) – 24wke	Mean change	74		-0.25 (SD 0.43)	33		0.4 (SD 0.574)		

[a] NR
[b] approximated to nearest integer (percentages only presented in text)
[c] SD calculated from reported SE
[d] from online supplement; SD calculated from reported SE
[e] Full analysis set, extracted from graph

		Metformin (500 mg bid)			Metformin (1000 mg bid)				
		N	k	mean	N	k	mean	Δ	p
Hypoglycaemic events:									
All hypoglycaemic events (no patients) – 24wk	Dichotomous	144	2	(1.4%)	147	5	(3.4%)		
Major/severe hypoglycaemic event – 24wk	Dichotomous	144	0	(0.0%)	147	1	(0.7%)		
Adverse events:									
GI: nausea – 24wk	Dichotomous	144	0	(0.0%)	147	5	(3.4%)		
Any adverse event(s) – 24wk	Dichotomous	144	75	(52.1%)	147	74	(50.3%)		
Study drug-related adverse event – 24wk	Dichotomous	144	14	(9.7%)	147	13	(8.8%)		
Gastrointestinal disorders (any) – 24wk	Dichotomous	144	14	(9.7%)	147	23	(15.6%)		
GI: diarrhoea – 24wk	Dichotomous	144	3	(2.1%)	147	8	(5.4%)		
GI: vomiting – 24wk	Dichotomous	144	0	(0.0%)	147	1	(0.7%)		
GI: gastritis – 24wk	Dichotomous	144	1	(0.7%)	147	0	(0.0%)		
GI: gatroenteritis – 24wk	Dichotomous	144	2	(1.4%)	147	1	(0.7%)		
GI: constipation – 24wk	Dichotomous	144	3	(2.1%)	147	0	(0.0%)		
Headache – 24wk	Dichotomous	144	7	(4.9%)	147	3	(2.0%)		
Infection (upper airway or other common) – 24wk	Dichotomous	144	6	(4.2%)	147	0	(0.0%)		
Nasopharyngitis – 24wk	Dichotomous	144	4	(2.8%)	147	4	(2.7%)		
paresthesia – 24wk	Dichotomous	144	3	(2.1%)	147	1	(0.7%)		
Temperature/influenza – 24wk	Dichotomous	144	7	(4.9%)	147	5	(3.4%)		
UTI – 24wk	Dichotomous	144	4	(2.8%)	147	3	(2.0%)		
Study drug exposure – 24wka	Continuous	144			147				
Dropouts:									
Total dropouts – 24wk	Dichotomous	144	17	(11.8%)	147	21	(14.3%)		
Dropout due to AEs – 24wk	Dichotomous	144	4	(2.8%)	147	6	(4.1%)		
drop out due to SAE – 24wk	Dichotomous	144	3	(2.1%)	147	6	(4.1%)		
Drop out due to unsatisfactory effect – 24wk	Dichotomous	144	4	(2.8%)	147	2	(1.4%)		
Other medication:									
Taking rescue medication – 24wkb	Dichotomous	144	19	(13.2%)	147	12	(8.2%)		

Full analysis set (FAS) or efficacy analysis pop									
Blood glucose: HbA1c (%) – 24wkc	Continuous	141		8 (SD 1.19)	138		7.6 (SD 1.17)		
HbA1c (%) – 24wkc	Mean change	141		-0.6 (SD 1.19)	138		-1.1 (SD 1.17)		
Fasting plasma glucose (mmol/l) – 24wkc	Mean change	136		-0.9 (SD 2.33)	132		-1.8 (SD 2.3)		
Fasting plasma glucose (mmol/l) – 24wkc	Continuous	136		9.9 (SD 2.33)	132		9 (SD 2.3)		
Body weight: Weight (kg) – 24wkd	Continuous	117		-0.7 (SD 3.24)	122		-0.5 (SD 3.31)		
Pre-study diet alone (i.e. drug naive)									
Blood glucose: HbA1c (%) – 12wke	Mean change	69		-1.05 (SD 0.581)	67		-1.28 (SD 0.573)		
HbA1c (%) – 24wke	Mean change	69		-1.1 (SD 0.581)	67		-1.45 (SD 0.819)		
Pre-study oral antidiabetics (i.e. not drug naive)									
Blood glucose: HbA1c (%) – 12wke	Mean change	72		-0.2 (SD 0.594)	71		-0.65 (SD 0.506)		
HbA1c (%) – 24wke	Mean change	72		-0.25 (SD 0.424)	71		-0.79 (SD 0.421)		
Baseline Hba1c <8.5%									
Blood glucose: HbA1c (%) – 24wkf	Continuous	68		-0.75 (SD 0.99)	74		-1 (SD 1.03)		
Baseline Hba1c <=8.5% and <11%									
Blood glucose: HbA1c (%) – 24wkf	Continuous	73		-0.78 (SD 1.03)	64		-1.39 (SD 1.04)		

[a] 160 days in metformin monotherapy group
[b] approximated to nearest integer (percentages only presented in text)
[c] SD calculated from reported SE
[d] from online supplement; SD calculated from reported SE
[e] Full analysis set, extracted from graph
[f] estimated from graph

		Metformin (500 mg bid)			Placebo				
		N	k	mean	N	k	mean	Δ	p
Hypoglycaemic events: All hypoglycaemic events (no patients) – 24wk	Dichotomous	144	2	(1.4%)	72	1	(1.4%)		
Major/severe hypoglycaemic event – 24wk	Dichotomous	144	0	(0.0%)	72	0	(0.0%)		
Adverse events: GI: nausea – 24wk	Dichotomous	144	0	(0.0%)	72	0	(0.0%)		
Any adverse event(s) – 24wk	Dichotomous	144	75	(52.1%)	72	39	(54.2%)		
Study drug-related adverse event – 24wk	Dichotomous	144	14	(9.7%)	72	10	(13.9%)		
Gastrointestinal disorders (any) – 24wk	Dichotomous	144	14	(9.7%)	72	10	(13.9%)		
GI: diarrhoea – 24wk	Dichotomous	144	3	(2.1%)	72	2	(2.8%)		
GI: vomiting – 24wk	Dichotomous	144	0	(0.0%)	72	1	(1.4%)		
GI: gastritis – 24wk	Dichotomous	144	1	(0.7%)	72	2	(2.8%)		
GI: gatroenteritis – 24wk	Dichotomous	144	2	(1.4%)	72	1	(1.4%)		
GI: constipation – 24wk	Dichotomous	144	3	(2.1%)	72	1	(1.4%)		
Headache – 24wk	Dichotomous	144	7	(4.9%)	72	1	(1.4%)		
Infection (upper airway or other common) – 24wk	Dichotomous	144	6	(4.2%)	72	2	(2.8%)		

Nasopharyngitis – 24wk	Dichotomous	144	4	(2.8%)	72	1	(1.4%)		
paresthesia – 24wk	Dichotomous	144	3	(2.1%)	72	1	(1.4%)		
Temperature/influenza – 24wk	Dichotomous	144	7	(4.9%)	72	3	(4.2%)		
UTI – 24wk	Dichotomous	144	4	(2.8%)	72	2	(2.8%)		
Study drug exposure – 24wk	Continuous	144		a	72		b		
Dropouts:									
Total dropouts – 24wk	Dichotomous	144	17	(11.8%)	72	18	(25.0%)		
Dropout due to AEs – 24wk	Dichotomous	144	4	(2.8%)	72	3	(4.2%)		
drop out due to SAE – 24wk	Dichotomous	144	3	(2.1%)	72	1	(1.4%)		
Drop out due to unsatisfactory effect – 24wk	Dichotomous	144	4	(2.8%)	72	6	(8.3%)		
Other medication:									
Taking rescue medication – 24wk	Dichotomous	144	19c		72	b			
Full analysis set (FAS) or efficacy analysis pop									
Blood glucose:									
HbA1c (%) – 24wkd	Mean change	141		-0.6 (SD 1.19)	65		0.1 (SD 0.806)	MD=-0.800 (CI: -0.996, -0.604)	<0.0001
HbA1c (%) – 24wkd	Continuous	141		8 (SD 1.19)	65		8.8 (SD 0.806)		
Fasting plasma glucose (mmol/l) – 24wkd	Mean change	136		-0.9 (SD 2.33)	61		0.6 (SD 2.34)	MD=-1.400 (CI: -2.184, -0.616)	<0.0001
Fasting plasma glucose (mmol/l) – 24wkd	Continuous	136		9.9 (SD 2.33)	61		11.4 (SD 2.34)		
Body weight:									
Weight (kg) – 24wke	Continuous	117		-0.7 (SD 3.24)	43		-0.7 (SD 2.62)		
Weight (kg) – 24wke	Continuous	144		-0.7 (SD 3.24)	72		-0.7 (SD 2.62)		
Pre-study diet alone (i.e. drug naive)									
Blood glucose:									
HbA1c (%) – 12wkf	Mean change	69		-1.05 (SD 0.581)	32		-0.15 (SD 0.622)		
HbA1c (%) – 24wkf	Mean change	69		-1.1 (SD 0.581)	32		-0.23 (SD 0.679)		
Pre-study oral antidiabetics (i.e. not drug naive)									
Blood glucose:									
HbA1c (%) – 12wkf	Mean change	72		-0.2 (SD 0.594)	33		0.45 (SD 0.574)		
HbA1c (%) – 24wkf	Mean change	72		-0.25 (SD 0.424)	33		0.4 (SD 0.574)		

[a] 160 days in metformin monotherapy group
[b] NR
[c] approximated to nearest integer (percentages only presented in text)
[d] SD calculated from reported SE
[e] from online supplement; SD calculated from reported SE
[f] Full analysis set, extracted from graph

	Metformin (1000 mg bid)			Placebo				
	N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**

Hypoglycaemic events: All hypoglycaemic events (no patients) – 24wk	Dichotomous	147	5	(3.4%)	72	1	(1.4%)		
Major/severe hypoglycaemic event – 24wk	Dichotomous	147	1	(0.7%)	72	0	(0.0%)		
Adverse events: GI: nausea – 24wk	Dichotomous	147	5	(3.4%)	72	0	(0.0%)		
Any adverse event(s) – 24wk	Dichotomous	147	74	(50.3%)	72	39	(54.2%)		
Study drug-related adverse event – 24wk	Dichotomous	147	13	(8.8%)	72	10	(13.9%)		
Gastrointestinal disorders (any) – 24wk	Dichotomous	147	23	(15.6%)	72	10	(13.9%)		
GI: diarrhoea – 24wk	Dichotomous	147	8	(5.4%)	72	2	(2.8%)		
GI: vomiting – 24wk	Dichotomous	147	1	(0.7%)	72	1	(1.4%)		
GI: gastritis – 24wk	Dichotomous	147	0	(0.0%)	72	2	(2.8%)		
GI: gatroenteritis – 24wk	Dichotomous	147	1	(0.7%)	72	1	(1.4%)		
GI: constipation – 24wk	Dichotomous	147	0	(0.0%)	72	1	(1.4%)		
Headache – 24wk	Dichotomous	147	3	(2.0%)	72	1	(1.4%)		
Infection (upper airway or other common) – 24wk	Dichotomous	147	0	(0.0%)	72	2	(2.8%)		
Nasopharyngitis – 24wk	Dichotomous	147	4	(2.7%)	72	1	(1.4%)		
paresthesia – 24wk	Dichotomous	147	1	(0.7%)	72	1	(1.4%)		
Temperature/influenza – 24wk	Dichotomous	147	5	(3.4%)	72	3	(4.2%)		
UTI – 24wk	Dichotomous	147	3	(2.0%)	72	2	(2.8%)		
Study drug exposure – 24wk	Continuous	147		a	72		b		
Dropouts: Total dropouts – 24wk	Dichotomous	147	21	(14.3%)	72	18	(25.0%)		
Dropout due to AEs – 24wk	Dichotomous	147	6	(4.1%)	72	3	(4.2%)		
drop out due to SAE – 24wk	Dichotomous	147	6	(4.1%)	72	1	(1.4%)		
Drop out due to unsatisfactory effect – 24wk	Dichotomous	147	2	(1.4%)	72	6	(8.3%)		
Other medication: Taking rescue medication – 24wk	Dichotomous	147	12c		72	b			
Full analysis set (FAS) or efficacy analysis pop Blood glucose: HbA1c (%) – 24wkd	Mean change	138		-1.1 (SD 1.17)	65		0.1 (SD 0.806)	MD=-1.200 (CI: -1.396, -1.004)	<0.0001
HbA1c (%) – 24wkd	Continuous	138		7.6 (SD 1.17)	65		8.8 (SD 0.806)		
Fasting plasma glucose (mmol/l) – 24wkd	Mean change	132		-1.8 (SD 2.3)	61		0.6 (SD 2.34)	MD=-2.300 (CI: -3.084, -1.516)	<0.0001
Fasting plasma glucose (mmol/l) – 24wkd	Continuous	132		9 (SD 2.3)	61		11.4 (SD 2.34)		
Body weight: Weight (kg) – 24wke	Continuous	122		-0.5 (SD 3.31)	43		-0.7 (SD 2.62)		
Weight (kg) – 24wke	Continuous	147		-0.5 (SD 3.31)	72		-0.7 (SD 2.62)		

Pre-study diet alone (i.e. drug naive) Blood glucose: HbA1c (%) – 12wkf	Mean change	67		-1.28 (SD 0.573)	32		-0.15 (SD 0.622)		
HbA1c (%) – 24wkf	Mean change	67		-1.45 (SD 0.819)	32		-0.23 (SD 0.679)		
Pre-study oral antidiabetics (i.e. not drug naive) Blood glucose: HbA1c (%) – 12wkf	Mean change	71		-0.65 (SD 0.506)	33		0.45 (SD 0.574)		
HbA1c (%) – 24wkf	Mean change	71		-0.79 (SD 0.421)	33		0.4 (SD 0.574)		

[a] 160 days in metformin monotherapy group
[b] NR
[c] approximated to nearest integer (percentages only presented in text)
[d] SD calculated from reported SE
[e] from online supplement; SD calculated from reported SE
[f] Full analysis set, extracted from graph

					Placebo				
		N	k	mean	N	k	mean	Δ	p
Full analysis set (FAS) or efficacy analysis pop Blood glucose: HbA1c (%) – 24wk	Mean change	140			65			MD=-1.700 (CI: -1.896, -1.504)	<0.0001
Fasting plasma glucose (mmol/l) – 24wk	Mean change	136			61			MD=-3.300 (CI: -4.084, -2.516)	<0.0001
Body weight: Weight (kg) – 24wk	Continuous	143			72				

	The primary efficacy analysis was an ANCOVA in the randomised full analysis set. The model included effects adjusted for baseline Hba1c, prior OAD and treatment. Hypoglycaemic events were analysed using logistic regression and kaplan-Meier analysis. P-values for between group comparisons for adverse events were not reported.

Table 48: Hanefeld et al. (2007)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** multinational **Authors' conclusions:** sitagliptin monotherapy improved indices of glycaemic control compared to placebo and was generally well-tolerated in patients with type 2 diabetes. The glycaemic response to treatment with sitagliptin 100 mg/day was similar between sitagliptin 100 mg once daily and 50 mg twice daily dose regimens **Source of funding:** sponsored by Merck & Co **Comments:** multinational double-blind, randomised, placebo controlled, parallel group dose range finding study. Study blinding was maintained using a double dummy technique with all patients taking study medications twice daily
Number and	**Total number of patients:** 555

characteristics of patients	**Inclusion criteria:** Male and female patients 21-75 years of age with type 2 diabetes either currently on OHA monotherapy (except thiazolidinediones) with Hba1c >= 6% and <=9% or not currently on an OHA with Hba1c >=6.5% and <10% were eligible to participate. **Exclusion criteria:** patients with type 1 diabetes, unstable cardiac disease, or elevated ALT, AST or creatinine phosphokinase (CPK) were excluded Pre-randomisation phase: at screening, patients not on an OHA with a Hba1c >=6.5% to <10% entered a diet and exercise run-in period of 2-6 weeks. Patients on OHA monotherapy with a Hba1c >=6% to <=9% had their OHA discontinued and then enetered a diet, exercise and drug washoff run-in period of 6 weeks. If Hba1c was >=6.5 and <10% and FPG was >=130 mg/dl and <=240 mg/dl after the diet and exercise (and for patients stopping an OHA , wash off) run-in period, patients entered a 2 week, single blind placebo run-in. Following this placebo run-in eligible patients had baseline measurements and then were randomised to treatment groups
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** some on oral hypoglycaemic drugs and/or insulin **Details of washout period:** Patients on OHA monotherapy with a Hba1c >=6% to <=9% had their OHA discontinued and then enetered a diet, exercise and drug washoff run-in period of 6 weeks (see pre-randomisation phase for more details)
Lifestyle advice	patients received counseling on diet and exercise consistent with ADA recommendations at study entry and throughout the study
Follow-up	**Total follow-up (wks):** 22 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 12 **Frequency of monitoring appointments:** Up to 8 weeks washout/placebo run-in period followed by 12 weeks of treatment. All glucose based efficacy parameters were collected at screening, at week -2, at randomisation (baseline), and at weeks 2, 4, 6, 8 and 12 whereas fasting lipids were measured at screening, at randomisation and week 12. Adverse events were collected by telephone for 14 days following completion of treatment.
Arms	**(1) Sitagliptin (25mg qd)** N: 111 Treatment duration (wks): 12 Washout period (d): 56 Comments: 6 week washout period and 2 week placebo run-in Treatment(s): Sitagliptin (Oral) – fixed-dose Set dose (mg/d):25 Frequency of dosing: once a day Compliance: treatment compliance assessed by returned tablet count Details of dosing regimen: Study blinding was maintained using a double dummy technique with all patients taking study medications twice daily **(2) Sitagliptin (50mg qd)** N: 112 Treatment duration (wks): 12 Washout period (d): 56 Comments: 6 week washout period and 2 week placebo run-in Treatment(s): Sitagliptin (Oral) – fixed-dose Set dose (mg/d):50 Frequency of dosing: once a day Compliance: treatment compliance assessed by returned tablet count Details of dosing regimen: Study blinding was maintained using a double dummy technique with all patients taking study medications twice daily **(3) Sitagliptin (100mg qd)** N: 110 Treatment duration (wks): 12 Washout period (d): 56 Comments: 6 week washout period and 2 week placebo run-in Treatment(s): Sitagliptin (Oral) – fixed-dose Set dose (mg/d):100 Frequency of dosing: once a day Compliance: treatment compliance assessed by returned tablet count Details of dosing regimen: Study blinding was maintained using a double dummy technique with all patients taking study medications twice daily **(4) Sitagliptin (50mg bid)** N: 111 Treatment duration (wks): 12 Washout period (d): 56 Comments: 6 week washout period and 2 week placebo run-in Treatment(s): Sitagliptin (Oral) – fixed-dose

Set dose (mg/d):100
Frequency of dosing: twice a day
Compliance: treatment compliance assessed by returned tablet count
Details of dosing regimen: Study blinding was maintained using a double dummy technique with all patients taking study medications twice daily

(5) placebo

N: 111

Treatment duration (wks): 12
Washout period (d): 56
Comments: 6 week washout period and 2 week placebo run-in

Treatment(s): Placebo (Oral) – fixed-dose
Frequency of dosing: once a day
Compliance: treatment compliance assessed by returned tablet count
Details of dosing regimen: Study blinding was maintained using a double dummy technique with all patients taking study medications twice daily

Outcomes

General

Efficacy analyses were based on the all patients treated (APT) population, consisting of all randomised patients who received at least one dose of study drug and who had both a baseline (randomisation visit) and at least oe post-randomisation measurement. Missing values were estimated by using the last observation carried forward method.

30 (27%) patients in placebo, 15 (13.6%) in 25 mg qd, 6 (5.5%) in 50 mg qd, 18 (16.4%) in 100 mg qd and 11 (9.9%) in 50 mg bid discontinued the study

Outcomes not extracted in this evidence table include mean daily glucose, fasting insulin, HOMA-beta, HOMA-IR, QUICKI and FFA

Baseline characteristics

		Sitagliptin (25mg qd)			Sitagliptin (50mg qd)				
		N	k	mean	N	k	mean	Δ	p
Demographics:									
Age (years)	Continuous	111		55.1 (SD 9.6)	112		55.3 (SD 10.3)		
Sex (n male)	Dichotomous	111	57	(51.4%)	112	51	(45.5%)		
Duration of diabetes (yrs)	Continuous	111		3.6 (SD 3.4)	112		3.3 (SD 3.9)		
Ethnicity-White	Dichotomous	111	98	(88.3%)	112	96	(85.7%)		
Ethnicity-Black	Dichotomous	111	4	(3.6%)	112	9	(8.0%)		
Ethnicity-Asian	Dichotomous	111	1	(0.9%)	112	0	(0.0%)		
Ethnicity-Other	Dichotomous	111	8	(7.2%)	112	7	(6.3%)		
Blood glucose:									
HbA1c (%) – 0wk	Continuous	111		7.7 (SD 0.9)	112		7.6 (SD 1)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	111		9.69585 (SD 2.56)	112		9.4572 (SD 2.1)		
Body weight:									
BMI (kg/m2)	Continuous	111		31.9 (SD 4.8)	112		31.6 (SD 4.9)		
Weight (kg) – 0wka	Continuous	111		90.03456 (SD 13.5)	112		89.18784 (SD 13.8)		
Previous blood glucose lowering drugs:									
Diet alone (i.e. drug naïve)	Dichotomous	111	41	(36.9%)	112	39	(34.8%)		
Oral antidiabetic medication	Dichotomous	111	70	(63.1%)	112	73	(65.2%)		

[a] estimated from BMI assuming mean height of 1.68m

		Sitagliptin (25mg qd)			Sitagliptin (100mg qd)				
		N	k	mean	N	k	mean	Δ	p
Demographics:									
Age (years)	Continuous	111		55.1 (SD 9.6)	110		56 (SD 7.9)		
Sex (n male)	Dichotomous	111	57	(51.4%)	110	61	(55.5%)		
Duration of diabetes (yrs)	Continuous	111		3.6 (SD 3.4)	110		3.6 (SD 3.9)		
Ethnicity-White	Dichotomous	111	98	(88.3%)	110	97	(88.2%)		
Ethnicity-Black	Dichotomous	111	4	(3.6%)	110	6	(5.5%)		

Ethnicity-Asian	Dichotomous	111	1	(0.9%)	110	0	(0.0%)		
Ethnicity-Other	Dichotomous	111	8	(7.2%)	110	7	(6.4%)		
Blood glucose:									
HbA1c (%) – 0wk	Continuous	111		7.7 (SD 0.9)	110		7.8 (SD 0.9)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	111		9.69585 (SD 2.56)	110		9.85125 (SD 2.3)		
Body weight:									
BMI (kg/m2)	Continuous	111		31.9 (SD 4.8)	110		31.6 (SD 5.8)		
Weight (kg) – 0wka	Continuous	111		90.03456 (SD 13.5)	110		89.18784 (SD 16.4)		
Previous blood glucose lowering drugs:									
Diet alone (i.e. drug naïve)	Dichotomous	111	41	(36.9%)	110	41	(37.3%)		
Oral antidiabetic medication	Dichotomous	111	70	(63.1%)	110	69	(62.7%)		

[a] estimated from BMI assuming mean height of 1.68m

		Sitagliptin (25mg qd)			Sitagliptin (50mg bid)				
		N	k	mean	N	k	mean	Δ	p
Demographics:									
Age (years)	Continuous	111		55.1 (SD 9.6)	111		55.2 (SD 9.5)		
Sex (n male)	Dichotomous	111	57	(51.4%)	111	49	(44.1%)		
Duration of diabetes (yrs)	Continuous	111		3.6 (SD 3.4)	111		4.5 (SD 5.9)		
Ethnicity-White	Dichotomous	111	98	(88.3%)	111	90	(81.1%)		
Ethnicity-Black	Dichotomous	111	4	(3.6%)	111	7	(6.3%)		
Ethnicity-Asian	Dichotomous	111	1	(0.9%)	111	1	(0.9%)		
Ethnicity-Other	Dichotomous	111	8	(7.2%)	111	13	(11.7%)		
Blood glucose:									
HbA1c (%) – 0wk	Continuous	111		7.7 (SD 0.9)	111		7.8 (SD 0.9)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	111		9.69585 (SD 2.56)	111		9.6681 (SD 2.37)		
Body weight:									
BMI (kg/m2)	Continuous	111		31.9 (SD 4.8)	111		32.7 (SD 4.8)		
Weight (kg) – 0wka	Continuous	111		90.03456 (SD 13.5)	111		92.29248 (SD 13.5)		
Previous blood glucose lowering drugs:									
Diet alone (i.e. drug naïve)	Dichotomous	111	41	(36.9%)	111	38	(34.2%)		
Oral antidiabetic medication	Dichotomous	111	70	(63.1%)	111	73	(65.8%)		

[a] estimated from BMI assuming mean height of 1.68m

		Sitagliptin (25mg qd)			placebo				
		N	k	mean	N	k	mean	Δ	p
Demographics:									
Age (years)	Continuous	111		55.1 (SD 9.6)	111		55.9 (SD 9.3)		
Sex (n male)	Dichotomous	111	57	(51.4%)	111	70	(63.1%)		
Duration of diabetes (yrs)	Continuous	111		3.6 (SD 3.4)	111		3.3 (SD 3.4)		
Ethnicity-White	Dichotomous	111	98	(88.3%)	111	87	(78.4%)		
Ethnicity-Black	Dichotomous	111	4	(3.6%)	111	8	(7.2%)		
Ethnicity-Asian	Dichotomous	111	1	(0.9%)	111	1	(0.9%)		
Ethnicity-Other	Dichotomous	111	8	(7.2%)	111	15	(13.5%)		
Blood glucose:									
HbA1c (%) – 0wk	Continuous	111		7.7 (SD 0.9)	111		7.6 (SD 0.9)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	111		9.69585 (SD 2.56)	111		9.8013 (SD 2.37)		

Body weight: BMI (kg/m2)	Continuous	111		31.9 (SD 4.8)	111		31.4 (SD 5.1)		
Weight (kg) – 0wka	Continuous	111		90.03456 (SD 13.5)	111		88.62336 (SD 14.4)		
Previous blood glucose lowering drugs: Diet alone (i.e. drug naïve)	Dichotomous	111	41	(36.9%)	111	39	(35.1%)		
Oral antidiabetic medication	Dichotomous	111	70	(63.1%)	111	72	(64.9%)		

[a] estimated from BMI assuming mean height of 1.68m

		Sitagliptin (50mg qd)			Sitagliptin (100mg qd)				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	112		55.3 (SD 10.3)	110		56 (SD 7.9)		
Sex (n male)	Dichotomous	112	51	(45.5%)	110	61	(55.5%)		
Duration of diabetes (yrs)	Continuous	112		3.3 (SD 3.9)	110		3.6 (SD 3.9)		
Ethnicity-White	Dichotomous	112	96	(85.7%)	110	97	(88.2%)		
Ethnicity-Black	Dichotomous	112	9	(8.0%)	110	6	(5.5%)		
Ethnicity-Asian	Dichotomous	112	0	(0.0%)	110	0	(0.0%)		
Ethnicity-Other	Dichotomous	112	7	(6.3%)	110	7	(6.4%)		
Blood glucose: HbA1c (%) – 0wk	Continuous	112		7.6 (SD 1)	110		7.8 (SD 0.9)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	112		9.4572 (SD 2.1)	110		9.85125 (SD 2.3)		
Body weight: BMI (kg/m2)	Continuous	112		31.6 (SD 4.9)	110		31.6 (SD 5.8)		
Weight (kg) – 0wka	Continuous	112		89.18784 (SD 13.8)	110		89.18784 (SD 16.4)		
Previous blood glucose lowering drugs: Diet alone (i.e. drug naïve)	Dichotomous	112	39	(34.8%)	110	41	(37.3%)		
Oral antidiabetic medication	Dichotomous	112	73	(65.2%)	110	69	(62.7%)		

[a] estimated from BMI assuming mean height of 1.68m

		Sitagliptin (50mg qd)			Sitagliptin (50mg bid)				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	112		55.3 (SD 10.3)	111		55.2 (SD 9.5)		
Sex (n male)	Dichotomous	112	51	(45.5%)	111	49	(44.1%)		
Duration of diabetes (yrs)	Continuous	112		3.3 (SD 3.9)	111		4.5 (SD 5.9)		
Ethnicity-White	Dichotomous	112	96	(85.7%)	111	90	(81.1%)		
Ethnicity-Black	Dichotomous	112	9	(8.0%)	111	7	(6.3%)		
Ethnicity-Asian	Dichotomous	112	0	(0.0%)	111	1	(0.9%)		
Ethnicity-Other	Dichotomous	112	7	(6.3%)	111	13	(11.7%)		
Blood glucose: HbA1c (%) – 0wk	Continuous	112		7.6 (SD 1)	111		7.8 (SD 0.9)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	112		9.4572 (SD 2.1)	111		9.6681 (SD 2.37)		
Body weight: BMI (kg/m2)	Continuous	112		31.6 (SD 4.9)	111		32.7 (SD 4.8)		
Weight (kg) – 0wka	Continuous	112		89.18784 (SD 13.8)	111		92.29248 (SD 13.5)		
Previous blood glucose lowering drugs: Diet alone (i.e. drug naïve)	Dichotomous	112	39	(34.8%)	111	38	(34.2%)		
Oral antidiabetic medication	Dichotomous	112	73	(65.2%)	111	73	(65.8%)		

[a] estimated from BMI assuming mean height of 1.68m

		Sitagliptin (50mg qd)			placebo				
		N	k	mean	N	k	mean	Δ	p
Demographics:									
Age (years)	Continuous	112		55.3 (SD 10.3)	111		55.9 (SD 9.3)		
Sex (n male)	Dichotomous	112	51	(45.5%)	111	70	(63.1%)		
Duration of diabetes (yrs)	Continuous	112		3.3 (SD 3.9)	111		3.3 (SD 3.4)		
Ethnicity-White	Dichotomous	112	96	(85.7%)	111	87	(78.4%)		
Ethnicity-Black	Dichotomous	112	9	(8.0%)	111	8	(7.2%)		
Ethnicity-Asian	Dichotomous	112	0	(0.0%)	111	1	(0.9%)		
Ethnicity-Other	Dichotomous	112	7	(6.3%)	111	15	(13.5%)		
Blood glucose:									
HbA1c (%) – 0wk	Continuous	112		7.6 (SD 1)	111		7.6 (SD 0.9)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	112		9.4572 (SD 2.1)	111		9.8013 (SD 2.37)		
Body weight:									
BMI (kg/m2)	Continuous	112		31.6 (SD 4.9)	111		31.4 (SD 5.1)		
Weight (kg) – 0wka	Continuous	112		89.18784 (SD 13.8)	111		88.62336 (SD 14.4)		
Previous blood glucose lowering drugs:									
Diet alone (i.e. drug naïve)	Dichotomous	112	39	(34.8%)	111	39	(35.1%)		
Oral antidiabetic medication	Dichotomous	112	73	(65.2%)	111	72	(64.9%)		

[a] estimated from BMI assuming mean height of 1.68m

		Sitagliptin (100mg qd)			Sitagliptin (50mg bid)				
		N	k	mean	N	k	mean	Δ	p
Demographics:									
Age (years)	Continuous	110		56 (SD 7.9)	111		55.2 (SD 9.5)		
Sex (n male)	Dichotomous	110	61	(55.5%)	111	49	(44.1%)		
Duration of diabetes (yrs)	Continuous	110		3.6 (SD 3.9)	111		4.5 (SD 5.9)		
Ethnicity-White	Dichotomous	110	97	(88.2%)	111	90	(81.1%)		
Ethnicity-Black	Dichotomous	110	6	(5.5%)	111	7	(6.3%)		
Ethnicity-Asian	Dichotomous	110	0	(0.0%)	111	1	(0.9%)		
Ethnicity-Other	Dichotomous	110	7	(6.4%)	111	13	(11.7%)		
Blood glucose:									
HbA1c (%) – 0wk	Continuous	110		7.8 (SD 0.9)	111		7.8 (SD 0.9)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	110		9.85125 (SD 2.3)	111		9.6681 (SD 2.37)		
Body weight:									
BMI (kg/m2)	Continuous	110		31.6 (SD 5.8)	111		32.7 (SD 4.8)		
Weight (kg) – 0wka	Continuous	110		89.18784 (SD 16.4)	111		92.29248 (SD 13.5)		
Previous blood glucose lowering drugs:									
Diet alone (i.e. drug naïve)	Dichotomous	110	41	(37.3%)	111	38	(34.2%)		
Oral antidiabetic medication	Dichotomous	110	69	(62.7%)	111	73	(65.8%)		

[a] estimated from BMI assuming mean height of 1.68m

		Sitagliptin (100mg qd)			placebo				
		N	k	mean	N	k	mean	Δ	p
Demographics:									
Age (years)	Continuous	110		56 (SD 7.9)	111		55.9 (SD 9.3)		

Sex (n male)	Dichotomous	110	61	(55.5%)	111	70	(63.1%)		
Duration of diabetes (yrs)	Continuous	110		3.6 (SD 3.9)	111		3.3 (SD 3.4)		
Ethnicity-White	Dichotomous	110	97	(88.2%)	111	87	(78.4%)		
Ethnicity-Black	Dichotomous	110	6	(5.5%)	111	8	(7.2%)		
Ethnicity-Asian	Dichotomous	110	0	(0.0%)	111	1	(0.9%)		
Ethnicity-Other	Dichotomous	110	7	(6.4%)	111	15	(13.5%)		
Blood glucose: HbA1c (%) – 0wk	Continuous	110		7.8 (SD 0.9)	111		7.6 (SD 0.9)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	110		9.85125 (SD 2.3)	111		9.8013 (SD 2.37)		
Body weight: BMI (kg/m2)	Continuous	110		31.6 (SD 5.8)	111		31.4 (SD 5.1)		
Weight (kg) – 0wka	Continuous	110		89.18784 (SD 16.4)	111		88.62336 (SD 14.4)		
Previous blood glucose lowering drugs: Diet alone (i.e. drug naïve)	Dichotomous	110	41	(37.3%)	111	39	(35.1%)		
Oral antidiabetic medication	Dichotomous	110	69	(62.7%)	111	72	(64.9%)		

[a] estimated from BMI assuming mean height of 1.68m

		Sitagliptin (50mg bid)			placebo				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	111		55.2 (SD 9.5)	111		55.9 (SD 9.3)		
Sex (n male)	Dichotomous	111	49	(44.1%)	111	70	(63.1%)		
Duration of diabetes (yrs)	Continuous	111		4.5 (SD 5.9)	111		3.3 (SD 3.4)		
Ethnicity-White	Dichotomous	111	90	(81.1%)	111	87	(78.4%)		
Ethnicity-Black	Dichotomous	111	7	(6.3%)	111	8	(7.2%)		
Ethnicity-Asian	Dichotomous	111	1	(0.9%)	111	1	(0.9%)		
Ethnicity-Other	Dichotomous	111	13	(11.7%)	111	15	(13.5%)		
Blood glucose: HbA1c (%) – 0wk	Continuous	111		7.8 (SD 0.9)	111		7.6 (SD 0.9)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	111		9.6681 (SD 2.37)	111		9.8013 (SD 2.37)		
Body weight: BMI (kg/m2)	Continuous	111		32.7 (SD 4.8)	111		31.4 (SD 5.1)		
Weight (kg) – 0wka	Continuous	111		92.29248 (SD 13.5)	111		88.62336 (SD 14.4)		
Previous blood glucose lowering drugs: Diet alone (i.e. drug naïve)	Dichotomous	111	38	(34.2%)	111	39	(35.1%)		
Oral antidiabetic medication	Dichotomous	111	73	(65.8%)	111	72	(64.9%)		

[a] estimated from BMI assuming mean height of 1.68m

Results

		Sitagliptin (25mg qd)			Sitagliptin (50mg qd)				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 12wka	Mean change	107		-0.28 (SD 0.753)	107		-0.44 (SD 0.756)		
HbA1c (%) – 12wk	Continuous	107		7.47 (SD 1.3)	107		7.22 (SD 1.02)		
Fasting plasma glucose (mmol/l) – 12wk	Mean change	108		-0.59385 (SD 1.85)	108		-0.8547 (SD 1.85)		
Hypoglycaemic events: All hypoglycaemic events (no patients) – 12wk	Dichotomous	110	1	(0.9%)	110	1	(0.9%)		

Adverse events: Any adverse event(s) – 12wk	Dichotomous	110	49	(44.5%)	110	50	(45.5%)		
Any serious adverse event(s) – 12wk	Dichotomous	110	1	(0.9%)	110	4	(3.6%)		
Serious AE drug related – 12wk	Dichotomous	110	0	(0.0%)	110	0	(0.0%)		
Study drug-related adverse event – 12wk	Dichotomous	110	12	(10.9%)	110	11	(10.0%)		
Death – 12wk	Dichotomous	110	0	(0.0%)	110	0	(0.0%)		
Gastrointestinal disorders (any) – 12wk	Dichotomous	110	13	(11.8%)	110	10	(9.1%)		
Headache – 12wk	Dichotomous	110	2	(1.8%)	110	2	(1.8%)		
Dropouts: Total dropouts – 12wk	Dichotomous	111	15	(13.5%)	112	6	(5.4%)		
Dropout due to AEs – 12wk	Dichotomous	111	2	(1.8%)	112	0	(0.0%)		
drop out due to drug related AE – 12wk	Dichotomous	111	2	(1.8%)	112	0	(0.0%)		
drop out due to SAE – 12wk	Dichotomous	111	0	(0.0%)	112	0	(0.0%)		
drop out due to drug related SAE – 12wk	Dichotomous	111	0	(0.0%)	112	0	(0.0%)		
Drop out due to unsatisfactory effect – 12wk	Dichotomous	111	8	(7.2%)	112	2	(1.8%)		
Lipids: Total cholesterol (mmol/l) – 12wk	Mean change	105		0.03879 (SD 0.324)	106		0.028446 (SD 0.326)		
HDL cholesterol (mmol/l) – 12wk	Mean change	105		0.082752 (SD 0.352)	106		0.16809 (SD 0.367)		
Triglycerides (mmol/l) – 12wk	Mean change	105		-0.044031 (SD 0.431)	106		-0.089191 (SD 0.439)		
LDL cholesterol (mmol/l) – 12wk	Mean change	105		0.126714 (SD 0.541)	106		0.074994 (SD 0.53)		

[a] SD calculated from reported 95% CI

		Sitagliptin (25mg qd)			Sitagliptin (100mg qd)				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Blood glucose: HbA1c (%) – 12wka	Mean change	107		-0.28 (SD 0.753)	106		-0.44 (SD 0.749)		
HbA1c (%) – 12wk	Continuous	107		7.47 (SD 1.3)	106		7.38 (SD 1.11)		
Fasting plasma glucose (mmol/l) – 12wk	Mean change	108		-0.59385 (SD 1.85)	108		-0.9435 (SD 1.82)		
Hypoglycaemic events: All hypoglycaemic events (no patients) – 12wk	Dichotomous	110	1	(0.9%)	110	2	(1.8%)		
Adverse events: Any adverse event(s) – 12wk	Dichotomous	110	49	(44.5%)	110	51	(46.4%)		
Any serious adverse event(s) – 12wk	Dichotomous	110	1	(0.9%)	110	3	(2.7%)		
Serious AE drug related – 12wk	Dichotomous	110	0	(0.0%)	110	0	(0.0%)		
Study drug-related adverse event – 12wk	Dichotomous	110	12	(10.9%)	110	11	(10.0%)		
Death – 12wk	Dichotomous	110	0	(0.0%)	110	0	(0.0%)		
Gastrointestinal disorders (any) – 12wk	Dichotomous	110	13	(11.8%)	110	10	(9.1%)		
Headache – 12wk	Dichotomous	110	2	(1.8%)	110	4	(3.6%)		
Dropouts: Total dropouts – 12wk	Dichotomous	111	15	(13.5%)	110	18	(16.4%)		
Dropout due to AEs – 12wk	Dichotomous	111	2	(1.8%)	110	5	(4.5%)		
drop out due to drug related AE – 12wk	Dichotomous	111	2	(1.8%)	110	1	(0.9%)		

drop out due to SAE – 12wk	Dichotomous	111	0	(0.0%)	110	2	(1.8%)		
drop out due to drug related SAE – 12wk	Dichotomous	111	0	(0.0%)	110	0	(0.0%)		
Drop out due to unsatisfactory effect – 12wk	Dichotomous	111	8	(7.2%)	110	9	(8.2%)		
Lipids: Total cholesterol (mmol/l) – 12wk	Mean change	105		0.03879 (SD 0.324)	104		0.098268 (SD 0.336)		
HDL cholesterol (mmol/l) – 12wk	Mean change	105		0.082752 (SD 0.352)	104		0.139644 (SD 0.363)		
Triglycerides (mmol/l) – 12wk	Mean change	105		-0.044031 (SD 0.431)	104		0.009032 (SD 0.435)		
LDL cholesterol (mmol/l) – 12wk	Mean change	105		0.126714 (SD 0.541)	104		0.191364 (SD 0.538)		

[a] SD calculated from reported 95% CI

		Sitagliptin (25mg qd)			Sitagliptin (50mg bid)				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 12wka	Mean change	107		-0.28 (SD 0.753)	108		-0.43 (SD 0.699)		
HbA1c (%) – 12wk	Continuous	107		7.47 (SD 1.3)	108		7.41 (SD 1.1)		
Fasting plasma glucose (mmol/l) – 12wk	Mean change	108		-0.59385 (SD 1.85)	108		-0.76035 (SD 1.85)		
Hypoglycaemic events: All hypoglycaemic events (no patients) – 12wk	Dichotomous	110	1	(0.9%)	111	1	(0.9%)		
Adverse events: Any adverse event(s) – 12wk	Dichotomous	110	49	(44.5%)	111	51	(45.9%)		
Any serious adverse event(s) – 12wk	Dichotomous	110	1	(0.9%)	111	3	(2.7%)		
Serious AE drug related – 12wk	Dichotomous	110	0	(0.0%)	111	1	(0.9%)		
Study drug-related adverse event – 12wk	Dichotomous	110	12	(10.9%)	111	16	(14.4%)		
Death – 12wk	Dichotomous	110	0	(0.0%)	111	0	(0.0%)		
Gastrointestinal disorders (any) – 12wk	Dichotomous	110	13	(11.8%)	111	9	(8.1%)		
Headache – 12wk	Dichotomous	110	2	(1.8%)	111	4	(3.6%)		
Dropouts: Total dropouts – 12wk	Dichotomous	111	15	(13.5%)	111	11	(9.9%)		
Dropout due to AEs – 12wk	Dichotomous	111	2	(1.8%)	111	2	(1.8%)		
drop out due to drug related AE – 12wk	Dichotomous	111	2	(1.8%)	111	1	(0.9%)		
drop out due to SAE – 12wk	Dichotomous	111	0	(0.0%)	111	1	(0.9%)		
drop out due to drug related SAE – 12wk	Dichotomous	111	0	(0.0%)	111	1	(0.9%)		
Drop out due to unsatisfactory effect – 12wk	Dichotomous	111	8	(7.2%)	111	2	(1.8%)		
Lipids: Total cholesterol (mmol/l) – 12wk	Mean change	105		0.03879 (SD 0.324)	103		0.054306 (SD 0.335)		
HDL cholesterol (mmol/l) – 12wk	Mean change	105		0.082752 (SD 0.352)	103		0.080166 (SD 0.362)		
Triglycerides (mmol/l) – 12wk	Mean change	105		-0.044031 (SD 0.431)	103		-0.019193 (SD 0.438)		
LDL cholesterol (mmol/l) – 12wk	Mean change	105		0.126714 (SD 0.541)	103		0.160332 (SD 0.549)		

[a] SD calculated from reported 95% CI

	Sitagliptin (25mg qd)	placebo	Δ	p

		N	k	mean	N	k	mean		
Blood glucose: HbA1c (%) – 12wka	Mean change	107		-0.28 (SD 0.753)	107		0.12 (SD 0.753)	MD=-0.390 (CI: -0.590, -0.190)	<0.001b
HbA1c (%) – 12wk	Continuous	107		7.47 (SD 1.3)	107		7.76 (SD 1.11)		
Fasting plasma glucose (mmol/l) – 12wk	Mean change	108		-0.59385 (SD 1.85)	108		0.0111 (SD 1.85)	MD=-0.611 (CI: -1.099, -0.122)	<0.05b
Body weight: Weight (kg) – 12wk	Continuous	111			111				c
Hypoglycaemic events: All hypoglycaemic events (no patients) – 12wk	Dichotomous	110	1	(0.9%)	111	0	(0.0%)		c
Adverse events: Any adverse event(s) – 12wk	Dichotomous	110	49	(44.5%)	111	38	(34.2%)		c
Any serious adverse event(s) – 12wk	Dichotomous	110	1	(0.9%)	111	2	(1.8%)		c
Serious AE drug related – 12wk	Dichotomous	110	0	(0.0%)	111	0	(0.0%)		c
Study drug-related adverse event – 12wk	Dichotomous	110	12	(10.9%)	111	10	(9.0%)		c
Death – 12wk	Dichotomous	110	0	(0.0%)	111	0	(0.0%)		c
Gastrointestinal disorders (any) – 12wk	Dichotomous	110	13	(11.8%)	111	15	(13.5%)		c
Headache – 12wk	Dichotomous	110	2	(1.8%)	111	3	(2.7%)		c
Dropouts: Total dropouts – 12wk	Dichotomous	111	15	(13.5%)	111	30	(27.0%)		
Dropout due to AEs – 12wk	Dichotomous	111	2	(1.8%)	111	4	(3.6%)		c
drop out due to drug related AE – 12wk	Dichotomous	111	2	(1.8%)	111	3	(2.7%)		c
drop out due to SAE – 12wk	Dichotomous	111	0	(0.0%)	111	1	(0.9%)		c
drop out due to drug related SAE – 12wk	Dichotomous	111	0	(0.0%)	111	0	(0.0%)		c
Drop out due to unsatisfactory effect – 12wk	Dichotomous	111	8	(7.2%)	111	9	(8.1%)		c
Lipids: Total cholesterol (mmol/l) – 12wk	Mean change	105		0.03879 (SD 0.324)	103		-0.002586 (SD 0.321)	MD=0.041 (CI: -0.047, 0.129)	
HDL cholesterol (mmol/l) – 12wk	Mean change	105		0.082752 (SD 0.352)	103		0.028446 (SD 0.362)	MD=0.054 (CI: -0.041, 0.150)	
Triglycerides (mmol/l) – 12wk	Mean change	105		-0.044031 (SD 0.431)	103		0.058708 (SD 0.433)	MD=-0.103 (CI: -0.220, 0.015)	
LDL cholesterol (mmol/l) – 12wk	Mean change	105		0.126714 (SD 0.541)	103		-0.010344 (SD 0.536)	MD=0.137 (CI: -0.010, 0.284)	

[a] SD calculated from reported 95% CI
[b] from trend test for sitagliptin qd vs. placebo
[c] not reported

	Sitagliptin (50mg qd)	Sitagliptin (100mg qd)	Δ	p

		N	k	mean	N	k	mean		
Blood glucose: HbA1c (%) – 12wka	Mean change	107		-0.44 (SD 0.756)	106		-0.44 (SD 0.749)		
HbA1c (%) – 12wk	Continuous	107		7.22 (SD 1.02)	106		7.38 (SD 1.11)		
Fasting plasma glucose (mmol/l) – 12wk	Mean change	108		-0.8547 (SD 1.85)	108		-0.9435 (SD 1.82)		
Hypoglycaemic events: All hypoglycaemic events (no patients) – 12wk	Dichotomous	110	1	(0.9%)	110	2	(1.8%)		
Adverse events: Any adverse event(s) – 12wk	Dichotomous	110	50	(45.5%)	110	51	(46.4%)		
Any serious adverse event(s) – 12wk	Dichotomous	110	4	(3.6%)	110	3	(2.7%)		
Serious AE drug related – 12wk	Dichotomous	110	0	(0.0%)	110	0	(0.0%)		
Study drug-related adverse event – 12wk	Dichotomous	110	11	(10.0%)	110	11	(10.0%)		
Death – 12wk	Dichotomous	110	0	(0.0%)	110	0	(0.0%)		
Gastrointestinal disorders (any) – 12wk	Dichotomous	110	10	(9.1%)	110	10	(9.1%)		
Headache – 12wk	Dichotomous	110	2	(1.8%)	110	4	(3.6%)		
Dropouts: Total dropouts – 12wk	Dichotomous	112	6	(5.4%)	110	18	(16.4%)		
Dropout due to AEs – 12wk	Dichotomous	112	0	(0.0%)	110	5	(4.5%)		
drop out due to drug related AE – 12wk	Dichotomous	112	0	(0.0%)	110	1	(0.9%)		
drop out due to SAE – 12wk	Dichotomous	112	0	(0.0%)	110	2	(1.8%)		
drop out due to drug related SAE – 12wk	Dichotomous	112	0	(0.0%)	110	0	(0.0%)		
Drop out due to unsatisfactory effect – 12wk	Dichotomous	112	2	(1.8%)	110	9	(8.2%)		
Lipids: Total cholesterol (mmol/l) – 12wk	Mean change	106		0.028446 (SD 0.326)	104		0.098268 (SD 0.336)		
HDL cholesterol (mmol/l) – 12wk	Mean change	106		0.16809 (SD 0.367)	104		0.139644 (SD 0.363)		
Triglycerides (mmol/l) – 12wk	Mean change	106		-0.089191 (SD 0.439)	104		0.009032 (SD 0.435)		
LDL cholesterol (mmol/l) – 12wk	Mean change	106		0.074994 (SD 0.53)	104		0.191364 (SD 0.538)		

[a] SD calculated from reported 95% CI

		Sitagliptin (50mg qd)			Sitagliptin (50mg bid)				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 12wka	Mean change	107		-0.44 (SD 0.756)	108		-0.43 (SD 0.699)		
HbA1c (%) – 12wk	Continuous	107		7.22 (SD 1.02)	108		7.41 (SD 1.1)		
Fasting plasma glucose (mmol/l) – 12wk	Mean change	108		-0.8547 (SD 1.85)	108		-0.76035 (SD 1.85)		
Hypoglycaemic events: All hypoglycaemic events (no patients) – 12wk	Dichotomous	110	1	(0.9%)	111	1	(0.9%)		
Adverse events: Any adverse event(s) – 12wk	Dichotomous	110	50	(45.5%)	111	51	(45.9%)		
Any serious adverse event(s) – 12wk	Dichotomous	110	4	(3.6%)	111	3	(2.7%)		
Serious AE drug related – 12wk	Dichotomous	110	0	(0.0%)	111	1	(0.9%)		
Study drug-related adverse event – 12wk	Dichotomous	110	11	(10.0%)	111	16	(14.4%)		b

Death – 12wk	Dichotomous	110	0	(0.0%)	111	0	(0.0%)			
Gastrointestinal disorders (any) – 12wk	Dichotomous	110	10	(9.1%)	111	9	(8.1%)			
Headache – 12wk	Dichotomous	110	2	(1.8%)	111	4	(3.6%)			
Dropouts:										
Total dropouts – 12wk	Dichotomous	112	6	(5.4%)	111	11	(9.9%)			
Dropout due to AEs – 12wk	Dichotomous	112	0	(0.0%)	111	2	(1.8%)			
drop out due to drug related AE – 12wk	Dichotomous	112	0	(0.0%)	111	1	(0.9%)			
drop out due to SAE – 12wk	Dichotomous	112	0	(0.0%)	111	1	(0.9%)			
drop out due to drug related SAE – 12wk	Dichotomous	112	0	(0.0%)	111	1	(0.9%)			
Drop out due to unsatisfactory effect – 12wk	Dichotomous	112	2	(1.8%)	111	2	(1.8%)			
Lipids:										
Total cholesterol (mmol/l) – 12wk	Mean change	106		0.028446 (SD 0.326)	103		0.054306 (SD 0.335)			
HDL cholesterol (mmol/l) – 12wk	Mean change	106		0.16809 (SD 0.367)	103		0.080166 (SD 0.362)			
Triglycerides (mmol/l) – 12wk	Mean change	106		-0.089191 (SD 0.439)	103		-0.019193 (SD 0.438)			
LDL cholesterol (mmol/l) – 12wk	Mean change	106		0.074994 (SD 0.53)	103		0.160332 (SD 0.549)			

[a] SD calculated from reported 95% CI
[b] not reported

		Sitagliptin (50mg qd)			placebo				
		N	k	mean	N	k	mean	Δ	p
Blood glucose:									
HbA1c (%) – 12wka	Mean change	107		-0.44 (SD 0.756)	107		0.12 (SD 0.753)	MD=-0.550 (CI: -0.750, -0.350)	<0.001b
HbA1c (%) – 12wk	Continuous	107		7.22 (SD 1.02)	107		7.76 (SD 1.11)		
Fasting plasma glucose (mmol/l) – 12wk	Mean change	108		-0.8547 (SD 1.85)	108		0.0111 (SD 1.85)	MD=-0.866 (CI: -1.354, -0.377)	<0.001b
Body weight:									
Weight (kg) – 12wk	Continuous	112			111				c
Hypoglycaemic events:									
All hypoglycaemic events (no patients) – 12wk	Dichotomous	110	1	(0.9%)	111	0	(0.0%)		c
Adverse events:									
Any adverse event(s) – 12wk	Dichotomous	110	50	(45.5%)	111	38	(34.2%)		c
Any serious adverse event(s) – 12wk	Dichotomous	110	4	(3.6%)	111	2	(1.8%)		
Serious AE drug related – 12wk	Dichotomous	110	0	(0.0%)	111	0	(0.0%)		c
Study drug-related adverse event – 12wk	Dichotomous	110	11	(10.0%)	111	10	(9.0%)		c
Death – 12wk	Dichotomous	110	0	(0.0%)	111	0	(0.0%)		c
Gastrointestinal disorders (any) – 12wk	Dichotomous	110	10	(9.1%)	111	15	(13.5%)		c
Headache – 12wk	Dichotomous	110	2	(1.8%)	111	3	(2.7%)		c
Dropouts:									
Total dropouts – 12wk	Dichotomous	112	6	(5.4%)	111	30	(27.0%)		
Dropout due to AEs – 12wk	Dichotomous	112	0	(0.0%)	111	4	(3.6%)		c

drop out due to drug related AE – 12wk	Dichotomous	112	0	(0.0%)	111	3	(2.7%)		c
drop out due to SAE – 12wk	Dichotomous	112	0	(0.0%)	111	1	(0.9%)		c
drop out due to drug related SAE – 12wk	Dichotomous	112	0	(0.0%)	111	0	(0.0%)		c
Drop out due to unsatisfactory effect – 12wk	Dichotomous	112	2	(1.8%)	111	9	(8.1%)		c
Lipids: Total cholesterol (mmol/l) – 12wk	Mean change	106		0.028446 (SD 0.326)	103		-0.002586 (SD 0.321)	MD=0.031 (CI: -0.057, 0.119)	
HDL cholesterol (mmol/l) – 12wk	Mean change	106		0.16809 (SD 0.367)	103		0.028446 (SD 0.362)	MD=0.137 (CI: 0.041, 0.233)	
Triglycerides (mmol/l) – 12wk	Mean change	106		-0.089191 (SD 0.439)	103		0.058708 (SD 0.433)	MD=-0.149 (CI: -0.265, -0.033)	
LDL cholesterol (mmol/l) – 12wk	Mean change	106		0.074994 (SD 0.53)	103		-0.010344 (SD 0.536)	MD=0.085 (CI: -0.059, 0.230)	
Hba1c>9.0% Blood glucose: HbA1c (%) – 12wk	Mean change	0			0			MD=-1.150 (CI: -2.270, -0.030)	d

[a] SD calculated from reported 95% CI
[b] from trend test for sitagliptin qd vs. placebo
[c] not reported
[d] 95% CI -2.27 to -0.03

		Sitagliptin (100mg qd)			Sitagliptin (50mg bid)			Δ	p
		N	k	mean	N	k	mean		
Blood glucose: HbA1c (%) – 12wka	Mean change	106		-0.44 (SD 0.749)	108		-0.43 (SD 0.699)		
HbA1c (%) – 12wk	Continuous	106		7.38 (SD 1.11)	108		7.41 (SD 1.1)		
Fasting plasma glucose (mmol/l) – 12wk	Mean change	108		-0.9435 (SD 1.82)	108		-0.76035 (SD 1.85)		
Hypoglycaemic events: All hypoglycaemic events (no patients) – 12wk	Dichotomous	110	2	(1.8%)	111	1	(0.9%)		
Adverse events: Any adverse event(s) – 12wk	Dichotomous	110	51	(46.4%)	111	51	(45.9%)		
Any serious adverse event(s) – 12wk	Dichotomous	110	3	(2.7%)	111	3	(2.7%)		
Serious AE drug related – 12wk	Dichotomous	110	0	(0.0%)	111	1	(0.9%)		
Study drug-related adverse event – 12wk	Dichotomous	110	11	(10.0%)	111	16	(14.4%)		
Death – 12wk	Dichotomous	110	0	(0.0%)	111	0	(0.0%)		
Gastrointestinal disorders (any) – 12wk	Dichotomous	110	10	(9.1%)	111	9	(8.1%)		
Headache – 12wk	Dichotomous	110	4	(3.6%)	111	4	(3.6%)		
Dropouts: Total dropouts – 12wk	Dichotomous	110	18	(16.4%)	111	11	(9.9%)		
Dropout due to AEs – 12wk	Dichotomous	110	5	(4.5%)	111	2	(1.8%)		
drop out due to drug related AE – 12wk	Dichotomous	110	1	(0.9%)	111	1	(0.9%)		
drop out due to SAE – 12wk	Dichotomous	110	2	(1.8%)	111	1	(0.9%)		

drop out due to drug related SAE – 12wk	Dichotomous	110	0	(0.0%)	111	1	(0.9%)		
Drop out due to unsatisfactory effect – 12wk	Dichotomous	110	9	(8.2%)	111	2	(1.8%)		
Lipids: Total cholesterol (mmol/l) – 12wk	Mean change	104		0.098268 (SD 0.336)	103		0.054306 (SD 0.335)		
HDL cholesterol (mmol/l) – 12wk	Mean change	104		0.139644 (SD 0.363)	103		0.080166 (SD 0.362)		
Triglycerides (mmol/l) – 12wk	Mean change	104		0.009032 (SD 0.435)	103		-0.019193 (SD 0.438)		
LDL cholesterol (mmol/l) – 12wk	Mean change	104		0.191364 (SD 0.538)	103		0.160332 (SD 0.549)		

[a] SD calculated from reported 95% CI

		Sitagliptin (100mg qd)			placebo				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 12wka	Mean change	106		-0.44 (SD 0.749)	107		0.12 (SD 0.753)	MD=-0.560 (CI: -0.750, -0.370)	<0.001b
HbA1c (%) – 12wk	Continuous	106		7.38 (SD 1.11)	107		7.76 (SD 1.11)		
Fasting plasma glucose (mmol/l) – 12wk	Mean change	108		-0.9435 (SD 1.82)	108		0.0111 (SD 1.85)	MD=-0.955 (CI: -1.443, -0.466)	<0.001b
Body weight: Weight (kg) – 12wk	Continuous	110			111				c
Hypoglycaemic events: All hypoglycaemic events (no patients) – 12wk	Dichotomous	110	2	(1.8%)	111	0	(0.0%)		c
Adverse events: Any adverse event(s) – 12wk	Dichotomous	110	51	(46.4%)	111	38	(34.2%)		c
Any serious adverse event(s) – 12wk	Dichotomous	110	3	(2.7%)	111	2	(1.8%)		c
Serious AE drug related – 12wk	Dichotomous	110	0	(0.0%)	111	0	(0.0%)		c
Study drug-related adverse event – 12wk	Dichotomous	110	11	(10.0%)	111	10	(9.0%)		c
Death – 12wk	Dichotomous	110	0	(0.0%)	111	0	(0.0%)		c
Gastrointestinal disorders (any) – 12wk	Dichotomous	110	10	(9.1%)	111	15	(13.5%)		c
Headache – 12wk	Dichotomous	110	4	(3.6%)	111	3	(2.7%)		c
Dropouts: Total dropouts – 12wk	Dichotomous	110	18	(16.4%)	111	30	(27.0%)		
Dropout due to AEs – 12wk	Dichotomous	110	5	(4.5%)	111	4	(3.6%)		c
drop out due to drug related AE – 12wk	Dichotomous	110	1	(0.9%)	111	3	(2.7%)		c
drop out due to SAE – 12wk	Dichotomous	110	2	(1.8%)	111	1	(0.9%)		c
drop out due to drug related SAE – 12wk	Dichotomous	110	0	(0.0%)	111	0	(0.0%)		c
Drop out due to unsatisfactory effect – 12wk	Dichotomous	110	9	(8.2%)	111	9	(8.1%)		c
Lipids: Total cholesterol (mmol/l) – 12wk	Mean change	104		0.098268 (SD 0.336)	103		-0.002586 (SD 0.321)	MD=0.101 (CI: 0.010, 0.191)	

HDL cholesterol (mmol/l) – 12wk	Mean change	104		0.139644 (SD 0.363)	103		0.028446 (SD 0.362)	MD=0.111 (CI: 0.013, 0.209)	
Triglycerides (mmol/l) – 12wk	Mean change	104		0.009032 (SD 0.435)	103		0.058708 (SD 0.433)	MD=-0.050 (CI: -0.168, 0.069)	
LDL cholesterol (mmol/l) – 12wk	Mean change	104		0.191364 (SD 0.538)	103		-0.010344 (SD 0.536)	MD=0.202 (CI: 0.054, 0.349)	
Hba1c>9.0%									
Blood glucose: HbA1c (%) – 12wk	Mean change	0			0			MD=-1.180 (CI: -2.260, -0.100)	d

[a] SD calculated from reported 95% CI
[b] from trend test for sitagliptin qd vs. placebo
[c] not reported
[d] 95% CI -2.26 to -0.09

		Sitagliptin (50mg bid)			placebo				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Blood glucose: HbA1c (%) – 12wka	Mean change	108		-0.43 (SD 0.699)	107		0.12 (SD 0.753)	MD=-0.540 (CI: -0.740, -0.340)	<0.001b
HbA1c (%) – 12wk	Continuous	108		7.41 (SD 1.1)	107		7.76 (SD 1.11)		
Fasting plasma glucose (mmol/l) – 12wk	Mean change	108		-0.76035 (SD 1.85)	108		0.0111 (SD 1.85)	MD=-0.777 (CI: -1.265, -0.289)	<0.05b
Body weight: Weight (kg) – 12wk	Continuous	111			111				c
Hypoglycaemic events: All hypoglycaemic events (no patients) – 12wk	Dichotomous	111	1	(0.9%)	111	0	(0.0%)		c
Adverse events: Any adverse event(s) – 12wk	Dichotomous	111	51	(45.9%)	111	38	(34.2%)		c
Any serious adverse event(s) – 12wk	Dichotomous	111	3	(2.7%)	111	2	(1.8%)		c
Serious AE drug related – 12wk	Dichotomous	111	1	(0.9%)	111	0	(0.0%)		c
Study drug-related adverse event – 12wk	Dichotomous	111	16	(14.4%)	111	10	(9.0%)		c
Death – 12wk	Dichotomous	111	0	(0.0%)	111	0	(0.0%)		c
Gastrointestinal disorders (any) – 12wk	Dichotomous	111	9	(8.1%)	111	15	(13.5%)		c
Headache – 12wk	Dichotomous	111	4	(3.6%)	111	3	(2.7%)		c
Dropouts: Total dropouts – 12wk	Dichotomous	111	11	(9.9%)	111	30	(27.0%)		
Dropout due to AEs – 12wk	Dichotomous	111	2	(1.8%)	111	4	(3.6%)		c
drop out due to drug related AE – 12wk	Dichotomous	111	1	(0.9%)	111	3	(2.7%)		c
drop out due to SAE – 12wk	Dichotomous	111	1	(0.9%)	111	1	(0.9%)		c
drop out due to drug related SAE – 12wk	Dichotomous	111	1	(0.9%)	111	0	(0.0%)		c
Drop out due to unsatisfactory effect – 12wk	Dichotomous	111	2	(1.8%)	111	9	(8.1%)		c

Lipids: Total cholesterol (mmol/l) – 12wk	Mean change	103		0.054306 (SD 0.335)	103		-0.002586 (SD 0.321)	MD=0.054 (CI: -0.034, 0.142)	
HDL cholesterol (mmol/l) – 12wk	Mean change	103		0.080166 (SD 0.362)	103		0.028446 (SD 0.362)	MD=0.049 (CI: -0.047, 0.145)	
Triglycerides (mmol/l) – 12wk	Mean change	103		-0.019193 (SD 0.438)	103		0.058708 (SD 0.433)	MD=-0.078 (CI: -0.196, 0.041)	
LDL cholesterol (mmol/l) – 12wk	Mean change	103		0.160332 (SD 0.549)	103		-0.010344 (SD 0.536)	MD=0.171 (CI: 0.023, 0.318)	

[a] SD calculated from reported 95% CI
[b] from pairwise comparison for 50 mg bid vs. placebo
[c] not reported

Change in baseline in primary efficacy variable (hba1c) at week 12 was analysed using ANCOVA model with terms for treatment, prior OHA status and baseline Hba1c as covariates. The dose response relationships were assessed using a step-down trend test. Change from baseline is LS change from baseline at 12 weeks.The same ANCOVA model was used to evaluate between treatment differences in other efficacy endpoints. Change from placebo is between treatment difference in LS mean change from baseline at week 12.

Table 49: Hermann et al. (1994)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** Unclear but assumed Sweden **Authors' conclusions:** Dose-effect titrated treatment with either metformin or glyburide promotes equal degrees of glycaemic control **Source of funding:** Lipha Pharmaceuticals **Comments:** Double-blind
Number and characteristics of patients	**Total number of patients:** 38 **Inclusion criteria:** Patients with NIDDM with FBG >=6.87 mmol/l **Exclusion criteria:** conditions requiring insulin treatment and contraindications to drugs Pre-randomisation phase: 6 week dietary treatment and a run-in of 2 weeks with dietary treatment and single-blind placebo
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** some on oral hypoglycaemic drugs and/or insulin **Details of washout period:** Those on oral therapy had this withdrawn 2-3 weeks before inclusion
Lifestyle advice	There was a 8 week dietary treatment period prior to randomisation
Follow-up	**Total follow-up (wks):** 26 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 26 **Frequency of monitoring appointments:** Patients had a wash out period of up to 6 weeks followed by a 2 week placebo run in period. After this, doses were titrated between 2 and 12 weeks, after which treatment was maintained at maximal dose for 6 months. Data reported at 2, 4 and 6 of maintenance period.
Arms	**(1) Metformin** N: 38 Treatment duration (wks): 26

Washout period (d): 0
Comments: Those taking oral agents stopped this before inclusion

Treatment(s): Metformin (Oral)

Minimum dose (mg/d): 1000
Maximum dose (mg/d): 3000
Details of dosing regimen: 1 to 3 g/day. Dose titration was performed during weeks 2-12 with escalation visits every 2 weeks if FBG<6.7 mmol/l. Dose level 1 was 1 g and dose level 3 was 3 g.

(2) Sulfonylurea

N: 34

Treatment duration (wks): 26
Washout period (d): 0
Comments: Those taking oral agents stopped this before inclusion

Treatment(s): Sulfonylurea (Oral)

Minimum dose (mg/d): 3.5
Maximum dose (mg/d): 10.5
Details of dosing regimen: Glyburide 3.5 to 10.5 mg/day micronized tablets (3.5 mg micronized tablets=5 mg non micronized). Dose level 1 was 3.5 mg and dose level 3 was 10.5 mg

Outcomes

General

Data not extracted from third trial arm (combination of metformin and glyburide).

Patients were randomised to monotherapy (metformin and glyburide) and doses were escalated through 6 levels. From dose levels 1 to 3, the individual drug doses were increased. From dose levels 4 to 6, single therapy became dual therapy. Only data from dose levels up to 3 have been extracted.

Baseline characteristics

		Metformin			Sulfonylurea				
		N	k	mean	N	k	mean	Δ	p
Blood pressure: Systolic blood pressure (mmHg) – 0wk	Continuous	38		150 (SD 12.3)	34		141 (SD 17.5)		
Diastolic blood pressure (mmHg) – 0wk	Continuous	38		85 (SD 12.3)	34		84 (SD 5.83)		
Lipids: Total cholesterol (mmol/l) – 0wk	Continuous	38		5.38 (SD 1.54)	34		5.66 (SD 0.991)		
HDL cholesterol (mmol/l) – 0wk	Continuous	38		0.81 (SD 0.37)	34		0.89 (SD 0.292)		
Triglycerides (mmol/l) – 0wk	Continuous	38		2.02 (SD 1.29)	34		2.01 (SD 2.16)		
LDL cholesterol (mmol/l) – 0wk	Continuous	38		3.66 (SD 1.54)	34		3.93 (SD 0.816)		
Monotherapy maintained Blood glucose: HbA1c (%) – 24wka	Continuous	19		6.9 (SD 1.31)	19		6.7 (SD 1.31)		
HbA1c (%) – 24wka	Continuous	19		6.9 (SD 1.31)	19		5.3 (SD 0.436)		
HbA1c (%) – 24wka	Continuous	19		5.8 (SD 0.872)	19		6.7 (SD 1.31)		
HbA1c (%) – 24wka	Continuous	19		5.8 (SD 0.872)	19		5.3 (SD 0.436)		
HbA1c (%) – 24wka	Mean change	19		-0.9 (SD 0.872)	19		-1.3 (SD 0.872)		
Fasting plasma glucose (mmol/l) – 0wka	Continuous	19		9.3 (SD 1.74)	19		8.6 (SD 1.74)		
Body weight: Weight (kg) – 0wka	Continuous	19		78.6 (SD 12.6)	19		82.6 (SD 11.8)		

[a] SD calculated from reported SE

Results

	Metformin			Sulfonylurea				
	N	k	mean	N	k	mean	Δ	p

Body weight: Weight (kg) – 16wka	Mean change	38		-0.8 (SD 3.08)	34		2.4 (SD 6.12)			
Hypoglycaemic events: minor hypoglycaemic events – 28wk	Dichotomous	34	12	(35.3%)	38	8	(21.1%)			
Major/severe hypoglycaemic event – 28wk	Dichotomous	34	0	(0.0%)	38	0	(0.0%)			
Adverse events: Any adverse event(s) – 24wk	Dichotomous	38	32	(84.2%)	34	26	(76.5%)			
cardiovascular AE – 24wk	Dichotomous	38	2	(5.3%)	34	3	(8.8%)			
cardiac: MI – 28wk	Dichotomous	34	2	(5.9%)	38	0	(0.0%)			
CV death – 28wk	Dichotomous	34	1	(2.9%)	38	0	(0.0%)			
Death – 28wk	Dichotomous	34	1	(2.9%)	38	0	(0.0%)			
Dizziness – 24wk	Dichotomous	38	6	(15.8%)	34	5	(14.7%)			
Dyspepsia – 24wk	Dichotomous	38	4	(10.5%)	34	2	(5.9%)			
GI: diarrhoea – 24wk	Dichotomous	38	19	(50.0%)	34	0	(0.0%)			
GI: abdominal pain – 24wk	Dichotomous	38	7	(18.4%)	34	2	(5.9%)			
Headache – 24wk	Dichotomous	38	4	(10.5%)	34	1	(2.9%)			
increased sweating – 24wk	Dichotomous	38	5	(13.2%)	34	5	(14.7%)			
metabolism and nutritional disorders – 24wk	Dichotomous	38	12	(31.6%)	34	13	(38.2%)			
Musculoskeletal and connective tissue disorders – 24wk	Dichotomous	38	1	(2.6%)	34	1	(2.9%)			
Nervous system disorders – 24wk	Dichotomous	38	8	(21.1%)	34	13	(38.2%)			
Skin reaction – 24wk	Dichotomous	38	6	(15.8%)	34	6	(17.6%)			
Tremor – 24wk	Dichotomous	38	2	(5.3%)	34	13	(38.2%)			
Dropouts: Dropout due to AEs – 28wk	Dichotomous	34	3	(8.8%)	38	9	(23.7%)			
Blood pressure: Systolic blood pressure (mmHg) – 24wk	Mean change	38		2.4 (SD 15.4)	34		-1 (SD 11.7)			
Diastolic blood pressure (mmHg) – 24wk	Mean change	38		0.6 (SD 7.39)	34		0.5 (SD 6.99)			
Lipids: Total cholesterol (mmol/l) – 24wk	Mean change	38		-0.18 (SD 0.55)	34		0.13 (SD 0.75)			
HDL cholesterol (mmol/l) – 24wk	Mean change	38		0.02 (SD 0.12)	34		0.03 (SD 0.11)			
Triglycerides (mmol/l) – 24wk	Mean change	38		0.09 (SD 0.86)	34		0.08 (SD 0.75)			
LDL cholesterol (mmol/l) – 24wk	Mean change	38		-0.15 (SD 0.43)	34		0.12 (SD 0.52)			
Monotherapy maintained										
Blood glucose: HbA1c (%) – 24wkb	Continuous	19		6.9 (SD 1.31)	19		5.3 (SD 0.436)			
HbA1c (%) – 24wkb	Continuous	19		5.8 (SD 0.872)	19		6.7 (SD 1.31)			
HbA1c (%) – 24wkb	Continuous	19		5.8 (SD 0.872)	19		5.3 (SD 0.436)			
HbA1c (%) – 24wkb	Mean change	19		-0.9 (SD 0.872)	19		-1.3 (SD 0.872)			
HbA1c (%) – 24wkb	Continuous	19		6.9 (SD 1.31)	19		6.7 (SD 1.31)			
Fasting plasma glucose (mmol/l) – 24wkb	Mean change	19		-2 (SD 1.74)	19		-2.1 (SD 2.18)			
Fasting plasma glucose (mmol/l) – 24wkb	Continuous	19		6.9 (SD 1.31)	19		6.6 (SD 0.872)			
Body weight: Weight (kg) – 24wkb	Mean change	19		-0.8 (SD 2.18)	19		2.8 (SD 3.05)			
Weight (kg) – 24wkb	Continuous	19		78.8 (SD 12.6)	19		86.2 (SD 14.4)			
Hypoglycaemic events: All hypoglycaemic events (no patients) – 24wk	Dichotomous	38	8	(21.1%)	34	12	(35.3%)			

	Adverse events: GI: nausea – 24wk	Dichotomous	38	9	(23.7%)	34	3	(8.8%)		
	[a] estimated from graph [b] SD calculated from reported SE									

Table 50: Herz et al. (2003)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** Canada and Spain **Authors' conclusions:** pioglitazone 30 and 45 mg produced significant improvements in Hba1c, insulin sensitivity and lipid profile in OAM naïve patients with type 2 diabetes with suboptimal glycaemic control and mild dyslipidemia **Source of funding:** sponsored by Eli Lilly and Company **Comments:** randomised, double-blind placebo controlled trial, no details on methods of randomisation, allocation concealment or blinding
Number and characteristics of patients	**Total number of patients:** 297 **Inclusion criteria:** patients with type 2 diabetes that was not controlled by diet and exercise who have had no previous treatment with insulin or OAMs. At screening Hba1c values for eligible patients were >=6.5% and <=9.8%, generally indicative of mild to moderate hyperglycaemia in type 2 diabetes. **Exclusion criteria:** patients were excluded for the following reasons: cardiac disease with marked limitation of functional capacity, serum TGs >500 mg/dl ot total cholesterol >300 mg/dl, serum creatinine>=1.8 mg/dl, renal transplantor current renal dialysis, serum ALT or AST >2.5 times the upper limit of normal, clinical signs or symptoms of liver disease, hemoglobin below the lower limit of normal, HIV infection, treatment with systemic corticosteroids (excluding topical and inhaled) within the previous 4 weeks, BMI <=25 kg/m2, signs or symptoms of substance abuse or life expectancy <3 years Pre-randomisation phase: there was a placebo lead in period in which all patients received placebo once daily for 3-5 weeks before being randomised to treatment period
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** All treatment naive/ no OADs at screening **Details of washout period:** All AHA naïve 3-5 week placebo run in period
Lifestyle advice	patients were asked to maintain a consistent diet and exercise regimen throughout the study
Follow-up	**Total follow-up (wks):** 21 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 16 **Frequency of monitoring appointments:** 3-5 week placebo run in followed by 16 week treatment phase
Arms	**(1) Pioglitazone (30 mg)** N: 99 Treatment duration (wks): 16 Washout period (d): 35 Treatment(s): Pioglitazone (Oral) – fixed-dose Set dose (mg/d):30 Frequency of dosing: once a day **(2) Pioglitazone (45 mg)** N: 99 Treatment duration (wks): 16 Washout period (d): 35 Treatment(s): Pioglitazone (Oral) – fixed-dose Set dose (mg/d):45 Frequency of dosing: once a day **(3) Placebo**

N: 99
Treatment duration (wks): 16
Washout period (d): 35
Treatment(s): Placebo (Oral)
Frequency of dosing: once a day

Outcomes

General

The primary time point for efficacy anlyses was study endpoint, defined as the last double blind visit at which data were collected. Data are reported for the ITT population, all randomised patients who received at least one dose of study medication and had both a baseline measurement and at least one measurement during the treatment period. Data describing least squares mean (LSM) changes from baseline to endpoint are expressed as percent absolute units.

Outcomes not extracted in this evidence table include insulin sensitivity measures, fasting insulin and lipid paramters (as units of measurement were not reported)

11 (11%) patients in placebo group, 7 (7%) in 30 mg group and 7 (7%) in 45 mg group discontinued the study

Hypoglycaemic events

All hypoglycaemic events (no events) (Hypoglycaemic events were defined by either of the following: (1) a sign or symptom pf hypoglycaemia recorded in the patient diary or (2) an SMBG <=50 mg/dl regardless of the presence of hypoglycaemic signs or symptoms)

Baseline characteristics

		Pioglitazone (30 mg)			Pioglitazone (45 mg)			Δ	p
		N	k	mean	N	k	mean		
Demographics: Age (years)	Continuous	99		59 (SD 11)	99		58.1 (SD 11)		
Sex (n male)	Dichotomous	99	59	(59.6%)	99	52	(52.5%)		
Duration of diabetes (months)	Continuous	99		22.5 (SD 38.3)	99		20.1 (SD 43.4)		
Ethnicity-White	Dichotomous	99	97	(98.0%)	99	93	(93.9%)		
Ethnicity-Asian	Dichotomous	99	1	(1.0%)	99	3	(3.0%)		
Ethnicity-Hispanic	Dichotomous	99	1	(1.0%)	99	3	(3.0%)		
Blood glucose: HbA1c (%) – 0wka	Continuous	95		7.5 (SD 0.877)	96		7.6 (SD 0.784)		
Body weight: BMI (kg/m2)	Continuous	99		31.7 (SD 4.6)	99		30.8 (SD 5.1)		
Weight (kg) – 0wk	Continuous	99		86.6 (SD 15.9)	99		84.1 (SD 16.8)		
Lipids: HDL cholesterol (mmol/l) – 0wkb	Continuous	99		1.14	99		1.13		
Triglycerides (mmol/l) – 0wkb	Continuous	99		1.91	99		1.99		
triglycerides <1.7 mmol/l – 0wk	Dichotomous	95	50	(52.6%)	96	50	(52.1%)		
HDL >1.15 (men) or >1.40 (women) – 0wk	Dichotomous	95	22	(23.2%)	96	27	(28.1%)		

[a] SD calculated from SE extracted from graph
[b] SDs not reported

		Pioglitazone (30 mg)			Placebo			Δ	p
		N	k	mean	N	k	mean		
Demographics: Age (years)	Continuous	99		59 (SD 11)	99		58 (SD 10.7)		
Sex (n male)	Dichotomous	99	59	(59.6%)	99	49	(49.5%)		
Duration of diabetes (months)	Continuous	99		22.5 (SD 38.3)	99		17.4 (SD 29.4)		
Ethnicity-White	Dichotomous	99	97	(98.0%)	99	96	(97.0%)		
Ethnicity-Asian	Dichotomous	99	1	(1.0%)	99	3	(3.0%)		
Ethnicity-Hispanic	Dichotomous	99	1	(1.0%)	99	0	(0.0%)		

Blood glucose: HbA1c (%) – 0wka	Continuous	95		7.5 (SD 0.877)	96		7.5 (SD 0.294)			
Body weight: BMI (kg/m2)	Continuous	99		31.7 (SD 4.6)	99		31.7 (SD 4.5)			
Weight (kg) – 0wk	Continuous	99		86.6 (SD 15.9)	99		86.3 (SD 17.4)			
Lipids: HDL cholesterol (mmol/l) – 0wkb	Continuous	99		1.14	99		1.2			
Triglycerides (mmol/l) – 0wkb	Continuous	99		1.91	99		1.72			
triglycerides <1.7 mmol/l – 0wk	Dichotomous	95	50	(52.6%)	97	54	(55.7%)			
HDL >1.15 (men) or >1.40 (women) – 0wk	Dichotomous	95	22	(23.2%)	97	35	(36.1%)			

[a] SD calculated from SE extracted from graph
[b] SDs not reported

		Pioglitazone (45 mg)			Placebo			Δ	p
		N	k	mean	N	k	mean		
Demographics: Age (years)	Continuous	99		58.1 (SD 11)	99		58 (SD 10.7)		
Sex (n male)	Dichotomous	99	52	(52.5%)	99	49	(49.5%)		
Duration of diabetes (months)	Continuous	99		20.1 (SD 43.4)	99		17.4 (SD 29.4)		
Ethnicity-White	Dichotomous	99	93	(93.9%)	99	96	(97.0%)		
Ethnicity-Asian	Dichotomous	99	3	(3.0%)	99	3	(3.0%)		
Ethnicity-Hispanic	Dichotomous	99	3	(3.0%)	99	0	(0.0%)		
Blood glucose: HbA1c (%) – 0wka	Continuous	96		7.6 (SD 0.784)	96		7.5 (SD 0.294)		
Body weight: BMI (kg/m2)	Continuous	99		30.8 (SD 5.1)	99		31.7 (SD 4.5)		
Weight (kg) – 0wk	Continuous	99		84.1 (SD 16.8)	99		86.3 (SD 17.4)		
Lipids: HDL cholesterol (mmol/l) – 0wkb	Continuous	99		1.13	99		1.2		
Triglycerides (mmol/l) – 0wkb	Continuous	99		1.99	99		1.72		
triglycerides <1.7 mmol/l – 0wk	Dichotomous	96	50	(52.1%)	97	54	(55.7%)		
HDL >1.15 (men) or >1.40 (women) – 0wk	Dichotomous	96	27	(28.1%)	97	35	(36.1%)		

[a] SD calculated from SE extracted from graph
[b] SDs not reported

Results

		Pioglitazone (30 mg)			Pioglitazone (45 mg)			Δ	p
		N	k	mean	N	k	mean		
Blood glucose: HbA1c (%) – 16wka	Mean change	95		-0.8	96		-0.9		
HbA1c (%) – 16wkb	Continuous	95		6.7 (SD 0.585)	96		6.7 (SD 0.764)		
HbA1c < 7% or <=7% – 16wk	Dichotomous	99	67	(67.7%)	99	66	(66.7%)		
Body weight: Weight (kg) – 16wkc	Mean change	99		0.35	99		0.82		
Hypoglycaemic events: All hypoglycaemic events (no events) – 16wk	Dichotomous	99			99				NS
All hypoglycaemic events (no patients) – 16wk	Dichotomous	95	10d	(10.5%)	96	11e	(11.5%)		

Adverse events: Any adverse event(s) – 16wk	Dichotomous	99	63	(63.6%)	99	79	(79.8%)		NS
Arthralgia – 16wk	Dichotomous	99	3	(3.0%)	99	10	(10.1%)		NS
Edema peripheral – 16wkd	Dichotomous	99	14	(14.1%)	99	16	(16.2%)		NS
Dropouts: Total dropouts – 16wk	Dichotomous	99	7	(7.1%)	99	7	(7.1%)		
Dropout due to AEs – 16wk	Dichotomous	99	2	(2.0%)	99	2	(2.0%)		NR
Drop out due to unsatisfactory effect – 16wk	Dichotomous	99	1	(1.0%)	99	0	(0.0%)		NR
Lipids: Total cholesterol (mmol/l) – 16wkf	Mean change	95		4 (SD 19.5)	96		0.4 (SD 17.6)		NS
HDL cholesterol (mmol/l) – 16wkf	Mean change	95		16.4 (SD 22.4)	96		19.5 (SD 21.6)		NS
Triglycerides (mmol/l) – 16wkf	Mean change	95		-6 (SD 44.8)	96		-16.5 (SD 45.1)		NS
LDL cholesterol (mmol/l) – 16wkf	Mean change	95		6.8 (SD 28.3)	96		2.3 (SD 28.4)		NS
triglycerides <1.7 mmol/l – 16wk	Dichotomous	95	57	(60.0%)	96	68	(70.8%)		NR
HDL >1.15 (men) or >1.40 (women) – 16wk	Dichotomous	95	50	(52.6%)	96	54	(56.3%)		NR
baseline Hba1c >=6.5% to <7% Blood glucose: HbA1c (%) – 16wkg	Mean change	33		-0.28 (SD 0.689)	30		-0.38 (SD 0.493)		
HbA1c < 7% or <=7% – 16wk	Dichotomous	33	31	(93.9%)	30	28	(93.3%)		
baseline Hba1c >=7% to <8% Blood glucose: HbA1c (%) – 16wkg	Mean change	37		-0.77 (SD 0.608)	36		-0.77 (SD 0.42)		
HbA1c < 7% or <=7% – 16wk	Dichotomous	37	29	(78.4%)	36	26	(72.2%)		
baseline Hba1c >=8% to <=9.8% Blood glucose: HbA1c (%) – 16wkg	Mean change	25		-1.4 (SD 0.75)	30		-1.5 (SD 0.767)		
HbA1c < 7% or <=7% – 16wk	Dichotomous	25	7	(28.0%)	30	12	(40.0%)		

[a] SD not reported
[b] SD calculated from SE extracted from graph
[c] No SDs reported
[d] approximated to nearest integer (percentages only presented in text)
[e] approximated to nearest integer (percentages only presented in text); approximated to nearest integer (percentages only presented in text)
[f] estimated fom graph
[g] estimated from graph

		Pioglitazone (30 mg)			Placebo				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Blood glucose: HbA1c (%) – 16wka	Mean change	95		-0.8	96		-0.2		<0.001
HbA1c (%) – 16wka	Mean change	99		-0.8	99		-0.2		<0.001
HbA1c (%) – 16wkb	Continuous	95		6.7 (SD 0.585)	96		7.3 (SD 0.588)		
HbA1c < 7% or <=7% – 16wk	Dichotomous	99	67	(67.7%)	99	41	(41.4%)		<0.001
Body weight: Weight (kg) – 16wkc	Mean change	99		0.35	99		-1.58		<0.001
Hypoglycaemic events: All hypoglycaemic events (no events) – 16wk	Dichotomous	99			99				NS
All hypoglycaemic events (no patients) – 16wk	Dichotomous	99	10d	(10.5%)	99	11e	(11.5%)		NS
All hypoglycaemic events (no patients) – 16wk	Dichotomous	95	10d	(10.5%)	96	11e	(11.5%)		NS

Adverse events: Any adverse event(s) – 16wk	Dichotomous	99	63	(63.6%)	99	68	(68.7%)	NS
Arthralgia – 16wk	Dichotomous	99	3	(3.0%)	99	2	(2.0%)	NS
Edema peripheral – 16wkd	Dichotomous	99	14	(14.1%)	99	16	(16.2%)	NS
Dropouts: Total dropouts – 16wk	Dichotomous	99	7	(7.1%)	99	11	(11.1%)	
Dropout due to AEs – 16wk	Dichotomous	99	2	(2.0%)	99	1	(1.0%)	NR
Drop out due to unsatisfactory effect – 16wk	Dichotomous	99	1	(1.0%)	99	5	(5.1%)	NR
Lipids: Total cholesterol (mmol/l) – 16wkf	Mean change	95		4 (SD 19.5)	97		2 (SD 16.7)	NS
HDL cholesterol (mmol/l) – 16wkf	Mean change	95		16.4 (SD 22.4)	97		9.1 (SD 19.7)	0.028
Triglycerides (mmol/l) – 16wkf	Mean change	95		-6 (SD 44.8)	97		1 (SD 39.4)	NS
LDL cholesterol (mmol/l) – 16wkf	Mean change	95		6.8 (SD 28.3)	96		3.5 (SD 23.5)	NS
triglycerides <1.7 mmol/l – 16wk	Dichotomous	95	57	(60.0%)	97	55	(56.7%)	NR
HDL >1.15 (men) or >1.40 (women) – 16wk	Dichotomous	95	50	(52.6%)	97	44	(45.4%)	NR
baseline Hba1c >=6.5% to <7% Blood glucose: HbA1c (%) – 16wkg	Mean change	33		-0.28 (SD 0.689)	29		-0.01 (SD 0.592)	NS
HbA1c < 7% or <=7% – 16wk	Dichotomous	33	31	(93.9%)	29	25	(86.2%)	
baseline Hba1c >=7% to <8% Blood glucose: HbA1c (%) – 16wkg	Mean change	37		-0.77 (SD 0.608)	42		-0.2 (SD 0.648)	<0.001
HbA1c < 7% or <=7% – 16wk	Dichotomous	37	29	(78.4%)	42	15	(35.7%)	0.002
baseline Hba1c >=8% to <=9.8% Blood glucose: HbA1c (%) – 16wkg	Mean change	25		-1.4 (SD 0.75)	25		-0.26 (SD 0.8)	<0.001
HbA1c < 7% or <=7% – 16wk	Dichotomous	25	7	(28.0%)	25	1	(4.0%)	

[a] SD not reported
[b] SD calculated from SE extracted from graph
[c] No SDs reported
[d] approximated to nearest integer (percentages only presented in text)
[e] approximated to nearest integer (percentages only presented in text); approximated to nearest integer (percentages only presented in text)
[f] estimated fom graph
[g] estimated from graph

		Pioglitazone (45 mg)			Placebo				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Blood glucose: HbA1c (%) – 16wka	Mean change	96		-0.9	96		-0.2		<0.001
HbA1c (%) – 16wka	Mean change	99		-0.9	99		-0.2		<0.001
HbA1c (%) – 16wkb	Continuous	96		6.7 (SD 0.764)	96		7.3 (SD 0.588)		
HbA1c < 7% or <=7% – 16wk	Dichotomous	99	66	(66.7%)	99	41	(41.4%)		0.001
Body weight: Weight (kg) – 16wkc	Mean change	99		0.82	99		-1.58		<0.001
Hypoglycaemic events: All hypoglycaemic events (no patients) – 16wkd	Dichotomous	96	11	(11.5%)	96	11	(11.5%)		NS
All hypoglycaemic events (no patients) – 16wkd	Dichotomous	99	11	(11.5%)	99	11	(11.5%)		NS
Adverse events: Any adverse event(s) – 16wk	Dichotomous	99	79	(79.8%)	99	68	(68.7%)		NS

Arthralgia – 16wk	Dichotomous	99	10	(10.1%)	99	2	(2.0%)		0.017
Edema peripheral – 16wke	Dichotomous	99	16	(16.2%)	99	16	(16.2%)		NS
Dropouts:									
Total dropouts – 16wk	Dichotomous	99	7	(7.1%)	99	11	(11.1%)		
Dropout due to AEs – 16wk	Dichotomous	99	2	(2.0%)	99	1	(1.0%)		NR
Drop out due to unsatisfactory effect – 16wk	Dichotomous	99	0	(0.0%)	99	5	(5.1%)		NR
Lipids:									
Total cholesterol (mmol/l) – 16wkf	Mean change	96		0.4 (SD 17.6)	97		2 (SD 16.7)		NS
HDL cholesterol (mmol/l) – 16wkf	Mean change	96		19.5 (SD 21.6)	97		9.1 (SD 19.7)		<0.001
Triglycerides (mmol/l) – 16wkf	Mean change	96		-16.5 (SD 45.1)	97		1 (SD 39.4)		0.007
LDL cholesterol (mmol/l) – 16wkf	Mean change	96		2.3 (SD 28.4)	96		3.5 (SD 23.5)		NS
triglycerides <1.7 mmol/l – 16wk	Dichotomous	96	68	(70.8%)	97	55	(56.7%)		NR
HDL >1.15 (men) or >1.40 (women) – 16wk	Dichotomous	96	54	(56.3%)	97	44	(45.4%)		NR
baseline Hba1c >=6.5% to <7%									
Blood glucose:									
HbA1c (%) – 16wkg	Mean change	30		-0.38 (SD 0.493)	29		-0.01 (SD 0.592)		NS
HbA1c < 7% or <=7% – 16wk	Dichotomous	30	28	(93.3%)	29	25	(86.2%)		
baseline Hba1c >=7% to <8%									
Blood glucose:									
HbA1c (%) – 16wkg	Mean change	36		-0.77 (SD 0.42)	42		-0.2 (SD 0.648)		<0.001
HbA1c < 7% or <=7% – 16wk	Dichotomous	36	26	(72.2%)	42	15	(35.7%)		0.01
baseline Hba1c >=8% to <=9.8%									
Blood glucose:									
HbA1c (%) – 16wkg	Mean change	30		-1.5 (SD 0.767)	25		-0.26 (SD 0.8)		<0.001
HbA1c < 7% or <=7% – 16wk	Dichotomous	30	12	(40.0%)	25	1	(4.0%)		0.03

[a] SD not reported
[b] SD calculated from SE extracted from graph
[c] No SDs reported
[d] approximated to nearest integer (percentages only presented in text); approximated to nearest integer (percentages only presented in text)
[e] approximated to nearest integer (percentages only presented in text)
[f] estimated fom graph
[g] estimated from graph

Continuous measures were asssed by a fixed effects ANCOVA, using last observation carried forward. The model included treatment, investigator and baseline value as covariates. Pairwise t-tests between pioglitazone and placebo were calculated from LSM values derived from the model and were adjusted for multiplicity using Hochberg's method. Differences among treatments for additional categorical variables were analysed using chi-squared

Table 51: Hoffmann & (1994)

General

Phase:
☑ monotherapy
☐ dual therapy
☐ triple therapy
☐ insulin monotherapy
☐ insulin+oral

Parallel / crossover: Parallel

Country: Germany

Authors' conclusions: Acarbose and glibenclamide are effectiev drugs for monotherapy of NIDDM patients when diet alone fails. Because postprandial insulin increase has been shown to be associated with increased risk for cardiovascular disease, acarbose, which lowers PP increase, may be superior to to glibenclamide, which elevates postprandial insulin increase

	Source of funding: Unclear **Comments:** Signle-blind (to allow investigators to adjust glibenclamide)
Number and characteristics of patients	**Total number of patients:** 96 **Inclusion criteria:** Patients with NIDDM, treated with diet alone, Hba1c 7-9%, 35-70 years with diabetes for at least 3 months and BMI <=35 kg/m2 **Exclusion criteria:** AST>=50 U/l, ALT >=50 U/L, tumors, pregnancy
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** All treatment naive/ no OADs at screening **Details of washout period:** NIDDM inadequately controlled with diet therapy, all AHA naïve
Lifestyle advice	No details reported
Follow-up	**Total follow-up (wks):** 24 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 24 **Frequency of monitoring appointments:** Visits every 6 weeks
Arms	**(1) Placebo** N: 30 Treatment duration (wks): 24 Washout period (d): 0 Comments: AHA naïve Treatment(s): Placebo (Oral) **(2) Glibenclamide** N: 27 Treatment duration (wks): 24 Washout period (d): 0 Comments: AHA naïve Treatment(s): Sulfonylurea (Oral) – flexible-dose (dose-adjusted) Mean dose (mg/d): 4.3 Minimum dose (mg/d): 3.5 Maximum dose (mg/d): 7 Details of dosing regimen: Glibenclamide 3.5 mg administered individually 1-3 times per day **(3) Acarbose** N: 28 Treatment duration (wks): 24 Washout period (d): 0 Comments: AHA naïve Treatment(s): Acarbose (Oral) – fixed-dose Set dose (mg/d):300 Frequency of dosing: three times a day Details of dosing regimen: Acarbose 100 mg TID with meals
Outcomes	
Baseline characteristics	

		Placebo			Glibenclamide				
		N	k	mean	N	k	mean	Δ	p
Demographics:									
Age (years)	Continuous	30		56.9 (SD 6.7)	27		59.5 (SD 5.7)		
Sex (n male)	Dichotomous	30	40	(133.3%)	27	48	(177.8%)		
Duration of diabetes (months)	Continuous	30		12.1 (SD 10.8)	27		17.6 (SD 13.1)		
Blood glucose:									
HbA1c (%) – 0wka	Continuous	30		8.29 (SD 0.37)	27		8.3 (SD 0.37)		
Adverse events:									
liver enzymes: abnormal ALT – 0wk	Continuous	30		14.7	27		12.6		
Liver enzymes: AST (U/l) – 0wk	Continuous	30		10.8	27		9.7		

[a] LS mean and SD

	Placebo	Acarbose	Δ	p

		N	k	mean	N	k	mean		
Demographics: Age (years)	Continuous	30		56.9 (SD 6.7)	28		58.8 (SD 6.9)		
Sex (n male)	Dichotomous	30	40	(133.3%)	28	46	(164.3%)		
Duration of diabetes (months)	Continuous	30		12.1 (SD 10.8)	28		12.7 (SD 10.8)		
Blood glucose: HbA1c (%) – 0wka	Continuous	30		8.29 (SD 0.37)	28		8.29 (SD 0.42)		
Adverse events: liver enzymes: abnormal ALT – 0wk	Continuous	30		14.7	28		13.7		
Liver enzymes: AST (U/l) – 0wk	Continuous	30		10.8	28		b		

[a] LS mean and SD
[b] NR

		Glibenclamide			Acarbose				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	27		59.5 (SD 5.7)	28		58.8 (SD 6.9)		
Sex (n male)	Dichotomous	27	48	(177.8%)	28	46	(164.3%)		
Duration of diabetes (months)	Continuous	27		17.6 (SD 13.1)	28		12.7 (SD 10.8)		
Blood glucose: HbA1c (%) – 0wka	Continuous	27		8.3 (SD 0.37)	28		8.29 (SD 0.42)		
Adverse events: liver enzymes: abnormal ALT – 0wk	Continuous	27		12.6	28		13.7		
Liver enzymes: AST (U/l) – 0wk	Continuous	27		9.7	28		b		

[a] LS mean and SD
[b] NR

Results

		Placebo			Glibenclamide				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 12wka	Continuous	30		8.23 (SD 0.363)	27		7.55 (SD 0.345)		
HbA1c (%) – 24wka	Continuous	30		8.42 (SD 0.335)	27		7.5 (SD 0.292)		
HbA1c (%) – 24wk	Mean change	30		0.16 (SD 0.39)	27		-0.76 (SD 0.39)		
Fasting plasma glucose (mmol/l) – 24wk	Mean change	30		0.16 (SD 0.67)	27		-1.25 (SD 0.89)		
Hypoglycaemic events: All hypoglycaemic events (no patients) – 24wk	Dichotomous	30	0	(0.0%)	27	2	(7.4%)		
Adverse events: liver enzymes: abnormal ALT – 24wk	Continuous	30		13.1	27		14.8		
Liver enzymes: AST (U/l) – 24wk	Continuous	30		9.7	27		12.4		
Dropouts: Total dropouts – 24wk	Dichotomous	30	0	(0.0%)	27	0	(0.0%)		
Lipids: Total cholesterol (mmol/l) – 24wk	Mean change	30		0.01 (SD 1.67)	27		-0.18 (SD 1.61)		
HDL cholesterol (mmol/l) – 24wk	Mean change	30		0.15 (SD 0.64)	27		-0.07 (SD 0.68)		
Triglycerides (mmol/l) – 24wk	Mean change	30		-0.28 (SD 0.95)	27		-0.43 (SD 1.36)		

[a] estimated from graph; 95% CI converted

		Placebo			Acarbose			Δ	p
		N	k	mean	N	k	mean		
Blood glucose: HbA1c (%) – 12wka	Continuous	30		8.23 (SD 0.363)	28		7.55 (SD 0.405)		
HbA1c (%) – 24wka	Continuous	30		8.42 (SD 0.335)	28		7.3 (SD 0.324)		
HbA1c (%) – 24wk	Mean change	30		0.16 (SD 0.39)	28		-0.98 (SD 0.45)		
Fasting plasma glucose (mmol/l) – 24wk	Mean change	30		0.16 (SD 0.67)	28		-1.2 (SD 0.89)		
Hypoglycaemic events: All hypoglycaemic events (no patients) – 24wk	Dichotomous	30	0	(0.0%)	28	0	(0.0%)		
Adverse events: liver enzymes: abnormal ALT – 24wk	Continuous	30		13.1	28		11.4		
Liver enzymes: AST (U/l) – 24wk	Continuous	30		9.7	28		b		
Dropouts: Total dropouts – 24wk	Dichotomous	30	0	(0.0%)	28	0	(0.0%)		
Lipids: Total cholesterol (mmol/l) – 24wk	Mean change	30		0.01 (SD 1.67)	28		-0.59 (SD 1.34)		
HDL cholesterol (mmol/l) – 24wk	Mean change	30		0.15 (SD 0.64)	28		0.09 (SD 0.44)		
Triglycerides (mmol/l) – 24wk	Mean change	30		-0.28 (SD 0.95)	28		-0.58 (SD 1.21)		

[a] estimated from graph; 95% CI converted
[b] NR

		Glibenclamide			Acarbose			Δ	p
		N	k	mean	N	k	mean		
Blood glucose: HbA1c (%) – 12wka	Continuous	27		7.55 (SD 0.345)	28		7.55 (SD 0.405)		
HbA1c (%) – 24wka	Continuous	27		7.5 (SD 0.292)	28		7.3 (SD 0.324)		
HbA1c (%) – 24wk	Mean change	27		-0.76 (SD 0.39)	28		-0.98 (SD 0.45)		
Fasting plasma glucose (mmol/l) – 24wk	Mean change	27		-1.25 (SD 0.89)	28		-1.2 (SD 0.89)		
Hypoglycaemic events: All hypoglycaemic events (no patients) – 24wk	Dichotomous	27	2	(7.4%)	28	0	(0.0%)		
Adverse events: liver enzymes: abnormal ALT – 24wk	Continuous	27		14.8	28		11.4		
Liver enzymes: AST (U/l) – 24wk	Continuous	27		12.4	28		b		
Dropouts: Total dropouts – 24wk	Dichotomous	27	0	(0.0%)	28	0	(0.0%)		
Lipids: Total cholesterol (mmol/l) – 24wk	Mean change	27		-0.18 (SD 1.61)	28		-0.59 (SD 1.34)		
HDL cholesterol (mmol/l) – 24wk	Mean change	27		-0.07 (SD 0.68)	28		0.09 (SD 0.44)		
Triglycerides (mmol/l) – 24wk	Mean change	27		-0.43 (SD 1.36)	28		-0.58 (SD 1.21)		

[a] estimated from graph; 95% CI converted
[b] NR

Table 52: Hoffmann & (1997)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** Germany **Authors' conclusions:** Acarbose and metformin are effective drugs for first line monotherapy of patients with NIDDM. With respect to plasma lipid profile, especially HDL and LDL cholesterol, acarbose may be superior to metformin **Source of funding:** Unclear **Comments:** Double-blind for acarbose/placebo and single blind for metformin
Number and characteristics of patients	**Total number of patients:** 96 **Inclusion criteria:** patients with NIDDM on diet alone with Hba1c 7-11%, aged 35 to 70 years, diagnosis of diabetes for at least 3 months, stable bodyweight and BMI <=35 kg/m2 **Exclusion criteria:** Biochemical liver or renal dysfuntion, serious acute disease, congestive heart failure
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** All treatment naive/ no OADs at screening **Details of washout period:** All AHA naïve
Lifestyle advice	Patients were to receive a diet tailored to individual energy requirements. Individual dietary enforcement was made at screening and during the study
Follow-up	**Total follow-up (wks):** 24 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 24 **Frequency of monitoring appointments:** Patients visited the centres every 6 weeks
Arms	**(1) Acarbose** N: 31 Treatment duration (wks): 24 Washout period (d): - Treatment(s): Acarbose (Oral) – fixed-dose Set dose (mg/d):300 Details of dosing regimen: 3x100mg/day **(2) Metformin** N: 31 Treatment duration (wks): 24 Washout period (d): - Treatment(s): Metformin (Oral) – fixed-dose Set dose (mg/d):1700 Details of dosing regimen: 850 mg bid **(3) Placebo** N: 32 Treatment duration (wks): - Washout period (d): - Treatment(s): Placebo (Oral)
Outcomes	
Baseline characteristics	

		Acarbose			Metformin			Δ	p
		N	k	mean	N	k	mean		
Demographics: Age (years)	Continuous	31		58.9 (SD 9.4)	31		55.9 (SD 7.8)		
Sex (n male)	Dichotomous	31	6a	(19.4%)	31	14b	(45.2%)		
Duration of diabetes (months)	Continuous	31		36.9 (SD 27.2)	31		25 (SD 17.4)		

Blood glucose: HbA1c (%) – 0wk	Continuous	31		9.6 (SD 0.9)	31		9.7 (SD 0.9)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	31		9.1 (SD 0.7)	31		8.8 (SD 0.6)		
Body weight: BMI (kg/m2)	Continuous	31		26.4 (SD 2.7)	31		27.4 (SD 2.2)		
Weight (kg) – 0wk	Continuous	31		73.9 (SD 10.3)	31		79 (SD 8.8)		
Lipids: Total cholesterol (mmol/l) – 0wk	Mean change	31		6.3 (SD 1.23)	31		5.74 (SD 1.1)		
HDL cholesterol (mmol/l) – 0wk	Mean change	31		1.42 (SD 0.37)	31		1.61 (SD 0.56)		
Triglycerides (mmol/l) – 0wk	Mean change	31		1.68 (SD 0.86)	31		1.41 (SD 0.91)		
LDL cholesterol (mmol/l) – 0wk	Mean change	31		4.08 (SD 1.23)	31		3.59 (SD 1.06)		
LDL/HDL ratio – 0wk	Continuous	31		3.15 (SD 1.62)	31		2.56 (SD 1.17)		

[a] approximated to nearest integer (percentages only presented in text)
[b] approximated to nearest integer (percentages only presented in text); approximated to nearest integer (percentages only presented in text)

		Acarbose			Placebo				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	31		58.9 (SD 9.4)	32		60.2 (SD 8.6)		
Sex (n male)	Dichotomous	31	6a	(19.4%)	32	12b	(37.5%)		
Duration of diabetes (months)	Continuous	31		36.9 (SD 27.2)	32		43.2 (SD 33.9)		
Blood glucose: HbA1c (%) – 0wk	Continuous	31		9.6 (SD 0.9)	32		9.4 (SD 0.9)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	31		9.1 (SD 0.7)	32		8.7 (SD 0.6)		
Body weight: BMI (kg/m2)	Continuous	31		26.4 (SD 2.7)	32		26.3 (SD 2.2)		
Weight (kg) – 0wk	Continuous	31		73.9 (SD 10.3)	32		74.9 (SD 9.7)		
Lipids: Total cholesterol (mmol/l) – 0wk	Mean change	31		6.3 (SD 1.23)	32		5.9 (SD 1.08)		
HDL cholesterol (mmol/l) – 0wk	Mean change	31		1.42 (SD 0.37)	32		1.54 (SD 0.43)		
Triglycerides (mmol/l) – 0wk	Mean change	31		1.68 (SD 0.86)	32		1.6 (SD 0.83)		
LDL cholesterol (mmol/l) – 0wk	Mean change	31		4.08 (SD 1.23)	32		3.62 (SD 1.27)		
LDL/HDL ratio – 0wk	Continuous	31		3.15 (SD 1.62)	32		2.63 (SD 1.41)		

[a] approximated to nearest integer (percentages only presented in text)
[b] approximated to nearest integer (percentages only presented in text); approximated to nearest integer (percentages only presented in text)

		Metformin			Placebo				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	31		55.9 (SD 7.8)	32		60.2 (SD 8.6)		
Sex (n male) a	Dichotomous	31	14	(45.2%)	32	12	(37.5%)		
Duration of diabetes (months)	Continuous	31		25 (SD 17.4)	32		43.2 (SD 33.9)		

Blood glucose: HbA1c (%) – 0wk	Continuous	31		9.7 (SD 0.9)	32		9.4 (SD 0.9)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	31		8.8 (SD 0.6)	32		8.7 (SD 0.6)		
Body weight: BMI (kg/m2)	Continuous	31		27.4 (SD 2.2)	32		26.3 (SD 2.2)		
Weight (kg) – 0wk	Continuous	31		79 (SD 8.8)	32		74.9 (SD 9.7)		
Lipids: Total cholesterol (mmol/l) – 0wk	Mean change	31		5.74 (SD 1.1)	32		5.9 (SD 1.08)		
HDL cholesterol (mmol/l) – 0wk	Mean change	31		1.61 (SD 0.56)	32		1.54 (SD 0.43)		
Triglycerides (mmol/l) – 0wk	Mean change	31		1.41 (SD 0.91)	32		1.6 (SD 0.83)		
LDL cholesterol (mmol/l) – 0wk	Mean change	31		3.59 (SD 1.06)	32		3.62 (SD 1.27)		
LDL/HDL ratio – 0wk	Continuous	31		2.56 (SD 1.17)	32		2.63 (SD 1.41)		

[a] approximated to nearest integer (percentages only presented in text); approximated to nearest integer (percentages only presented in text)

Results

		Acarbose			Metformin				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 12wka	Continuous	31		8.7 (SD 0.909)	31		8.95 (SD 0.71)		
HbA1c (%) – 24wka	Continuous	31		8.5 (SD 0.909)	31		8.8 (SD 0.852)		
Fasting plasma glucose (mmol/l) – 24wka	Continuous	31		7.881852 (SD 0.631)	31		7.937358 (SD 0.473)		
Body weight: Weight (kg) – 24wk	Continuous	31		73.1 (SD 10.2)	31		78.5 (SD 8.4)		
Dropouts: Total dropouts – 24wk	Dichotomous	31	3	(9.7%)	31	1	(3.2%)		
Lipids: Total cholesterol (mmol/l) – 24wk	Continuous	31		5.41 (SD 1.04)	31		5.83 (SD 0.85)		
HDL cholesterol (mmol/l) – 24wk	Continuous	31		1.65 (SD 0.61)	31		1.61 (SD 0.54)		
Triglycerides (mmol/l) – 24wk	Continuous	31		1.23 (SD 0.62)	31		1.28 (SD 0.6)		
LDL cholesterol (mmol/l) – 24wk	Continuous	31		3.19 (SD 0.96)	31		3.64 (SD 0.98)		
LDL/HDL ratio – 24wk	Continuous	31		2.31 (SD 1.38)	31		2.56 (SD 1.09)		

[a] estimated from graph; converted 95% CI

		Acarbose			Placebo				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 12wka	Continuous	31		8.7 (SD 0.909)	32		9.5 (SD 0.866)		
HbA1c (%) – 24wka	Continuous	31		8.5 (SD 0.909)	32		9.7 (SD 0.895)		
Fasting plasma glucose (mmol/l) – 24wk	Continuous	31		7.881852 (SD 0.631) a	32		b		
Body weight: Weight (kg) – 24wk	Continuous	31		73.1 (SD 10.2)	32		75.1 (SD 9.5)		
Dropouts: Total dropouts – 24wk	Dichotomous	31	3	(9.7%)	32	1	(3.1%)		
Lipids: Total cholesterol (mmol/l) – 24wk	Continuous	31		5.41 (SD 1.04)	32		5.83 (SD 1.21)		
HDL cholesterol (mmol/l) – 24wk	Continuous	31		1.65 (SD 0.61)	32		1.39 (SD 0.33)		
Triglycerides (mmol/l) – 24wk	Continuous	31		1.23 (SD 0.62)	32		1.46 (SD 0.61)		

LDL cholesterol (mmol/l) – 24wk	Continuous	31		3.19 (SD 0.96)	32		3.8 (SD 1.12)		
LDL/HDL ratio – 24wk	Continuous	31		2.31 (SD 1.38)	32		3.01 (SD 1.5)		

[a] estimated from graph; converted 95% CI
[b] unclear on graph

		Metformin			Placebo				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 12wka	Continuous	31		8.95 (SD 0.71)	32		9.5 (SD 0.866)		
HbA1c (%) – 24wka	Continuous	31		8.8 (SD 0.852)	32		9.7 (SD 0.895)		
Fasting plasma glucose (mmol/l) – 24wk	Continuous	31		7.937358 (SD 0.473) a	32		b		
Body weight: Weight (kg) – 24wk	Continuous	31		78.5 (SD 8.4)	32		75.1 (SD 9.5)		
Dropouts: Total dropouts – 24wk	Dichotomous	31	1	(3.2%)	32	1	(3.1%)		
Lipids: Total cholesterol (mmol/l) – 24wk	Continuous	31		5.83 (SD 0.85)	32		5.83 (SD 1.21)		
HDL cholesterol (mmol/l) – 24wk	Continuous	31		1.61 (SD 0.54)	32		1.39 (SD 0.33)		
Triglycerides (mmol/l) – 24wk	Continuous	31		1.28 (SD 0.6)	32		1.46 (SD 0.61)		
LDL cholesterol (mmol/l) – 24wk	Continuous	31		3.64 (SD 0.98)	32		3.8 (SD 1.12)		
LDL/HDL ratio – 24wk	Continuous	31		2.56 (SD 1.09)	32		3.01 (SD 1.5)		

[a] estimated from graph; converted 95% CI
[b] unclear on graph

Table 53: Holman et al. (1999)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** UK (from UKPDS trial) **Authors' conclusions:** Acarbose significantly improved glycaemic control over 3 years in patients with established type 2 diabetes, irrespective of concomitant therapy for diabetes. Careful titration of acarbose is needed in view of the increased noncompliance rate seen secondary to the known side effects **Source of funding:** Supported by Bayer UK **Comments:** Double-blind placebo controlled trial
Number and characteristics of patients	**Total number of patients:** 222 **Inclusion criteria:** Unclear (see full UKPDS paper or appropriate cochrane review for details) **Exclusion criteria:** Unclear (see full UKPDS paper or appropriate cochrane review for details)
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** some on oral hypoglycaemic drugs and/or insulin **Details of washout period:** Data from subgroup analyses of people on diet alone were extracted

Lifestyle advice	-
Follow-up	**Total follow-up (wks):** 156 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 156 **Frequency of monitoring appointments:** Patients were seen at 4 monthly intervals
Arms	**(1) Placebo** N: 107 Treatment duration (wks): 156 Washout period (d): 0 Comments: Only subgroup analyses in patients on diet alone were extracted Treatment(s): Placebo (Oral) **(2) Acarbose (100mg TID)** N: 115 Treatment duration (wks): 157 Washout period (d): 0 Comments: Only subgroup analyses in patients on diet alone were extracted Treatment(s): Acarbose (Oral) – fixed-dose Set dose (mg/d):300 Frequency of dosing: three times a day Details of dosing regimen: Acarbose 50 mg once, BID & TID at two-week intervals; 4 months after start dosage increased in 3 weeks period with 50 mg per step to 100 mg TID
Outcomes	**General** Data were only extracted for patients who were controlled on diet alone at baseline (i.e. drug naïve). These were limited to between group comparisons for Hba1c levels at study endpoint.
Baseline characteristics	
Results	

		Placebo			Acarbose (100mg TID)				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
ITT Blood glucose: HbA1c (%) – 3yr	Continuous	107			115			MD=-0.200 (CI: -0.680, 0.280)	0.4a
PP Blood glucose: HbA1c (%) – 3yr	Continuous	73			49			MD=-0.610 (CI: -1.310, 0.090)	0.092a

[a] SE calculated from reported 95% CI

	Baseline details not reported for patients on diet alone

Table 54: Horton et al. (2000)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** USA **Authors' conclusions:** Nateglinide and metformin monotherapy each improved overall glycaemic control but by different mechanisms. Nateglinide decreased mealtime glucose excursions, whereas metformin

	primarily affected FPG. In combination, nateglinide and metformin had complementary effects, improving Hba1c, FPG and postprandial hyperglycaemia **Source of funding:** financial support from Novartis **Comments:** prospective, double blind randomised placebo-controlled study. Randomisation method involved a computerised system and a double-dummy technique was used to maintain double-blinding (patients in the monoptherapy groups received their assigned active treatment plus identical placebo for the alternative therapy, whereas patients in the placebo group received both dummy nateglinide and metformin tablets. All patients therefore received 6 tablets each day).
Number and characteristics of patients	**Total number of patients:** 701 **Inclusion criteria:** patients were included in the study if they were aged 30 years and over and had been diagnosed with type 2 diabetes for at least 3 months. BMI was required to be 20-35 kg/m2 **Exclusion criteria:** type 1 diabetes, secondary forms of diabetes, a history of significant diabetic complications or renal impairment Pre-randomisation phase: patients underwent a 4 week washout period, all patients had to have been treated with diet alone (all OHAs discontinued) during the 4 week washout period before enrollment in the 4 week single blind placebo run-in period. Patients with Hba1c levels between 6.8% and 11% during run-in and with an FPG <=15 mmol/l were able to proceed to treatment randomisation.
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** some on oral hypoglycaemic drugs and/or insulin **Details of washout period:** all OHAs were discontinued for at least 4 weeks before the 4 week placebo run-in period (trial does not report proportions of patients taking OHAs before this time but separate subgroup analysis of previously drug naïve patients are reported in Horton 2004)
Lifestyle advice	patients were expected to maintain a constant diet throughout both phases of the study
Follow-up	**Total follow-up (wks):** 28 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 24 **Frequency of monitoring appointments:** clinic visits were scheduled for -4 and -2 during the run-in period, at randomisation (week 0) and weeks 4, 8, 12, 16 and 24 during treatment
Arms	**(1) Metformin** N: 178 Treatment duration (wks): 24 Washout period (d): 56 Comments: Patients were on diet and exercise for 4 weeks before starting a 4 week single-blind placebo run in Treatment(s): Metformin (Oral) – forced titration Maximum dose (mg/d): 1500 Frequency of dosing: three times a day Details of dosing regimen: metformin was titrated according to the approved package labeling to 500 mg (immediately after the start of three main meals) **(2) Placebo** N: 172 Treatment duration (wks): 24 Washout period (d): 56 Comments: Patients were on diet and exercise for 4 weeks before starting a 4 week single-blind placebo run in Treatment(s): Placebo (Oral) – fixed-dose
Outcomes	**General** the ITT population was used for assessment of change from baseline in Hba1c at week 24 and for all secondary efficacy variables, using the last observation carried forward method for patients who did not complete the study. Only 2/4 arms have been extracted into this evidence table, data relating to the nateglinide monotherapy arm was not extracted (as this is not licensed for monotherapy) and data relating to the combined nateglinide plus metformin arm were not extracted. All outcomes except area under the curve (AUC) measurements were extracted. 45 (25%) patients in the metformin arm and 66 (38%) patients in the placebo group discontinued the study See Horton (2004) for outcomes **Hypoglycaemic events** **suspected hypoglycaemia was determined by self-monitoring of blood glucose, patients were taught how to recognise, treat and monitor hypoglycaemia and were instructed to note all symptomatic and asymptomatic events in a study diary. All suspected symptomatic hypoglycaemic events were recorded as adverse events, even in the absence of a confimatory blood glucose measurement** symptomatic (unconfirmed) hypoglycaemia (symptoms suggestive of hypoglycaemia) confirmed hypoglycaemia (confirmed hypoglycaemia was defined as symptoms consistent with

hypoglycaemia confirmed by a blood glucose measurement <=2.8 mmol/l)

Baseline characteristics

		Metformin			Placebo				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	178		56.8 (SD 10.9)	172		59.6 (SD 10.9)		
Sex (n male)	Dichotomous	178	121	(68.0%)	172	104	(60.5%)		
Duration of diabetes (yrs)	Continuous	178		4.5 (SD 5.5)	172		4.6 (SD 4.7)		
Ethnicity-White	Dichotomous	178	141	(79.2%)	172	135	(78.5%)		
Ethnicity-African American	Dichotomous	178	17	(9.6%)	172	29	(16.9%)		
Ethnicity-Asian	Dichotomous	178	4	(2.2%)	172	1	(0.6%)		
Ethnicity-Other	Dichotomous	178	16	(9.0%)	172	7	(4.1%)		
Blood glucose: HbA1c (%) – 0wk	Continuous	178		8.4 (SD 1.2)	172		8.3 (SD 1.1)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	178		11 (SD 2.6)	172		10.7 (SD 2.3)		
Body weight: BMI (kg/m2)	Continuous	178		29.6 (SD 4.3)	172		29.2 (SD 3.9)		
Weight (kg) – 0wka	Continuous	178		83.54304 (SD 12.1)	172		82.41408 (SD 11)		
treatment-naive (reported in Horton et al. 2004) Demographics: Age (years) b	Continuous	104		55.4 (SD 11.2)	104		59 (SD 11.2)		
Sex (n male)	Dichotomous	104	70	(67.3%)	104	67	(64.4%)		
Duration of diabetes (yrs)	Continuous	104		3.7 (SD 4.08)	104		4.2 (SD 4.08)		
Blood glucose: HbA1c (%) – 0wk	Continuous	98		8.3 (SD 1.02)	98		8.2 (SD 1.02)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	101		10 (SD 2.04)	99		10.4 (SD 1.99)		
2h postprandial glucose excursion (mmol/l) – 0wk	Continuous	80		2.3 (SD 1.79)	77		2.1 (SD 1.75)		
Body weight: BMI (kg/m2)	Continuous	104		29.9 (SD 4.08)	104		29.5 (SD 4.08)		
Weight (kg) – 0wka	Continuous	104		84.38976 (SD 11.5)	104		83.2608 (SD 11.5)		

[a] estimated from BMI assuming mean height of 1.68m
[b] SD calculated from reported SE

Results

		Metformin			Placebo				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 24wk	Mean change	178			172			MD=-1.200	<0.0001
Fasting plasma glucose (mmol/l) – 24wk	Mean change	178			172				<0.0001
Hypoglycaemic events: Major/severe hypoglycaemic event – 24wk	Dichotomous	178			172				NR
symptomatic (confirmed) – 24wk	Dichotomous	178			172				NR
Adverse events: Any adverse event(s) – 24wk	Dichotomous	178			172				NR
cardiovascular AE – 24wk	Dichotomous	178			172				NR
Death – 24wk	Dichotomous	178			172				NR
Gastrointestinal disorders (any) – 24wk	Dichotomous	178			172				NR

	GI: diarrhoea – 24wk	Dichotomous	178			172				NR
	Dropouts:									
	Total dropouts – 24wk	Dichotomous	178	45	(25.3%)	172	66	(38.4%)		
	Dropout due to AEs – 24wk	Dichotomous	178	12	(6.7%)	172	9	(5.2%)		
	baseline Hba1c >=9.5%									
	Blood glucose:									
	HbA1c (%) – 24wk	Mean change	0			0			MD=-1.500	a
	treatment-naive (reported in Horton et al. 2004)									
	Blood glucose:									
	HbA1c (%) – 24wkb	Mean change	98		-0.8 (SD 0.99)	98		0.5 (SD 0.99)		<0.001
	HbA1c < 7% or <=7% – 24wkc	Dichotomous	98	40	(40.8%)	98	17	(17.3%)		NR
	Fasting plasma glucose (mmol/l) – 24wk	Mean change	101		-1.2 (SD 3.01) b	99		0.27 (SD 2.98) d		<0.001
	2h postprandial glucose excursion (mmol/l) – 24wk	Mean change	80		-1 (SD 1.79)	77		-0.5 (SD 1.75)		
	Body weight:									
	Weight (kg) – 24wk	Mean change	104		e	104		-0.2 (SD 4.08) b		NR
	Hypoglycaemic events:									
	symptomatic (unconfirmed) hypoglycaemia – 24wk	Dichotomous	104	11	(10.6%)	104	3	(2.9%)		
	confirmed hypoglycaemia – 24wk	Dichotomous	104	1	(1.0%)	104	0	(0.0%)		
	Adverse events:									
	GI: nausea – 24wk	Dichotomous	104	10	(9.6%)	104	4	(3.8%)		
	Back pain – 24wk	Dichotomous	104	5	(4.8%)	104	7	(6.7%)		
	Chest pain – 24wk	Dichotomous	104	3	(2.9%)	104	4	(3.8%)		
	Cough – 24wk	Dichotomous	104	4	(3.8%)	104	3	(2.9%)		
	Dizziness – 24wk	Dichotomous	104	4	(3.8%)	104	4	(3.8%)		
	Dyspepsia – 24wk	Dichotomous	104	8	(7.7%)	104	4	(3.8%)		
	Fatigue – 24wk	Dichotomous	104	6	(5.8%)	104	2	(1.9%)		
	GI: diarrhoea – 24wk	Dichotomous	104	21	(20.2%)	104	7	(6.7%)		
	GI: abdominal pain – 24wk	Dichotomous	104	7	(6.7%)	104	5	(4.8%)		
	GI: constipation – 24wk	Dichotomous	104	6	(5.8%)	104	3	(2.9%)		
	Headache – 24wk	Dichotomous	104	4	(3.8%)	104	12	(11.5%)		
	Infection (upper airway or other common) – 24wk	Dichotomous	104	11	(10.6%)	104	14	(13.5%)		
	Palpitations – 24wk	Dichotomous	104	0	(0.0%)	104	0	(0.0%)		
	pharyngitis – 24wk	Dichotomous	104	2	(1.9%)	104	1	(1.0%)		
	Sinusitis or sinus abnormality – 24wk	Dichotomous	104	3	(2.9%)	104	7	(6.7%)		
	Temperature/influenza – 24wk	Dichotomous	104	9	(8.7%)	104	4	(3.8%)		

[a] No of patients for subgroup not reported
[b] SD calculated from reported SE
[c] approximated to nearest integer (percentages only presented in text)
[d] estimated from graph
[e] not reported

	See Horton (2004) for outcomes An ANCOVA model that included effects for treatment, centre, baseline measure, treatment by centre interaction and treatment by baseline interaction was used to compare the effects of the four treatment groups

Table 55: Hotta et al. (1993)

General	**Phase:**

	☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** Unclear but assumed Japan **Authors' conclusions:** The present study demonstrated that initial combination therapy with netwglinide and metformin substantially reduces both fasting and postprandial glucose and is a safe and effective means of achieving therapeutic targets in drug naïve patients with type 2 diabetes **Source of funding:** Unclear **Comments:** Double-blind, placebo controlled trial
Number and characteristics of patients	**Total number of patients:** 37 **Inclusion criteria:** Patients with NIDDM, aged 35 to 75 years, without serious complications and who had 2 hour postprandial blood glucose 11.2 mmol/l or higher after diet as sole treatment for at least 2-3 months **Exclusion criteria:** No details reported Pre-randomisation phase: There was a 4 week placebo controlled run-in period
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** All treatment naive/ no OADs at screening **Details of washout period:** All AHA naïve
Lifestyle advice	Details not reported
Follow-up	**Total follow-up (wks):** 28 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 24 **Frequency of monitoring appointments:** HbA1c levels were determined at weeks 0, 8, 16 and 24
Arms	**(1) Placebo** N: 18 Treatment duration (wks): 24 Washout period (d): 28 Comments: All AHA naïve Treatment(s): Placebo (Oral) **(2) Acarbose (100mg TID)** N: 19 Treatment duration (wks): 24 Washout period (d): 28 Comments: All AHA naïve Treatment(s): Acarbose (Oral) – fixed-dose Set dose (mg/d):300 Frequency of dosing: three times a day Details of dosing regimen: Acarbose 100 mg TID
Outcomes	**General** Overall, data from 24 trials have been extracted into this evidence table. Data was not extracted for the following RCTs for the reasons provided below; 1) Campbell (1998) was abstract only and insufficient data for meta-analysis 2) Calle-Pascual (1996)-letter only 3) Haffner (1997)-unclear previous OADs 4) Drent (2002), Johnston (1998a), Johnston (1998b), Pagano (1995)-comparisons with miglitol 5) Hillebrand (1987)-paper was not found as there was an incorrect citation 6) Holmes (2001) comparison with nateglinide 7) Kawamori (2003) comparisons with miglitol and voglibose 8) Rybka (1999) paper not available from British library 9) Takami (2002) comparison with voglibose 10) Hoffman (1990)-Not in English 11) Kovacevic (1997)-unclear definition of basic principles of care 12) Van der Laar (2004a)-newly diagnosed diabetes but no mention of previous OADs or if treatment naïve 13) Zheng (1995)-Not in English Data for the following RCTs have been extracted elsewhere within this review question; Hoffman (1997)

Baseline characteristics

		Placebo			Acarbose (100mg TID)				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	18		47.9 [rng 31–67]	19		49.8 [rng 31–66]		
Sex (n male)	Dichotomous	18	14	(77.8%)	19	14	(73.7%)		
Duration of diabetes (yrs)	Continuous	18		4.8 [rng 0.7–11]	19		4.6 [rng 0.3–14]		
Blood glucose: HbA1c (%) – 0wka	Continuous	13		10.3 (SD 1.44)	16		11.1 (SD 2)		
Fasting plasma glucose (mmol/l) – 0wka	Continuous	15		8.8 (SD 2.32)	16		8.9 (SD 2)		
Body weight: BMI (kg/m2)	Continuous	18		22.9 [rng 18–26.8]	19		23.5 [rng 20–28.3]		
Weight (kg) – 0wka	Continuous	18		60.8 (SD 9.76)	19		60.7 (SD 6.97)		
Lipids: Total cholesterol (mmol/l) – 0wk	Continuous	13		5.1 (SD 0.721)	16		5.5 (SD 1.2)		
HDL cholesterol (mmol/l) – 0wk	Continuous	13		1.2 (SD 0.361)	16		1.2 (SD 0.4)		
Triglycerides (mmol/l) – 0wk	Continuous	13		1.7 (SD 0.721)	16		1.5 (SD 0.8)		

[a] SD calculated from reported SE

Results

		Placebo			Acarbose (100mg TID)				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 16wka	Continuous	18		10.5 (SD 2.55)	19		10.1 (SD 1.74)		
HbA1c (%) – 24wk	Mean change	13		-0.42 (SD 1.3)	16		-1.38 (SD 1.75)		
HbA1c (%) – 24wkb	Continuous	13		9.9 (SD 1.8)	16		9.7 (SD 2.4)		
Fasting plasma glucose (mmol/l) – 16wka	Continuous	18		8.9 (SD 2.12)	19		8.2 (SD 1.96)		
Fasting plasma glucose (mmol/l) – 24wk	Mean change	13		-0.04 (SD 1.29)	16		-0.71 (SD 1.85)		
Fasting plasma glucose (mmol/l) – 24wk	Continuous	18		8.7 (SD 2.55)	19		8.2 (SD 1.74) a		
Fasting plasma glucose (mmol/l) – 24wk	Continuous	18		8.7 (SD 2.55)	19		8.2 (SD 2.18)		
Fasting plasma glucose (mmol/l) – 24wk	Continuous	18		8.8 (SD 1.91) a	19		8.2 (SD 2.18)		
Fasting plasma glucose (mmol/l) – 24wka	Continuous	18		8.8 (SD 1.91)	19		8.2 (SD 1.74)		
Body weight: Weight (kg) – 24wk	Mean change	15		-0.82 (SD 1.09)	16		-0.81 (SD 3.22)		
Weight (kg) – 24wkb	Continuous	18		60 (SD 8.91)	19		59.9 (SD 6.97)		
Adverse events: Any adverse event(s) – 24wk	Dichotomous	18	11	(61.1%)	19	15	(78.9%)		
Flatulence – 24wk	Dichotomous	18	7	(38.9%)	19	10	(52.6%)		
GI: diarrhoea – 24wk	Dichotomous	18	1	(5.6%)	19	1	(5.3%)		
Dropouts: Dropout due to AEs – 24wk	Dichotomous	18	0	(0.0%)	19	1	(5.3%)		
Lipids: Total cholesterol (mmol/l) – 24wk	Mean change	13		0.12 (SD 0.57)	16		0.04 (SD 0.68)		
Total cholesterol (mmol/l) – 24wk	Continuous	13		5.2 (SD 1.27)	16		5.5 (SD 1.31)		
HDL cholesterol (mmol/l) – 24wk	Mean change	12		0.15 (SD 0.17)	16		0.06 (SD 0.18)		

	HDL cholesterol (mmol/l) – 24wk	Continuous	12		1.3 (SD 0.424)	16		1.3 (SD 0.436)		
	Triglycerides (mmol/l) – 24wk	Mean change	13		0.15 (SD 0.58)	16		-0.18 (SD 0.55)		
	Triglycerides (mmol/l) – 24wk	Continuous	13		1.8 (SD 0.849)	16		1.3 (SD 0.872)		

[a] estimated from graph; ANCOVA
[b] SD calculated from reported SE

Table 56: Iwamoto et al. (2010)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** Japan **Authors' conclusions:** Treatement with sitagliptin for 12 weeks provided significant and clinically meaningful reductions in Hba1c, FPG and 2-h PPG across the dose range studies and was generally well tolerated in Japanese patients with type 2 diabetes **Source of funding:** Supported by Merck Research Laboratories and Banyu Pharmaceutical company **Comments:** Phase II, randomized, double-blind, placebo controlled, parallel-arm study. Patients were allocated to treatment assignment using an allocation schedule created by a Japanese third party vendor that packaged the clinical supplies and provided them to the clinical site. Numbered containers were used to implement allocation and each patient was assigned the next number in the sequence upon being enrolled. All study personnel, including investigators, study site personnel, patients, monitors, and central laboratory personnel, remained blinded to treatment allocation throughout the study; the code was revealed to the researchers only after case report forms were completed, the database was locked, and statistical analysis plans were finalised.
Number and characteristics of patients	**Total number of patients:** 363 **Inclusion criteria:** Male and female Japanese patients aged 20 to 75 years with type 2 diabetes were eligible to participate if they had inadequate glycemic control and, at screening, were either taking an oral anti-hyperglycemic agent (OHA) or had not taken an OHA for at least 8 weeks. At screening/Visit 1, the HbA1c inclusion criteria ranged from =6.5% to <10% for patients not on an OHA (for at least 8 weeks) and =6% to =9% for patients on OHA monotherapy (within 8 weeks prior to Visit 1) **Exclusion criteria:** Patients with type 1 diabetes, history of diabetic ketoacidosis, serum C-peptide =0.7 ng/dL at screening, treatment with insulin, PPAR-gamma agonist (pioglitazone) or any combination OHA therapy in the 8 weeks prior to screening, unstable cardiac disease, active liver or gallbladder disease, inadequately controlled hypertension (systolic or diastolic blood pressure >160 mm Hg or >100 mm Hg, respectively), elevated serum creatinine (>1.3 mg/dL in men and >1.2 mg/dL in women), and elevations >2-fold the upper limit of normal (ULN) in alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) were excluded. Pre-randomisation phase: The study included a screening diet/ exercise run-in period of up to 8 weeks, including a 2-week single-blind placebo run-in period. At Visit 2, patients who had been on a diet and exercise program for at least 6 weeks and who had not taken an OHA for at least 6 weeks were eligible to directly enter the placebo run-in period. All other patients underwent a 6-week diet and exercise program (and wash-off period for patients on OHA at screening) prior to entering the placebo run-in period. This design ensured that patients received =8 weeks of diet and exercise therapy without OHA treatment before randomization. Patients with an HbA1c =6.5 and <10% and a fasting plasma glucose (FPG) =270 mg/dL upon entering the placebo run-in period and with =75% compliance with the single-blind placebo were randomised
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** some on oral hypoglycaemic drugs and/or insulin **Details of washout period:** All other patients underwent a 6-week diet and exercise program (and wash-off period for patients on OHA at screening) prior to entering the placebo run-in period
Lifestyle advice	patients received diet and exercise therapy during the active treatment phase
Follow-up	**Total follow-up (wks):** 22

	Length of titration period (wks): 0 **Length of maintenance period (wks):** 12 **Frequency of monitoring appointments:** Up to 8 week wash out period, 12 week treatment period and safety telephone follow up on adverse events 14 days later HbA1c, FPG were measured at baseline (i.e., Week 0 prior to the first dose of study medication) and at various time points throughout the study
Arms	**(1) Sitagliptin (25 mg)** N: 80 Treatment duration (wks): 12 Washout period (d): 56 Comments: There was an 8 week period consisting of diet/exercise and placebo run-in Treatment(s): Sitagliptin (Oral) – fixed-dose Set dose (mg/d):25 Frequency of dosing: once a day Details of dosing regimen: administered once daily before breakfast for 12 weeks **(2) Sitagliptin (50 mg)** N: 72 Treatment duration (wks): 12 Washout period (d): 56 Comments: There was an 8 week period consisting of diet/exercise and placebo run-in Treatment(s): Sitagliptin (Oral) – fixed-dose Set dose (mg/d):50 Frequency of dosing: once a day Details of dosing regimen: administered once daily before breakfast for 12 weeks **(3) Sitagliptin (100 mg)** N: 70 Treatment duration (wks): 12 Washout period (d): 56 Comments: There was an 8 week period consisting of diet/exercise and placebo run-in Treatment(s): Sitagliptin (Oral) – fixed-dose Frequency of dosing: once a day Details of dosing regimen: administered once daily before breakfast for 12 weeks **(4) Placebo** N: 73 Treatment duration (wks): 12 Washout period (d): 56 Comments: There was an 8 week period consisting of diet/exercise and placebo run-in Treatment(s): Placebo (Oral) – fixed-dose Frequency of dosing: once a day Details of dosing regimen: administered once daily before breakfast for 12 weeks
Outcomes	**General** Efficacy analyses were performed on the full analysis set (FAS) consisting of all randomized patients who received at least one dose of study drug and who had valid measurements both at baseline and at least one post-treatment measurement. Missing data were handled using the last observation carried forward method. Safety analyses were performed on the all-patients- as-treated population (APaT) consisting of all patients who took at least one dose of study drug. One arm relating to sitagliptin (200 mg qd) was not extracted in this evidence table as this dose is over the recommended dose in the summary product characteristics. Outcomes not extracted include glycosated albumin, HOMA-beta, area under the curve measures, insulinogenic index, 1.5-anhydroglucitol. 3 (3.8%) patients in 25 mg, 1 (1.4%) in the 50 mg, 2 (2.9%) in the 100 mg and 5 (6.8%) in the placebo groups discontinued the study. **Hypoglycaemic events** All hypoglycaemic events (no patients) (Hypoglycaemia was assessed by the study site investigator through reviewing patient self-reports of signs and symptoms of hypoglycaemia. A fingerstick BG determination concurrent with the episode was not required to assess an episode as hypoglycaemia, although investigators could include the measurement if it was available in their assessment of the episode)
Baseline characteristics	**Error! Not a valid filename.**
Results	**Error! Not a valid filename.**
	The primary efficacy endpoint, the change from baseline in HbA1c at Week 12, was analyzed using an analysis of covariance (ANCOVA) model with erms for treatment, prior OHA use, and baseline HbA1c value as covariates. The between-group differences (relative to placebo) and associated 95% confidence intervals (CIs) for efficacy endpoints were assessed by testing the differences in the least squares (LS) mean changes

	from baseline at Week 12. A stepwise linear contrast test based on the ANCOVA model was used to examine the dose-response relationship for placebo and the sitagliptin 25-, 50-, 100-, and 200-mg groups. For overall AEs, drug-related AEs, hypoglycemia, and selected gastrointestinal-related AEs (i.e., nausea, vomiting, and diarrhea), the comparisons with placebo were conducted by Fisher's exact test, and between-group differences (relative to placebo) and associated 95% CIs were reported.

Table 57: Jain et al. (2006)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** Multicentre (assumed USA) **Authors' conclusions:** with long-term treatment, both glyburide and pioglitazone resulted in comparable glycaemic control; however pioglitazone was associated with less hypoglycaemia and fewer withdrawals due to lack of efficacy or adverse events **Source of funding:** Sponsored by Takeda Pharmaceuticals and supported by grants from Eli Lilly and Merck and Co and GlaxoSmithKline **Comments:** randomised, multicentre, double-blind, active comparator trial but no details of randomisation methods, allocation concealment or blinding
Number and characteristics of patients	**Total number of patients:** 502 **Inclusion criteria:** patients with recently diagnosed type 2 diabetes (<=2 years) unsuccessfully treated with diet and exercise. Patients were treatment naïve men and non pregnant, non lactating women 18-80 years olf age, from the US or Puerto Rico were eligible for enrollment. Treatment naïve was defined as documented type 2 diabetes of less than 2 years duration and not treated with the drugs listed below. At screening patients were required to have Hba1c between 7.5 and 11.5%, fasting C-peptide of i.0 ng/ml or greater and fasting plasma glucose level above 120 mg/dl **Exclusion criteria:** any patient whose treatment had previously failed due to lack of efficacy or signs of intolerance, or who had recently (less than 3 months) undergone treatment with rosiglitazone, pioglitaznoe or troglitazone could not participate in the study. Additional exclusion criteria included previous drug or alcohol abuse, previous treatment with any meglitinide analog, alpha-glucosidase inhibitor, metformin, insulin or sulfonylurea treatment for 3 months or more, use of hydrochlorothiazide greater than 25 mg/day, glucocorticoids, steroid joint injections, niacin greater than 250 mg/day, or anti diabetic agents other than the study drugs listed during the trial, concurrent participation or enrollment in another investigational study, serum creatinine above 1.5 mg/dl for men and above 1.4 mg/dl for women, greater than 1+ dipstick proteinuria or equivalent, anemia with hemoglobin levels below 12 g/dl in men and below 10 g/dl in women, diastolic blood pressure above 100 mmHg or systolic blood pressure above 180 mmHg, BMI <20 kg/m2 or >40 kg/m2, ALT level more than 1.5 times the upper limit of normal or active liver disease or jaundice, or triglyceride level greater than 500 mg/dl. Patients were also excluded if they had a chronic condition expected to require recurrent glucocorticoid use, New York Heart Sssociation class III or IV heart failure, an acure cardiovascular event within 6 months before screening including myocardial infarction, cerebrovascular accident, evidence of an ongoing cardiac disturbance, evidence of acute or unstable chronic pulmonary disease or leisons at chest radiography, or a history of cancer not in remission for at least 5 years Pre-randomisation phase: no details (16 week titration and 40 week maintenance period).
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** some on oral hypoglycaemic drugs and/or insulin **Details of washout period:** Exclusion criteria included time limited previous use of AHAs. Unclear whether all participants were completely drug naïve.
Lifestyle advice	no details reported
Follow-up	**Total follow-up (wks):** 56 **Length of titration period (wks):** 16 **Length of maintenance period (wks):** 40 **Frequency of monitoring appointments:** no details reported
Arms	**(1) Pioglitazone** N: 251 Treatment duration (wks): 56 Washout period (d): 0 Treatment(s): Pioglitazone (Oral) – flexible-dose (dose-adjusted) Median dose (mg/d): 45

Minimum dose (mg/d): 15
Maximum dose (mg/d): 45
Frequency of dosing: once a day
Compliance: mean treatment compliance was 96.8% (assumed this is overall as not reported by treatment group)
Details of dosing regimen: Starting dose 15 mg/day

16 week titration period: increased by 15mg/d every 4 weeks to a maximum dose of 45mg/d depending on glucose control (FBG maintained between 69 and 141 mg/dl)

After 16 week titration period, patients began 40 week double blind traetment in which the optimal study drug dosage was maintained for each patient.

During the 40 week maintenance period, the range of mean ± SD daily dose at each visit was 34.9 ± 11.64 to 37.6 ± 11.30 mg for pioglitazone. The median daily dose at each visit was 45mg for pioglitazone

(2) Glyburide

N: 251

Treatment duration (wks): 56
Washout period (d): 0

Treatment(s): Sulfonylurea (Oral) – flexible-dose (dose-adjusted)

Median dose (mg/d): 10
Minimum dose (mg/d): 5
Maximum dose (mg/d): 15
Frequency of dosing: once a day
Compliance: mean treatment compliance was 96.8% (assumed this is overall as not reported by treatment group)
Details of dosing regimen: Starting dose: 5 mg/d glyburide

16 week titration period: increased by 5mg/d every 4 weeks to a maximum of 15mg/d depending on glucose control (FBG levels maintained between 69 and 141 mg/dl)

After 16 week titration period, patients began 40 week double blind traetment in which the optimal study drug dosage was maintained for each patient

During the 40 week maintenance period, the range of mean ± SD daily dose at each visit was 9.9 ± 4.33 to 10.5 ± 4.31 mg for glyburide. The median daily dose at each visit was 10 mg for glyburide

Outcomes

General

All analyses were performed using ITT population defined as any randomly assigned patients receiving one or more doses of study drug . The last observation carried forward was used for missing values ibn analysing the difference from baseline to each measure after baseline.

123 (49%) in glyburide and 117 (47%) in the pioglitazone group did not complete the study

All outcomes were extracted in this evidence table

Hypoglycaemic events

All hypoglycaemic events (no patients) (a hypoglycaemic event was reported if a patients had 2 or more usual symptoms of hypoglycaemic concurrently, one symptom before ingesting a glucose- or lactose-containing substance, or a blood glucose level below 60mg/dl (with home monitoring) or below 70 mg/dl (with clinical laboratory tests))

Baseline characteristics

		Pioglitazone			Glyburide				
		N	k	mean	N	k	mean	Δ	p
Demographics:									
Age (years)	Continuous	251		52.1 (SD 11.3)	251		52.1 (SD 12.4)		
Sex (n male)	Dichotomous	251	133	(53.0%)	251	141	(56.2%)		
Duration of diabetes (months)	Continuous	251		9.6 (SD 13.8)	251		9.4 (SD 15.2)		
Ethnicity-White	Dichotomous	251	153	(61.0%)	251	165	(65.7%)		
Ethnicity-African American	Dichotomous	251	40	(15.9%)	251	34	(13.5%)		
Ethnicity-Asian	Dichotomous	251	4	(1.6%)	251	0	(0.0%)		
Ethnicity-Hispanic	Dichotomous	251	52	(20.7%)	251	50	(19.9%)		
Ethnicity-Other	Dichotomous	251	2	(0.8%)	251	2	(0.8%)		
Blood glucose:									
HbA1c (%) – 0wk	Continuous	251		9.2 (SD 1.2)	251		9.2 (SD 1.26)		
Fasting plasma glucose (mg/dl)	Continuous	251		189.4 (SD 51.5)	251		183.8 (SD 53.8)		
Body weight:									
BMI (kg/m2)	Continuous	251		32.5 (SD 5.75)	251		32.8 (SD 5.71)		
Weight (kg) – 0wk	Continuous	251		93.9 (SD 19.7)	251		94.3 (SD 20)		

Waist/hip ratio	Continuous	251		0.93 (SD 0.073)	251		0.94 (SD 0.075)		
Height (cm)	Continuous	251		169.9 (SD 10)	251		169.5 (SD 10.7)		

Results

		Pioglitazone			Glyburide				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Blood glucose: HbA1c (%) – 16wka	Mean change	251		-2.04 (SD 1.19)	251		-2.45 (SD 1.19)		
HbA1c (%) – 24wka	Mean change	251		-2.22 (SD 1.19)	251		-2.34 (SD 1.19)		
HbA1c (%) – 32wkb	Mean change	251		-2.16	251		-2.24		
HbA1c (%) – 40wkb	Mean change	251		-2.13	251		2.2		
HbA1c (%) – 48wkb	Mean change	251		-2.12	251		-2.06		
HbA1c (%) – 56wka	Mean change	251		-2.07 (SD 1.19)	251		-2.02 (SD 1.58)	MD=-0.050	0.669
HbA1c < 7% or <=7% – 56wk	Dichotomous	148	102	(68.9%)	148	99	(66.9%)		NR
Body weight: Weight (kg) – 56wk	Mean change	251		3.66 (SD 6.14)	251		1.95 (SD 5.35)		<0.001
Hypoglycaemic events: All hypoglycaemic events (no events) – 56wk	Dichotomous	251			251				NR
All hypoglycaemic events (no events) – 56wkc	Count	75460	24		74284	176			
All hypoglycaemic events (no patients) – 56wk	Dichotomous	251	11	(4.4%)	251	61	(24.3%)		<0.001
recurrent hypoglycaemia – 56wkd	Dichotomous	251	6	(2.4%)	251	33	(13.1%)		0.0001
Adverse events: Any adverse event(s) – 56wk	Dichotomous	251	205	(81.7%)	251	209	(83.3%)		
Any serious adverse event(s) – 56wk	Dichotomous	251	23	(9.2%)	251	22	(8.8%)		NR
Study drug-related adverse event – 56wk	Dichotomous	251	69	(27.5%)	251	92	(36.7%)		NR
Arthralgia – 56wk	Dichotomous	251	13	(5.2%)	251	19	(7.6%)		NR
Back pain – 56wk	Dichotomous	251	12	(4.8%)	251	18	(7.2%)		NR
Bone fracture – 56wk	Dichotomous	251	0	(0.0%)	251	2	(0.8%)		NR
Bronchitis – 56wk	Dichotomous	251	19	(7.6%)	251	8	(3.2%)		NR
cardiovascular AE – 56wk	Dichotomous	251	11	(4.4%)	251	22	(8.8%)		0.0478
cardiac: serious event – 56wk	Dichotomous	251	3	(1.2%)	251	8	(3.2%)		NR
cardiac: CAD – 56wk	Dichotomous	251	0	(0.0%)	251	4	(1.6%)		NR
cardiac: CHF – 56wk	Dichotomous	251	1	(0.4%)	251	1	(0.4%)		NR
cardiac: MI – 56wk	Dichotomous	251	2	(0.8%)	251	2	(0.8%)		NR
cancer – 56wk	Dichotomous	251	0	(0.0%)	251	2	(0.8%)		NR
Chest pain – 56wk	Dichotomous	251	1	(0.4%)	251	2	(0.8%)		NR
Death – 56wk	Dichotomous	251	0	(0.0%)	251	2	(0.8%)		NR
Edema peripheral – 56wk	Dichotomous	251	14	(5.6%)	251	8	(3.2%)		NR
GI: diarrhoea – 56wk	Dichotomous	251	15	(6.0%)	251	16	(6.4%)		NR

	Headache – 56wk	Dichotomous	251	19	(7.6%)	251	22	(8.8%)		NR
	Infection (upper airway or other common) – 56wk	Dichotomous	251	32	(12.7%)	251	31	(12.4%)		NR
	liver enzymes: abnormal ALT – 56wk	Dichotomous	209	9	(4.3%)	206	25	(12.1%)		0.008
	pain (limbs) – 56wk	Dichotomous	251	10	(4.0%)	251	14	(5.6%)		NR
	Sinusitis or sinus abnormality – 56wk	Dichotomous	251	15	(6.0%)	251	24	(9.6%)		NR
	Dropouts:									
	Total dropouts – 56wk	Dichotomous	251	117	(46.6%)	251	123	(49.0%)		
	Dropout due to AEs – 56wk	Dichotomous	251	14	(5.6%)	251	25	(10.0%)		0.067
	Drop out due to unsatisfactory effect – 56wk	Dichotomous	251	18	(7.2%)	251	29	(11.6%)		0.092
	Dropout due to hypoglycaemia – 56wk	Dichotomous	251	0	(0.0%)	251	9	(3.6%)		0.004

[a] SD estimated from SE extracted from graph
[b] graph
[c] (Used in the analysis); Patient days estimated assuming dropout occurred halfway through the study
[d] >= 2 events

	Categoric data treatment comparisons were performed by using a Cochran-Mantel-Haenzel test controlling for pooled centre. The primary efficacy measure was analysed using a two way ANCOVA with terms for treatment and centre as the main effects, baseline as a covariate and treatment by centre interaction term

Table 58: Johnston et al. (1998)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** USA **Authors' conclusions:** Treatment with miglitol offers the elderly type 2 diabetic patient significant reductions in daylong glycaemia as measured by Hba1c. The greater Hba1c reductions with once daily glyburide occurred at a cost of significant increases in weight, insulin levels and the incidence of clinical and subclinical hypoglycaemia. **Source of funding:** Bayer employees were involved in the conduct and analyiss of the trial **Comments:** Double-blind
Number and characteristics of patients	**Total number of patients:** 184 **Inclusion criteria:** patients with type 2 diabetes, aged 60 years and older, treated with diet alone for at least 12 weeks before randomisation, Hba1c betw een 6.5 and 10%, FBG >140 mg/dl 2 weeks before randomisation **Exclusion criteria:** unable to understand and comply with diet and glucose monitoring guidelines, serious illness that prevents them from completing the study Pre-randomisation phase: 6 week placebo run-in period
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** some on oral hypoglycaemic drugs and/or insulin **Details of washout period:** Patients were on sulfonylurea prior to screening but were required to have been only on diet treatment at least 12 weeks prior to randomisation 6 week single-blind run in period where participants were given placebo and diet advice to facilitate weight reduction (1lb/week) in overweight individuals
Lifestyle advice	During the placebo run-in period patients received instruction in an ADA approved diet aimed at facilitating 1lb/week weight reduction in overweight individuals (monitored via diaries at baseline, 6 months and 1 year)
Follow-up	**Total follow-up (wks):** 56 **Length of titration period (wks):** 40 **Length of maintenance period (wks):** 56

	Frequency of monitoring appointments: 17 visits over the entire trial period starting from screening to 56 week follow up Length of titration period variable but up to 40 weeks
Arms	**(1) Glyburide** N: 104 Treatment duration (wks): 56 Washout period (d): 42 Treatment(s): Sulfonylurea (Oral) – flexible-dose (dose-adjusted) Mean dose (mg/d): 8.9 Minimum dose (mg/d): 1.25 Maximum dose (mg/d): 20 Details of dosing regimen: glyburide 20 mg once daily (morning), the dosing began at 1.25 mg/day and was stepped up & individually titrated: every 2 weeks increase: 2.5/5/7.5/10/15/20 mg. In general, doses were increased if FPG>140 mg/dl and decreased if there was a risk of hypoglycaemia Study visits were every 2 weeks to faciliate dose titration Median glyburide dose at end of study for efficacy population was 3.75mg/day and for the safety population 5mg/d **(2) Placebo** N: 101 Treatment duration (wks): 56 Washout period (d): 42 Treatment(s): Placebo (Oral)
Outcomes	**General** Data from 2/4 arms were extracted in this evidence table (arms relating to miglitol were not extracted as it was not included within the scope)

Baseline characteristics

		Glyburide			Placebo				
		N	k	mean	N	k	mean	Δ	p
Full analysis set (FAS) or efficacy analysis pop									
Demographics:									
Age (years) a	Continuous	92		67.7 (SD 5.75)	92		68.5 (SD 5.75)		
Sex (n male) b	Dichotomous	92	54	(58.7%)	92	61	(66.3%)		
Duration of diabetes (yrs) a	Continuous	92		7.2 (SD 7.67)	92		7 (SD 7.67)		
Blood glucose:									
HbA1c (%) – 0wka	Continuous	92		8.4 (SD 1.02)	92		8.4 (SD 1)		
Fasting plasma glucose (mg/dl) – 0wka	Continuous	92		195 (SD 41.8)	92		195 (SD 45.2)		
Previous blood glucose lowering drugs:									
Sulfonylureab	Dichotomous	92	56	(60.9%)	92	55	(59.8%)		

[a] Least square mean; SD estimated from reported SE
[b] approximated to nearest integer (percentages only presented in text)

Results

		Glyburide			Placebo				
		N	k	mean	N	k	mean	Δ	p
Body weight:									
Weight (kg) – 56wka	Mean change	104		2.3	101		-1.1		
Hypoglycaemic events:									
Symptomatic hypoglycaemia – 56wkb	Dichotomous	104	48	(46.2%)	101	8	(7.9%)		
Adverse events:									
GI: nausea – 56wkb	Dichotomous	104	6	(5.8%)	101	5	(5.0%)		
cardiovascular AE – 56wkb	Dichotomous	101	29	(28.7%)	101	22	(21.8%)		
Edema peripheral – 56wkb	Dichotomous	104	11	(10.6%)	104	6	(5.8%)		
Flatulence – 56wkb	Dichotomous	104	14	(13.5%)	101	14	(13.9%)		
GI: diarrhoea – 56wk	Dichotomous	104	12c	(11.5%)	101	11b	(10.9%)		

Dropouts:										
Total dropouts – 56wk	Dichotomous	104	12	(11.5%)	101	9	(8.9%)		
Dropout due to AEs – 56wkb	Dichotomous	104	6	(5.8%)	101	6	(5.9%)		
Lipids:									
Triglycerides (mmol/l) – 56wka	Mean change	104		0.01129	101		0.0114029		
Triglycerides (mmol/l) – 56wk	Mean change	104		0.01129a	101	4			
Full analysis set (FAS) or efficacy analysis pop									
Blood glucose:									
HbA1c (%) – 56wka	Mean change	92		-0.93	92		-0.01		
Fasting plasma glucose (mg/dl) – 56wka	Continuous	92		-30.5	92		1		

[a] SD not reported
[b] approximated to nearest integer (percentages only presented in text)
[c] approximated to nearest integer (percentages only presented in text); approximated to nearest integer (percentages only presented in text)

Table 59: Josse et al. (2003)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** Canada **Authors' conclusions:** - **Source of funding:** Bayer **Comments:** -
Number and characteristics of patients	**Total number of patients:** 192 **Inclusion criteria:** Elderly patients aged >65 years with type 2 diabetes (no further details reported) treated on diet alone, >35kg/m2 **Exclusion criteria:** patients taking insulin therapy or oral agents, major debilitating disease, documented gastrointestinal, Hba1c <110 or >150% of upper limit of normal (6.4%), recent major cardiovascular event or abnormal liver or renal function Pre-randomisation phase: 6 week run in period (no further details provided)
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** - **Details of washout period:** Unclear whether all patients had no history of AHA use; patients at time of enrollment were not on insulin or AHA and states in abstract that they were treated on diet alone. There was a 6 week run in period but no details were provided.
Lifestyle advice	Patients were advised to adjust dietary intake to ensure total caloric intake and nutrient composition was similar throughout the study
Follow-up	**Total follow-up (wks):** 58 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 52 **Frequency of monitoring appointments:** Patients seen every 6 weeks
Arms	**(1) Acarbose** N: 93 Treatment duration (wks): 52 Washout period (d): 42 Treatment(s): Acarbose (Oral) – flexible-dose (dose-adjusted) Minimum dose (mg/d): 50 Maximum dose (mg/d): 300

Frequency of dosing: three times a day
Details of dosing regimen: Acarbose, week 1: 50 mg once daily at supper, week 2: 50 mg BID at breakfast and supper, week 3: 50 mg TID with meals, week 4-52 titrated upward to 100 mg TID when post-load blood glucose > 12 mmol/l, downtitrated to 50mg TID in case of intolerance

(2) Placebo

N: 99

Treatment duration (wks): 52

Washout period (d): 42

Treatment(s): Placebo (Oral)

Outcomes

Baseline characteristics

		Acarbose		
		N	**k**	**mean**
Demographics:				
Age (years)	Continuous	93		69.7 (SD 4.82182538049648) a
Sex (n male)	Dichotomous	93	65	(69.9%)
Duration of diabetes (yrs)	Continuous	93		5.8 (SD 6.75055553269507) a
Blood glucose:				
HbA1c (%) – 52wk	Continuous	93		7.4 (SD 0.964365076099296) a
HbA1c (%) – 52wk	Continuous	93		7.4 (SD 0.964365076099296) a
Fasting plasma glucose (mmol/l) – 52wk	Continuous	93		8.4 (SD 1.92873015219859) a
Fasting plasma glucose (mmol/l) – 52wk	Continuous	93		8.4 (SD 1.92873015219859) a
Body weight:				
BMI (kg/m2)	Continuous	93		28.3 (SD 3.85746030439718) a
Weight (kg)	Continuous	93		79.4 (SD 12.5367459892908) a

[a] SD calculated from reported SE

		Placebo		
		N	**k**	**mean**
Demographics:				
Age (years)	Continuous	99		70.3 (SD 4.9749371855331) a
Sex (n male)	Dichotomous	99	60	(60.6%)
Duration of diabetes (yrs)	Continuous	99		4.8 (SD 4.9749371855331) a
Blood glucose:				
HbA1c (%) – 52wk	Continuous	99		7.3 (SD 0.99498743710662) a
HbA1c (%) – 52wk	Continuous	99		7.3 (SD 0.99498743710662) a
Fasting plasma glucose (mmol/l) – 52wk	Continuous	99		8.5 (SD 1.98997487421324) a
Fasting plasma glucose (mmol/l) – 52wk	Continuous	99		8.5 (SD 1.98997487421324) a
Body weight:				
BMI (kg/m2)	Continuous	99		28.6 (SD 3.97994974842648) a
Weight (kg)	Continuous	99		81.3 (SD 15.9197989937059) a

[a] SD calculated from reported SE

Results

		Acarbose		
		N	**k**	**mean**
Blood glucose:				
HbA1c (%) – 52wk	Mean change	93		-0.3 (SD 0.964365076099296) a
HbA1c (%) – 52wk	Mean change	93		-0.3 (SD 0.964365076099296) a
Fasting plasma glucose (mmol/l) – 52wk	Mean change	93		-0.3 (SD 1.92873015219859) a
Fasting plasma glucose (mmol/l) – 52wk	Mean change	93		-0.3 (SD 1.92873015219859) a
Hypoglycaemic events:				
All hypoglycaemic events (no patients) – 52wk	Dichotomous	93	0	(0.0%)

Adverse events: GI: nausea – 52wk	Dichotomous	93	10	(10.8%)
Dropouts: Total dropouts – 52wk	Dichotomous	93	13	(14.0%)
Dropout due to AEs – 52wk	Dichotomous	93	10	(10.8%)

[a] SD calculated from reported SE

		Placebo		
		N	k	mean
Blood glucose: HbA1c (%) – 52wk	Mean change	99		0.3 (SD 0.99498743710662) a
HbA1c (%) – 52wk	Mean change	99		0.3 (SD 0.99498743710662) a
Fasting plasma glucose (mmol/l) – 52wk	Mean change	99		0.4 (SD 1.98997487421324) a
Fasting plasma glucose (mmol/l) – 52wk	Mean change	99		0.4 (SD 1.98997487421324) a
Hypoglycaemic events: All hypoglycaemic events (no patients) – 52wk	Dichotomous	99	0	(0.0%)
Adverse events: GI: nausea – 52wk	Dichotomous	99	3	(3.0%)
Dropouts: Total dropouts – 52wk	Dichotomous	99	5	(5.1%)
Dropout due to AEs – 52wk	Dichotomous	99	3	(3.0%)

[a] SD calculated from reported SE

Table 60: Jovanovic et al. (2000)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** USA **Authors' conclusions:** Repaglinide was well tolerated in a preprandial fixed dose regimen of 1 mg or 4 mg, assigned without adjustment for clinical parameters **Source of funding:** supported by Novo Nordisk Pharmaceuticals **Comments:** multicenter, double blind placebo controlled trial. Randomly assigned in blocks of five (1 to placebo, 2 to each repaglinide group). No other details relating to method of randomisation or allocation concealment. Blinding was achieved by encapsulation of 2 tablets (0.5 mg, 2 mg or 0 mg repaglinide) in each capsule of study medication to produce uniform appearance of all doses administered.
Number and characteristics of patients	**Total number of patients:** 361 **Inclusion criteria:** aged 40-75 years, with type 2 diabetes for at least 6 months and were using an OHA or following a diet and exercise program. Enrolled patients had a body weight between 90% and 150% of that considered ideal. Patients who had not been previously treated with an OHA (naïve) had Hba1c levels >6.5% before enrollment, OHA treated patients had Hba1c levels <12%. Patients who had previously received OHAs were not enrolled unless their FPG levels increased by at least 25 mg/dl in the 2 weeks following discontinuation of their previous treatment. **Exclusion criteria:** history of chronic insulin treatment, sevre uncontrolled hypertension, cardiac disorders, elevated serum creatinine levels (>1.6 g/l), elevated liver transaminase levels, previous exposure to repaglinide or concurrent therapy with corticosteroids. Any patient having 2 consecutive FPG values in excess of 350 mg/dl could be discontinued from the study for lack of efficacy at the discretion of the investigator Pre-randomisation phase: patients discontinued existing OHA treatment and entered a 2 week washout period

Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** some on oral hypoglycaemic drugs and/or insulin **Details of washout period:** 2 week washout period
Lifestyle advice	No details reported
Follow-up	**Total follow-up (wks):** 26 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 24 **Frequency of monitoring appointments:** patients returned to the clinic at weeks 2, 6, 12, 18 and 24.
Arms	**(1) Repaglinide (1mg)** N: 140 Treatment duration (wks): 24 Washout period (d): 14 Treatment(s): repaglinide (Oral) – fixed-dose Set dose (mg/d):1 Frequency of dosing: three times a day Details of dosing regimen: study medication was administered preprandially (15 mins before the three principal daily meals) **(2) Repaglinide (4mg)** N: 146 Treatment duration (wks): 24 Washout period (d): 14 Treatment(s): repaglinide (Oral) – fixed-dose Set dose (mg/d):4 Frequency of dosing: three times a day Details of dosing regimen: study medication was administered preprandially (15 mins before the three principal daily meals) **(3) placebo** N: 75 Treatment duration (wks): 24 Washout period (d): 14 Treatment(s): Placebo (Oral) – fixed-dose Frequency of dosing: three times a day Details of dosing regimen: study medication was administered preprandially (15 mins before the three principal daily meals)
Outcomes	**General** Safety analyses included all patients who received at least one dose of the study medication. Efficacy was assessed using the ITT population. 45 (60%) patients in placebo group, 32 (23%) in 1 mg group and 45 (31%) in 4 mg group discontinued the study All outcomes were extracted in this evidence table Only data from drug naïve subgroup used in analyses as inadequate washout period applied (2 weeks) **Hypoglycaemic events** **hypoglycaemic events relate to subjective symptoms that could be hypoglycaemia (eg. Sweating, strong hunger, dizziness, tremor), even when unconfirmed by blood glucose measurement. Subjective symptoms or blood glucose value <45 mg/dl were all classified as hypoglycaemic events of mild to moderate severity.** Major/severe hypoglycaemic event (Severe hypoglycaemic events were defined as sevrely impaired consciousness caused by hypoglycaemia, which required the assistance of another person and hospitalisation.)

Baseline characteristics

		Repaglinide (1mg)			Repaglinide (4mg)				
		N	k	mean	N	k	mean	Δ	p
Demographics:									
Age (years)	Continuous	140		57.9	146		57.6		
Sex (n male)	Dichotomous	140	96	(68.6%)	146	87	(59.6%)		
Duration of diabetes (yrs)	Continuous	140		6.6 (SD 6.5)	146		6.3 (SD 5.6)		
Ethnicity-African American	Dichotomous	140	14	(10.0%)	146	18	(12.3%)		
Ethnicity-Asian	Dichotomous	140	0	(0.0%)	146	2	(1.4%)		

Ethnicity-Other	Dichotomous	140	19	(13.6%)	146	16	(11.0%)		
Ethnicity-European	Dichotomous	140	107	(76.4%)	146	110	(75.3%)		
Blood glucose: HbA1c (%) – 0wk	Continuous	140		8.9 (SD 1.9)	146		8.7 (SD 1.7)		
Fasting plasma glucose (mg/dl) – 2wk	Continuous	140		250 (SD 78)	146		241 (SD 70)		
Body weight: BMI (kg/m2)	Continuous	140		29.4 (SD 4.5)	146		29.5 (SD 4.4)		
Diabetic complications: Retinopathy	Dichotomous	140	9	(6.4%)	146	8	(5.5%)		
Nephropathy	Dichotomous	140	2	(1.4%)	146	2	(1.4%)		
Neuropathy	Dichotomous	140	31	(22.1%)	146	28	(19.2%)		
Macroangiopathy	Dichotomous	140	15	(10.7%)	146	7	(4.8%)		
Previous blood glucose lowering drugs: Diet alone (i.e. drug naïve)	Dichotomous	140	39	(27.9%)	146	40	(27.4%)		
Sulfonylurea	Dichotomous	140	89	(63.6%)	146	83	(56.8%)		
Combination therapy	Dichotomous	140	6	(4.3%)	146	16	(11.0%)		
Other than sulphonylurea	Dichotomous	140	6	(4.3%)	146	7	(4.8%)		

		Repaglinide (1mg)			**placebo**				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Demographics: Age (years)	Continuous	140		57.9	75		58.5		
Sex (n male)	Dichotomous	140	96	(68.6%)	75	49	(65.3%)		
Duration of diabetes (yrs)	Continuous	140		6.6 (SD 6.5)	75		6.8 (SD 6.6)		
Ethnicity-African American	Dichotomous	140	14	(10.0%)	75	11	(14.7%)		
Ethnicity-Asian	Dichotomous	140	0	(0.0%)	75	1	(1.3%)		
Ethnicity-Other	Dichotomous	140	19	(13.6%)	75	12	(16.0%)		
Ethnicity-European	Dichotomous	140	107	(76.4%)	75	51	(68.0%)		
Blood glucose: HbA1c (%) – 0wk	Continuous	140		8.9 (SD 1.9)	75		8.6 (SD 1.4)		
Fasting plasma glucose (mg/dl) – 2wk	Continuous	140		250 (SD 78)	75		246 (SD 60)		
Body weight: BMI (kg/m2)	Continuous	140		29.4 (SD 4.5)	75		29.8 (SD 4.3)		
Diabetic complications: Retinopathy	Dichotomous	140	9	(6.4%)	75	6	(8.0%)		
Nephropathy	Dichotomous	140	2	(1.4%)	75	3	(4.0%)		
Neuropathy	Dichotomous	140	31	(22.1%)	75	17	(22.7%)		
Macroangiopathy	Dichotomous	140	15	(10.7%)	75	4	(5.3%)		
Previous blood glucose lowering drugs: Diet alone (i.e. drug naïve)	Dichotomous	140	39	(27.9%)	75	17	(22.7%)		
Sulfonylurea	Dichotomous	140	89	(63.6%)	75	46	(61.3%)		
Combination therapy	Dichotomous	140	6	(4.3%)	75	10	(13.3%)		
Other than sulphonylurea	Dichotomous	140	6	(4.3%)	75	2	(2.7%)		

	Repaglinide (4mg)			**placebo**				
	N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**

Demographics: Age (years)	Continuous	146		57.6	75		58.5		
Sex (n male)	Dichotomous	146	87	(59.6%)	75	49	(65.3%)		
Duration of diabetes (yrs)	Continuous	146		6.3 (SD 5.6)	75		6.8 (SD 6.6)		
Ethnicity-African American	Dichotomous	146	18	(12.3%)	75	11	(14.7%)		
Ethnicity-Asian	Dichotomous	146	2	(1.4%)	75	1	(1.3%)		
Ethnicity-Other	Dichotomous	146	16	(11.0%)	75	12	(16.0%)		
Ethnicity-European	Dichotomous	146	110	(75.3%)	75	51	(68.0%)		
Blood glucose: HbA1c (%) – 0wk	Continuous	146		8.7 (SD 1.7)	75		8.6 (SD 1.4)		
Fasting plasma glucose (mg/dl) – 2wk	Continuous	146		241 (SD 70)	75		246 (SD 60)		
Body weight: BMI (kg/m2)	Continuous	146		29.5 (SD 4.4)	75		29.8 (SD 4.3)		
Diabetic complications: Retinopathy	Dichotomous	146	8	(5.5%)	75	6	(8.0%)		
Nephropathy	Dichotomous	146	2	(1.4%)	75	3	(4.0%)		
Neuropathy	Dichotomous	146	28	(19.2%)	75	17	(22.7%)		
Macroangiopathy	Dichotomous	146	7	(4.8%)	75	4	(5.3%)		
Previous blood glucose lowering drugs: Diet alone (i.e. drug naïve)	Dichotomous	146	40	(27.4%)	75	17	(22.7%)		
Sulfonylurea	Dichotomous	146	83	(56.8%)	75	46	(61.3%)		
Combination therapy	Dichotomous	146	16	(11.0%)	75	10	(13.3%)		
Other than sulphonylurea	Dichotomous	146	7	(4.8%)	75	2	(2.7%)		

Results

		Repaglinide (1mg)			Repaglinide (4mg)				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Blood glucose: HbA1c (%) – 12wka	Mean change	136		-0.7 (SD 1.75)	145		-0.7 (SD 1.81)		
HbA1c (%) – 24wka	Mean change	136		-0.65 (SD 1.75)	145		-0.7 (SD 1.81)		
HbA1c < 7% or <=7% – 24wk	Dichotomous	129	41	(31.8%)	134	43	(32.1%)		
Hba1c <8% – 24wk	Dichotomous	129	65	(50.4%)	134	70	(52.2%)		
Fasting plasma glucose (mg/dl) – 12wka	Mean change	135		-60 (SD 63.9)	143		-58 (SD 41.9)		
Fasting plasma glucose (mg/dl) – 24wka	Mean change	135		-47 (SD 63.9)	143		-49 (SD 71.7)		
Hypoglycaemic events: All hypoglycaemic events (no patients) – 24wk	Dichotomous	140	38	(27.1%)	146	51	(34.9%)		
Major/severe hypoglycaemic event – 24wk	Dichotomous	140	0	(0.0%)	146	0	(0.0%)		
symptomatic (confirmed) – 24wkb	Dichotomous	140	0	(0.0%)	146	2	(1.4%)		
symptomatic (unconfirmed) hypoglycaemia – 24wkc	Dichotomous	140	30	(21.4%)	146	47	(32.2%)		
Symptomatic hypoglycaemia – 24wkd	Dichotomous	140	13	(9.3%)	146	16	(11.0%)		
asymptomatic (confirmed) – 24wkb	Dichotomous	140	1	(0.7%)	146	1	(0.7%)		
Adverse events: GI: nausea – 24wke	Dichotomous	140	7	(5.0%)	146	7	(4.8%)		
Any adverse event(s) – 24wk	Dichotomous	140	108	(77.1%)	146	117	(80.1%)		
Arthralgia – 24wk	Dichotomous	140	10	(7.1%)	146	9	(6.2%)		
Back pain – 24wk	Dichotomous	140	10	(7.1%)	146	9	(6.2%)		
cardiovascular AE – 24wk	Dichotomous	140	13	(9.3%)	146	20	(13.7%)		
Chest pain – 24wkf	Dichotomous	140	4	(2.9%)	146	4	(2.7%)		

Dizziness – 24wk	Dichotomous	140	3	(2.1%)	146	14	(9.6%)		
Fatigue – 24wk	Dichotomous	140	9	(6.4%)	146	8	(5.5%)		
GI: diarrhoea – 24wk	Dichotomous	140	8	(5.7%)	146	8	(5.5%)		
Headache – 24wk	Dichotomous	140	16	(11.4%)	146	21	(14.4%)		
Hyperglycaemia – 24wk	Dichotomous	140	2	(1.4%)	146	3	(2.1%)		
Infection (upper airway or other common) – 24wk	Dichotomous	140	18	(12.9%)	146	19	(13.0%)		
Pain (any) – 24wk	Dichotomous	140	7	(5.0%)	146	5	(3.4%)		
paresthesia – 24wk	Dichotomous	140	8	(5.7%)	146	2	(1.4%)		
Sinusitis or sinus abnormality – 24wk	Dichotomous	140	11	(7.9%)	146	7	(4.8%)		
Dropouts:									
Total dropouts – 24wke	Dichotomous	140	32	(22.9%)	146	45	(30.8%)		
Dropout due to AEs – 24wke	Dichotomous	140	9	(6.4%)	146	12	(8.2%)		
Drop out due to unsatisfactory effect – 24wk	Dichotomous	140	11	(7.9%)	146	17	(11.6%)		
Dropout due to hypoglycaemia – 24wk	Dichotomous	140	1	(0.7%)	146	2	(1.4%)		
Pre-study diet alone (i.e. drug naive)									
Blood glucose:									
HbA1c (%) – 12wkg	Mean change	38		-1.45 (SD 1.23)	40		-2 (SD 1.58)		
HbA1c (%) – 24wkg	Mean change	38		-1.35 (SD 1.85)	40		-1.93 (SD 1.58)		
Fasting plasma glucose (mg/dl) – 12wkg	Mean change	37		-36 (SD 63.9)	39		-53 (SD 62.4)		
Fasting plasma glucose (mg/dl) – 24wkg	Mean change	37		-27 (SD 66.9)	39		-48 (SD 62.4)		
Hypoglycaemic events:									
All hypoglycaemic events (no patients) – 24wkh	Dichotomous	39	15	(38.5%)	40	22	(55.0%)		
Pre-study oral antidiabetics (i.e. not drug naive)									
Hypoglycaemic events:									
All hypoglycaemic events (no patients) – 24wk	Dichotomous	101	23	(22.8%)	106	29	(27.4%)		

[a] Data extracted from graph; SD calculated from assumed SE
[b] BG confirmed <45 mg/dl
[c] BG >=45 mg/dl
[d] no BG reading
[e] DO NOT USE - inadequate washout period for total population
[f] approximated to nearest integer (percentages only presented in text)
[g] (Used in the analysis); Data extracted from graph; SD calculated from assumed SE
[h] (Used in the analysis)

		Repaglinide (1mg)			placebo				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Blood glucose:									
HbA1c (%) – 12wka	Mean change	136		-0.7 (SD 1.75)	74		1.25 (SD 2.15)		
HbA1c (%) – 24wka	Mean change	135		-0.65 (SD 1.75)	74		1.3 (SD 3.01)		<0.001
HbA1c (%) – 24wka	Mean change	136		-0.65 (SD 1.75)	74		1.3 (SD 3.01)		<0.001
HbA1c < 7% or <=7% – 24wk	Dichotomous	129	41		75	b			
Hba1c <8% – 24wk	Dichotomous	129	65		75	b			
Fasting plasma glucose (mg/dl) – 12wka	Mean change	135		-60 (SD 63.9)	74		-2 (SD 73.1)		
Fasting plasma glucose (mg/dl) – 24wk	Mean change	135		-47 (SD 63.9) a	74		6 (SD 90.3) c		

Hypoglycaemic events:										
All hypoglycaemic events (no patients) – 24wk	Dichotomous	140	38	(27.1%)	75	8	(10.7%)		
Major/severe hypoglycaemic event – 24wk	Dichotomous	140	0	(0.0%)	75	0	(0.0%)		
symptomatic (confirmed) – 24wkd	Dichotomous	140	0	(0.0%)	75	0	(0.0%)		
symptomatic (unconfirmed) hypoglycaemia – 24wke	Dichotomous	140	30	(21.4%)	75	2	(2.7%)		
Symptomatic hypoglycaemia – 24wkf	Dichotomous	140	13	(9.3%)	75	5	(6.7%)		
asymptomatic (confirmed) – 24wkd	Dichotomous	140	1	(0.7%)	75	1	(1.3%)		
Adverse events:										
GI: nausea – 24wkg	Dichotomous	140	7	(5.0%)	75	2	(2.7%)		
Any adverse event(s) – 24wk	Dichotomous	140	108	(77.1%)	75	53	(70.7%)		
Arthralgia – 24wk	Dichotomous	140	10	(7.1%)	75	4	(5.3%)		
Back pain – 24wk	Dichotomous	140	10	(7.1%)	75	4	(5.3%)		
cardiovascular AE – 24wk	Dichotomous	140	13	(9.3%)	75	6	(8.0%)		0.807
Chest pain – 24wkh	Dichotomous	140	4	(2.9%)	75	1	(1.3%)		
Dizziness – 24wk	Dichotomous	140	3	(2.1%)	75	7	(9.3%)		
Fatigue – 24wk	Dichotomous	140	9	(6.4%)	75	7	(9.3%)		
GI: diarrhoea – 24wk	Dichotomous	140	8	(5.7%)	75	1	(1.3%)		
Headache – 24wk	Dichotomous	140	16	(11.4%)	75	6	(8.0%)		
Hyperglycaemia – 24wk	Dichotomous	140	2	(1.4%)	75	6	(8.0%)		
Infection (upper airway or other common) – 24wk	Dichotomous	140	18	(12.9%)	75	3	(4.0%)		
Pain (any) – 24wk	Dichotomous	140	7	(5.0%)	75	8	(10.7%)		
paresthesia – 24wk	Dichotomous	140	8	(5.7%)	75	2	(2.7%)		
Sinusitis or sinus abnormality – 24wk	Dichotomous	140	11	(7.9%)	75	0	(0.0%)		
Dropouts:										
Total dropouts – 24wkg	Dichotomous	140	32	(22.9%)	75	45	(60.0%)		
Dropout due to AEs – 24wkg	Dichotomous	140	9	(6.4%)	75	12	(16.0%)		
Drop out due to unsatisfactory effect – 24wk	Dichotomous	140	11	(7.9%)	75	23	(30.7%)		
Dropout due to hypoglycaemia – 24wk	Dichotomous	140	1	(0.7%)	75	0	(0.0%)		
Pre-study diet alone (i.e. drug naive)										
Blood glucose:										
HbA1c (%) – 12wki	Mean change	38		-1.45 (SD 1.23)	17		0.63 (SD 1.65)		
HbA1c (%) – 24wki	Mean change	38		-1.35 (SD 1.85)	17		1 (SD 2.68)		NRj
Fasting plasma glucose (mg/dl) – 12wki	Mean change	37		-36 (SD 63.9)	17		-8 (SD 66)		
Fasting plasma glucose (mg/dl) – 24wki	Mean change	37		-27 (SD 66.9)	17		8.5 (SD 78.3)		
Hypoglycaemic events:										
All hypoglycaemic events (no patients) – 24wkk	Dichotomous	39	15	(38.5%)	17	1	(5.9%)		
Pre-study oral antidiabetics (i.e. not drug naive)										
Hypoglycaemic events:										
All hypoglycaemic events (no patients) – 24wk	Dichotomous	101	23	(22.8%)	58	7	(12.1%)		

[a] Data extracted from graph; SD calculated from assumed SE
[b] not reported
[c] Data extracted from graph (inconsistency in reported value in text); SD calculated from assumed SE
[d] BG confirmed <45 mg/dl
[e] BG >=45 mg/dl
[f] no BG reading
[g] DO NOT USE - inadequate washout period for total population
[h] approximated to nearest integer (percentages only presented in text)
[i] (Used in the analysis); Data extracted from graph; SD calculated from assumed SE
[j] changes from screening p<0.001
[k] (Used in the analysis)

		Repaglinide (4mg)			placebo			Δ	p
		N	k	mean	N	k	mean		
Blood glucose: HbA1c (%) – 12wka	Mean change	145		-0.7 (SD 1.81)	74		1.25 (SD 2.15)		
HbA1c (%) – 24wka	Mean change	143		-0.7 (SD 1.81)	74		1.3 (SD 3.01)		<0.001
HbA1c (%) – 24wka	Mean change	145		-0.7 (SD 1.81)	74		1.3 (SD 3.01)		<0.001
HbA1c < 7% or <=7% – 24wk	Dichotomous	134	43		75	b			
Hba1c <8% – 24wk	Dichotomous	134	70		75	b			
Fasting plasma glucose (mg/dl) – 12wka	Mean change	143		-58 (SD 41.9)	74		-2 (SD 73.1)		
Fasting plasma glucose (mg/dl) – 24wk	Mean change	143		-49 (SD 71.7) a	74		6 (SD 90.3) c		
Hypoglycaemic events: All hypoglycaemic events (no patients) – 24wk	Dichotomous	146	51	(34.9%)	75	8	(10.7%)		
Major/severe hypoglycaemic event – 24wk	Dichotomous	146	0	(0.0%)	75	0	(0.0%)		
symptomatic (confirmed) – 24wkd	Dichotomous	146	2	(1.4%)	75	0	(0.0%)		
symptomatic (unconfirmed) hypoglycaemia – 24wke	Dichotomous	146	47	(32.2%)	75	2	(2.7%)		
Symptomatic hypoglycaemia – 24wkf	Dichotomous	146	16	(11.0%)	75	5	(6.7%)		
asymptomatic (confirmed) – 24wkd	Dichotomous	146	1	(0.7%)	75	1	(1.3%)		
Adverse events: GI: nausea – 24wkg	Dichotomous	146	7	(4.8%)	75	2	(2.7%)		
Any adverse event(s) – 24wk	Dichotomous	146	117	(80.1%)	75	53	(70.7%)		
Arthralgia – 24wk	Dichotomous	146	9	(6.2%)	75	4	(5.3%)		
Back pain – 24wk	Dichotomous	146	9	(6.2%)	75	4	(5.3%)		
cardiovascular AE – 24wk	Dichotomous	146	20	(13.7%)	75	6	(8.0%)		0.273
Chest pain – 24wkh	Dichotomous	146	4	(2.7%)	75	1	(1.3%)		
Dizziness – 24wk	Dichotomous	146	14	(9.6%)	75	7	(9.3%)		
Fatigue – 24wk	Dichotomous	146	8	(5.5%)	75	7	(9.3%)		
GI: diarrhoea – 24wk	Dichotomous	146	8	(5.5%)	75	1	(1.3%)		
Headache – 24wk	Dichotomous	146	21	(14.4%)	75	6	(8.0%)		
Hyperglycaemia – 24wk	Dichotomous	146	3	(2.1%)	75	6	(8.0%)		
Infection (upper airway or other common) – 24wk	Dichotomous	146	19	(13.0%)	75	3	(4.0%)		
Pain (any) – 24wk	Dichotomous	146	5	(3.4%)	75	8	(10.7%)		
paresthesia – 24wk	Dichotomous	146	2	(1.4%)	75	2	(2.7%)		
Sinusitis or sinus abnormality – 24wk	Dichotomous	146	7	(4.8%)	75	0	(0.0%)		
Dropouts: Total dropouts – 24wkg	Dichotomous	146	45	(30.8%)	75	45	(60.0%)		
Dropout due to AEs – 24wkg	Dichotomous	146	12	(8.2%)	75	12	(16.0%)		
Drop out due to unsatisfactory effect – 24wk	Dichotomous	146	17	(11.6%)	75	23	(30.7%)		
Dropout due to hypoglycaemia – 24wk	Dichotomous	146	2	(1.4%)	75	0	(0.0%)		
Pre-study diet alone (i.e. drug naive) Blood glucose: HbA1c (%) – 12wki	Mean change	40		-2 (SD 1.58)	17		0.63 (SD 1.65)		
HbA1c (%) – 24wki	Mean change	40		-1.93 (SD 1.58)	17		1 (SD 2.68)		NR
Fasting plasma glucose (mg/dl) – 12wki	Mean change	39		-53 (SD 62.4)	17		-8 (SD 66)		

	Fasting plasma glucose (mg/dl) – 24wki	Mean change	39		-48 (SD 62.4)	17		8.5 (SD 78.3)		
	Hypoglycaemic events: All hypoglycaemic events (no patients) – 24wkj	Dichotomous	40	22	(55.0%)	17	1	(5.9%)		
	Pre-study oral antidiabetics (i.e. not drug naive) Hypoglycaemic events: All hypoglycaemic events (no patients) – 24wk	Dichotomous	106	29	(27.4%)	58	7	(12.1%)		

[a] Data extracted from graph; SD calculated from assumed SE
[b] not reported
[c] Data extracted from graph (inconsistency in reported value in text); SD calculated from assumed SE
[d] BG confirmed <45 mg/dl
[e] BG >=45 mg/dl
[f] no BG reading
[g] DO NOT USE - inadequate washout period for total population
[h] approximated to nearest integer (percentages only presented in text)
[i] (Used in the analysis); Data extracted from graph; SD calculated from assumed SE
[j] (Used in the analysis)

	Between treatment comparisons were made using calculations based on last observation carried forward, by ANOVA with treatment and center included in the model as fixed effect. P-values for between group comparison for other adverse events (including hypoglycaemia) were not reported

Table 61: Kato et al. (2009)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** Japan **Authors' conclusions:** Using a low dose regimen, pioglitazone significantly improved blood pressure and hepatic function and may be more effective than metformin to reduce risk factors in Japanese diabetic patients with metabolic syndrome at preventing atherosclerosis **Source of funding:** Unclear **Comments:** Random assignment was performed by opening sealed envelopes with sequential numbers at the time of allocation.
Number and characteristics of patients	**Total number of patients:** 50 **Inclusion criteria:** Japanese patients recently diagnosed with type 2 diabetes associated with metabolic syndrome (all patients had fatty liver). Patients who had no history of treatment with oral antinhyperglycaemic drugs, antihyperlipidemic drugs or antihypertensive drugs were studies. All patients were on continuous dietary and exercise therapy following intiation of the analysis for not less than 3 months, including a one month pre-treatment baseline measurement period (observation period) **Exclusion criteria:** patients with diabetic retinopathy, nephropathy or neuropathy whose condition was unstable or underwent sudden progression were excluded from the study. Furthermore, those patients with liver dysfunction, renal dysfunction or anaemia were also excluded. In addition, patients with myocardial infarction, angina, congestive heart failure or a history of cerebrovascular disease were also excluded Pre-randomisation phase: After one month of dietary and exercise therapy, the subjects were randomly assigned to 12 weeks of therapy
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** All treatment naive/ no OADs at screening **Details of washout period:** All AHA naïve
Lifestyle advice	All patients were on continuous dietary and exercise therapy following intiation of the analysis for not less than 3 months, including a one month pre-treatment baseline measurement period (observation period). Patients were instructed to keep their total energy intake within 1200-1800 kcal, the fat ratio of caloric intake to <25-30% and to do 150 min or more of exercise per week. Patients were instructed to reduce their caloric intake to less than the regular caloric intake of the study population (200-2500 kcal/day) from the observation

	period through the end of the study period. During the study period, dietary and exercise therapy were continued. All patients received nutritional instruction from a national registered dietician at the monthly visits from the observation period through the end of the study period. Adherence to the dietary and exercise therapy was 84% (21/25) in pioglitazone group and 80% (20/25) in the metformin group.
Follow-up	**Total follow-up (wks):** 16 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 12 **Frequency of monitoring appointments:** Over the 12 week treatment period, consultations and tests were performed monthly
Arms	**(1) Pioglitazone** N: 25 Treatment duration (wks): 12 Washout period (d): 0 Treatment(s): Pioglitazone (Oral) – fixed-dose Set dose (mg/d):15 Details of dosing regimen: No other details reported **(2) Metformin** N: 25 Treatment duration (wks): 12 Washout period (d): 0 Treatment(s): Metformin (Oral) – fixed-dose Set dose (mg/d):500 Details of dosing regimen: No other details reported
Outcomes	**General** No dropout details were reported and it was assumed that no patients from either group discontinued the study. Outcomes not extracted in this evidence table include measures of insulin resistence, heart rate and liver enzymes (ALT and AST)

Baseline characteristics

		Pioglitazone			Metformin			Δ	p
		N	k	mean	N	k	mean		
Demographics: Age (years)	Continuous	25		51.4 (SD 15.2)	25		58.6 (SD 12.4)		
Sex (n male)	Dichotomous	25	12	(48.0%)	25	14	(56.0%)		
Blood glucose: HbA1c (%) – 0wk	Continuous	25		7.4 (SD 1.8)	25		7.1 (SD 1.4)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	25		7.3 (SD 1.4)	25		7.6 (SD 1.4)		
Body weight: BMI (kg/m2) – 0wk	Continuous	25		28.4 (SD 6.4)	25		27.5 (SD 3.4)		
Waist circumference (cms) – 0wk	Continuous	25		95.6 (SD 10.8)	25		95.4 (SD 7.9)		
Blood pressure: Systolic blood pressure (mmHg) – 0wk	Continuous	25		133.5 (SD 19)	25		131.2 (SD 12.4)		
Diastolic blood pressure (mmHg) – 0wk	Continuous	25		78.9 (SD 9.3)	25		77.5 (SD 5.7)		
Lipids: HDL cholesterol (mmol/l) – 0wk	Continuous	25		1.48 (SD 0.5)	25		1.4 (SD 0.31)		
Triglycerides (mmol/l) – 0wk	Continuous	25		1.61 (SD 1.08)	25		1.63 (SD 0.69)		
LDL cholesterol (mmol/l) – 0wk	Continuous	25		3.26 (SD 0.74)	25		3.46 (SD 0.83)		

Results

	Pioglitazone	Metformin	Δ	p

		N	k	mean	N	k	mean		
Blood glucose: HbA1c (%) – 0wk	Percentage change from baseline	25			25				>0.05
HbA1c (%) – 12wk	Continuous	25		6.3 (SD 1.2)	25		6.3 (SD 0.9)		
Fasting plasma glucose (mmol/l) – 0wk	Percentage change from baseline	25			25				>0.05
Fasting plasma glucose (mmol/l) – 12wka	Percentage change from baseline	25		-5 (SD -15.3)	25		-5.8 (SD -16.1)		
Fasting plasma glucose (mmol/l) – 12wk	Continuous	25		6.9 (SD 1.4)	25		7.1 (SD 1.3)		
Postprandial plasma glucose (mmol/l) – 0wk	Percentage change from baseline	25			25				>0.05
Postprandial plasma glucose (mmol/l) – 12wk	Continuous	25		10.5 (SD 3.9)	25		12.8 (SD 3.6)		
Postprandial plasma glucose (mmol/l) – 12wk	Percentage change from baseline	25		-17.4 (SD -65.1)	25		-14.3 (SD -56.1)		
Body weight: BMI (kg/m2) – 0wk	Percentage change from baseline	25			25				<0.01
BMI (kg/m2) – 12wk	Continuous	25		28.5 (SD 6.9)	25		26.6 (SD 3.5)		
BMI (kg/m2) – 12wka	Percentage change from baseline	25		0.2 (SD 4.08)	25		-3.3 (SD 3.06)		
Waist circumference (cms) – 0wk	Percentage change from baseline	25			25				>0.05
Waist circumference (cms) – 12wk	Percentage change from baseline	25		-0.5 (SD 0.765)	25		-2.7 (SD -8.93)		
Waist circumference (cms) – 12wk	Continuous	25		95.1 (SD 11.7)	25		93.1 (SD 9.3)		
Adverse events: cardiovascular AE – 0wk	Dichotomous	25			25				NR
cardiovascular AE – 12wk	Dichotomous	25	0	(0.0%)	25	0	(0.0%)		
Edema peripheral – 0wk	Dichotomous	25			25				NR
Edema peripheral – 12wk	Dichotomous	25	2	(8.0%)	25	0	(0.0%)		
Blood pressure: Systolic blood pressure (mmHg) – 0wk	Percentage change from baseline	25			25				<0.05
Systolic blood pressure (mmHg) – 12wk	Continuous	25		126.9 (SD 17.2)	25		131.7 (SD 15.7)		
Systolic blood pressure (mmHg) – 12wk	Percentage change from baseline	25		-4.7 (SD -18.9)	25		0.5 (SD 10.7)		
Diastolic blood pressure (mmHg) – 0wk	Percentage change from baseline	25			25				>0.05
Diastolic blood pressure (mmHg) – 12wk	Continuous	25		75 (SD 8.4)	25		76.4 (SD 8.2)		
Diastolic blood pressure (mmHg) – 12wk	Percentage change from baseline	25		4.6 (SD 6.12)	25		1.3 (SD 8.16)		
Lipids: HDL cholesterol (mmol/l) – 0wk	Percentage change from baseline	25			25				>0.05
HDL cholesterol (mmol/l) – 12wk	Percentage change from baseline	25		-18.2 (SD -70.9)	25		-10.9 (SD -41.6)		
HDL cholesterol (mmol/l) – 12wk	Continuous	25		1.72 (SD 0.54)	25		1.55 (SD 0.37)		
Triglycerides (mmol/l) – 0wk	Percentage change from baseline	25			25				>0.05
Triglycerides (mmol/l) – 12wk	Percentage change from baseline	25		-5.4 (SD -0.765)	25		-0.7 (SD 35.7)		
Triglycerides (mmol/l) – 12wk	Continuous	25		1.41 (SD 0.75)	25		1.51 (SD 0.84)		
LDL cholesterol (mmol/l) – 0wk	Percentage change from baseline	25			25				>0.05

	LDL cholesterol (mmol/l) – 12wk	Percentage change from baseline	25		-2.1 (SD 18.1)	25		0 (SD 18.1)		
	LDL cholesterol (mmol/l) – 12wk	Continuous	25		3.27 (SD 0.68)	25		3.42 (SD 0.87)		

[a] SD calculated from reported 95% CI

	For statistical evaluation, the paired t-test was used for pre and post treatment values. Change from baseline (%) to final value (last observation carried forward). Treatments were compared using adjusted mean ratios from baseline (pioglitazone/metformin) with baseline values as covariate data. For comparisons of data between the pioglitazone group and the metformin group, 95% confidence intervals were presented. In the testing of rates of change in therapeutic effects between the two groups, for items without equality of variance, Welch's test was used, while for items with equality of variance, the unpaired t-teat was used.

Table 62: Kawamori et al. (2012)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** Japan **Authors' conclusions:** Linagliptin showed superior glucose-lowering efficacy and comparable safety and tolerability to both placebo and voglibose in Japanese patients with typen 2 diabetes **Source of funding:** supported by Boehringer Ingelheim **Comments:** This is a randomized, double-blind study with both a placebo- and an active-controlled parallel group. Randomization will be based on the Zelen rule and follow a predefined allocation ratio of 2:2:2:1 (linagliptin 5 mg: linagliptin 10 mg: voglibose: placebo). Allocation to treatment groups is balanced for the potentially confounding effects of patient background and baseline characteristics, HbA1c (stratified into two categories; < 8.5% and = 8.5%), the number of pre-study use of antidiabetic drugs, gender and study site. Treatment allocation is conducted by a sponsor-independent contractor. Following informed consent, the investigator completes a registration form that is sent to the allocation center. The registration form includes data on the subjects' inclusion and exclusion criteria. After receiving the registration form, the allocation center sends a registration report to the investigator. The investigator confirms that the patient satisfies the study criteria and sends a second registration form to the allocation center once the 4-week washout period is completed. The allocation center randomizes the patient according to the predefined criteria above and this information is provided to the investigator. Randomization is done once at the enrollment of study. An independent external clinical event committee conducted blinded ajudication of any suspected cardiovascular or cerebrovascular AEs.
Number and characteristics of patients	**Total number of patients:** 561 **Inclusion criteria:** The study enrolled male and non-pregnant female patients with type 2 diabetes aged 20-80 years with a BMI <=40 kg/m2 and inadequate glycaemic control (Hba1c 7-10% in those previously untreated with OADs or Hba1c 7-9% at screening and 7-10% after washout in those already receiving one or two OADs for >=10 weeks) **Exclusion criteria:** fasting plasma glucose >13.3 mmol/l during washout or placebo run-in, myocardial infarction, stroke or TIA within the previous 6 months, impaired hepatic function, treatment with a glitazone, insulin or anti-obesity drugs within the previous 3 months or any investigational agent within the previous 2 months and/or a history of known intolerance, allergy or hypersensitivity to voglibose or any other concomitant drugs Pre-randomisation phase: there was a 2 week washout phase for patients who previously received one or two OADs and this was followed by a 2 week placebo run-in period
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** some on oral hypoglycaemic drugs and/or insulin **Details of washout period:** See baseline characteristics for details. There was a 2 week washout phase (for those previously on OADs) and 2 week placebo run-in (for all individuals including those who were AHA naïve)
Lifestyle advice	no details reported
Follow-up	**Total follow-up (wks):** 16 **Length of titration period (wks):** 0

	Length of maintenance period (wks): 12 **Frequency of monitoring appointments:** no details reported
Arms	**(1) Linagliptin 5 mg** N: 159 Treatment duration (wks): 12 Washout period (d): 28 Comments: washout period of 2 weeks and placebo run-in period of 2 weeks Treatment(s): Linagliptin (Oral) – fixed-dose Set dose (mg/d):5 Frequency of dosing: once a day Details of dosing regimen: no further details reported **(2) Placebo** N: 80 Treatment duration (wks): 12 Washout period (d): 28 Comments: washout period of 2 weeks and placebo run-in period of 2 weeks Treatment(s): Placebo (Oral) – fixed-dose Frequency of dosing: once a day Details of dosing regimen: at week 12, patients receiving placebo were randomised to linagliptin 5 mg or 10 mg (data not extracted)
Outcomes	**General** Data from 2/4 of the arms in this study were not extracted into this evidence table: Linaglitpin 10 mg (as this is over the recommended dose of 5 mg specified in the summary product characteristics) and voglibose (as this is not licensed in the UK). In addition, only 12 week data from the Linagliptin 5 mg and placebo arms have been extracted as following 12 weeks, patients in the placebo arm were randomised to linagliptin 5 mg or 10 mg. Outcomes not extracted in this evidence table include fasting insulin and measures of insulin resistance, and glycated albumin Efficacy analyses at week 12 were performed using the full analysis set (all randomised patients who had baseline and >=1 dose of study medication). Safety analyses at week 12 were performed on the treated set (all randomised patients who receieved >=1 dose of study medication). A total of 3 (1.9%) patients in linagliptin arm and 6 (7.5%) in the placebo arm discontinued the study **Quality of life** Satisfaction (measures using Diabetes Treatment satisfaction Questionnaire (DTSQ))
Baseline characteristics	

		Linagliptin 5 mg			Placebo				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	159		60.3 (SD 9.4)	80		59.7 (SD 8.9)		
Sex (n male)	Dichotomous	159	111	(69.8%)	80	57	(71.3%)		
Blood glucose: HbA1c (%) – 0wk	Continuous	159		8.07 (SD 0.66)	80		7.95 (SD 0.67)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	159		9.1 (SD 1.8)	80		9 (SD 1.7)		
Body weight: BMI (kg/m2) – 0wk	Continuous	159		24.6 (SD 4)	80		24.3 (SD 3.4)		
Weight (kg) – 0wka	Continuous	159		69.43104 (SD 11.3)	80		68.58432 (SD 9.6)		
Diabetic complications: Microvascular	Dichotomous	159	57	(35.8%)	80	28	(35.0%)		
Macrovascular	Dichotomous	159	77	(48.4%)	80	36	(45.0%)		
metabolic syndrome	Dichotomous	159	59	(37.1%)	80	31	(38.8%)		
Previous blood glucose lowering drugs: Diet alone (i.e. drug naïve)	Dichotomous	159	87	(54.7%)	80	43	(53.8%)		
any monotherapy (1 previous OAD)	Dichotomous	159	58	(36.5%)	80	29	(36.3%)		
any dual therapy (2 previous OAD)	Dichotomous	159	14	(8.8%)	80	8	(10.0%)		
Renal function: eGFR	Continuous	159		113.9 (SD 24.9)	80		111.4 (SD 26.3)		

[a] estimated from BMI assuming mean height of 1.68m

Results

		Linagliptin 5 mg			Placebo				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 12wka	Mean change	159		-0.24 (SD 0.757)	80		0.63 (SD 0.716)	MD=-0.870 (CI: -1.040, -0.700)	<0.0001
HbA1c (%) – 12wka	Continuous	159		7.58 (SD 1.01)	80		8.34 (SD 1.25)		
HbA1c < 7% or <=7% – 12wk	Dichotomous	159	42	(26.4%)	80	8	(10.0%)		0.0038
Fasting plasma glucose (mmol/l) – 12wka	Mean change	159		-0.7 (SD 1.26)	80		0.4 (SD 0.894)	MD=-1.100 (CI: -1.400, -0.800)	<0.0001
Fasting plasma glucose (mmol/l) – 12wka	Continuous	159		8.2 (SD 1.26)	80		9.3 (SD 1.79)		
Body weight: BMI (kg/m2) – 12wk	Mean change	159		-0.02 (SD 0.63)	80		-0.13 (SD 0.537)	MD=0.110 (CI: -0.030, 0.250)	>0.05
Weight (kg) – 12wk	Mean change	159		-0.06 (SD 1.51)	80		-0.39 (SD 1.43)	MD=0.330 (CI: -0.040, 0.700)	>0.05
Waist circumference (cms) – 12wk	Mean change	159		0 (SD 2.77)	80		-0.5 (SD 2.59)	MD=0.500 (CI: -0.160, 1.160)	>0.05
Hypoglycaemic events: All hypoglycaemic events (no patients) – 12wk	Dichotomous	159	0	(0.0%)	80	0	(0.0%)		
Adverse events: Any adverse event(s) – 12wk	Dichotomous	159	89	(56.0%)	80	45	(56.3%)		
Any serious adverse event(s) – 12wk	Dichotomous	159	1	(0.6%)	80	1	(1.3%)		
Serious AE drug related – 12wk	Dichotomous	159	0	(0.0%)	80	0	(0.0%)		
Study drug-related adverse event – 12wk	Dichotomous	159	15	(9.4%)	80	8	(10.0%)		
Gastrointestinal disorders (any) – 12wk	Dichotomous	159	29	(18.2%)	80	11	(13.8%)		
hypersensitivity – 12wk	Dichotomous	159	0	(0.0%)	80	0	(0.0%)		
Infection (upper airway or other common) – 12wk	Dichotomous	159	38	(23.9%)	80	12	(15.0%)		
metabolism and nutritional disorders – 12wk	Dichotomous	159	4	(2.5%)	80	7	(8.8%)		
Musculoskeletal and connective tissue disorders – 12wk	Dichotomous	159	10	(6.3%)	80	8	(10.0%)		
Nervous system disorders – 12wk	Dichotomous	159	9	(5.7%)	80	4	(5.0%)		
renal or urinary disorder – 12wk	Dichotomous	159	3	(1.9%)	80	2	(2.5%)		
Skin reaction – 12wk	Dichotomous	159	13	(8.2%)	80	2	(2.5%)		
Dropouts: Total dropouts – 12wk	Dichotomous	159	3	(1.9%)	80	6	(7.5%)		
Dropout due to AEs – 12wk	Dichotomous	159	3	(1.9%)	80	6	(7.5%)		
drop out due to drug related AE – 12wk	Dichotomous	159	1	(0.6%)	80	2	(2.5%)		

	drop out due to SAE – 12wk	Dichotomous	159	1	(0.6%)	80	0	(0.0%)		
	Lipids: Total cholesterol (mmol/l) – 12wk	Mean change	159		-0.118956 (SD 0.62)	80		-0.072408 (SD 0.625)	MD=-0.047 (CI: -0.197, 0.103)	>0.05
	HDL cholesterol (mmol/l) – 12wk	Mean change	159		-0.033618 (SD 0.196)	80		-0.036204 (SD 0.208)	MD=0.003 (CI: -0.047, 0.052)	>0.05
	Triglycerides (mmol/l) – 12wk	Mean change	159		-0.046289 (SD 0.954)	80		-0.118545 (SD 0.929)	MD=0.073 (CI: -0.154, 0.300)	>0.05
	LDL cholesterol (mmol/l) – 12wk	Mean change	159		-0.111198 (SD 0.554)	80		-0.02586 (SD 0.532)	MD=-0.083 (CI: -0.215, 0.049)	>0.05
	Quality of life: Satisfaction – 12wk	Mean change	159		3 (SD 7.57)	80		1.9 (SD 7.16)	MD=1.100 (CI: -0.700, 2.900)	>0.05
	Pre-study diet alone (i.e. drug naive) Blood glucose: HbA1c (%) – 12wkb	Mean change	87		-0.75	43		-0.16	MD=-0.590 (CI: -0.790, -0.390)	c
	HbA1c (%) – 12wkb	Mean change	87		-0.75	43		-0.16	MD=-0.590 (CI: -0.790, -0.390)	
	Baseline Hba1c >=8 Blood glucose: HbA1c (%) – 12wk	Mean change	88						MD=-1.090 (CI: -1.345, -0.835)	<0.0001d
	<= 1 years since diagnosis Blood glucose: HbA1c (%) – 12wk	Mean change	19			7			MD=-0.660 (CI: -1.230, -0.090)	
	eGFR >=90 ml/min Blood glucose: HbA1c (%) – 12wk	Mean change	135						MD=-0.890 (CI: -1.090, -0.690)	d
	eGFR 60 to <90 ml/min Blood glucose: HbA1c (%) – 12wk	Mean change	20						MD=-0.750 (CI: -1.200, -0.300)	d

[a] SD calculated from reported SE
[b] SD not reported
[c] SD calculated from reported 95% CI
[d] number of patients in placebo not reported

ANCOVA with baseline value as covariate and treatment and previous OAD thetrapy as varaibles was used to evaluate changes in continuous efficacy endpoints. Last observation carried forward was used to impute missing data for Hba1c, FPG, body weight. BMI and wasit circumference. Fisher's exact test was used to evaluate changes in categorical efficacy endpoints. P-values for between group comparisons for adverse events were not reported

Table 63: Kikuchi et al. (2009)

General

Phase:
☑ monotherapy
☐ dual therapy
☐ triple therapy
☐ insulin monotherapy
☐ insulin+oral
Parallel / crossover: Parallel

	Country: Japan **Authors' conclusions:** Vildagliptin 50mg bid was considered to be the most effective and tolerated dose, and therefore can be considered the recommended clinical dose for Japanese patients with type 2 diabetes **Source of funding:** funded by Novartis Pharma **Comments:** multi-centre randomised, double blind, placebo controlled trial with no details of randomisation, allocation concelament or blinding methods
Number and characteristics of patients	**Total number of patients:** 291 **Inclusion criteria:** patients diagnosed with type 2 diabetes, inadequately controlled on diet and exercise. Male and female outpatients (aged 20-75 years) with a BMI 20-35 kg/m2, Hba1c 6.5-10% and fasting plasma glucose <270 mg/dl were eligible to participate. Patients were required to be without OAD treatment and should be on dietary therapy (essential) and/or exercise for at least 8 weeks before run-in visit **Exclusion criteria:** history of type 1 or secondary forms of diabetes, acute metabolic diabetic complications, MI, unstable angina or coronary artery bypass surgery within the previous 6 months. CHF and liver disease also precluded participation. Patients with any of the following laboratory abnormalities were also excluded: ALT, AST and total bilirubin greater than two times the upper limit of normal, serum creatinine >2.0 mg/dl, clinically signifiacnt thyroid stimulating hormone levels or fasting tryglyerides >700 mg/dl Pre-randomisation phase: there was a 2 week run-in phase followed by 12 weeks of active treatment. Assumed baseline was after the 2 week run-in phase as illustrated in the reported graphs
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** some on oral hypoglycaemic drugs and/or insulin **Details of washout period:** Unclear whether all patients were AHA naïve
Lifestyle advice	patients were instructed to maintain their prior diet, exercise program and daily routine during the trial
Follow-up	**Total follow-up (wks):** 14 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 12 **Frequency of monitoring appointments:** Efficacy and tolerability were assessed during 4 visits at weeks 0, 2, 4, 8 and 12 of treatment
Arms	**(1) Vildagliptin (10 mg bid)** N: 71 Treatment duration (wks): 12 Washout period (d): 14 Treatment(s): Vildagliptin (Oral) – fixed-dose Set dose (mg/d):20 Frequency of dosing: twice a day Details of dosing regimen: vildagliptin 10 mg (bid) was taken 30 minutes before breakfast and an evening meal **(2) Vildagliptin (25 mg bid)** N: 72 Treatment duration (wks): 12 Washout period (d): 14 Treatment(s): Vildagliptin (Oral) – fixed-dose Set dose (mg/d):50 Frequency of dosing: twice a day Details of dosing regimen: vildagliptin 25 mg (bid) was taken 30 minutes before breakfast and an evening meal **(3) Vildagliptin (50 mg bid)** N: 76 Treatment duration (wks): 12 Washout period (d): 14 Treatment(s): Vildagliptin (Oral) – fixed-dose Set dose (mg/d):100 Frequency of dosing: twice a day Details of dosing regimen: vildagliptin 50 mg (bid) was taken 30 minutes before breakfast and an evening meal **(4) placebo** N: 72 Treatment duration (wks): 12 Washout period (d): 14 Treatment(s): Placebo (Oral) – fixed-dose Frequency of dosing: twice a day Details of dosing regimen: placebo was taken bid **(5) Vildagliptin (10, 25 and 50mg bid)** N: 219

	Treatment duration (wks): 12 Washout period (d): 14 Comments: Combined individual vildagliptin groups Treatment(s): Vildagliptin (Oral) Details of dosing regimen: Variable doses
Outcomes	**General** Primary and secondary analyses were performed in the full analysis set (FAS) population which was defined as all randomised patients excluding those with GCP violations, untreated patients, and those whose efficacy data (after randomisation) were not available. 6 (3%) in the vildagliptin groups and 6 (8%) in the placebo groups discontinued. 3 patients were discontinued due to unsatisfactory therapeutic effects and 5 for adverse events Outcomes not extracted in this evidence table include glucose, insulin and glucagon
Baseline characteristics	

		Vildagliptin (10 mg bid)			Vildagliptin (25 mg bid)			Δ	p
		N	k	mean	N	k	mean		
Demographics: Age (years)	Continuous	71		58.9 (SD 8.6)	72		57.8 (SD 8.5)		
Sex (n male)	Dichotomous	71	52	(73.2%)	72	46	(63.9%)		
Duration of diabetes (yrs)	Continuous	71		4.5 (SD 4.2)	72		4.7 (SD 4.5)		
Blood glucose: HbA1c (%) – 0wk	Continuous	71		7.4 (SD 0.8)	72		7.4 (SD 0.9)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	71		8.94105 (SD 1.94)	72		9.0243 (SD 1.82)		
2-h post prandial glucose (mmol/l) – 0wk	Continuous	71		15.8952 (SD 5.61)	72		14.76855 (SD 6.5)		
Body weight: BMI (kg/m2)	Continuous	71		24.4 (SD 2.7)	72		24.3 (SD 2.5)		
Weight (kg) – 0wk	Continuous	71		64.2 (SD 10.4)	72		63.6 (SD 9.7)		
BMI >25 kg/m2	Dichotomous	71	21	(29.6%)	72	17	(23.6%)		

		Vildagliptin (10 mg bid)			Vildagliptin (50 mg bid)			Δ	p
		N	k	mean	N	k	mean		
Demographics: Age (years)	Continuous	71		58.9 (SD 8.6)	76		58.8 (SD 8.6)		
Sex (n male)	Dichotomous	71	52	(73.2%)	76	51	(67.1%)		
Duration of diabetes (yrs)	Continuous	71		4.5 (SD 4.2)	76		4.7 (SD 4.3)		
Blood glucose: HbA1c (%) – 0wk	Continuous	71		7.4 (SD 0.8)	76		7.4 (SD 0.8)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	71		8.94105 (SD 1.94)	76		8.9133 (SD 1.85)		
2-h post prandial glucose (mmol/l) – 0wk	Continuous	71		15.8952 (SD 5.61)	76		15.7731 (SD 5.42)		
Body weight: BMI (kg/m2)	Continuous	71		24.4 (SD 2.7)	76		24.3 (SD 2.8)		
Weight (kg) – 0wk	Continuous	71		64.2 (SD 10.4)	76		62.7 (SD 9.3)		
BMI >25 kg/m2	Dichotomous	71	21	(29.6%)	76	23	(30.3%)		

	Vildagliptin (10 mg bid)	placebo	Δ	p

		N	k	mean	N	k	mean		
Demographics: Age (years)	Continuous	71		58.9 (SD 8.6)	72		60.4 (SD 8.1)		
Sex (n male)	Dichotomous	71	52	(73.2%)	52	46	(88.5%)		
Duration of diabetes (yrs)	Continuous	71		4.5 (SD 4.2)	72		7.1 (SD 5.5)		
Blood glucose: HbA1c (%) – 0wk	Continuous	71		7.4 (SD 0.8)	72		7.4 (SD 0.8)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	71		8.94105 (SD 1.94)	72		9.00765 (SD 1.66)		
2-h post prandial glucose (mmol/l) – 0wk	Continuous	71		15.8952 (SD 5.61)	72		15.8175 (SD 4.94)		
Body weight: BMI (kg/m2)	Continuous	71		24.4 (SD 2.7)	72		24.6 (SD 3.1)		
Weight (kg) – 0wk	Continuous	71		64.2 (SD 10.4)	72		63.8 (SD 10.1)		
BMI >25 kg/m2	Dichotomous	71	21	(29.6%)	72	25	(34.7%)		

		Vildagliptin (25 mg bid)			Vildagliptin (50 mg bid)				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	72		57.8 (SD 8.5)	76		58.8 (SD 8.6)		
Sex (n male)	Dichotomous	72	46	(63.9%)	76	51	(67.1%)		
Duration of diabetes (yrs)	Continuous	72		4.7 (SD 4.5)	76		4.7 (SD 4.3)		
Blood glucose: HbA1c (%) – 0wk	Continuous	72		7.4 (SD 0.9)	76		7.4 (SD 0.8)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	72		9.0243 (SD 1.82)	76		8.9133 (SD 1.85)		
2-h post prandial glucose (mmol/l) – 0wk	Continuous	72		14.76855 (SD 6.5)	76		15.7731 (SD 5.42)		
Body weight: BMI (kg/m2)	Continuous	72		24.3 (SD 2.5)	76		24.3 (SD 2.8)		
Weight (kg) – 0wk	Continuous	72		63.6 (SD 9.7)	76		62.7 (SD 9.3)		
BMI >25 kg/m2	Dichotomous	72	17	(23.6%)	76	23	(30.3%)		

		Vildagliptin (25 mg bid)			placebo				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	72		57.8 (SD 8.5)	72		60.4 (SD 8.1)		
Sex (n male)	Dichotomous	72	46	(63.9%)	52	46	(88.5%)		
Duration of diabetes (yrs)	Continuous	72		4.7 (SD 4.5)	72		7.1 (SD 5.5)		
Blood glucose: HbA1c (%) – 0wk	Continuous	72		7.4 (SD 0.9)	72		7.4 (SD 0.8)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	72		9.0243 (SD 1.82)	72		9.00765 (SD 1.66)		
2-h post prandial glucose (mmol/l) – 0wk	Continuous	72		14.76855 (SD 6.5)	72		15.8175 (SD 4.94)		
Body weight: BMI (kg/m2)	Continuous	72		24.3 (SD 2.5)	72		24.6 (SD 3.1)		
Weight (kg) – 0wk	Continuous	72		63.6 (SD 9.7)	72		63.8 (SD 10.1)		
BMI >25 kg/m2	Dichotomous	72	17	(23.6%)	72	25	(34.7%)		

		Vildagliptin (50 mg bid)			placebo				
		N	k	mean	N	k	mean	Δ	p
Demographics:									
Age (years)	Continuous	76		58.8 (SD 8.6)	72		60.4 (SD 8.1)		
Sex (n male)	Dichotomous	76	51	(67.1%)	52	46	(88.5%)		
Duration of diabetes (yrs)	Continuous	76		4.7 (SD 4.3)	72		7.1 (SD 5.5)		
Blood glucose:									
HbA1c (%) – 0wk	Continuous	76		7.4 (SD 0.8)	72		7.4 (SD 0.8)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	76		8.9133 (SD 1.85)	72		9.00765 (SD 1.66)		
2-h post prandial glucose (mmol/l) – 0wk	Continuous	76		15.7731 (SD 5.42)	72		15.8175 (SD 4.94)		
Body weight:									
BMI (kg/m2)	Continuous	76		24.3 (SD 2.8)	72		24.6 (SD 3.1)		
Weight (kg) – 0wk	Continuous	76		62.7 (SD 9.3)	72		63.8 (SD 10.1)		
BMI >25 kg/m2	Dichotomous	76	23	(30.3%)	72	25	(34.7%)		

Results

		Vildagliptin (10, 25 and 50mg bid)		
		N	k	mean
Dropouts:				
Total dropouts – 12wk	Dichotomous	219	6	(2.7%)

		Vildagliptin (10 mg bid)			Vildagliptin (25 mg bid)				
		N	k	mean	N	k	mean	Δ	p
Blood glucose:									
HbA1c (%) – 12wka	Mean change	71		-0.53 (SD 0.758)	72		-0.67 (SD 0.764)		
Fasting plasma glucose (mmol/l) – 12wka	Mean change	71		-0.61605 (SD 0.889)	72		-0.78255 (SD 0.989)		
2-h post prandial glucose (mmol/l) – 12wkb	Mean change	18		-3.46875 (SD 4.77)	19		-3.20235 (SD 4.71)		
Body weight:									
Weight (kg) – 12wkc	Mean change	71		-0.2 (SD 12.6)	72		0.2 (SD 11)		
Hypoglycaemic events:									
All hypoglycaemic events (no patients) – 12wk	Dichotomous	71	3	(4.2%)	72	0	(0.0%)		
Major/severe hypoglycaemic event – 12wk	Dichotomous	71	0	(0.0%)	72	0	(0.0%)		
Adverse events:									
Any adverse event(s) – 12wk	Dichotomous	71	44	(62.0%)	72	45	(62.5%)		
Any serious adverse event(s) – 12wk	Dichotomous	71	0	(0.0%)	72	1	(1.4%)		
Death – 12wk	Dichotomous	71	0	(0.0%)	72	0	(0.0%)		
URT inflammation – 12wk	Dichotomous	71	3	(4.2%)	72	4	(5.6%)		
Infection (upper airway or other common) – 12wk	Dichotomous	71	0	(0.0%)	72	1	(1.4%)		
Nasopharyngitis – 12wk	Dichotomous	71	14	(19.7%)	72	12	(16.7%)		
pruritus – 12wk	Dichotomous	71	1	(1.4%)	72	4	(5.6%)		

Dropouts: Dropout due to AEs – 12wkd	Dichotomous	71	1	(1.4%)	72	1	(1.4%)		
Baseline Hba1c >=8 Blood glucose: HbA1c (%) – 12wk	Mean change	0		-0.6 (SD 0) e	0		-0.9 (SD 0) f		
BMI 22-25 kg/m2 Blood glucose: HbA1c (%) – 12wkc	Mean change	50		-0.6 (SD 0.707)	55		-0.7 (SD 0.742)		

[a] SE estimated from graph
[b] in patients who took meal test
[c] assumed SE reported in paper and converted
[d] Inconsistency in reported text (states overall 5 people dropped out due to adverse events across all trial arms)
[e] SE 0.2% sample size based on baseline Hba1c not reported
[f] SE 0.2%

		Vildagliptin (10 mg bid)			Vildagliptin (50 mg bid)				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Blood glucose: HbA1c (%) – 12wka	Mean change	71		-0.53 (SD 0.758)	76		-0.92 (SD 0.785)	MD=-0.400	<0.0001
Fasting plasma glucose (mmol/l) – 12wka	Mean change	71		-0.61605 (SD 0.889)	76		-1.37085 (SD 1.06)		
2-h post prandial glucose (mmol/l) – 12wkb	Mean change	18		-3.46875 (SD 4.77)	21		-3.44655 (SD 4.55)		
Body weight: Weight (kg) – 12wkc	Mean change	71		-0.2 (SD 12.6)	76		0.5 (SD 12.2)		
Hypoglycaemic events: All hypoglycaemic events (no patients) – 12wk	Dichotomous	71	3	(4.2%)	76	2	(2.6%)		
Major/severe hypoglycaemic event – 12wk	Dichotomous	71	0	(0.0%)	76	0	(0.0%)		
Adverse events: Any adverse event(s) – 12wk	Dichotomous	71	44	(62.0%)	76	47	(61.8%)		
Any serious adverse event(s) – 12wk	Dichotomous	71	0	(0.0%)	76	0	(0.0%)		
Death – 12wk	Dichotomous	71	0	(0.0%)	76	0	(0.0%)		
URT inflammation – 12wk	Dichotomous	71	3	(4.2%)	76	0	(0.0%)		
Infection (upper airway or other common) – 12wk	Dichotomous	71	0	(0.0%)	76	0	(0.0%)		
Nasopharyngitis – 12wk	Dichotomous	71	14	(19.7%)	76	15	(19.7%)		
pruritus – 12wk	Dichotomous	71	1	(1.4%)	76	0	(0.0%)		
Dropouts: Dropout due to AEs – 12wkd	Dichotomous	71	1	(1.4%)	76	1	(1.3%)		
Baseline Hba1c >=8 Blood glucose: HbA1c (%) – 12wk	Mean change	0		-0.6 (SD 0) e	0		-1.3 (SD 0) f		
BMI 22-25 kg/m2 Blood glucose: HbA1c (%) – 12wkc	Mean change	50		-0.6 (SD 0.707)	53		-0.9 (SD 0.728)		

[a] SE estimated from graph
[b] in patients who took meal test
[c] assumed SE reported in paper and converted
[d] Inconsistency in reported text (states overall 5 people dropped out due to adverse events across all trial arms)
[e] SE 0.2% sample size based on baseline Hba1c not reported
[f] SE 0.1%

	Vildagliptin (10 mg bid)	placebo	Δ	p

		N	k	mean	N	k	mean		
Blood glucose: HbA1c (%) – 12wka	Mean change	71		-0.53 (SD 0.758)	72		0.28 (SD 0.849)	MD=-0.800 (CI: -0.996, -0.604)	<0.001
Fasting plasma glucose (mmol/l) – 12wka	Mean change	71		-0.61605 (SD 0.889)	72		0.1332 (SD 0.942)		<0.001
2-h post prandial glucose (mmol/l) – 12wkb	Mean change	18		-3.46875 (SD 4.77)	20		0.20535 (SD 4.52)		<0.001
Body weight: Weight (kg) – 12wkc	Mean change	71		-0.2 (SD 12.6)	72		-0.5 (SD 9.33)		NS
Hypoglycaemic events: All hypoglycaemic events (no patients) – 12wk	Dichotomous	71	3	(4.2%)	72	1	(1.4%)		
Major/severe hypoglycaemic event – 12wk	Dichotomous	71	0	(0.0%)	72	0	(0.0%)		
Adverse events: Any adverse event(s) – 12wk	Dichotomous	71	44	(62.0%)	72	53	(73.6%)		
Any serious adverse event(s) – 12wk	Dichotomous	71	0	(0.0%)	72	2	(2.8%)		
Death – 12wk	Dichotomous	71	0	(0.0%)	72	0	(0.0%)		
URT inflammation – 12wk	Dichotomous	71	3	(4.2%)	72	1	(1.4%)		
Infection (upper airway or other common) – 12wk	Dichotomous	71	0	(0.0%)	72	4	(5.6%)		
Nasopharyngitis – 12wk	Dichotomous	71	14	(19.7%)	72	18	(25.0%)		
pruritus – 12wk	Dichotomous	71	1	(1.4%)	72	0	(0.0%)		
Dropouts: Dropout due to AEs – 12wkd	Dichotomous	71	1	(1.4%)	72	1	(1.4%)		
Baseline Hba1c >=8									
Blood glucose: HbA1c (%) – 12wk	Mean change	0		-0.6 (SD 0) e	0		0.7 (SD 0) f		
BMI 22-25 kg/m2									
Blood glucose: HbA1c (%) – 12wkc	Mean change	50		-0.6 (SD 0.707)	47		0.3 (SD 0.686)		

[a] SE estimated from graph
[b] in patients who took meal test
[c] assumed SE reported in paper and converted
[d] Inconsistency in reported text (states overall 5 people dropped out due to adverse events across all trial arms)
[e] SE 0.2% sample size based on baseline Hba1c not reported
[f] SE 0.3%

		Vildagliptin (25 mg bid)			Vildagliptin (50 mg bid)				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 12wka	Mean change	72		-0.67 (SD 0.764)	76		-0.92 (SD 0.785)	MD=-0.200	0.01
Fasting plasma glucose (mmol/l) – 12wka	Mean change	72		-0.78255 (SD 0.989)	76		-1.37085 (SD 1.06)		
2-h post prandial glucose (mmol/l) – 12wkb	Mean change	19		-3.20235 (SD 4.71)	21		-3.44655 (SD 4.55)		
Body weight: Weight (kg) – 12wkc	Mean change	72		0.2 (SD 11)	76		0.5 (SD 12.2)		
Hypoglycaemic events: All hypoglycaemic events (no patients) – 12wk	Dichotomous	72	0	(0.0%)	76	2	(2.6%)		

Major/severe hypoglycaemic event – 12wk	Dichotomous	72	0	(0.0%)	76	0	(0.0%)		
Adverse events:										
Any adverse event(s) – 12wk	Dichotomous	72	45	(62.5%)	76	47	(61.8%)		
Any serious adverse event(s) – 12wk	Dichotomous	72	1	(1.4%)	76	0	(0.0%)		
Death – 12wk	Dichotomous	72	0	(0.0%)	76	0	(0.0%)		
URT inflammation – 12wk	Dichotomous	72	4	(5.6%)	76	0	(0.0%)		
Infection (upper airway or other common) – 12wk	Dichotomous	72	1	(1.4%)	76	0	(0.0%)		
Nasopharyngitis – 12wk	Dichotomous	72	12	(16.7%)	76	15	(19.7%)		
pruritus – 12wk	Dichotomous	72	4	(5.6%)	76	0	(0.0%)		
Dropouts:										
Dropout due to AEs – 12wkd	Dichotomous	72	1	(1.4%)	76	1	(1.3%)		
Baseline Hba1c >=8										
Blood glucose:										
HbA1c (%) – 12wk	Mean change	0		-0.9 (SD 0) e	0		-1.3 (SD 0) f		
BMI 22-25 kg/m2										
Blood glucose:										
HbA1c (%) – 12wkc	Mean change	55		-0.7 (SD 0.742)	53		-0.9 (SD 0.728)		

[a] SE estimated from graph
[b] in patients who took meal test
[c] assumed SE reported in paper and converted
[d] Inconsistency in reported text (states overall 5 people dropped out due to adverse events across all trial arms)
[e] SE 0.2%
[f] SE 0.1%

		Vildagliptin (25 mg bid)			placebo				
		N	k	mean	N	k	mean	Δ	p
Blood glucose:									
HbA1c (%) – 12wka	Mean change	72		-0.67 (SD 0.764)	72		0.28 (SD 0.849)	MD=-1.000 (CI: -1.196, -0.804)	<0.001
Fasting plasma glucose (mmol/l) – 12wka	Mean change	72		-0.78255 (SD 0.989)	72		0.1332 (SD 0.942)		<0.001
2-h post prandial glucose (mmol/l) – 12wkb	Mean change	19		-3.20235 (SD 4.71)	20		0.20535 (SD 4.52)		<0.001
Body weight:									
Weight (kg) – 12wkc	Mean change	72		0.2 (SD 11)	72		-0.5 (SD 9.33)		NS
Hypoglycaemic events:									
All hypoglycaemic events (no patients) – 12wk	Dichotomous	72	0	(0.0%)	72	1	(1.4%)		
Major/severe hypoglycaemic event – 12wk	Dichotomous	72	0	(0.0%)	72	0	(0.0%)		
Adverse events:									
Any adverse event(s) – 12wk	Dichotomous	72	45	(62.5%)	72	53	(73.6%)		
Any serious adverse event(s) – 12wk	Dichotomous	72	1	(1.4%)	72	2	(2.8%)		
Death – 12wk	Dichotomous	72	0	(0.0%)	72	0	(0.0%)		
URT inflammation – 12wk	Dichotomous	72	4	(5.6%)	72	1	(1.4%)		
Infection (upper airway or other common) – 12wk	Dichotomous	72	1	(1.4%)	72	4	(5.6%)		
Nasopharyngitis – 12wk	Dichotomous	72	12	(16.7%)	72	18	(25.0%)		
pruritus – 12wk	Dichotomous	72	4	(5.6%)	72	0	(0.0%)		

Dropouts: Dropout due to AEs – 12wkd	Dichotomous	72	1	(1.4%)	72	1	(1.4%)		
Baseline Hba1c >=8 Blood glucose: HbA1c (%) – 12wk	Mean change	0		-0.9 (SD 0) e	0		0.7 (SD 0) f		
BMI 22-25 kg/m2 Blood glucose: HbA1c (%) – 12wkc	Mean change	55		-0.7 (SD 0.742)	47		0.3 (SD 0.686)		

[a] SE estimated from graph
[b] in patients who took meal test
[c] assumed SE reported in paper and converted
[d] Inconsistency in reported text (states overall 5 people dropped out due to adverse events across all trial arms)
[e] SE 0.2%
[f] SE 0.3%

		Vildagliptin (50 mg bid)			placebo				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Blood glucose: HbA1c (%) – 12wka	Mean change	76		-0.92 (SD 0.785)	72		0.28 (SD 0.849)	MD=-1.200 (CI: -1.396, -1.004)	<0.001
Fasting plasma glucose (mmol/l) – 12wka	Mean change	76		-1.37085 (SD 1.06)	72		0.1332 (SD 0.942)		<0.001
2-h post prandial glucose (mmol/l) – 12wkb	Mean change	21		-3.44655 (SD 4.55)	20		0.20535 (SD 4.52)		<0.001
Body weight: Weight (kg) – 12wkc	Mean change	76		0.5 (SD 12.2)	72		-0.5 (SD 9.33)		NS
Hypoglycaemic events: All hypoglycaemic events (no patients) – 12wk	Dichotomous	76	2	(2.6%)	72	1	(1.4%)		
Major/severe hypoglycaemic event – 12wk	Dichotomous	76	0	(0.0%)	72	0	(0.0%)		
Adverse events: Any adverse event(s) – 12wk	Dichotomous	76	47	(61.8%)	72	53	(73.6%)		
Any serious adverse event(s) – 12wk	Dichotomous	76	0	(0.0%)	72	2	(2.8%)		
Death – 12wk	Dichotomous	76	0	(0.0%)	72	0	(0.0%)		
URT inflammation – 12wk	Dichotomous	76	0	(0.0%)	72	1	(1.4%)		
Infection (upper airway or other common) – 12wk	Dichotomous	76	0	(0.0%)	72	4	(5.6%)		
Nasopharyngitis – 12wk	Dichotomous	76	15	(19.7%)	72	18	(25.0%)		
pruritus – 12wk	Dichotomous	76	0	(0.0%)	72	0	(0.0%)		
Dropouts: Dropout due to AEs – 12wkd	Dichotomous	76	1	(1.3%)	72	1	(1.4%)		
Baseline Hba1c >=8 Blood glucose: HbA1c (%) – 12wk	Mean change	0		-1.3 (SD 0) e	0		0.7 (SD 0) f		
BMI 22-25 kg/m2 Blood glucose: HbA1c (%) – 12wkc	Mean change	53		-0.9 (SD 0.728)	47		0.3 (SD 0.686)		

[a] SE estimated from graph
[b] in patients who took meal test
[c] assumed SE reported in paper and converted
[d] Inconsistency in reported text (states overall 5 people dropped out due to adverse events across all trial arms)
[e] SE 0.1%

	[f] SE 0.3%
	Changes from baseline in the primary and secondary endpoints were analysed using an ANCOVA model with treatment and region as a factor and baseline Hba1c as the covariate. Adjusted (least squares) mean changes reported. P-values from between group compari

Table 64: Kikuchi et al. (2012)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** - **Authors' conclusions:** - **Source of funding:** - **Comments:** -
Number and characteristics of patients	**Total number of patients:** 213 **Inclusion criteria:** Drug naïve Japanese adults (20-75 years) with T2DM, HbA1c >=7.4% **Exclusion criteria:** -
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** All treatment naive/ no OADs at screening **Details of washout period:** No wash out. All patients were drug naïve.
Lifestyle advice	Not reported
Follow-up	**Total follow-up (wks):** 34 **Length of titration period (wks):** 17 **Length of maintenance period (wks):** 28 **Frequency of monitoring appointments:** -
Arms	**(1) Pioglitizone** N: 159 Treatment duration (wks): 28 Washout period (d): 0 Comments: Starting dose of 15mg/d At week 4, uptitrated to 30mg/d if no adverse events occurred At week 17, uptitrated to 45mg/d if HbA1c >=6.5% at week 16 and no adverse events occurred; otherwise maintained at 30mg/d No reduction in dose of study drug was permitted Treatment(s): Pioglitazone (Oral) – forced titration Minimum dose (mg/d): 15 Maximum dose (mg/d): 45 Details of dosing regimen: Starting dose of 15mg/d At week 4, uptitrated to 30mg/d if no adverse events occurred At week 17, uptitrated to 45mg/d if HbA1c >=6.5% at week 16 and no adverse events occurred; otherwise maintained at 30mg/d No reduction in dose of study drug was permitted **(2) Placebo** N: 54 Treatment duration (wks): 28 Washout period (d): 0 Treatment(s): Placebo (Oral)
Outcomes	**General** Data were not extracted from the third trial arm receiving rosiglitazone.

	Missing data were imputed using LOCF

Baseline characteristics

		Pioglitizone			Placebo				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	159		56 (SD 10.3)	54		53.9 (SD 10)		
Sex (n male)	Dichotomous	159	99	(62.3%)	54	33	(61.1%)		
Duration of diabetes (yrs)	Continuous	159		4.2 (SD 4.5)	54		4.2 (SD 3.9)		
Blood glucose: HbA1c (%) – 28wk	Continuous	159		8.8 (SD 1.3)	54		9 (SD 1.4)		
Fasting plasma glucose (mg/dl) – 0wk	Continuous	159		184.5 (SD 43.8)	54		190.8 (SD 46.6)		
Body weight: BMI (kg/m2)	Continuous	159		24.9 (SD 3.5)	54		25 (SD 3.6)		
Weight (kg) – 0wka	Continuous	159		70.27776 (SD 9.88)	54		70.56 (SD 10.2)		

[a] estimated from BMI assuming mean height of 1.68m

Results

		Pioglitizone			Placebo				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 16wka	Mean change	159		-0.91 (SD 1.01)	54		0.21 (SD 1.1)		
HbA1c (%) – 16wk	Continuous	159			54			MD=-1.260 (CI: -1.554, -0.966)	
HbA1c (%) – 28wk	Continuous	159		8.8 (SD 1.3)	54		9 (SD 1.4)	MD=-1.640 (CI: -1.960, -1.320)	b
Body weight: Weight (kg) – 28wk	Continuous	159		2.8 (SD 2.1)	54		-1 (SD 1.7)		
Dropouts: Total dropouts – 28wk	Dichotomous	159	22	(13.8%)	54	11	(20.4%)		
Dropout due to AEs – 28wk	Dichotomous	159	14	(8.8%)	54	1	(1.9%)		

[a] Data extracted from graph, assumed mistakenly reported as SD and not SE
[b] SEM calculated from reported 95% CI

Table 65: Kirkman et al. (2006)

General

Phase:
☑ monotherapy
☐ dual therapy
☐ triple therapy
☐ insulin monotherapy
☐ insulin+oral

Parallel / crossover: Parallel

Country: USA

Authors' conclusions: Ameliorating postprandial hyperglycemia did not appear to delay progression of early type 2 diabetes. Factors other than postprandial hyperglycemia may be greater determinants of progression of diabetes

Source of funding: supported by an investigator-initiated grant from Bayer with additional support from the National Institutes of Health

Comments: Blinded randomisation was stratified by site and randomisation to a hyperglycaemic clamp procedure. Detailed methods of randomisation and allocation concealment not reported

Number and characteristics of patients	**Total number of patients:** 239 **Inclusion criteria:** Individuals at least 25 years old with obesity, a history of gestational diabetes or a family history of diabetes were targeted. These participants were screened for diabetes and those with a 2-h postload plasma glucose =200 mg/dl (11.1 mmol/l) and FPG <140 mg/dl were considered to have early diabetes and were screened for enrollment. **Exclusion criteria:** BMI<24 kg/m2, cancer within 5 years, infectious disease including HIV infection, a cardiac event within the previous 6 month, uncontrolled hypertension or hypertension that could not be controlled with agents other than beta blockersor thiazide diuretics, elevated aspartate aminotransferase, serum creatinine >1.4 mg/dl in men or 1.3 mg/dl in women, fasting plasma triglycerides >600 mg/dl despite treatment, any significant disease or medication that could interfere with medication tolerance or with outcomes, suspected inability to adhere to the protocol or inability to give informed consent Pre-randomisation phase: For screening details see inclusion criteria. Within 6 weeks of the qualifying OGTT, participants were admitted for a 2-day study initiation visit. All participants had a medical history and physical examination before randomisation.
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** All treatment naive/ no OADs at screening **Details of washout period:** All diagnosed with early diabetes
Lifestyle advice	A registered dietitian counseled subjects on an appropriate diet for type 2 diabetes. Subjects whose FPG was >=140 mg/dl had intensified dietary counseling. No further details about lifestyle advice was reported.
Follow-up	**Total follow-up (wks):** 260 **Length of titration period (wks):** - **Length of maintenance period (wks):** 260 **Frequency of monitoring appointments:** Within 6 weeks of the qualifying OGTT, subjects were admitted for a 2 day study initiation visit (including medical history and physical exam). Participants visited the study clinic at 3 month intervals and had FPG measured, among other measurements. Annually, each subject completed a visit at which multiple measures were done (OGTT, history, and physical examination, seven-field fundus photographs, electrocardiogram, and laboratory tests for renal and hepatic function). At years 1 and 2, Meal Profile Studies (MPS) and hyperglycemic clamps were repeated. Hba1c was measured every 6 months, total and HDL cholesterol and triglycerides were measured annually
Arms	**(1) Acarbose** N: 120 Treatment duration (wks): 260 Washout period (d): 0 Comments: Participants were newly diagnosed therefore assumed to be treatment naïve (no washout period necessary). Treatment duration was not specifically reported but assumed to last the duration of the study (i.e. 5 years) Treatment(s): Acarbose (Oral) – forced titration Minimum dose (mg/d): 25 Maximum dose (mg/d): 300 Participants achieving full dose (n): 99 Frequency of dosing: three times a day Compliance: Compliance was assessed by pill counts. Mean pill consumption was 79.5% of prescribed dose in the acarbose group at year 1 and 79% at year 5 Details of dosing regimen: Initiated at a dose of 25 mg once daily with the evening meal, then titrated at weekly intervals by 25mg daily to the maximum dose of 100mg t.i.d with meals. The study drug was down-titrated as needed in participants who complained of gastrointestinal side effects. Efforts were made to reach a daily dosage of at least 50mg t.i.d. After study titration 91% of participants receiving Acarbose had achieved the full dose **(2) Placebo** N: 119 Treatment duration (wks): 260 Washout period (d): 0 Comments: Participants were newly diagnosed therefore assumed to be treatment naïve (no washout period necessary). Treatment duration was not specifically reported but assumed to last the duration of the study (i.e. 5 years) Treatment(s): Placebo (Oral) Participants achieving full dose (n): 107 Compliance: Mean pill consumption was 84.6% of prescribed dose in the placebo group at year 1 and 83.8% at year 5. Details of dosing regimen: Identical placebo given. After study titration 97% of participants receiving placebo had achieved the full dose
Outcomes	**General** Meal Profile Studies, hyperglycaemic clamp, insulin sensitivity, proinsulin and insulin resistance were also measured but are not reported in this evidence table. The primary outcome was development of frank

hyperglycaemia (two consecutive quarterly FPG >=140 mg/dl)

219 participants completed the initiation visit, received the study drug, returned for at least one follow up visit and are included in the intention to treat analysis. Over the 5 year trial, 95 participants terminated follow-up prematurely (53 in the acarbose group and 42 in the placebo group).

Baseline characteristics

		All study participants		
		N	**k**	**mean**
Demographics:				
Age (years) – yr	Continuous	219		53.7 (SD 11.4)
Sex (n male)	Dichotomous	219	74	(33.8%)
Ethnicity-White	Dichotomous	219	171	(78.1%)
Ethnicity-African American	Dichotomous	219	41	(18.7%)
Ethnicity-Asian	Dichotomous	219	3	(1.4%)
Ethnicity-Other	Dichotomous	219	4	(1.8%)
Blood glucose:				
HbA1c (%) – yr	Continuous	219		6.34 (SD 0.64)
HbA1c (%) – yr	Continuous	219		6.34 (SD 0.64)
Fasting plasma glucose (mmol/l) – yr	Continuous	219		6.7377 (SD 0.76035)
Fasting plasma glucose (mmol/l) – yr	Continuous	219		6.7377 (SD 0.76035)
2-h plasma glucose (mg/dl) – yr	Continuous	219		236.2 (SD 31)
2-h plasma glucose (mg/dl) – yr	Continuous	219		236.2 (SD 31)
Body weight:				
BMI (kg/m2)	Continuous	219		35.2 (SD 7.1)
Weight (kg)	Continuous	219		98.6 (SD 21.2)
Waist circumference (cms)	Continuous	219		104.648 (SD 12.954)
Blood pressure:				
Diagnosis of hypertension	Dichotomous	219	107	(48.9%)
Systolic blood pressure (mmHg)	Continuous	219		132.6 (SD 17.3)
Diastolic blood pressure (mmHg)	Continuous	219		75.4 (SD 11)
Lipids:				
Total cholesterol (mmol/l)	Continuous	219		5.0427 (SD 1.000782)
HDL cholesterol (mmol/l)	Continuous	219		0.993024 (SD 0.222396)
Triglycerides (mmol/l)	Continuous	219		2.177841 (SD 1.15158)
LDL cholesterol (mmol/l)	Continuous	219		3.054066 (SD 0.933546)
Diabetic complications:				
Retinopathy	Dichotomous	219	25	(11.4%)
Microalbuminuria	Dichotomous	219	6	(2.7%)
Sensory neuropathy	Dichotomous	219	33	(15.1%)

		Acarbose			Placebo				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Demographics:									
Age (years) – 0yr	Continuous	109		53.7 (SD 11)	110		53.7 (SD 11.7)		
Sex (n male)	Dichotomous	109	36	(33.0%)	110	38	(34.5%)		
Ethnicity-White	Dichotomous	109	84	(77.1%)	110	87	(79.1%)		
Ethnicity-African American	Dichotomous	109	21	(19.3%)	110	20	(18.2%)		
Ethnicity-Asian	Dichotomous	109	2	(1.8%)	110	1	(0.9%)		
Ethnicity-Other	Dichotomous	109	2	(1.8%)	110	2	(1.8%)		
Blood glucose:									
HbA1c (%) – 0yr	Continuous	106		6.35 (SD 0.64)	106		6.32 (SD 0.62)		
Fasting plasma glucose (mmol/l) – 0yr	Continuous	109		6.77655 (SD 0.771)	110		6.7044 (SD 0.744)		

2-h plasma glucose (mg/dl) – 0yr	Continuous	109		236.5 (SD 31.8)	110		235.8 (SD 30.4)			
Peak postprandial glucose, first meal (mmol/l) – 0yr	Continuous	108		10.5339 (SD 1.85)	110		10.51725 (SD 1.69)			
Peak postprandial glucose, second meal (mmol/l) – 0yr	Continuous	108		7.8588 (SD 1.53)	110		7.81995 (SD 1.42)			
Body weight: BMI (kg/m2)	Continuous	109		35.1 (SD 7.2)	110		35.2 (SD 7.1)			
Weight (kg)	Continuous	109		97.4 (SD 19.1)	110		99.9 (SD 23.1)			
Waist circumference (cms)	Continuous	109		104.648 (SD 14.2)	110		104.648 (SD 11.7)			
Blood pressure: Diagnosis of hypertension	Dichotomous	109	54	(49.5%)	110	53	(48.2%)			
Systolic blood pressure (mmHg)	Continuous	109		133.3 (SD 16.4)	110		132 (SD 18.2)			
Diastolic blood pressure (mmHg)	Continuous	109		75.6 (SD 11.1)	110		75.2 (SD 11)			
Lipids: Total cholesterol (mmol/l)	Continuous	109		5.045286 (SD 0.967)	110		5.0427 (SD 1.03)			
HDL cholesterol (mmol/l)	Continuous	109		0.987852 (SD 0.217)	110		0.99561 (SD 0.228)			
Triglycerides (mmol/l)	Continuous	109		2.207195 (SD 1.29)	110		2.148487 (SD 1.01)			
LDL cholesterol (mmol/l)	Continuous	109		3.043722 (SD 0.936)	110		3.061824 (SD 0.934)			
Diabetic complications: Retinopathy	Dichotomous	109	11	(10.1%)	110	14	(12.7%)			
Microalbuminuria	Dichotomous	109	3	(2.8%)	110	3	(2.7%)			
Sensory neuropathy	Dichotomous	109	15	(13.8%)	110	18	(16.4%)			

Results

		Acarbose			Placebo				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Blood glucose: HbA1c (%) – 1yr	Continuous	81		6.16 (SD 0.74)	76		6.22 (SD 0.6)		>0.05a
HbA1c (%) – 2yr	Continuous	63		6.02 (SD 0.49)	63		6.26 (SD 0.62)		>0.05a
HbA1c (%) – 3yr	Continuous	45		6.17 (SD 0.6)	49		6.24 (SD 0.56)		>0.05a
HbA1c (%) – 4yr	Continuous	41		6.44 (SD 0.72)	40		6.4 (SD 0.64)		>0.05a
HbA1c (%) – 5yr	Continuous	15		6.03 (SD 0.71)	16		6.41 (SD 0.89)		>0.05a
Fasting plasma glucose (mmol/l) – 1yrb	Continuous	74		6.34365 (SD 0.899)	78		6.4491 (SD 0.932)		>0.05a
Fasting plasma glucose (mmol/l) – 2yrb	Continuous	60		6.25485 (SD 0.938)	59		6.48795 (SD 0.871)		>0.05a
Fasting plasma glucose (mmol/l) – 3yrb	Continuous	50		6.42135 (SD 0.832)	52		6.4047 (SD 0.727)		>0.05a
Fasting plasma glucose (mmol/l) – 4yrb	Continuous	39		6.9042 (SD 1.12)	45		6.5601 (SD 1.01)		>0.05a
Fasting plasma glucose (mmol/l) – 5yrb	Continuous	20		6.8598 (SD 1.1)	29		6.88755 (SD 1.27)		>0.05a
2-h plasma glucose (mg/dl) – 1yrb	Continuous	74		202.9 (SD 45.5)	78		211.9 (SD 50.4)		>0.05a

	2-h plasma glucose (mg/dl) – 2yrb	Continuous	60		201.1 (SD 47.2)	59		204.3 (SD 45.2)	>0.05a
	2-h plasma glucose (mg/dl) – 3yrb	Continuous	50		202.3 (SD 50.1)	52		206 (SD 51.7)	>0.05a
	2-h plasma glucose (mg/dl) – 4yrb	Continuous	39		224.6 (SD 61.4)	45		223.1 (SD 52.4)	>0.05a
	2-h plasma glucose (mg/dl) – 5yrb	Continuous	20		222.2 (SD 35.7)	29		237 (SD 55.4)	>0.05a
	Peak postprandial glucose, first meal (mmol/l) – 1yr	Continuous	81		9.1353 (SD 1.59)	82		10.18425 (SD 1.65)	<0.01a
	Peak postprandial glucose, first meal (mmol/l) – 2yr	Continuous	63		9.14085 (SD 1.39)	62		10.2231 (SD 1.65)	<0.01a
	Peak postprandial glucose, second meal (mmol/l) – 1yr	Continuous	81		6.78765 (SD 0.938)	82		7.57575 (SD 1.18)	<0.01a
	Peak postprandial glucose, second meal (mmol/l) – 2yr	Continuous	63		6.6378 (SD 0.805)	61		7.4037 (SD 0.988)	<0.01a
	Dropouts:								
	Total dropouts – 5yrc	Dichotomous	120	64	(53.3%)	119	51	(42.9%)	
	Dropout due to AEs – 5yrc	Dichotomous	120	13	(10.8%)	119	5	(4.2%)	d
	Dropout due to AEs – 5yrc	Dichotomous	109	13	(10.8%)	110	5	(4.2%)	d

[a] Repeated measures ANOVA and random effects models
[b] in OGTT
[c] From online supplementary data
[d] not reported

	Kaplan-Meier product limit estimation was used to assess the primary outcome of time to development of frank fasting hyperglycaemia (not extracted in this evidence table). Repeated measures ANOVA and random effects models were used to analyse other longitudinal outcomes (tukey's correction used to adjust for multiple tests)

Table 66: Kovacevic I,Profozic V,Skrabalo Z,Cabrijan T,Zjacic-Rotkvic V,Goldoni (1997)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** Unclear (assumed Croatia) **Authors' conclusions:** Therapeutic use of acarbose and glibenclamide significantly improved glucose metabolism in patients with NIDDM inadequately treated with basic principles of care; BPT (assumed diet and lifestyle) **Source of funding:** Unclear **Comments:** Glibenclamide (single blind) placebo (double-blind)
Number and characteristics of patients	**Total number of patients:** 102 **Inclusion criteria:** patients with NIDDM for at least 3 months, Hba1c 7-11%, aged 35-70 years and with stable bodyweight (not >35 BMI) **Exclusion criteria:** patients with severe liver disease, kidney disease, other severe diseases, pregnancy
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** All treatment naive/ no OADs at screening **Details of washout period:** Patients were controlled on basic principles of treatment alone (assumed diet/exercise), NIDDM
Lifestyle advice	patients were uncontrolled on basic principles of treatment alone (assumed to be diet/exercise) and received diet therapy 6 weeks prior to randomisation which was maintained with drug allocation
Follow-up	**Total follow-up (wks):** 30

Length of titration period (wks): 0
Length of maintenance period (wks): 24
Frequency of monitoring appointments: 6 week pre-randomisation where patients were on diet therapy
6 visits (1 pre-randomisation and 5 at week 0, 6, 12, 18 and 24)

Arms

(1) Acarbose
N: 34
Treatment duration (wks): 24
Washout period (d): 0
Comments: Treatment naïve (assumed) - had 6 week of diet therapy prior to randomisation
Treatment(s): Acarbose (Oral) – fixed-dose
Set dose (mg/d):300
Frequency of dosing: three times a day
Details of dosing regimen: 100 mg tid with main meals

(2) Glibenclamide
N: 34
Treatment duration (wks): 24
Washout period (d): 0
Comments: Treatment naïve (assumed) - had 6 week of diet therapy prior to randomisation
Treatment(s): Sulfonylurea (Oral) – flexible-dose (dose-adjusted)
Minimum dose (mg/d): 3.5
Maximum dose (mg/d): 10.5
Details of dosing regimen: Administered before breakfast and dinner

(3) Placebo
N: 34
Treatment duration (wks): 24
Washout period (d): 0
Comments: Treatment naïve (assumed) - had 6 week of diet therapy prior to randomisation
Treatment(s): Placebo (Oral)

Outcomes

General
1/33 in acarbose, 1/33 in glibenclamide and 6/31 placebo patients discontinued the study

Baseline characteristics

		All study participants		
		N	k	mean
Demographics:				
Age (years)	Continuous	97		57.54 (SD 8.08)
Sex (n male)	Dichotomous	97	47	(48.5%)
Duration of diabetes (yrs)	Continuous	97		4.5a
Body weight:				
BMI (kg/m2)	Continuous	97		28.73 (SD 2.83)
Weight (kg)	Continuous	97		81.087552 (SD 7.987392) b

[a] SD not reported
[b] estimated from BMI assuming mean height of 1.68m

		Acarbose			Glibenclamide			Δ	p
		N	k	mean	N	k	mean		
Blood glucose:									
HbA1c (%) – 0wk	Continuous	33		8.3 (SD 0.7)	33		9 (SD 1)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	33		11.7 (SD 3.11)	33		13.9 (SD 4.2)		

		Acarbose			Placebo			Δ	p
		N	k	mean	N	k	mean		
Blood glucose:									
HbA1c (%) – 0wk	Continuous	33		8.3 (SD 0.7)	31		8.3 (SD 1.09)		

Fasting plasma glucose (mmol/l) – 0wk	Continuous	33		11.7 (SD 3.11)	31		11.9 (SD 3.3)		

		Glibenclamide			Placebo				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 0wk	Continuous	33		9 (SD 1)	31		8.3 (SD 1.09)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	33		13.9 (SD 4.2)	31		11.9 (SD 3.3)		

Results

		Acarbose			Glibenclamide				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 24wk	Continuous	33		7.6 (SD 0.9)	33		7.4 (SD 1.2)		
Fasting plasma glucose (mmol/l) – 12wk	Continuous	33		9.5 (SD 2)	33		9.9 (SD 2.7)		
Fasting plasma glucose (mmol/l) – 24wk	Continuous	33		9.8 (SD 2.2)	33		9.9 (SD 2.7)		
Adverse events: Any adverse event(s) – 24wk	Dichotomous	33	18	(54.5%)	33	5	(15.2%)		
Dropouts: Total dropouts – 24wk	Dichotomous	34	1	(2.9%)	34	1	(2.9%)		
Dropout due to AEs – 24wk	Dichotomous	34	0	(0.0%)	34	0	(0.0%)		

		Acarbose			Placebo				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 24wk	Continuous	33		7.6 (SD 0.9)	31		8.5 (SD 1.7)		
Fasting plasma glucose (mmol/l) – 12wk	Continuous	33		9.5 (SD 2)	31		11.7 (SD 3)		
Fasting plasma glucose (mmol/l) – 24wk	Continuous	33		9.8 (SD 2.2)	31		11.2 (SD 3.55)		
Adverse events: Any adverse event(s) – 24wk	Dichotomous	33	18	(54.5%)	31	5	(16.1%)		
Dropouts: Total dropouts – 24wk	Dichotomous	34	1	(2.9%)	34	3	(8.8%)		
Dropout due to AEs – 24wk	Dichotomous	34	0	(0.0%)	34	3	(8.8%)		

		Glibenclamide			Placebo				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 24wk	Continuous	33		7.4 (SD 1.2)	31		8.5 (SD 1.7)		
Fasting plasma glucose (mmol/l) – 12wk	Continuous	33		9.9 (SD 2.7)	31		11.7 (SD 3)		
Fasting plasma glucose (mmol/l) – 24wk	Continuous	33		9.9 (SD 2.7)	31		11.2 (SD 3.55)		
Adverse events: Any adverse event(s) – 24wk	Dichotomous	33	5	(15.2%)	31	5	(16.1%)		

	Dropouts:										
	Total dropouts – 24wk	Dichotomous	34	1	(2.9%)	34	3	(8.8%)			
	Dropout due to AEs – 24wk	Dichotomous	34	0	(0.0%)	34	3	(8.8%)			

	Assumed SDs reported for all continuous outcomes

Table 67: Lawrence et al. (2004)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** Unclear but assumed UK **Authors' conclusions:** For the same improvement in glycaemic control, pioglitazone and metformin produce favourable changes in HDL and LDL subfractions compared with gliclazide in overweight type 2 diabetic patients **Source of funding:** Takeda **Comments:** Open label trial
Number and characteristics of patients	**Total number of patients:** 64 **Inclusion criteria:** patients with diet treated type 2 diabetes, Hba1c >7% or <7.5% for those on low dose oral therapy with BMI>27 kg/m2 **Exclusion criteria:** diet treated patients with a Hba1c >10%, current liipid-lowering therapy, previously intolerant to study medicationsrecent myocardial infarction, contrindication to study medications, uncontrolled angina or hypertension Pre-randomisation phase: There was a 3 month run-in phase on diet alone
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** some on oral hypoglycaemic drugs and/or insulin **Details of washout period:** There was a 3 month run-in phase on diet alone
Lifestyle advice	Diet treatment (no details provided)
Follow-up	**Total follow-up (wks):** 36 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 24 **Frequency of monitoring appointments:** Patients had a 3 month run in phase of diet therapy only and were seen 6 weeks pre-randomisation and at weeks 0 (baseline), 4, 8,12,18 and 24
Arms	**(1) Pioglitazone (30 mg)** N: 21 Treatment duration (wks): 24 Washout period (d): 90 Comments: There was a 3 month run-in phase on diet alone Treatment(s): Pioglitazone (Oral) – fixed-dose Set dose (mg/d):30 Minimum dose (mg/d): 30 Maximum dose (mg/d): 45 Frequency of dosing: once a day Details of dosing regimen: Pioglitazone 30 mg od (up to 45 mg od). If FBG>7 mmol/l treatment was uptitrated to a max of 45 mg od. 13 patients were uptitrated to 45 mg/day **(2) Metformin** N: 21 Treatment duration (wks): 24 Washout period (d): 90 Comments: There was a 3 month run-in phase on diet alone

Treatment(s): Metformin (Oral)
Minimum dose (mg/d): 1000
Maximum dose (mg/d): 3000
Details of dosing regimen: Metformin 500 mg bid (up to 1g tds). If FBG>7 mmol/l treatment was uptitrated to a max of 1 g tds. 11 patients were uptitrated to 3 g/day

(3) Gliclazide

N: 22

Treatment duration (wks): 24
Washout period (d): 90
Comments: There was a 3 month run-in phase on diet alone

Treatment(s): Sulfonylurea (Oral)
Minimum dose (mg/d): 80
Maximum dose (mg/d): 320
Details of dosing regimen: Gliclazide 80 mg od (up to 160 mg bid). If FBG>7 mmol/l treatment was uptitrated to a max of 160 mg bd. 5 patients were titrated to 320 mg/day.

Outcomes

Baseline characteristics

		Pioglitazone (30 mg)			Metformin				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	20		60.4 (SD 7.5)	20		59.5 (SD 9.3)		
Sex (n male)	Dichotomous	20	14	(70.0%)	20	12	(60.0%)		
Blood glucose: HbA1c (%) – 0wk	Continuous	20		7.43 (SD 0.9)	20		8.04 (SD 0.9)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	20		9.45 (SD 2.1)	20		9.77 (SD 2.3)		
Body weight: BMI (kg/m2) – 0wk	Continuous	20		med: 30.6 [rng 29.4–35.2]	20		med: 29.2 [rng 28.1–31.6]		
Weight (kg) – 0wka	Continuous	20		med: 86.36544 [rng 82.97856–99.34848]	20		med: 82.41408 [rng 79.30944–89.18784]		
Lipids: Total cholesterol (mmol/l) – 0wk	Continuous	21		5.4 (SD 0.77)	21		5.63 (SD 0.73)		
HDL cholesterol (mmol/l) – 0wk	Continuous	21		1.28 (SD 0.3)	21		1.26 (SD 0.24)		
Triglycerides (mmol/l) – 0wk	Continuous	21		2.29 (SD 1.68)	21		2.28 (SD 1.24)		
TC/HDL ratio – 0wk	Continuous	21		4.5 (SD 1.3)	21		4.62 (SD 1.01)		
Previous blood glucose lowering drugs: Oral antidiabetic medication	Dichotomous	20	12	(60.0%)	20	14	(70.0%)		

[a] estimated from BMI assuming mean height of 1.68m

		Pioglitazone (30 mg)			Gliclazide				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	20		60.4 (SD 7.5)	20		63.5 (SD 11.4)		
Sex (n male)	Dichotomous	20	14	(70.0%)	20	13	(65.0%)		
Blood glucose: HbA1c (%) – 0wk	Continuous	20		7.43 (SD 0.9)	20		7.85 (SD 0.9)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	20		9.45 (SD 2.1)	20		10.1 (SD 2.1)		
Body weight: BMI (kg/m2) – 0wk	Continuous	20		med: 30.6 [rng 29.4–35.2]	20		med: 28.7 [rng 28.3–34.4]		

Weight (kg) – 0wka	Continuous	20		med: 86.36544 [rng 82.97856–99.34848]	20		med: 81.00288 [rng 79.87392–97.09056]	
Lipids: Total cholesterol (mmol/l) – 0wk	Continuous	21		5.4 (SD 0.77)	22		5.35 (SD 0.83)	
HDL cholesterol (mmol/l) – 0wk	Continuous	21		1.28 (SD 0.3)	22		1.3 (SD 0.25)	
Triglycerides (mmol/l) – 0wk	Continuous	21		2.29 (SD 1.68)	22		1.77 (SD 1.05)	
TC/HDL ratio – 0wk	Continuous	21		4.5 (SD 1.3)	22		4.46 (SD 1.17)	
Previous blood glucose lowering drugs: Oral antidiabetic medication	Dichotomous	20	12	(60.0%)	20	15	(75.0%)	

[a] estimated from BMI assuming mean height of 1.68m

		Metformin			Gliclazide				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	20		59.5 (SD 9.3)	20		63.5 (SD 11.4)		
Sex (n male)	Dichotomous	20	12	(60.0%)	20	13	(65.0%)		
Blood glucose: HbA1c (%) – 0wk	Continuous	20		8.04 (SD 0.9)	20		7.85 (SD 0.9)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	20		9.77 (SD 2.3)	20		10.1 (SD 2.1)		
Body weight: BMI (kg/m2) – 0wk	Continuous	20		med: 29.2 [rng 28.1–31.6]	20		med: 28.7 [rng 28.3–34.4]		
Weight (kg) – 0wka	Continuous	20		med: 82.41408 [rng 79.30944–89.18784]	20		med: 81.00288 [rng 79.87392–97.09056]		
Lipids: Total cholesterol (mmol/l) – 0wk	Continuous	21		5.63 (SD 0.73)	22		5.35 (SD 0.83)		
HDL cholesterol (mmol/l) – 0wk	Continuous	21		1.26 (SD 0.24)	22		1.3 (SD 0.25)		
Triglycerides (mmol/l) – 0wk	Continuous	21		2.28 (SD 1.24)	22		1.77 (SD 1.05)		
TC/HDL ratio – 0wk	Continuous	21		4.62 (SD 1.01)	22		4.46 (SD 1.17)		
Previous blood glucose lowering drugs: Oral antidiabetic medication	Dichotomous	20	14	(70.0%)	20	15	(75.0%)		

[a] estimated from BMI assuming mean height of 1.68m

Results

		Pioglitazone (30 mg)			Metformin				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 24wk	Continuous	20		6.62 (SD 0.5)	20		6.9 (SD 0.5)		
HbA1c (%) – 24wk	Mean change	20		-0.81 (SD 0.63)	20		-1.12 (SD 0.84)		
Fasting plasma glucose (mmol/l) – 24wk	Continuous	20		6.8 (SD 1.1)	20		7.3 (SD 1)		
Body weight: BMI (kg/m2) – 24wka	Mean change	20		1.5	20		-0.6		
BMI (kg/m2) – 24wk	Continuous	20		med: 32.1 [rng 29.8–37]	20		med: 28.6 [rng 27.3–30.4]		

Weight (kg) – 24wkb	Mean change	20		4.2336	20		-1.69344		
Weight (kg) – 24wkc	Continuous	20		med: 90.59904 [rng 84.10752–104.4288]	20		med: 80.72064 [rng 77.05152–85.80096]		
Adverse events:									
Edema peripheral – 24wk	Dichotomous	20	1	(5.0%)	20	0	(0.0%)		
Dropouts:									
Total dropouts – 24wk	Dichotomous	21	1	(4.8%)	21	1	(4.8%)		
Dropout due to AEs – 24wk	Dichotomous	21	1	(4.8%)	21	1	(4.8%)		
Lipids:									
Total cholesterol (mmol/l) – 24wk	Continuous	20		5.44 (SD 0.82)	20		5.27 (SD 0.91)		
HDL cholesterol (mmol/l) – 24wk	Continuous	20		1.36 (SD 0.29)	20		1.21 (SD 0.22)		
Triglycerides (mmol/l) – 24wk	Continuous	20		2 (SD 1.3)	20		1.98 (SD 1.29)		
TC/HDL ratio – 24wk	Continuous	20		4.23 (SD 1.19)	20		4.49 (SD 1.05)		

[a] Not in paper, was this calculated?
[b] Not in paper, was this calculated?; estimated from BMI assuming mean height of 1.68m
[c] estimated from BMI assuming mean height of 1.68m

		Pioglitazone (30 mg)			Gliclazide				
		N	k	mean	N	k	mean	Δ	p
Blood glucose:									
HbA1c (%) – 24wk	Continuous	20		6.62 (SD 0.5)	20		6.64 (SD 0.5)		
HbA1c (%) – 24wk	Mean change	20		-0.81 (SD 0.63)	20		-1.21 (SD 0.82)		
Fasting plasma glucose (mmol/l) – 24wk	Continuous	20		6.8 (SD 1.1)	20		7.4 (SD 1.4)		
Body weight:									
BMI (kg/m2) – 24wka	Mean change	20		1.5	20		1.9		
BMI (kg/m2) – 24wk	Continuous	20		med: 32.1 [rng 29.8–37]	20		med: 30.6 [rng 28–35.7]		
Weight (kg) – 24wkb	Mean change	20		4.2336	20		5.36256		
Weight (kg) – 24wkc	Continuous	20		med: 90.59904 [rng 84.10752–104.4288]	20		med: 86.36544 [rng 79.0272–100.75968]		
Adverse events:									
Edema peripheral – 24wk	Dichotomous	20	1	(5.0%)	20	0	(0.0%)		
Dropouts:									
Total dropouts – 24wk	Dichotomous	21	1	(4.8%)	22	2	(9.1%)		
Dropout due to AEs – 24wk	Dichotomous	21	1	(4.8%)	22	2	(9.1%)		
Lipids:									
Total cholesterol (mmol/l) – 24wk	Continuous	20		5.44 (SD 0.82)	20		5.13 (SD 0.91)		
HDL cholesterol (mmol/l) – 24wk	Continuous	20		1.36 (SD 0.29)	20		1.24 (SD 0.26)		
Triglycerides (mmol/l) – 24wk	Continuous	20		2 (SD 1.3)	20		1.9 (SD 1.06)		
TC/HDL ratio – 24wk	Continuous	20		4.23 (SD 1.19)	20		4.34 (SD 1.7)		

[a] Not in paper, was this calculated?
[b] Not in paper, was this calculated?; estimated from BMI assuming mean height of 1.68m
[c] estimated from BMI assuming mean height of 1.68m

		Metformin			Gliclazide			Δ	p
		N	k	mean	N	k	mean		
Blood glucose: HbA1c (%) – 24wk	Continuous	20		6.9 (SD 0.5)	20		6.64 (SD 0.5)		
HbA1c (%) – 24wk	Mean change	20		-1.12 (SD 0.84)	20		-1.21 (SD 0.82)		
Fasting plasma glucose (mmol/l) – 24wk	Continuous	20		7.3 (SD 1)	20		7.4 (SD 1.4)		
Body weight: BMI (kg/m2) – 24wka	Mean change	20		-0.6	20		1.9		
BMI (kg/m2) – 24wk	Continuous	20		med: 28.6 [rng 27.3–30.4]	20		med: 30.6 [rng 28–35.7]		
Weight (kg) – 24wkb	Mean change	20		-1.69344	20		5.36256		
Weight (kg) – 24wkc	Continuous	20		med: 80.72064 [rng 77.05152–85.80096]	20		med: 86.36544 [rng 79.0272–100.75968]		
Adverse events: Edema peripheral – 24wk	Dichotomous	20	0	(0.0%)	20	0	(0.0%)		
Dropouts: Total dropouts – 24wk	Dichotomous	21	1	(4.8%)	22	2	(9.1%)		
Dropout due to AEs – 24wk	Dichotomous	21	1	(4.8%)	22	2	(9.1%)		
Lipids: Total cholesterol (mmol/l) – 24wk	Continuous	20		5.27 (SD 0.91)	20		5.13 (SD 0.91)		
HDL cholesterol (mmol/l) – 24wk	Continuous	20		1.21 (SD 0.22)	20		1.24 (SD 0.26)		
Triglycerides (mmol/l) – 24wk	Continuous	20		1.98 (SD 1.29)	20		1.9 (SD 1.06)		
TC/HDL ratio – 24wk	Continuous	20		4.49 (SD 1.05)	20		4.34 (SD 1.7)		

[a] Not in paper, was this calculated?
[b] Not in paper, was this calculated?; estimated from BMI assuming mean height of 1.68m
[c] estimated from BMI assuming mean height of 1.68m

Table 68: Lee & (1998)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** USA **Authors' conclusions:** The results indicate that metformin decreases calorie intake in a dose-dependent manner and leads to a reduction in bodyweight in NIDDM patients with obesity **Source of funding:** Unclear **Comments:** Double-blind
Number and characteristics of patients	**Total number of patients:** 48 **Inclusion criteria:** diet treated NIDDM women with obesity who failed to lose more than 1.5 kg of weight per month over the 3 preceeding months after being instructed to reduce their caloric intake by 30% were entered into the study

	Exclusion criteria: Major medical illness, cardiac, renal or hepatic disorder Pre-randomisation phase: There was a 4 week single blind placebo lead in period
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** All treatment naive/ no OADs at screening **Details of washout period:** Unclear history of AHA for patients but were on diet therapy for 3 months prior to enrollment and had a 4 week placebo run in period
Lifestyle advice	patients were put onto an ADA diet
Follow-up	**Total follow-up (wks):** 34 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 24 **Frequency of monitoring appointments:** All had a 4 week placebo run in period. Subjects returned 2 weeks after starting treatment and then every 4 weeks for 24 weeks. After 24 week treatment, participants were monitored for 6 weeks with placebo treatment
Arms	**(1) Placebo** N: 24 Treatment duration (wks): 24 Washout period (d): 28 Treatment(s): Placebo (Oral) Frequency of dosing: twice a day **(2) Metformin** N: 24 Treatment duration (wks): 24 Washout period (d): 28 Treatment(s): Metformin (Oral) – fixed-dose Set dose (mg/d):1700 Frequency of dosing: twice a day Details of dosing regimen: 850 mg/12 h
Outcomes	

Baseline characteristics

		Placebo			Metformin				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years) [a]	Continuous	24		59 (SD 14.7)	24		61 (SD 9.8)		
Duration of diabetes (yrs) [a]	Continuous	24		3 (SD 9.8)	24		4 (SD 4.9)		
Blood glucose: HbA1c (%) – 0wka	Continuous	24		8.1 (SD 0.98)	24		8.3 (SD 0.98)		
Fasting plasma glucose (mmol/l) – 0wka	Continuous	24		8.5 (SD 1.96)	24		8.9 (SD 3.92)		
Body weight: BMI (kg/m2) [a]	Continuous	24		39.6 (SD 5.88)	24		40 (SD 8.82)		
Weight (kg) – 0wka	Continuous	24		108.6 (SD 18.6)	24		112.8 (SD 33.3)		

[a] SD calculated from reported SE

Results

		Placebo			Metformin				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 24wka	Continuous	24		8.3 (SD 0.98)	24		7.4 (SD 0.98)		
Fasting plasma glucose (mmol/l) – 24wka	Continuous	24		7.9 (SD 3.92)	24		6.7 (SD 1.96)		
Body weight: Weight (kg) – 12wka	Continuous	24		109.2 (SD 16.7)	24		107.5 (SD 32.8)		
Weight (kg) – 24wka	Continuous	24		108.8 (SD 16.7)	24		103.5 (SD 32.3)		
Weight (kg) – 24wka	Mean change	24		-1 (SD 0.49)	24		-8.8 (SD 1.47)		

	Dropouts:									
	Total dropouts – 24wk	Dichotomous	24	8	(33.3%)	24	8	(33.3%)		
	[a] SD calculated from reported SE									

Table 69: Madsbad et al. (2001)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** Scandinavia **Authors' conclusions:** Repaglinide is shown to be an effective and safe treatment of patients with type 2 diabetes, and is better than glipizide in controlling Hba1c and FBG levels overall and in treatment naïve patients **Source of funding:** not reported **Comments:** Multicentre, multinational, double-blind asymmetrically randomised parallel group study. No methods of randomisation or allocation concealment reported
Number and characteristics of patients	**Total number of patients:** 256 **Inclusion criteria:** People with type 2 diabetes who were diet or OHA treated, aged 40-75 years with BMI >=21 and <=35kg/m2, Hba1c 6.5% or above and 10% or lower were eligible **Exclusion criteria:** serum creatinine 140 µmol/l, signs of liver disease, proliferative retinopathy, severe uncontrolled hypertension (SBP>200 mmHg or DBP>110mmHg), were pregnant or were using corticosteroids Pre-randomisation phase: Initial screening visit the week prior to randomisation included medical history and physical examination. (Please note that graphs indicate that the baseline is before titration period therefore follow-up months has been relabelled to 14 months)
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** some on oral hypoglycaemic drugs and/or insulin **Details of washout period:** Participants were randomised following cessation of any previous antidiabetic medication (unclear but seems to be 1 week)
Lifestyle advice	No details reported
Follow-up	**Total follow-up (wks):** 58 **Length of titration period (wks):** 6 **Length of maintenance period (wks):** 52 **Frequency of monitoring appointments:** Seems that patients stopped previous OADs 1 week prior to randomisation. After three 2 week titration visits, the participant entered a 12 month maintenance period with visits to the outpatient clinic after 1 month and subsequently every 3 months.
Arms	**(1) Repaglinide** N: 175 Treatment duration (wks): 52 Washout period (d): 7 Comments: patients stopped taking previous oral antidiabetic (seems to be 1 week prior to randomisation) Treatment(s): repaglinide (Oral) – flexible-dose (dose-adjusted) Minimum dose (mg/d): 1.5 Maximum dose (mg/d): 12 Frequency of dosing: three times a day Compliance: No details reported Details of dosing regimen: There were 4 dose levels in both groups: Dose level 1 was 0.5mg with meals, Dose level 2 was 1mg with meals, Dose level 3 was 2mg with meals and Dose level 4 was 4 mg with meals. Participants who were previously treated with OHAs and had a FBG>9.0 mmol/l on their previous treatment started on dose level 2, otherwise all participants started at dose level 1. Patients with FBG>7.8 mmol/l (representing poor glycaemic control by the guidelines used) and clinically significant hypoglycaemia had their dose increased to the next level. If FBG<4.4 mmol/l or if the

participant experienced clinically significant hypoglycaemia, the dose was reduced by one level. All participants were required to have 3 main meals daily. At the end of the trial across all participants, 52% were taking dose level 4 and this distribution did not differ significantly between the two treatment groups.

(2) Glipizide

N: 81

Treatment duration (wks): 52
Washout period (d): 7
Comments: patients stopped taking previous oral antidiabetic (seems to be 1 week prior to randomisation)

Treatment(s): Sulfonylurea (Oral) – flexible-dose (dose-adjusted)
Minimum dose (mg/d): 5
Maximum dose (mg/d): 15
Frequency of dosing: variable
Compliance: No details reported
Details of dosing regimen: Dose level 1 was 5mg before breakfast, Dose level 2 was 7.5 mg before breakfast, Dose level 3 was 10 mg before breakfast and Dose level 4 was 10 mg before breakfast and 5 mg before dinner. Placebo tablets were used in this group for lunch and dinner.

Outcomes

General

35 (20%) patients in the repaglinide group and 23 (28.4%) in the glipizide group discontinued the study.

Outcomes not reported in this evidence table include fasting insulin and fasting C-peptide

The ITT population was used for efficacy endpoint analyses.

Unclear reporting but it seems that patients were randomised 1 week after cessation of previous OADs. Population comprised 12% who were treatment naïve (23 in repaglinide and 7 in glipizide). Therefore only data for treatment naïve subgroup were extracted.

Hypoglycaemic events

No specific definitions relating to hypoglycaemia were reported

confirmed hypoglycaemia (BG <2.5 mmol/l)

Baseline characteristics

		Repaglinide			Glipizide				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	175		60.2 (SD 8.1)	81		62 (SD 8.8)		
Sex (n male)	Dichotomous	175	107	(61.1%)	81	52	(64.2%)		
Duration of diabetes (yrs)	Continuous	175		8.1 (SD 6)	81		7 (SD 4.9)		
Blood glucose: HbA1c (%) – 0wk	Continuous	175		7.3 (SD 1.2)	81		7.2 (SD 1.4)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	175		11 (SD 3)	81		10.8 (SD 2.7)		
Body weight: BMI (kg/m2)	Continuous	175		28 (SD 3.6)	81		28 (SD 3.5)		
Weight (kg) – 0mo	Continuous	175		82.9 (SD 13.4)	81		83.6 (SD 14.5)		
Diabetic complications: Retinopathy	Dichotomous	175	18	(10.3%)	81	6	(7.4%)		
Nephropathy	Dichotomous	175	10	(5.7%)	81	2	(2.5%)		
Neuropathy	Dichotomous	175	17	(9.7%)	81	9	(11.1%)		
Previous blood glucose lowering drugs: Diet alone (i.e. drug naïve)	Dichotomous	175	23	(13.1%)	81	7	(8.6%)		
Sulfonylurea	Dichotomous	175	108	(61.7%)	81	53	(65.4%)		
Other	Dichotomous	175	8	(4.6%)	81	5	(6.2%)		
Combination therapy	Dichotomous	175	36	(20.6%)	81	16	(19.8%)		

Results

	Repaglinide			Glipizide				
	N	k	mean	N	k	mean	Δ	p

Blood glucose: HbA1c (%) – 14wk	Mean change	175			81			MD=-0.590 (CI: -0.970, -0.210)	<0.05a
Fasting plasma glucose (mmol/l) – 14wk	Mean change	175			7			MD=-0.900 (CI: -1.700, -0.100)	<0.05b
Body weight: Weight (kg) – 14mo	Continuous	175			81				c
Hypoglycaemic events: minor hypoglycaemic events – 14mo	Dichotomous	175			81				c
minor hypoglycaemic events – 14mo	Dichotomous	175			81			RR=0.802 (CI: 0.450, 1.431)	0.576d
Major/severe hypoglycaemic event – 14mo	Dichotomous	175			81				c
confirmed hypoglycaemia – 14mo	Dichotomous	175			81				c
Adverse events: Study drug-related adverse event – 14mo	Dichotomous	175			81				c
Dropouts: Dropout due to AEs – 14mo	Dichotomous	175			81				c
Drop out due to unsatisfactory effect – 14mo	Dichotomous	175			81				c
Lipids: Total cholesterol (mmol/l) – 14mo	Mean change	175			81			MD=-0.070 (CI: -0.266, 0.126)	>0.05e
HDL cholesterol (mmol/l) – 14mo	Mean change	175			81			MD=-0.030 (CI: -0.030, -0.030)	>0.05e
Triglycerides (mmol/l) – 14mo	Mean change	175			81			MD=0.000 (CI: -0.392, 0.392)	>0.05e
Pre-study diet alone (i.e. drug naive) Blood glucose: HbA1c (%) – 14wk	Mean change	23			7				<0.05e
HbA1c (%) – 58wkf	Mean change	23		-1.5	7		-0.3		
Fasting plasma glucose (mmol/l) – 14wk	Mean change	23			7				<0.05e
Fasting plasma glucose (mmol/l) – 58wkf	Continuous	23		-2.4	7		1		
Pre-study oral antidiabetics (i.e. not drug naive) Blood glucose: HbA1c (%) – 14wk	Mean change	152			74				<0.05e
Pre-study Sulfonylurea alone Blood glucose: HbA1c (%) – 14wk	Mean change	108			53			MD=0.700	<0.05e

[a] SD reported
[b] ANOVA
[c] not reported
[d] chi-square test (Yates's correction) (calculated by reviewer)
[e] student's t-test
[f] No SDs reported

Baseline characteristics of the intention to treat population. Change from baseline data was analysed using ANOVA with treatment, centre and treatment by centre interaction as fixed effects. Changes from baseline for lipid levels and laboratory tests were analysed using a t-test.

Table 70: Madsbad et al. (2004)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** Scandinavia and UK **Authors' conclusions:** Patients treated with glimepiride had decreased Hba1c and fasting blood glucose, but slightly increased body weight. No safety issues were raised for liraglutide, observed adverse events were mild and transient **Source of funding:** Sponsored by Novo Nordisk which established the protocol in conjunction with an academic committee that was responsible for data review and this article **Comments:** Multicentre, double-blind, randomised, parallel group, dosage-response study in six treatment arms. In addition, an open label sulfonylurea arm was included as a reference group. No details of randomisation or allocation concealment methods reported. The trial was double-blind for the 5 dose levels of Liraglutide and placebo and open label for glimepiride. The blinding was kept until database release.
Number and characteristics of patients	**Total number of patients:** 193 **Inclusion criteria:** men and women aged 30 years and over with type 2 diabetes, BMI less than or equal to 40kg/m2, currently being treated with diet or an OHA and had a HbA1c level less than or equal to 9.5% on OHA or 7.5 to 10% on diet alone. **Exclusion criteria:** liver or renal disease, heart failure, unstable angina, myocardial infarction within the previous 12 months, concomitant treatment with thiazolidinediones or other investigational drugs, other significant condition likely to affect a patients diabetes and or ability to complete the trial, women who are pregnant, breast feeding or not using an adequate method of contraception. Patients were withdrawn from the trial if fasting plasma glucose was >15 mmol/l Pre-randomisation phase: Fasting blood glucose had to be 6-13 mmol/l at randomisation, patients were withdrawn from the trial if fasting plasma glucose was >15 mmol/l
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** some on oral hypoglycaemic drugs and/or insulin **Details of washout period:** Current treatment with oral antidiabetic medication was discontinued at screening and patients entered a 4 week washout period
Lifestyle advice	Patients were instructed to maintain their diet, exercise program and daily routines during the course of the trial
Follow-up	**Total follow-up (wks):** 12 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 12 **Frequency of monitoring appointments:** Each patient was seen on 7 occasions: screening, baseline, after 1, 4, 8 and 12 weeks of treatment and at follow-up
Arms	**(1) Glimepiride** N: 27 Treatment duration (wks): 12 Washout period (d): 30 Comments: there was a 4 week washout phase Treatment(s): Sulfonylurea (Oral) – flexible-dose (dose-adjusted) Mean dose (mg/d): 2.7 Minimum dose (mg/d): 1 Frequency of dosing: variable Compliance: compliance was assessed by drug accountability and plasma concentration measures Details of dosing regimen: Glimepiride was supplied as 1 and 2 mg tablets, with the dosage adjusted according to glycaemic control during the first 4 weeks, with the aim to achieve a fasting plasma glucose <7 mmol/l **(2) Placebo** N: 29 Treatment duration (wks): 12 Washout period (d): 30 Comments: there was a 4 week washout phase Treatment(s): Placebo (Subcutaneous) – fixed-dose Frequency of dosing: once a day Compliance: see liraglutide 0.6 mg Details of dosing regimen: placebo was administered in the morning before breakfast.

Outcomes

General

Only data from 2/7 arms were extracted in this evidence table as liraglutide is not currently licensed for monotherapy. Outcomes reported in the trial but not reported as part of this evidence table includes proinsulin-to-insulin ratio, beta cell function, fasting insulin, fasting C-peptide, fasting glucagon

5 (17%) patients in the placebo group and 1 (3.7%) patient in the glimepiride group did not complete the study

All analyses were performed on the ITT population (all patients who received at least one dose of a trial drug) which was n=26 in glimepiride and n=29 in placebo group

Hypoglycaemic events

confirmed hypoglycaemia (blood glucose <2.8 mmol/l)

Adverse events

Any adverse event(s) (Based on spontaneous reporting of adverse events)

Baseline characteristics

		Glimepiride			Placebo				
		N	k	mean	N	k	mean	Δ	p
ITT									
Demographics:									
Age (years)	Continuous	26		57 (SD 9.2)	29		57 (SD 9.4)		
Sex (n male)	Dichotomous	26	16	(61.5%)	29	20	(69.0%)		
Duration of diabetes (yrs)	Continuous	26		3.8 (SD 3.4)	29		3.4 (SD 2.9)		
Blood glucose:									
HbA1c (%) – 0wk	Continuous	26		7.8 (SD 0.9)	29		7.4 (SD 1.2)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	26		10.6 (SD 2.4)	29		9.7 (SD 2.9)		
Body weight:									
BMI (kg/m2)	Continuous	26		30.2 (SD 4.6)	29		30.3 (SD 4.2)		
Weight (kg) – 0wka	Continuous	26		85.23648 (SD 13)	29		85.51872 (SD 11.9)		
Previous blood glucose lowering drugs:									
Diet alone (i.e. drug naïve)	Dichotomous	26	7	(26.9%)	29	4	(13.8%)		
Oral antidiabetic medication	Dichotomous	26	19	(73.1%)	29	25	(86.2%)		

[a] estimated from BMI assuming mean height of 1.68m

Results

		Glimepiride			Placebo				
		N	k	mean	N	k	mean	Δ	p
Blood glucose:									
HbA1c (%) – 12wk	Continuous	26			29			MD=-0.740	0.0001a
Fasting plasma glucose (mmol/l) – 12wk	Continuous	26			29			MD=-2.600	<0.0001a
Body weight:									
Weight (kg) – 12wk	Continuous	26			29			MD=0.940	0.0622a
Hypoglycaemic events:									
symptomatic (unconfirmed) hypoglycaemia – 12wk	Dichotomous	26			29				NR
confirmed hypoglycaemia – 12wk	Dichotomous	26			29				NR
Adverse events:									
GI: nausea – 12wk	Dichotomous	26			29				NR
Any adverse event(s) – 12wk	Dichotomous	26	9	(34.6%)	29	16	(55.2%)		NR
GI: diarrhoea – 12wk	Dichotomous	26	0	(0.0%)	29	0	(0.0%)		NR
GI: vomiting – 12wk	Dichotomous	26	1	(3.8%)	29	0	(0.0%)		NR
GI: constipation – 12wk	Dichotomous	26	0	(0.0%)	29	0	(0.0%)		NR
Dropouts:									
Total dropouts – 12wk	Dichotomous	27	1	(3.7%)	29	5	(17.2%)		
Dropout due to AEs – 12wk	Dichotomous	27	0	(0.0%)	29	0	(0.0%)		NR

	Drop out due to unsatisfactory effect – 12wk	Dichotomous	27	0	(0.0%)	29	3	(10.3%)		NR
	ITT									
	Blood glucose:									
	HbA1c (%) – 12wkb	Continuous	26		7.2	29		7.3		
	Fasting plasma glucose (mmol/l) – 12wkb	Continuous	26		8.6	29		9.5		
	Body weight:									
	Weight (kg) – 12wkb	Mean change	26		0.73	29		0		

[a] mixed effect model
[b] estimated from graph, no SDs reported

Approximately two thirds of the GI events reported during liraglutide treatment were resolved within 1-3 days. Blood glucose outcomes and weight were analysed in a mixed effects model with treatment, visit, centre as fixed effects and patient as random effect. The interaction term, baseline Hba1c by visit was included in the model as a covariate. Adjusted endpoint levels at 12 week follow-up were calculated for all treatment groups using this model. Blood glucose outcomes and weight were analysed in a mixed effects model with treatment, visit, centre as fixed effects and patient as random effect. The interaction term, baseline Hba1c by visit was included in the model as a covariate. Adjusted endpoint levels at 12 week follow-up were calculated for all treatment groups using this model.

Table 71: Marbury et al. (1999)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** USA **Authors' conclusions:** Repaglinide at doses 0.5-4 mg administered three times preprandially, was well tolerated and provided safe and consistently effective glycaemic control during this one year study. Patients receiving repaglinide received the same therapeutic benefits as those using glyburide, and may have received some additional benefits. **Source of funding:** Not reported but one author worked at NorvoNordisk (USA) **Comments:** Multicenter, double blind randomised trial but no details of randomisation or allocation concelament methods
Number and characteristics of patients	**Total number of patients:** 576 **Inclusion criteria:** 37-75 years old, BMI 20-40 kg/m2 with type 2 diabetes for at least 6 months and had been treated either by prescribed diet and exercise therapy or another OHA **Exclusion criteria:** chronic insulin use, severe uncontrolled hypertension, cardiac disorders, proliferative retinopathy and elevated serum creatinine (>1.6 mg/dl), aspartate aminotransferase (>120 U/l) or alanine aminotransferase (>195 U/l). Patients with known contraindications to glyburide and those who had received repaglinide or systemic corticosteroids previously were also excluded. Pre-randomisation phase: The titration phase was separate to the 12 month maintenance phase therefore follow-up for endpoint outcomes have been relabelled to 14 month (changes in efficacy outcomes were from screening/first-dose baseline to treatment endpoint were measured)
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** some on oral hypoglycaemic drugs and/or insulin **Details of washout period:** patients discontinued OHAs on the morning of the first post randomisation visit
Lifestyle advice	Trougout the study patients ate three meals per day
Follow-up	**Total follow-up (wks):** 60 **Length of titration period (wks):** 8 **Length of maintenance period (wks):** 52 **Frequency of monitoring appointments:** Patients visited the clinic after an overnight fast every 10-14 days during dose adjustment and every 2 months during the maintenance period.
Arms	**(1) Repaglinide**

N: 383

Treatment duration (wks): 52
Washout period (d): 0
Comments: patients discontinued OHAs on the morning of the first post randomisation visit. No details of washout period. Only data from AHA naïve people extracted

Treatment(s): repaglinide (Oral) – flexible-dose (dose-adjusted)

Minimum dose (mg/d): 1.5
Maximum dose (mg/d): 12
Participants achieving full dose (n): 184
Frequency of dosing: three times a day
Details of dosing regimen: During weeks 1-8 doses of each drug were titrated towards a target FPG range of 80-140 mg/dl. Repaglinide was started at 0.5mg preprandially (with 3 daily meals) and adjusted in increments of 1,2 or 4 mg. Patients with an FPG>160 mg/dl who had previously taken any OHA other than repaglinide could begin the study at a higher dose (1 mg repaglinide). The final adjusted dose was maintained for 12 months, but the dose could be reduced for patients <80 mg/dl or with hypoglycaemic events judged clinically unacceptable.

55% of patients received the maximum dose allowed and 61% received the study drug for more than 12 months

(2) Glyburide

N: 193

Treatment duration (wks): 52
Washout period (d): 0
Comments: patients discontinued OHAs on the morning of the first post randomisation visit. No details of washout period. Only data from AHA naïve people extracted

Treatment(s): Sulfonylurea (Oral) – flexible-dose (dose-adjusted)

Minimum dose (mg/d): 2.5
Maximum dose (mg/d): 15
Participants achieving full dose (n): 88
Frequency of dosing: variable
Details of dosing regimen: Glyburide administered according to dosing schedules at time of study. Glyburide 2.5 mg was given once daily before breakfast with two identical placebo tablets before lunch and before dinner. The dose was increased as necessary to 5, 10 or 15 mg daily (administered as 10 mg before breakfast and 5 mg before dinner). Patients with FPG>160 mg/dl who had previously taken OHA could start at a higher dose 5 mg of glyburide if the investigator deemed it necessary. The final adjusted dose was maintained for 12 months, but the dose could be reduced for patients <80 mg/dl or with hypoglycaemic events judged clinically unacceptable.

65% received the study drug for more than 12 months and 52% received the maximum dose allowed.

Outcomes

General

Outcomes including fasting insulin, C-peptide and fibrogen are reported in the trial but are not included in this evidence table.

146 (40%) participants in repaglinide group and 67 (37%) in glyburide group did not complete the study.

The primary analysis for evaluating efficacy was based on each participant's last treatment evaluation (last observation carried forward).

As there was no washout period, only data from AHA naïve people were extracted.

Hypoglycaemic events

All hypoglycaemic events (no patients) (Patients were instructed to report all hypoglycaemic events and if possible to record their blood glucose value at the time of the event. Mild to moderate hypoglycaemic events were defined as symptoms of sweating, strong hunger, dizziness, tremors and/or a blood glucose level <45 mg/dl. Severe hypoglycaemia was characterised as severely impaired consiousness requiring assistance from a third party, medical care or hospitalisation.)

Baseline characteristics

		Repaglinide			Glyburide				
		N	k	mean	N	k	mean	Δ	p
Demographics:									
Age (years)	Continuous	362		58.3 (SD 9.4)	182		58.7 (SD 9)		
Sex (n male)	Dichotomous	362	242	(66.9%)	182	120	(65.9%)		
Duration of diabetes (yrs)	Continuous	362		7.2 (SD 6.2)	182		8.3 (SD 6.8)		
Ethnicity-White	Dichotomous	362	279	(77.1%)	182	144	(79.1%)		
Ethnicity-Black	Dichotomous	362	33	(9.1%)	182	16	(8.8%)		
Ethnicity-Other	Dichotomous	362	50	(13.8%)	182	22	(12.1%)		

Blood glucose: HbA1c (%) – 0mo	Continuous	362		8.7 (SD 1.7)	182		8.9 (SD 1.6)		
Fasting plasma glucose (mmol/l) – 0mo	Continuous	362		11.1555 (SD 3.4)	182		11.3775 (SD 3.26)		
Body weight: BMI (kg/m2)	Continuous	362		29.4 (SD 3.7)	181		29.1 (SD 3.7)		
Weight (kg) – 0moa	Continuous	362		82.97856 (SD 10.4)	181		82.13184 (SD 10.4)		
Previous blood glucose lowering drugs: Diet alone (i.e. drug naïve)	Dichotomous	362	47	(13.0%)	182	23	(12.6%)		
Oral antidiabetic medication	Dichotomous	362	315	(87.0%)	182	159	(87.4%)		

[a] estimated from BMI assuming mean height of 1.68m

Results

		Repaglinide			Glyburide				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Blood glucose: HbA1c (%) – 14mo	Mean change	338			171			MD=-0.020 (CI: -0.276, 0.236)	0.874a
HbA1c (%) – 14mo	Mean change	338			171			MD=-0.020 (CI: -0.270, 0.230)	>0.05b
Fasting plasma glucose (mmol/l) – 14mo	Mean change	327			166			MD=0.172 (CI: -0.391, 0.735)	>0.05b
Hypoglycaemic events: All hypoglycaemic events (no patients) – 14mo	Dichotomous	383			193			OR=0.768 (CI: 0.488, 1.208)	0.305c
All hypoglycaemic events (no patients) – 14mo	Dichotomous	383			193				d
Adverse events: Any adverse event(s) – 14mo	Dichotomous	383			193				d
Any adverse event(s) – 14mo	Dichotomous	383			193			OR=1.090 (CI: 0.745, 1.596)	0.728c
Any serious adverse event(s) – 14mo	Dichotomous	383			193				d
Any serious adverse event(s) – 14mo	Dichotomous	383			193			OR=1.710 (CI: 0.874, 3.347)	0.154c
cardiovascular AE – 14mo	Dichotomous	362			182				d
Death – 14mo	Dichotomous	383			193				d
Dizziness – 14mo	Dichotomous	383			193				d
Dizziness – 14mo	Dichotomous	383			193			OR=0.922 (CI: 0.336, 2.531)	0.918c
Headache – 14mo	Dichotomous	383			193			OR=1.427 (CI: 0.506, 4.020)	0.669c
Headache – 14mo	Dichotomous	383			193				d
Hyperglycaemia – 14mo	Dichotomous	383			193			OR=0.802 (CI: 0.259, 2.486)	0.932c
Hyperglycaemia – 14mo	Dichotomous	383			193				d
Increased appetite – 14mo	Dichotomous	383			193			OR=11.948 (CI: 0.700, 203.829)	0.061c
Increased appetite – 14mo	Dichotomous	383			193				d
Tremor – 14mo	Dichotomous	383			193			OR=1.533 (CI: 0.549, 4.281)	0.562c
Tremor – 14mo	Dichotomous	383			193				d

Dropouts: Dropout due to AEs – 14mo	Dichotomous	383			193				d
Drop out due to unsatisfactory effect – 14mo	Dichotomous	362			182				d
Lipids: Total cholesterol (mmol/l) – 14mo	Mean change	362			182			MD=0.030 (CI: -0.116, 0.177)	>0.05e
HDL cholesterol (mmol/l) – 14mo	Mean change	362			182			MD=-0.018 (CI: -0.056, 0.020)	>0.05e
Triglycerides (mmol/l) – 14mo	Mean change	362			182			MD=0.147 (CI: -0.353, 0.647)	>0.05e
LDL cholesterol (mmol/l) – 14mo	Continuous	338			171			MD=0.038 (CI: -0.091, 0.168)	>0.05e
Pre-study diet alone (i.e. drug naive) Blood glucose: HbA1c (%) – 3mof	Continuous	45		7.7 (SD 0.0671)	21		8.2 (SD 0.0458)		
HbA1c (%) – 5mof	Continuous	45		7.6 (SD 0.0671)	21		8 (SD 0.0458)		
HbA1c (%) – 14mog	Mean change	45		-1.3 (SD 1.41)	21		-1.1 (SD 1.47)		
Fasting plasma glucose (mmol/l) – 3moh	Continuous	45			21				
Fasting plasma glucose (mmol/l) – 5mof	Continuous	45		9.658044 (SD 2.98)	21		9.658044 (SD 3.31)		
Fasting plasma glucose (mmol/l) – 14mo	Mean change	43		-1.7205 (SD 0.0322)	21		-0.03885 (SD 3.08)		
Body weight: Weight (kg) – 3mof	Mean change	45		1.2 (SD 2.35)	21		1.8 (SD 3.44)		
Weight (kg) – 5mof	Mean change	45		1.95 (SD 2.35)	21		2.85 (SD 3.21)		
Weight (kg) – 14moi	Mean change	45		2.45 (SD 4.02)	21		3.64 (SD 4.81)		
Pre-study oral antidiabetics (i.e. not drug naive) Body weight: Weight (kg) – 14mo	Mean change	293			150				>0.05e

[a] student's t-test (calculated by reviewer)
[b] paired t test
[c] chi-square test (Yates's correction) (calculated by reviewer)
[d] not reported
[e] two sample t test
[f] estimated from graph
[g] SD calculated from reported SE
[h] unclear error bars on graph
[i] SD calculated from SE estimated from graph

two sample t-test was used to assess treatment difference in change from baseline data

Table 72: Mather et al. (2001)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral

	Parallel / crossover: Parallel **Country:** Canada **Authors' conclusions:** Metformin treatment improved both insulin resistance and endothelial function, with a strong statistucal link between these variables **Source of funding:** Dr Howard MacEwan Diabetes Center Research Fund **Comments:** Unclear if double-blind
Number and characteristics of patients	**Total number of patients:** 43 **Inclusion criteria:** Patients with stable weight and diet controlled type 2 diabetes **Exclusion criteria:** patients with known coronary or peripheral vascular disease, hypertension, hypercholesterolemiaknown diabetic retinopathy, renal or hepatic impairment
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** All treatment naive/ no OADs at screening **Details of washout period:** Unclear. States that diet controlled T2DM included but no details on history of AHAs
Lifestyle advice	No details reported
Follow-up	**Total follow-up (wks):** 12 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 12 **Frequency of monitoring appointments:** -
Arms	**(1) Placebo** N: 15 Treatment duration (wks): 12 Washout period (d): 0 Comments: Stated diet treated T2DM Treatment(s): Placebo (Oral) **(2) Metformin** N: 28 Treatment duration (wks): 12 Washout period (d): 0 Comments: Stated diet treated T2DM Treatment(s): Metformin (Oral) – fixed-dose Set dose (mg/d):1000 Frequency of dosing: twice a day Details of dosing regimen: Metformin given 500 mg bid
Outcomes	**General** Overall, data from 14 trials have been extracted into this evidence table. Data was not extracted for the following RCTs for the reasons provided below; 1) Amador-Licona (2000)-Previous OADs not reported 2) Chiasson (2001b)-comparison with miglitol 3) Horton (2000b)-comparison with nateglinide (not recommended for monotherapy) 4) Inzucchi (1998) comparison with troglitazone 5) Hallsten (2002b) comparison with rosiglitazone 6) UKPDSa as there were no dosing details reported 7) Charpentier (2001)-termed monotherapy but unclear whether OADs were discontinued and unclear washout 8) Grant (1996)-unclear whether OADs were discontinued 9) Tamez (1997b), Teupe (1991) and UKPDS (met vs. conventional) as these were not placebo controlled trials 10) Fanghanel (1996) comparison with insulin monotherapy (this comparison was not prioritised for inclusion) 11) Noury (1991)-unclear if previous OADs were washed off or discontinued 12) Dalzell (1986)-abstract only 13) DeFronzo (1995a)-some patients were taking sulfonylurea and these patients were switched (unclear if any assigned to metforin were washed off treatment duration was <12 months) Data for the following RCTs have been extracted elsewhere within this review question; Goldstein (2003), Uehara (1999), Moses (1999), Chiasson (2001a), Pavo (2003) NB: DeFronzo (1995b) relates to results from protocol 1 from the full paper
Baseline characteristics	

	Placebo			Metformin				
	N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**

Demographics: Age (years) a	Continuous	15		54.8 (SD 10.1)	29		50.7 (SD 9.69)		
Sex (n male)	Dichotomous	15	11	(73.3%)	29	15	(51.7%)		
Blood glucose: HbA1c (%) – 0wka	Continuous	15		7.2 (SD 1.94)	29		6.8 (SD 1.08)		
Fasting plasma glucose (mmol/l) – 0wka	Continuous	15		7.43 (SD 2.13)	29		7 (SD 1.24)		
Body weight: BMI (kg/m2) – 0wka	Continuous	15		33.1 (SD 7.36)	29		32.1 (SD 7)		
Blood pressure: Systolic blood pressure (mmHg)	Continuous	15		124 (SD 15.5)	29		126 (SD 10.8)		
Diastolic blood pressure (mmHg)	Continuous	15		78 (SD 3.87)	29		80 (SD 5.39)		
Lipids: Total cholesterol (mmol/l) – 0wk	Continuous	15		4.59 (SD 0.852)	29		5.38 (SD 0.969)		
HDL cholesterol (mmol/l) – 0wk	Continuous	15		1.18 (SD 0.31)	29		1.15 (SD 0.323)		
LDL cholesterol (mmol/l) – 0wk	Continuous	15		2.68 (SD 0.775)	29		3.36 (SD 0.808)		

[a] SD calculated from reported SE

Results

		Placebo			Metformin				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 12wka	Continuous	15		6.9 (SD 1.16)	29		6.5 (SD 1.08)		
Fasting plasma glucose (mmol/l) – 12wka	Continuous	15		7.39 (SD 2.63)	29		6.5 (SD 1.08)		
Body weight: BMI (kg/m2) – 12wka	Continuous	15		33 (SD 8.91)	29		32.1 (SD 7)		
Lipids: Total cholesterol (mmol/l) – 12wk	Continuous	15		4.64 (SD 0.87)	29		5.41 (SD 0.82)		
HDL cholesterol (mmol/l) – 12wk	Continuous	15		1.19 (SD 0.32)	29		1.2 (SD 0.36)		
LDL cholesterol (mmol/l) – 12wk	Continuous	15		2.8 (SD 0.83)	29		3.37 (SD 0.56)		

[a] SD calculated from reported SE

Table 73: Mohan et al. (2009)

General

Phase:
☑ monotherapy
☐ dual therapy
☐ triple therapy
☐ insulin monotherapy
☐ insulin+oral

Parallel / crossover: Parallel

Country: China, Korea and India

Authors' conclusions: In this study, sitagliptin monotherapy for 18 weeks significantly improved glycaemic control and was well-tolerated in patients with type 2 diabetes from China, India and Korea

Source of funding: Sponsored by Merck & Co Inc (some staff were previous employees and may have held stock in the company)

Comments: Randomisation using computrer generated schedule, drugs were supplied in coded containers and all patient care personnel, patients, lab staffand clinical sponsor's clinical monitor and associated statistical and scientific collaborators remained blinded to treatment allocations until study was complete and the database was locked.

Number and characteristics of patients	**Total number of patients:** 530 **Inclusion criteria:** aged 18 years and over with a diagnosis of type 2 diabetes within the previous 5 years. At the time of screening, patients were required to have a Hba1c >=7.5% and <=11% **Exclusion criteria:** patients who had received pioglitazone, rosiglitazone or insulin within the previous 12 weeks, were pregnant or breast feeding, people with type 1 diabetes, unstable cardiac disease or moderate to severe renal insufficiency were excluded. Patients were discontinued during the maintenance phase if FPG >15 mmol/l in weeks 0-8, FPG>13.3 mmol/l in weeks 6-12 or FPG>11.1 mmol/l in weeks 12-18 Pre-randomisation phase: Before randomisation patients followed a diet and exercise run-in period of 3-6 weeks (3 weeks for patients who had not received antihyperglycaemic agent [AHA] within the previous 3 months and 6 weeks for those who had discontinued AHA therapy at screening or within 3 months prior). This was followed by a 2 week single-blind placebo run-in period before randomisation. Eligibility to enter the 2 week single-blind placebo run-in was contingent on having Hba1c between 7.5 and 11%. At the end of the placebo run-in eligibility depended on having FPG between 7.2 and 15.6 mmol/l and treatment compliance to single blind placebo of 75% and over based on tablet counts.
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** some on oral hypoglycaemic drugs and/or insulin **Details of washout period:** 3 weeks washout for drug naïve patients and 6 weeks for those discontinuing therapy at screening or within the 3 months prior, followed by a 2 week single blind placebo run in period
Lifestyle advice	no details reported but diet and exercise formed part of the run-in phase
Follow-up	**Total follow-up (wks):** 26 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 18 **Frequency of monitoring appointments:** no details reported
Arms	**(1) Sitagliptin** N: 352 Treatment duration (wks): 18 Washout period (d): 56 Comments: washout periods varied depending on previous AHA (6 weeks for those discontinuing therapy and 3 weeks for thode not receiving AHA within the previous 3 months). There was also a 2 week placebo run-in period. Treatment(s): Sitagliptin (Oral) – fixed-dose Set dose (mg/d):100 Frequency of dosing: once a day Compliance: Patients with low compliance during the placebo run-in were not eligible for the maintenance phase. The rate of treatment compliance was the same in both groups (98%) Details of dosing regimen: no other details reported **(2) Placebo** N: 178 Treatment duration (wks): 18 Washout period (d): 56 Comments: washout periods varied depending on previous AHA (6 weeks for those discontinuing therapy and 3 weeks for thode not receiving AHA within the previous 3 months) Treatment(s): Placebo (Oral) Details of dosing regimen: image matched placebo was given
Outcomes	**General** Outcomes not reported in this evidence table include fasting insulin, proinsulin, c-peptide, HOMA-Beta, HOMA-IR, QUICKI, postprandial insulin, postprandial c-peptide, insulinogenic index, insulin sensitivity 45 (25%) in the placebo group and 46 (13%) in sitagliptin arm discontinued the study Efficacy outcomes were analysed using the full analysis set (FAS) populations defined for each endpoint as the set of randomised patients who had received at least one dose of the study medication and had a baseline measurement with at least one post randomisation measurement. Missing data were handled using the method of last observation carried forward (LOCF). Safety and tolerability were anlaysed using the all-patients treated population composed of all randomised patients who had received as least one dose of the study medication.

Baseline characteristics

		Sitagliptin			Placebo				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	352		50.9 (SD 9.3)	178		50.9 (SD 9.3)		
Sex (n male)	Dichotomous	352	200	(56.8%)	178	106	(59.6%)		

Duration of diabetes (yrs)	Continuous	352		2.1 (SD 1.7)	178		1.9 (SD 1.6)		
Blood glucose: HbA1c (%) – 0wk	Continuous	339		8.7 (SD 1)	169		8.7 (SD 1.1)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	339		10.5 (SD 2.4)	169		10.5 (SD 2.5)		
Body weight: BMI (kg/m2)	Continuous	352		25.1 (SD 3.4)	178		24.9 (SD 3.4)		
Weight (kg) – 0wk	Continuous	352		66.8 (SD 10.2)	178		66.6 (SD 11.4)		
Previous blood glucose lowering drugs: Diet alone (i.e. drug naïve)	Dichotomous	352	132	(37.5%)	178	58	(32.6%)		
China Demographics: Duration of diabetes (yrs)	Continuous	163		2.1 (SD 1.8)	82		1.7 (SD 1.6)		
Blood glucose: HbA1c (%) – 0wk	Continuous	163		8.6 (SD 1)	82		8.6 (SD 1)		
Previous blood glucose lowering drugs: Diet alone (i.e. drug naïve)	Dichotomous	163	60	(36.8%)	82	31	(37.8%)		
India Demographics: Duration of diabetes (yrs)	Continuous	127		1.8 (SD 1.5)	63		1.7 (SD 1.6)		
Blood glucose: HbA1c (%) – 0wk	Continuous	127		9 (SD 1.1)	63		9 (SD 1.2)		
Previous blood glucose lowering drugs: Diet alone (i.e. drug naïve)	Dichotomous	127	53	(41.7%)	63	21	(33.3%)		
Korea Demographics: Duration of diabetes (yrs)	Continuous	62		2.6 (SD 1.6)	33		2.9 (SD 1.5)		
Blood glucose: HbA1c (%) – 0wk	Continuous	62		8.5 (SD 0.9)	33		8.6 (SD 0.9)		
Previous blood glucose lowering drugs: Diet alone (i.e. drug naïve)	Dichotomous	62	19	(30.6%)	33	6	(18.2%)		

Results

		Sitagliptin			Placebo				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Blood glucose: HbA1c (%) – 12wka	Continuous	339		8 (SD 0.368)	169		8.94 (SD 0.91)		
HbA1c (%) – 18wkb	Mean change	339		-0.7 (SD 0.939)	169		0.3 (SD 1.33)	MD=-1.000 (CI: -1.200, -0.800)	<0.001c
HbA1c (%) – 18wkb	Continuous	339		8 (SD 1.3)	169		9.1 (SD 1.6)		
HbA1c < 7% or <=7% – 18wk	Dichotomous	339	70	(20.6%)	169	9	(5.3%)		<0.001
HbA1c < 7% or <=7% – 18wk	Dichotomous	339	70	(20.6%)	169	9	(5.3%)	OR=6.600 (CI: 2.005, 21.731)	d
Fasting plasma glucose (mmol/l) – 12wka	Continuous	339		9.1 (SD 1.66)	169		10.5 (SD 1.3)		
Fasting plasma glucose (mmol/l) – 18wkb	Mean change	339		-1.4 (SD 2.82)	169		0.3 (SD 2.65)	MD=-1.700 (CI: -2.100, -1.300)	<0.001c

2-h post prandial glucose (mmol/l) – 18wk	Continuous	352			178			MD=-3.100 (CI: -3.800, -2.400)	<0.001c
2-h post prandial glucose (mmol/l) – 18wk	Continuous	352			178				e
2-h post prandial glucose (mmol/l) – 18wkb	Mean change	297		-3.5 (SD 3.52)	131		-0.4 (SD 3.5)		
1-h postprandial gluocse (mmol/l) – 18wkb	Continuous	352			178				e
Body weight:									
Weight (kg) – 18wk	Continuous	352			178				e
Weight (kg) – 18wkf	Mean change	352		0.6 (SD 1.88)	178		0 (SD 2.67)		
Hypoglycaemic events:									
All hypoglycaemic events (no patients) – 18wk	Dichotomous	352	0	(0.0%)	178	0	(0.0%)		e
Adverse events:									
GI: nausea – 18wk	Dichotomous	352	0	(0.0%)	178	0	(0.0%)		e
Any adverse event(s) – 18wk	Dichotomous	352	82	(23.3%)	178	27	(15.2%)		e
Any serious adverse event(s) – 18wk	Dichotomous	352	6	(1.7%)	178	2	(1.1%)		e
Serious AE drug related – 18wk	Dichotomous	352	1	(0.3%)	178	1	(0.6%)		
Study drug-related adverse event – 18wk	Dichotomous	352	10	(2.8%)	178	3	(1.7%)		
Death – 18wk	Dichotomous	352	1	(0.3%)	178	0	(0.0%)		e
Gastrointestinal disorders (any) – 18wk	Dichotomous	352	18	(5.1%)	178	1	(0.6%)		e
GI: diarrhoea – 18wk	Dichotomous	352	0	(0.0%)	178	0	(0.0%)		e
GI: vomiting – 18wk	Dichotomous	352	0	(0.0%)	178	0	(0.0%)		e
GI: abdominal pain – 18wk	Dichotomous	352	3	(0.9%)	178	0	(0.0%)		e
Laboratory adverse event drug related – 18wkg	Dichotomous	352	9	(2.6%)	178	3	(1.7%)		
Laboratory adverse events – 18wkg	Dichotomous	352	23	(6.5%)	178	12	(6.7%)		
Dropouts:									
Total dropouts – 18wk	Dichotomous	352	46	(13.1%)	178	45	(25.3%)		
Dropout due to AEs – 18wk	Dichotomous	352	6	(1.7%)	178	4	(2.2%)		e
drop out due to drug related AE – 18wk	Dichotomous	352	2	(0.6%)	178	1	(0.6%)		
drop out due to SAE – 18wk	Dichotomous	352	3	(0.9%)	178	2	(1.1%)		
drop out due to drug related SAE – 18wk	Dichotomous	352	1	(0.3%)	178	1	(0.6%)		
China									
Blood glucose:									
HbA1c (%) – 18wkb	Mean change	158		-0.9 (SD 0.641)	79		-0.2 (SD 0.924)	MD=-0.700 (CI: -0.900, -0.500)	<0.001c
Fasting plasma glucose (mmol/l) – 18wkb	Mean change	158		-1 (SD 1.92)	79		0 (SD 1.81)	MD=-1.000 (CI: -1.500, -0.500)	<0.001c
2-h post prandial glucose (mmol/l) – 18wk	Continuous	144			66			MD=-2.800 (CI: -3.500, -2.100)	<0.001c
2-h post prandial glucose (mmol/l) – 18wkb	Mean change	144		-3.5 (SD 3.06)	66		-0.7 (SD 2.9)		

India									
Blood glucose: HbA1c (%) – 18wkb	Mean change	119		-0.6 (SD 1.15)	59		0.7 (SD 0.81)	MD=-1.400 (CI: -1.700, -1.100)	h
Fasting plasma glucose (mmol/l) – 18wkb	Mean change	119		-1.8 (SD 2.78)	59		0.3 (SD 2.35)	MD=-2.200 (CI: -2.900, -1.500)	h
2-h post prandial glucose (mmol/l) – 18wkb	Mean change	100		-3.3 (SD 3.57)	41		-0.5 (SD 3.59)		
2-h post prandial glucose (mmol/l) – 18wk	Continuous	100			41			MD=-2.800 (CI: -4.000, -1.600)	h
Korea									
Blood glucose: HbA1c (%) – 18wkb	Mean change	62		-0.8 (SD 1.21)	31		0.6 (SD 1.17)	MD=-1.400 (CI: -1.900, -0.900)	h
Fasting plasma glucose (mmol/l) – 18wkb	Mean change	62		-1.9 (SD 2.41)	31		1.1 (SD 2.27)	MD=-3.000 (CI: -4.000, -2.000)	h
2-h post prandial glucose (mmol/l) – 18wkb	Mean change	53		-4.2 (SD 3.71)	24		0.8 (SD 3.5)		
2-h post prandial glucose (mmol/l) – 18wk	Continuous	53			24			MD=-5.000 (CI: -6.800, -3.200)	h
Hba1c>=10%									
Blood glucose: HbA1c (%) – 18wk	Mean change	0			0			MD=-1.400 (CI: -2.000, -0.800)	i

[a] estimated from graph
[b] [DO NOT USE - OUTSIDE TIME RANGE]
[c] ANCOVA between group difference
[d] Fishers exact test (CI using wilsons method)
[e] not reported
[f] [DO NOT USE - OUTSIDE TIME RANGE]; SD calculated from reported SE
[g] approximated to nearest integer (percentages only presented in text)
[h] prespecified p-values not determined for this subgroup
[i] total n=72 but no arm specific numbers reported

ANCOVA was used to compare treatment groups for continuous efficacy parameters, focusing on change from baseline at week 18 with covariates including treatment allocation, baseline value, prior AHA status and nationality. The between group differences for efficacy endpoints were assessed by testing the difference least-square mean (LS-mean) change from baseline at week 18. Between group differences in the incidence of hypoglycaemia and pre-specified gastrointestinal AEs were analysed using Fishers exact test.

Table 74: Moses et al. (2001)

General

Phase:
☑ monotherapy
☐ dual therapy
☐ triple therapy
☐ insulin monotherapy
☐ insulin+oral

Parallel / crossover: Parallel

Country: 13 countries

Authors' conclusions: Mealtime dosing with repaglinide is effective in improving overall glycemic control in type 2 diabetic patients for which control is suboptimal using diet alone. Patients are able to vary their meal pattern from a conventional regimen of three meals daily without compromising control or increasing the risk of adverse events

Source of funding: Novo Nordisk

Comments: Double-blind

Number and characteristics of patients

Total number of patients: 408

Inclusion criteria: patients with type 2 diabetes, at least 40 years of age, treated by diet alone with no history of previous AHAs

	Exclusion criteria: Patients who had previously received oral antidiabetic agents were excluded, as were patients withhepatic disease, significant cardiovascular disease (including severe uncontrolled hypertension), or other diabetic complications indicative of a late disease state. Patients whose HbA1c deteriorated by >=1% during the study were withdrawn
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** All treatment naive/ no OADs at screening **Details of washout period:** All AHA naïve
Lifestyle advice	No details provided
Follow-up	**Total follow-up (wks):** 16 **Length of titration period (wks):** 4 **Length of maintenance period (wks):** 12 **Frequency of monitoring appointments:** Assessments occurred at baseline and after 4, 12 and 16 weeks
Arms	**(1) Repaglinide** N: 260 Treatment duration (wks): 16 Washout period (d): 0 Comments: AHA naïve Treatment(s): repaglinide (Oral) – flexible-dose (dose-adjusted) Minimum dose (mg/d): 1 Maximum dose (mg/d): 4 Frequency of dosing: three times a day Details of dosing regimen: Repaglinide 0.5 mg at mealtimes. In each case, one tablet was taken immediately before each main meal, in accordance with the dietary pattern of the individual patient (two to four times daily). If a meal was skipped or postponed, the trial medication for that meal was also skipped or postponed, and if a meal was added, trial medication was also added. Patients on repaglinide initially received a prandial dose of 0.5 mg, with the dose being doubled after 4 weeks if FPG exceeded 7.8 mmol/l. **(2) placebo** N: 134 Treatment duration (wks): 16 Washout period (d): 0 Comments: AHA naïve Treatment(s): Placebo (Oral)
Outcomes	**General** All calculations of efficacy were performed on an intention-to-treat population, defined as all patients who were randomised and exposed to at least one dose of trial medication and who yielded data from at least one visit after treatment initiation. Safety analyses were based on the population of patients randomised and exposed to at least one dose of trial medication. Where observations were missing, the last observation for that patient was used for analysis (last observation carried forward). The study was completed by 316/408 patients: 219/260 in the repaglinide group and 97/134 in the placebo group. Withdrawal was significantly more frequent in the placebo group than in the repaglinide group (P = 0.013), the principal reason being ineffective therapy
Baseline characteristics	

		Repaglinide			placebo				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Demographics: Age (years)	Continuous	260		57.5 (SD 9)	134		57.4 (SD 8.6)		
Sex (n male) a	Dichotomous	260	139	(53.5%)	134	77	(57.5%)		
Duration of diabetes (yrs)	Continuous	260		2.99 (SD 4.58)	134		3.07 (SD 4.69)		
Blood glucose: HbA1c (%) – 0wkb	Continuous	260		7.8 (SD 1.8)	134		7.6 (SD 1.5)		
Fasting plasma glucose (mmol/l) – 0wkb	Continuous	260		9.9 (SD 3.1)	134		9.6 (SD 2.7)		
Body weight: BMI (kg/m2)	Continuous	260		30 (SD 5)	134		30.9 (SD 5.5)		
Weight (kg) – 0wk	Continuous	260		84 (SD 16.1)	134		86.6 (SD 16.7)		

Diabetic complications:										
Retinopathy	Dichotomous	260	1	(0.4%)	134	0	(0.0%)		
Nephropathy	Dichotomous	260	2	(0.8%)	134	0	(0.0%)		
Neuropathy	Dichotomous	260	0	(0.0%)	134	0	(0.0%)		
Macroangiopathy	Dichotomous	260	0	(0.0%)	134	0	(0.0%)		

[a] Calculated from reported percentages
[b] Reported as SE, but assumed SD

Results

		Repaglinide			placebo				
		N	k	mean	N	k	mean	Δ	p
Blood glucose:									
HbA1c (%) – 16wka	Mean change	260		-1.14	134		-0.15		
HbA1c (%) – 16wkb	Continuous	260		6.59 (SD 1.61)	134		7.39 (SD 2.32)		
Fasting plasma glucose (mmol/l) – 16wkb	Continuous	260		8.05 (SD 3.22)	134		9.05 (SD 4.63)		
Hypoglycaemic events:									
minor hypoglycaemic events – 16wkc	Dichotomous	260	44	(16.9%)	134	4	(3.0%)		
Major/severe hypoglycaemic event – 16wk	Dichotomous	260	3d		134	e			
Adverse events:									
Any adverse event(s) – 16wk	Dichotomous	260	75f	(28.8%)	134	40g	(29.9%)		
Dropouts:									
Total dropouts – 16wk	Dichotomous	270	51	(18.9%)	138	41	(29.7%)		
Dropout due to AEs – 16wk	Dichotomous	270	9	(3.3%)	138	2	(1.4%)		
Study completers/observed cases									
Body weight:									
Weight (kg) – 16wkb	Continuous	219		84.6 (SD 13.3)	97		86.7 (SD 14.8)		

[a] mean change; SD not reported
[b] estimated from graph
[c] approximated to nearest integer (percentages only presented in text); approximated to nearest integer (percentages only presented in text)
[d] No of patients; reported there were no events that required hospitalisation or IV glucose/glucagon
[e] NR; reported there were no events that required hospitalisation or IV glucose/glucagon
[f] approximated to nearest integer (percentages only presented in text); excluding hypos
[g] approximated to nearest integer (percentages only presented in text); excluding hypos; approximated to nearest integer (percentages only presented in text)

Table 75: Nakamura et al. (2004)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** Japan **Authors' conclusions:** Pioglitazone but not glibenclamide or voglibose, appears to be effective in reducing UAE, IMT and PWV in normotemsive type 2 diabetes patients with microalbuminuria **Source of funding:** Unclear **Comments:** Unclear blinding
Number and characteristics	**Total number of patients:** 45 **Inclusion criteria:** type 2 diabetes and microalbuminuria treated witrh diet alone, Hba1c>6.5%

of patients	**Exclusion criteria:** patients with ketoacidosis, malignancy, heart disease, cerebrovascular disease, liver or non-diabetic renal disease
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** All treatment naive/ no OADs at screening **Details of washout period:** States treated with diet alone, no details of history of AHAs
Lifestyle advice	No details reported
Follow-up	**Total follow-up (wks):** 52 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 52 **Frequency of monitoring appointments:** measurements were taken at baseline, 6 and 12 months
Arms	**(1) Pioglitazone** N: 15 Treatment duration (wks): 52 Washout period (d): 0 Comments: Treated on diet alone Treatment(s): Pioglitazone (Oral) – fixed-dose Set dose (mg/d):30 **(2) Glibenclamide** N: 15 Treatment duration (wks): 52 Washout period (d): 0 Comments: Treated on diet alone Treatment(s): Sulfonylurea (Oral) – fixed-dose Set dose (mg/d):5 Details of dosing regimen: glibenclamide 5 mg/day
Outcomes	

Baseline characteristics

		Pioglitazone			Glibenclamide				
		N	k	mean	N	k	mean	Δ	p
Demographics:									
Age (years)	Continuous	15		56.5 (SD 12)	15		55 (SD 11.5)		
Sex (n male)	Dichotomous	15	9	(60.0%)	15	8	(53.3%)		
Duration of diabetes (yrs)	Continuous	15		17.5 (SD 4.5)	15		17 (SD 4.8)		
Blood glucose:									
HbA1c (%) – 0wk	Continuous	15		7.9 (SD 1.3)	15		7.8 (SD 1.4)		

Results

		Pioglitazone			Glibenclamide				
		N	k	mean	N	k	mean	Δ	p
Blood glucose:									
HbA1c (%) – 26wk	Continuous	15		6.8 (SD 1.2)	15		6.7 (SD 1.3)		
HbA1c (%) – 52wk	Continuous	15		6.2 (SD 1)	15		6.3 (SD 1.1)		
Dropouts:									
Total dropouts – 52wk	Dichotomous	15	0	(0.0%)	15	0	(0.0%)		
Dropout due to AEs – 52wk	Dichotomous	15	0	(0.0%)	15	0	(0.0%)		

Table 76: Nonaka et al. (2008)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** Japan **Authors' conclusions:** In this study, once daily sitagliptin 100 mg for 12 weeks improved fasting and postprandial glycaemic control and was generally well tolerated in Japanese patients with type 2 diabetes **Source of funding:** Study was sponsored by Banyu Pharmaceutical Co Ltd (a subsidary of Merck & Co the manufacturer of sitagliptin) **Comments:** Randomised, double-blind, placebo controlled study. Patients were randomised using a computer generated allocation schedule. Laboratory technicians were blinded to treatment group.
Number and characteristics of patients	**Total number of patients:** 152 **Inclusion criteria:** patients with type 2 diabetes aged 20 to 69 years were eligible if they were not on treatment with an oral antihyperglycaemic agent (OHA) or only on a single OHA over the 8 weeks prior to screening. Patients with a Hba1c level >= 6.5% and <10% and a fasting blood glucose >=126 and <=240 mg/dl were eligible to participate **Exclusion criteria:** type 1 diabetes, any treatment with insulin or pioglitazone in the 8 weeks prior to screening, unstable cardiac disease, elevated serum creatinine (>1.3 mg/dl) in men and >1.2mg/dl in women), and elevations over 2-fold the upper limit of normal in either alanine aminotransferase (ALT), aspartate aminotransferase (AST), or creatinr phosphokinase (CPK) Pre-randomisation phase: Patients who had not been on diet and exercise therapy for at least 6 weeks underwent a 6 week program of diet and exercise and then entered a 2 week single-blind, placebo run-in period. Patients who had been taking an OHA underwent a 6 week washout and then entered the placebo run-in period. Patients who had already had at least 6 weeks of diet and exercise therapy without any OHA entered directly into the placebo run-in period. Patients with a Hba1c >=6.5% and <10% and an FPG >= 126 and <=240 mg/dl were eligible to eneter the placebo run-in period. Patients with adequate compliance at the end of the placebo run-in period were randomised
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** some on oral hypoglycaemic drugs and/or insulin **Details of washout period:** There was a 6-week washout period for patients previously taking OHAs (see pre-randomisation details) plus a 2 week single blind placebo run in
Lifestyle advice	Patients received counselling regarding exercise and diet therapy at every visit throughout the study
Follow-up	**Total follow-up (wks):** 20 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 12 **Frequency of monitoring appointments:** No details reported related to the frequency of monitoring but at each visit, investigators patients diaries and confirmed adverse experiences and compliance
Arms	**(1) Sitagliptin** N: 76 Treatment duration (wks): 12 Washout period (d): 56 Comments: 6 week washout period and 2 week placebo run-in period Treatment(s): Sitagliptin (Oral) – fixed-dose Set dose (mg/d):100 Frequency of dosing: once a day Compliance: Assessed by tablet count Details of dosing regimen: No further details of dosing regime reported **(2) Placebo** N: 76 Treatment duration (wks): 12 Washout period (d): 56 Comments: 6 week washout period and 2 week placebo run-in period Treatment(s): Placebo (Oral) Compliance: as sitagliptin arm Details of dosing regimen: Details not reported but assumed same as sitagliptin arm to maintain blinding
Outcomes	**General** Outcomes not reported in this evidence table include fasting insulin, C-peptide, HOMA-IR, HOMA-beta, insulinogenic index, glucose total AUC, insulin total AUC and c-peptide AUC. Subgroup analyses by OHA

status, baseline Hba1c, FPG, gender, age, BMI and known duration of diabetes were specified but were not explicitly reported therefoer were not extracted.

2 patients in the sitagliptin arm and 8 patients in the placebo arm did not complete the study

Primary analysis conducted on all-patients-treated set, which was the population of randomised patients who had taken at least one dose of the study drug and had at least one post-randomisation measurement. The last observation carried forward method was used to impute missing values. The safety evaluation was conducted on all patients who took at least one dose of the study drug.

Adverse events

Study drug-related adverse event (Two clinical adverse experiences that were considered to be drug-related with sitagliptin were gastritis and hypoesthesia. Three events were considered for placebo (exfoliative dermatitis with cellulitis, decreased blood pressure and headache))

Baseline characteristics

		All study participants		
		N	k	mean
Demographics:				
Age (years)	Continuous	151		55.3 (SD 8.3)
Sex (n male)	Dichotomous	151	95	(62.9%)
Duration of diabetes (yrs)	Continuous	151		4 (SD 4.4)
Blood glucose:				
HbA1c (%) – wk	Continuous	151		7.6 (SD 0.9)
HbA1c (%) – wk	Continuous	151		7.6 (SD 0.9)
Hba1c <=8%	Dichotomous	151	106	(70.2%)
Hba1c >8%	Dichotomous	151	45	(29.8%)
Fasting plasma glucose (mmol/l) – wk	Continuous	151		9.07425 (SD 1.8648)
Fasting plasma glucose (mmol/l) – wk	Continuous	151		9.07425 (SD 1.8648)
Body weight:				
BMI (kg/m2)	Continuous	151		25.2 (SD 3.4)
Weight (kg) – 0wk	Continuous	151		71.12448 (SD 9.59616) a
Previous blood glucose lowering drugs:				
Diet alone (i.e. drug naïve)	Dichotomous	151	65	(43.0%)

[a] estimated from BMI assuming mean height of 1.68m

		Sitagliptin			Placebo				
		N	k	mean	N	k	mean	Δ	p
Demographics:									
Age (years)	Continuous	75		55.6 (SD 8.6)	76		55 (SD 8)		
Sex (n male)	Dichotomous	75	45	(60.0%)	76	50	(65.8%)		
Duration of diabetes (yrs)	Continuous	75		4 (SD 4.1)	76		4.1 (SD 4.6)		
Blood glucose:									
HbA1c (%) – 0wk	Continuous	75		7.54 (SD 0.85)	75		7.69 (SD 0.86)		
Hba1c <=8%	Dichotomous	75	53	(70.7%)	76	53	(69.7%)		
Hba1c >8%	Dichotomous	75	22	(29.3%)	76	23	(30.3%)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	75		9.0576 (SD 2.01)	76		9.0909 (SD 1.72)		
Body weight:									
BMI (kg/m2)	Continuous	75		25.2 (SD 3.5)	76		25.1 (SD 3.2)		
Weight (kg) – 0wka	Continuous	75		71.12448 (SD 9.88)	76		70.84224 (SD 9.03)		
Previous blood glucose lowering drugs:									
Diet alone (i.e. drug naïve)	Dichotomous	75	36	(48.0%)	76	29	(38.2%)		

[a] estimated from BMI assuming mean height of 1.68m

Results

	Sitagliptin			Placebo				
	N	k	mean	N	k	mean	Δ	p

Blood glucose: HbA1c (%) – 12wka	Mean change	75		-0.65 (SD 0.663)	75		0.41 (SD 0.663)	MD=-1.050 (CI: -1.270, -0.830)	<0.001b
HbA1c (%) – 12wk	Continuous	75		6.9 (SD 1)	75		8.09 (SD 1.04)		
HbA1c < 7% or <=7% – 12wkc	Dichotomous	75	44	(58.7%)	75	11	(14.7%)		<0.001d
HbA1c <= 6.5% – 12wkc	Dichotomous	75	26	(34.7%)	75	4	(5.3%)		<0.001d
Fasting plasma glucose (mmol/l) – 12wk	Mean change	75		-1.24875 (SD 1.71)	75		0.5217 (SD 1.35)	MD=-1.770 (CI: -2.203, -1.338)	<0.001b
2-h post prandial glucose (mmol/l) – 12wk	Mean change	43		-3.84615 (SD 2.97)	32		0.666 (SD 4.57)	MD=-4.512 (CI: -5.872, -3.152)	<0.001b
1-h postprandial gluocse (mmol/l) – 12wke	Continuous	75			76				
0.5-h postprandial (mmol/l) – 12wke	Continuous	75			32				
Body weight: Weight (kg) – 12wka	Mean change	75		-0.1 (SD 1.33)	76		-0.7 (SD 1.33)	MD=0.700 (CI: 0.200, 1.200)	<0.01b
Hypoglycaemic events: All hypoglycaemic events (no patients) – 12wk	Dichotomous	75	0	(0.0%)	76	0	(0.0%)		>0.05
Adverse events: Any adverse event(s) – 12wk	Dichotomous	75	44	(58.7%)	76	49	(64.5%)		>0.05
Any serious adverse event(s) – 12wk	Dichotomous	75	1f	(1.3%)	76	3g	(3.9%)		>0.05
Study drug-related adverse event – 12wk	Dichotomous	75	2	(2.7%)	76	3	(3.9%)		>0.05
Gastrointestinal disorders (any) – 12wk	Dichotomous	75	16	(21.3%)	76	13	(17.1%)		>0.05
Laboratory adverse events – 12wk	Dichotomous	75	9	(12.0%)	76	15c	(19.7%)		>0.05
Nervous system disorders – 12wk	Dichotomous	75	8	(10.7%)	76	5	(6.6%)		>0.05
Dropouts: Total dropouts – 12wk	Dichotomous	76	3	(3.9%)	76	9	(11.8%)		
Dropout due to AEs – 12wk	Dichotomous	76	0	(0.0%)	76	3	(3.9%)		h
dropout due to laboratory AE – 12wk	Dichotomous	76	0	(0.0%)	76	1	(1.3%)		

[a] SD calculated from reported 95% CI; least squares mean
[b] ANCOVA
[c] approximated to nearest integer (percentages only presented in text)
[d] not reported assumed fishers exact
[e] graph
[f] overdose
[g] MI, overdose, dermatitis with cellulitis
[h] not reported

The between group comparison of change in Hba1c from baseline to 12 weeks was performed using an ANCOVA model in which treatment was the factor and baseline Hba1c was the covariate. Between group comparisons for secondary endpoints were performed using an ANCOVA model similar to the one described for Hba1c. Between group differences in the incidence of hypoglycaemia were performed using Fisher's exact test. For adverse events, the incidence and 95% CI were calculated for each treatment group, and the between group difference and 95% CI of the difference were calculated.

Table 77: Pan et al. (2008)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** conducted in China, Romania and Spain **Authors' conclusions:** Vildagliptin is effective and well tolerated in patients with Type 2 diabetes, demonstrating similar glycaemic reductions to acarbose, but with better tolerability **Source of funding:** Novartis Pharmaceuticals Corporation **Comments:** 24 week, double-blind, randomised, active controlled parallel group trial. No details of blinding, randomisation methods and allocation concelament reported
Number and characteristics of patients	**Total number of patients:** 661 **Inclusion criteria:** patients with T2DM and HbA1c between 7.5 and 11.0% at the screening visit while receiving no OGLA. Patients who had taken no OGLA for at least 12 weeks prior to screening, and no OGLA for > 3 consecutive months at any time in the past, were considered to be representative of a drug-naive population. Male and female (non-fertile or of childbearing potential using a medically approved birth-control method) patients aged =18 years, with a body mass index (BMI) 20–40 kg/m2 (inclusive) and with fasting plasma glucose (FPG) < 15.0 mmol/l were eligible to participate. **Exclusion criteria:** history of Type 1 or secondary forms of diabetes, acute metabolic diabetic complications within the past 6 months, myocardial infarction, unstable angina or coronary artery bypass surgery within the previous 6 months. Congestive heart failure, New York Heart Association Class III or IV and liver disease (such as cirrhosis or chronic active hepatitis) or chronic intestinal disorders also precluded participation. Patients with any of the following laboratory abnormalities were also excluded: ALT or AST > 3 times the ULN; direct bilirubin > 1.3 times the ULN; serum creatinine levels > 220 µmol/l; TSH outside normal range; fasting triglycerides > 7.9 mmol/l. Pre-randomisation phase: Eligible patients were randomized at visit 2 (week 0, baseline)
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** some on oral hypoglycaemic drugs and/or insulin **Details of washout period:** Inclusion: patients not on OADs at least 12 weeks prior to enrollment
Lifestyle advice	No details reported
Follow-up	**Total follow-up (wks):** 26 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 24 **Frequency of monitoring appointments:** Screening visits - 2 weeks prior to randomisation. Efficacy and tolerability were assessed during four additional visits, at weeks 4, 12, 16 and 24 of active treatment.
Arms	**(1) Vildagliptin** N: 441 Treatment duration (wks): 24 Washout period (d): 0 Comments: Inclusion: patients not on OADs at least 12 weeks prior to enrollment Treatment(s): Vildagliptin (Oral) – fixed-dose Set dose (mg/d):100 Frequency of dosing: twice a day Details of dosing regimen: 50 mg given twice daily **(2) Acarbose** N: 220 Treatment duration (wks): 24 Washout period (d): 0 Comments: Inclusion: patients not on OADs at least 12 weeks prior to enrollment Treatment(s): Acarbose (Oral) – flexible-dose (dose-adjusted) Maximum dose (mg/d): 300 Details of dosing regimen: acarbose up to 300 mg daily (given in three divided doses). No other details reported but assumed flexible-dose regime
Outcomes	**General** All main outcome are reported in this evidence table 42 patients in vildagliptin group and 28 patients in the acarbose group did not complete the study. The ITT population included last observation carried forward for patients who discontinued prematurely. The ITT population for Hba1c was reported as 389 in vildagliptin and 187 in acarbose at week 24 (the

randomised population was used where outcome specific denominators were not reported)

Hypoglycaemic events

All hypoglycaemic events (no patients) (Hypoglycaemia was defined as symptoms suggestive of low blood glucose confirmed by SMBG measurement < 3.1 mmol/l plasma glucose equivalent.)

Major/severe hypoglycaemic event (Severe hypoglycaemia was defined as any episode requiring the assistance of another party.)

Baseline characteristics

		Vildagliptin			Acarbose				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	441		51.8 (SD 10.1)	220		51.9 (SD 10.3)		
Sex (n male)	Dichotomous	441	265	(60.1%)	220	139	(63.2%)		
Duration of diabetes (yrs)	Continuous	441		1.2 (SD 2.4)	220		1.3 (SD 2.4)		
Ethnicity-White	Dichotomous	441	42	(9.5%)	220	18	(8.2%)		
Ethnicity-Asian	Dichotomous	441	399	(90.5%)	220	202	(91.8%)		
Blood glucose: Fasting plasma glucose (mmol/l) – 0wk	Continuous	441		10 (SD 2.4)	220		10.2 (SD 2.5)		
Body weight: BMI (kg/m2)	Continuous	441		26.4 (SD 3.6)	220		25.8 (SD 3.5)		
Weight (kg) – 0wka	Continuous	441		74.51136 (SD 10.2)	220		72.81792 (SD 9.88)		
ITT Blood glucose: HbA1c (%) – 0wk	Continuous	441		8.6 (SD 0.9)	220		8.6 (SD 1)		

[a] estimated from BMI assuming mean height of 1.68m

Results

		Vildagliptin			Acarbose				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 24wk	Mean change	389			187			MD=-0.100 (CI: -0.296, 0.096)	0.307a
HbA1c < 7% or <=7% – 24wk	Dichotomous	427	198	(46.4%)	215	101	(47.0%)		b
HbA1c <= 6.5% – 24wk	Dichotomous	431	139	(32.3%)	215	76	(35.3%)		b
Fasting plasma glucose (mmol/l) – 24wkc	Mean change	441		-1.2 (SD 2.1)	220		-1.5 (SD 2.97)	MD=0.300 (CI: -0.092, 0.692)	0.112a
Body weight: Weight (kg) – 24wkc	Mean change	441		-0.4 (SD 2.1)	220		-1.7 (SD 2.97)	MD=1.300 (CI: 0.908, 1.692)	<0.001a
Hypoglycaemic events: All hypoglycaemic events (no patients) – 24wk	Dichotomous	441			220				b
Major/severe hypoglycaemic event – 24wk	Dichotomous	441			220				b
Adverse events: Any adverse event(s) – 24wk	Dichotomous	440			220				NS
Any serious adverse event(s) – 24wk	Dichotomous	440			220				NS
Death – 24wk	Dichotomous	440			220				b
Dizziness – 24wk	Dichotomous	440			220				NS
Fatigue – 24wk	Dichotomous	440			220				NS
Flatulence – 24wk	Dichotomous	440			220				NS

Gastrointestinal disorders (any) – 24wk	Dichotomous	440			220				<0.001d
GI: diarrhoea – 24wk	Dichotomous	440			220				NS
GI: abdominal distension – 24wk	Dichotomous	440			220				NS
Infection (upper airway or other common) – 24wk	Dichotomous	440			220				NS
Nasopharyngitis – 24wk	Dichotomous	440			220				NS
Palpitations – 24wk	Dichotomous	440			220				NS
Dropouts:									
Total dropouts – 24wk	Dichotomous	441	42	(9.5%)	220	28	(12.7%)		
Dropout due to AEs – 24wk	Dichotomous	441	11	(2.5%)	220	7	(3.2%)		NS
Drop out due to unsatisfactory effect – 24wk	Dichotomous	441	6	(1.4%)	220	8	(3.6%)		b
ITT									
Blood glucose:									
HbA1c (%) – 16wke	Continuous	389		7.25 (SD 0.394)	187		7.31 (SD 0.957)		
HbA1c (%) – 24wkc	Mean change	431		-1.4 (SD 1.97)	216		-1.3 (SD 1.37)		
Safety population									
Hypoglycaemic events:									
All hypoglycaemic events (no patients) – 24wk	Dichotomous	440	0	(0.0%)	220	0	(0.0%)		
Major/severe hypoglycaemic event – 24wk	Dichotomous	440	0	(0.0%)	220	0	(0.0%)		
Adverse events:									
Any adverse event(s) – 24wk	Dichotomous	440	154	(35.0%)	220	113	(51.4%)		
Any serious adverse event(s) – 24wk	Dichotomous	440	7	(1.6%)	220	2	(0.9%)		
Death – 24wk	Dichotomous	440	0	(0.0%)	220	0	(0.0%)		
Dizziness – 24wk	Dichotomous	440	17	(3.9%)	220	9	(4.1%)		
Fatigue – 24wk	Dichotomous	440	4	(0.9%)	220	5	(2.3%)		
Flatulence – 24wk	Dichotomous	440	11	(2.5%)	220	26	(11.8%)		
Gastrointestinal disorders (any) – 24wk	Dichotomous	440	54	(12.3%)	220	56	(25.5%)		
GI: diarrhoea – 24wk	Dichotomous	440	11	(2.5%)	220	6	(2.7%)		
GI: abdominal distension – 24wk	Dichotomous	440	12	(2.7%)	220	20	(9.1%)		
Infection (upper airway or other common) – 24wk	Dichotomous	440	15	(3.4%)	220	11	(5.0%)		
Nasopharyngitis – 24wk	Dichotomous	440	18	(4.1%)	220	14	(6.4%)		
Palpitations – 24wk	Dichotomous	440	16	(3.6%)	220	3	(1.4%)		
BMI >=30kg/m2									
Blood glucose:									
HbA1c (%) – 24wkc	Mean change	61		-1.2 (SD 1.56)	22		-1.3 (SD 0.938)		
BMI <30.0 kg/m2									
Blood glucose:									
HbA1c (%) – 24wkc	Mean change	379		-1.5 (SD 1.95)	198		-1.3 (SD 1.41)		
<3 months since diagnosis									
Blood glucose:									
HbA1c (%) – 24wkc	Mean change	258		-1.8 (SD 1.61)	131		-1.7 (SD 1.14)		0.565f

Fasting plasma glucose (mmol/l) – 24wkc	Mean change	258		-1.5 (SD 1.61)	131		-1.7 (SD 1.14)		0.319f
Body weight: Weight (kg) – 24wkc	Mean change	258		-0.6 (SD 3.21)	131		-1.8 (SD 3.43)		<0.001f
>=3 months since diagnosis Blood glucose: HbA1c (%) – 24wkc	Mean change	173		-0.9 (SD 1.32)	85		-0.7 (SD 1.84)		0.211f
Fasting plasma glucose (mmol/l) – 24wkc	Mean change	173		-0.8 (SD 2.63)	85		-1.1 (SD 2.77)		0.286f
Body weight: Weight (kg) – 24wkc	Mean change	173		-0.2 (SD 2.63)	85		-1.6 (SD 2.77)		<0.001f
Hba1c>9.0% Blood glucose: HbA1c (%) – 24wkc	Mean change	147		-2 (SD 1.21)	63		-2.1 (SD 1.59)		

[a] SD reported
[b] not reported
[c] assumed SE reported
[d] assumed chi squared, no other details reported
[e] estimated from graph
[f] No other details reported

AM? in primary and secondary end-points were analysed using an ANCOVA model with treatment and pooled centre as the classification variables and baseline value as the covariate. Several criteria were pre-specified to classify patients as responders to treatment. The percentage of patients (i) achieving end-point HbA1c < 7.0%, (ii) achieving end-point HbA1c ? 6.5%, (iii) experiencing a reduction of HbA1c ? 1.0%, (iv) experiencing a reduction of HbA1c ?0.7%, (v) experiencing a reduction of HbA1c ? 0.5% and (vi) meeting at least one of the aforementioned criteria in the two treatment groups were each compared by Chi-squared tests.

Table 78: Pan et al. (2012)

General

Phase:
☑ monotherapy
☐ dual therapy
☐ triple therapy
☐ insulin monotherapy
☐ insulin+oral

Parallel / crossover: Parallel

Country: China, India, the Phillippines and South Korea

Authors' conclusions: Saxagliptin improved glycaemic control and was well tolerated in drug naïve Asian patients with type 2 diabetes

Source of funding: Funded by Astra Zeneca and Bristol-Myers Squibb

Comments: 24 week, multicentre, randomised, parallel group, double blind, placebo controlled, phase 3 study. Computer generated allocation sequence was used. To maintain blinding, study drug packaging and tablets were identical

Number and characteristics of patients

Total number of patients: 568

Inclusion criteria: Men and non-pregnant, non-breast feeding women aged 18 years and over with type 2 diabetes who were drug naïve. Patients were considered drug naïve if they had never received medications for type 2 diabetes or had received such for <6 months since diagnosis. In addition, patients should not have received drug therapy for >3 consecutive days or 7 non-consecutive days during the 8 weeks prior to enrollment. Patients were required to have fasting c-peptide >0.33 nmol/l and Hba1c 7.2 to 10% at lead-in and 7.0-10% at randomisation.

Exclusion criteria: Type 1 diabetes, history of diabetic ketoacidosis or hyperosmolar non-ketonic coma, symptoms of poorly controlled diabetes, significant cardiovascular history within 6 months of visit. Patients with a history of haemoglobinopathies, unstable or rapidly progressing renal disease based on clinical judgement, autoimmune skin disorder, GI surgery that could alter drug absorption, a history of drug or alcohol abuse in the past year, any clinically significant abnormality that may compromise study participation were also excluded. Patients with serum creatinine >=1.4 mg/dl (women) or >=1.5 mg/dl. Those who

	received insulin therapy within 1 year of enrollment or previous treatment with any DPP-4 inhibitor were not included Pre-randomisation phase: There was a 4 week, single-blind lead in period before the 24 week double blind treatment period. Visit 4 (start of the double blind treatment period) was baseline (week 0) and patients were randomised at this visit.
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** all on oral hypoglycaemic drugs and/or insulin **Details of washout period:** 4 week run in (details not provided)
Lifestyle advice	Patients were given specific counselling on dietary and lifestyle modifications according to usual clinical routine during the lead-in period. This was reinforced during the treatment period to last study visit.
Follow-up	**Total follow-up (wks):** 28 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 24 **Frequency of monitoring appointments:** No details reported
Arms	**(1) Saxagliptin (5mg)** N: 284 Treatment duration (wks): 24 Washout period (d): 0 Treatment(s): Saxagliptin (Oral) – fixed-dose Set dose (mg/d):5 Frequency of dosing: once a day Details of dosing regimen: Rescue therapy with open label metformin was permitted during the treatment period for unacceptable fasting plasma glucose (FPG): if FPG>13.3 mmol/l at visits 6 or 7, if FPG >12.2 mmol/l at visit 8 or FPG>11.1 mmol/l at visits 9, 10 or 11. If a follow-up visit within 3-5 days confirmed FPG was elevated, the patient was started on metformin 500 mg once daily and the dose was titrated at the discretion of the investigator to a maximum of 2000 mg/day **(2) Placebo** N: 284 Treatment duration (wks): 24 Washout period (d): 0 Treatment(s): Placebo (Oral) – fixed-dose Frequency of dosing: once a day Details of dosing regimen: as saxagliptin group
Outcomes	**General** The efficacy analysis set included all randomised patients who had received at least one dose of study medication, had baseline data, and had data for at least one post-baseline efficacy endpoint, data on or after rescue medication were excluded. Primary and secondary efficacy analyses were conducted on the full analysis set using LOCF for patients who discontinued early or received rescue medication. Missing efficacy data were replaced by post-dose data, but before rescue medication. The primary safety analysis was conducted on data from randomised patients who received at least one dose of study medication and excluded data collected on or after the use of rescue medication. 22/284 (7.7%) patients in the saxagliptin group and 36/284 (12.7%) in placebo group discontinued the study Outcomes not extracted in this evidence table include postprandial blood glucose levels, fasting insulin, c-peptide, glucagon and measures of insulin resistance **Hypoglycaemic events** All hypoglycaemic events (no patients) (Reported hypoglycaemia was defined as signs and symptoms consistent with hypoglycaemia with or without a documented glucose measurement) minor hypoglycaemic events (No specific definition) symptomatic (confirmed) (Events with associated symptoms of hypoglycaemia and a documented plasma glucose <=2.8 mmol/l) moderate hypoglycaemia (No specific definition)
Baseline characteristics	

		Saxagliptin (5mg)			Placebo				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	284		51.2 (SD 10)	284		51.6 (SD 10.3)		
Sex (n male)	Dichotomous	284	160	(56.3%)	284	155	(54.6%)		
Duration of diabetes (yrs)	Continuous	284		0.8 (SD 1.4)	284		1.2 (SD 2.6)		

Blood glucose: Fasting plasma glucose (mmol/l) – 0wk	Continuous	284		9.1 (SD 2.1)	284		9.1 (SD 2.5)		
Body weight: BMI (kg/m2) – 0wk	Continuous	284		25.9 (SD 3.4)	284		25.9 (SD 3.7)		
Weight (kg) – 0wk	Continuous	284		69.2 (SD 11.4)	284		69.2 (SD 12.4)		
Waist circumference (cms) – 0wk	Continuous	284		89.9 (SD 0.6)	284		90.6 (SD 0.6)		
Lipids: Total cholesterol (mmol/l)	Mean change	284		5 (SD 0.06)	284		5 (SD 0.07)		
HDL cholesterol (mmol/l)	Mean change	284		1.2 (SD 0.02)	284		1.1 (SD 0.02)		
Triglycerides (mmol/l)	Mean change	284		1.9 (SD 0.08)	284		2.1 (SD 0.11)		
LDL cholesterol (mmol/l)	Mean change	284		3 (SD 0.05)	284		2.9 (SD 0.06)		
Full analysis set (FAS) or efficacy analysis pop Blood glucose: HbA1c (%) – 0wk	Continuous	284		8.1 (SD 0.8)	284		8.2 (SD 0.8)		

Results

		Saxagliptin (5mg)			Placebo				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Blood glucose: HbA1c (%) – 24wk	Mean change	284			284			MD=-0.500 (CI: -0.650, -0.350)	<0.0001
HbA1c < 7% or <=7% – 24wk	Dichotomous	284			284				<0.0001
Fasting plasma glucose (mmol/l) – 24wk	Mean change	284			284				<0.0001
Body weight: BMI (kg/m2) – 24wk	Mean change	284			284				NR
Weight (kg) – 24wk	Mean change	284			284				NR
Waist circumference (cms) – 24wk	Mean change	284			284				NR
Other medication: Taking rescue medication – 24wk	Dichotomous	284	14	(4.9%)	284	27	(9.5%)		
Safety population Hypoglycaemic events: All hypoglycaemic events (no patients) – 24wk	Dichotomous	284	5a	(1.8%)	284	2b	(0.7%)		
minor hypoglycaemic events – 24wkc	Dichotomous	284			284				
symptomatic (confirmed) – 24wk	Dichotomous	284	0	(0.0%)	284	0	(0.0%)		
moderate hypoglycaemia – 24wk	Dichotomous	284	c		284	1			
Adverse events: Any adverse event(s) – 24wk	Dichotomous	284	124	(43.7%)	284	102	(35.9%)		
Serious AE drug related – 24wk	Dichotomous	284	8	(2.8%)	284	4	(1.4%)		
Study drug-related adverse event – 24wk	Dichotomous	284	23	(8.1%)	284	11	(3.9%)		
Cough – 24wk	Dichotomous	284	7	(2.5%)	284	5	(1.8%)		

	Death – 24wk	Dichotomous	284	1	(0.4%)	284	0	(0.0%)		
	Dizziness – 24wk	Dichotomous	284	7	(2.5%)	284	7	(2.5%)		
	GI: diarrhoea – 24wk	Dichotomous	284	9	(3.2%)	284	4	(1.4%)		
	Headache – 24wk	Dichotomous	284	4	(1.4%)	284	7	(2.5%)		
	Infection (upper airway or other common) – 24wk	Dichotomous	284	16	(5.6%)	284	21	(7.4%)		
	Nasopharyngitis – 24wk	Dichotomous	284	9	(3.2%)	284	8	(2.8%)		
	Temperature/influenza – 24wk	Dichotomous	284	2	(0.7%)	284	6	(2.1%)		
	UTI – 24wk	Dichotomous	284	6	(2.1%)	284	11	(3.9%)		
	Study drug exposure – 24wkd	Continuous	284		156	284		147		
	Dropouts:									
	Dropout due to AEs – 24wk	Dichotomous	284	3	(1.1%)	284	3	(1.1%)		
	Full analysis set (FAS) or efficacy analysis pop									
	Blood glucose:									
	HbA1c (%) – 16wke	Mean change	277		-0.89 (SD 0.666)	274		-0.32 (SD 0.662)		
	HbA1c (%) – 24wkf	Mean change	277		-0.953 (SD 1.04)	274		-0.415 (SD 1.02)		
	HbA1c < 7% or <=7% – 24wk	Dichotomous	277	127g	(45.8%)	274	79h	(28.8%)		
	Fasting plasma glucose (mmol/l) – 24wki	Mean change	280		-0.9 (SD 3.51)	279		-0.17 (SD 3.84)		
	Body weight:									
	BMI (kg/m2) – 24wkj	Mean change	284		-0.12	284		-0.43		
	Weight (kg) – 24wkj	Mean change	284		-0.32	284		-1.14		
	Waist circumference (cms) – 24wk	Mean change	284		0.35k	284		-0.2j		

[a] approximated to nearest integer (percentages only presented in text)
[b] approximated to nearest integer (percentages only presented in text); approximated to nearest integer (percentages only presented in text); approximated to nearest integer (percentages only presented in text)
[c] unclear no of events per group
[d] days
[e] estimated from graph
[f] estimated from graph; SD calculated from SE
[g] assumed same denominator as Hba1c (%); approximated to nearest integer (percentages only presented in text)
[h] assumed same denominator as Hba1c (%)
[i] adjusted mean change, SE estimated from graph
[j] unclear denominator, no SE reported
[k] unclear denominator, no SE reported
nator

	Changes in baseline to week 24 were assesed using ANCOVA with treatment and country as fixed main effects and baseline as the covariate. The proportion of patients achieving Hba1c<7% at week 24 was analysed using Fisher's exact test. AE data were summarised descriptively.

Table 79: Pavo et al. (2003)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel

	Country: Russia and Hungary **Authors' conclusions:** The more pronounced improvement in indicators of insulin sensitivity by pioglitazone as compared with metformin monotherapy in patients recently diagnosed with type 2 diabetes who are Oam naïve may be of interest for further clinical evaluation **Source of funding:** Unclear **Comments:** Double-blind
Number and characteristics of patients	**Total number of patients:** 205 **Inclusion criteria:** Patients with recently diagnosed type 2 diabetes with Hba1c 7.5 to 11% and were at least 40 years old. **Exclusion criteria:** patients with a history of lactic acidosis, liver disease, congestive heart failure, impaired kidney or liver function, BMI <25 kg/m2 or >40 kg/m2, cancer or use of OAMs Pre-randomisation phase: There was a 3-5 week lead in period with placebo before randomisation. There was also an 8 week titration period before the maintenance period.
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** All treatment naive/ no OADs at screening **Details of washout period:** 4 week placebo run in period, all OAD naïve
Lifestyle advice	Patients also received diabetes education and individualised dietary and physical activity
Follow-up	**Total follow-up (wks):** 36 **Length of titration period (wks):** 8 **Length of maintenance period (wks):** 24 **Frequency of monitoring appointments:** 4 week placebo run in
Arms	**(1) Metformin** N: 100 Treatment duration (wks): 32 Washout period (d): 28 Comments: OAD naïve Treatment(s): Metformin (Oral) – flexible-dose (dose-adjusted) Mean dose (mg/d): 2292 Minimum dose (mg/d): 850 Maximum dose (mg/d): 2550 Details of dosing regimen: 850 mg/day titrated to max 2550 mg/day (forced uptitration at visit 2 and uptitration if FBG>=7 mmol/l at visit 3) **(2) Pioglitazone** N: 105 Treatment duration (wks): 32 Washout period (d): 28 Comments: OAD naïve Treatment(s): Pioglitazone (Oral) – flexible-dose (dose-adjusted) Mean dose (mg/d): 41.5 Minimum dose (mg/d): 30 Maximum dose (mg/d): 45 Details of dosing regimen: 30 mg/day titrated to max 45 mg/day
Outcomes	
Baseline characteristics	

		Metformin			Pioglitazone				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	100		55.8 (SD 8.4)	105		54.2 (SD 9.1)		
Sex (n male)	Dichotomous	100	56	(56.0%)	105	46a	(43.8%)		
Duration of diabetes (months)	Continuous	100		6.3 (SD 3.9)	105		5.6 (SD 3.8)		
Blood glucose: HbA1c (%) – 0wk	Continuous	100		8.6	105		8.6		
Body weight: BMI (kg/m2)	Continuous	100		31.1 (SD 4.4)	105		31.3 (SD 4.2)		
Weight (kg) – 0wk	Continuous	100		88.9 (SD 15.9)	105		86.6 (SD 15.6)		

[a] approximated to nearest integer (percentages only presented in text)

Results

		Metformin			Pioglitazone			Δ	p
		N	k	mean	N	k	mean		
Blood glucose: HbA1c (%) – 24wka	Continuous	100		7.3 (SD 0.7)	105		7.55 (SD 1.02)		
HbA1c (%) – 32wka	Continuous	100		7.45 (SD 1)	105		7.52 (SD 1.02)		
HbA1c (%) – 32wkb	Mean change	100		-1.5	105		-1.3		
Fasting plasma glucose (mmol/l) – 16wka	Continuous	100		9.25 (SD 2)	105		9.4 (SD 2.56)		
Fasting plasma glucose (mmol/l) – 24wka	Continuous	100		9.25 (SD 2)	105		9.1 (SD 2.05)		
Fasting plasma glucose (mmol/l) – 32wkb	Mean change	100		-2.8	105		-3		
Fasting plasma glucose (mmol/l) – 32wka	Continuous	100		9.5 (SD 2)	105		8.95 (SD 2.05)		
Body weight: Weight (kg) – 32wkc	Mean change	100		-2.4 (SD 4)	105		0.7 (SD 4.1)		
Adverse events: Any adverse event(s) – 32wkd	Dichotomous	100	51	(51.0%)	105	49	(46.7%)		
Edema peripheral – 32wk	Dichotomous	100	4	(4.0%)	105	13	(12.4%)		
liver enzymes: abnormal ALT – 32wk	Continuous	100		1.2 (SD 16)	105		-6.8 (SD 16.4)		
Liver enzymes: AST (U/l) – 32wk	Continuous	100		0.7 (SD 9)	105		-2.2 (SD 9.22)		
Dropouts: Total dropouts – 32wk	Dichotomous	100	9	(9.0%)	105	5	(4.8%)		
Dropout due to AEs – 32wk	Dichotomous	100	0	(0.0%)	105	2	(1.9%)		
Blood pressure: Systolic blood pressure (mmHg) – 32wk	Continuous	100		-6.7 (SD 12)	105		-6.2 (SD 12.3)		
Diastolic blood pressure (mmHg) – 32wk	Continuous	100		-3.9 (SD 6)	105		-3.9 (SD 6.15)		

[a] estimated from graph
[b] SD not reported
[c] SD calculated from reported SE
[d] approximated to nearest integer (percentages only presented in text)

Table 80: Pi-Sunyer et al. (2007)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** conducted at 98 centres in the US (88), India (4) and Slovakia (6) **Authors' conclusions:** Vildagliptin is effective and well-tolerated in drug-naïve patienrs with type 2 diabetes and 100 mg vildagliptin provides similar clinical benefit whether given as single or in divided doses **Source of funding:** Funded by Novartis Pharmaceuticals Corporation **Comments:** 24-week, double-blind, randomised trial but details of randomisation, blinding or allocation concelament not reported
Number and characteristics	**Total number of patients:** 354 **Inclusion criteria:** patients diagnosed with type 2 diabetes with a Hba1c between 7.5% and 10% at the

of patients	screening visit while receiving no pharmacological treatment. Patients who had taken no oral antidiabetic drug (OAD) for at least 12 weeks prior to screening and no OAD for over 3 consecutive months at any time in the past were considered to be representative of a drug naïve population. Male and female (non-fertile or of child bearing potential using a medically approved birth control method), aged 18-80 years inclusive with a BMI 22-45 kg/m2 and with FPG <15 mmol/l were eligible to participate **Exclusion criteria:** history of type 1 or secondary forms of diabetes, acute metabolic diabetic complications, myocardial infarction, unstable angina, or coronary artery bypass surgery within the previous 6 months. Congestive heart failure (NYHA class III or IV), and liver disease also precluded participation. Patients with any of the following laboratory abnormalities were also excluded: ALT or AST greater than three times the upper limit of normal (ULN), direct bilirubin >1.3 times the ULN, serum creatinine levels >220 µmol/l, clinically significant abnormal thyroid stimulating hormone or fasting triglycerides (TG) >7.9 mmol/l Pre-randomisation phase: Each patient attended one screening visit (week -2) during which inclusion/exclusion criteria were assessed. Eligible patients were randomised as visit 2 (baseline) week 0
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** some on oral hypoglycaemic drugs and/or insulin **Details of washout period:** Drug naïve defined as those not taking any OADs at least 12 weeks prior to screening and no history of 3 consecutive months of OADs
Lifestyle advice	No details of lifestyle advice reported
Follow-up	**Total follow-up (wks):** 26 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 24 **Frequency of monitoring appointments:** Efficacy and tolerability were assessed during 5 additional visits at weeks 4, 8, 12, 16 and 24 of treatment
Arms	**(1) Vildagliptin (50mg b.i.d)** N: 83 Treatment duration (wks): 24 Washout period (d): 14 Comments: 2 week screening period (no details provided) Treatment(s): Vildagliptin (Oral) – fixed-dose Set dose (mg/d):100 Frequency of dosing: twice a day Details of dosing regimen: Vildagliptin 50mg bid **(2) Vildagliptin (100 mg qd)** N: 91 Treatment duration (wks): 24 Washout period (d): 14 Comments: 2 week screening period (no details provided) Treatment(s): Vildagliptin (Oral) – fixed-dose Set dose (mg/d):100 Frequency of dosing: once a day Details of dosing regimen: vildagliptin 100 mg qd **(3) Placebo** N: 92 Treatment duration (wks): 24 Washout period (d): 14 Comments: 2 week screening period (no details provided) Treatment(s): Placebo (Oral) Details of dosing regimen: No details reported but assumed taken orally to maintain blinding **(4) Vildagliptin 50 mg qd** N: 88 Treatment duration (wks): 24 Washout period (d): 14 Comments: 2 week screening period (no details provided) Treatment(s): Vildagliptin (Oral) – fixed-dose Set dose (mg/d):50 Frequency of dosing: once a day Details of dosing regimen: vildagliptin 50 mg qd
Outcomes	**General** NB: 50mg vildagliptin qd is only recommended in patients taking sulfonylurea and those with end stage renal disease). Outcomes not reported in this evidence table include lipid parameters (data not shown in full paper). ITT population defined as those who received at least one dose of study medication and had a baseline and at least one post baseline asssesment using last observation carried forward (LOCF) for patients who

discontinued early

23.9% discontinued in the vildagliptin 50 mg qd group, 19.3% in the vildagliptin 50 mg bid, 16.5% in vildagliptin 100 mg qd group and 31.5% in placebo group. Of these 3 (3.6%), 5 (5.5%) and 14 (15.2%) were due to unsatisfactory therapeutic effect in the 50 mg b.i.d, 100 mg qd and placebo groups respectively

Blood glucose

HbA1c (%) (The primary efficacy variable was the change from baseline in hba1c at study endpoint in the ITT population)

Hypoglycaemic events

Major/severe hypoglycaemic event (Severe hypoglycaemia was defined as any episode requiring the assistance of another party)

symptomatic (confirmed) (Confirmed hypoglycaemia was defined as symptoms suggestive of low blood glucose confirmed by self-monitored blood glucose (SMBG) measureemtn <3.1 mmol/l plasma glucose equivalent.)

asymptomatic (confirmed) (Instances of SMBG <3.1 without accompanying symptoms were recorded as asymptomatic low blood glucose.)

Baseline characteristics

		Vildagliptin (50mg b.i.d)			Vildagliptin (100 mg qd)				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	83		50.2 (SD 12.7)	91		52 (SD 11.7)		
Sex (n male)	Dichotomous	83	47	(56.6%)	91	49	(53.8%)		
Duration of diabetes (yrs)	Continuous	83		2.4 (SD 3.2)	91		2.1 (SD 2.9)		
Ethnicity-White	Dichotomous	83	44	(53.0%)	91	53	(58.2%)		
Ethnicity-Black	Dichotomous	83	5	(6.0%)	91	11	(12.1%)		
Ethnicity-Asian (Indian subcontinent)	Dichotomous	83	15	(18.1%)	91	15	(16.5%)		
Ethnicity-Asian (non-Indian subcontinent)	Dichotomous	83	1	(1.2%)	91	1	(1.1%)		
Blood glucose: Hba1c <=8%	Dichotomous	83	38	(45.8%)	91	33	(36.3%)		
Hba1c >8%	Dichotomous	83	45	(54.2%)	91	58	(63.7%)		
Fasting plasma glucose (mmol/l) – 0wka	Continuous	79		10.9 (SD 3.56)	89		10 (SD 2.83)		
Body weight: BMI (kg/m2)	Continuous	83		32.2 (SD 6)	91		31.9 (SD 5)		
Weight (kg) – 0wka	Continuous	79		90.4 (SD 18.7)	89		90.5 (SD 19.8)		
Height (cm)	Continuous	83		167 (SD 9.2)	91		168 (SD 10.5)		
ITT Blood glucose: HbA1c (%) – 0wka	Continuous	79		8.4 (SD 0.9)	89		8.3 (SD 0.8)		

[a] SD calculated from reported SE

		Vildagliptin (50mg b.i.d)			Placebo				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	83		50.2 (SD 12.7)	92		52 (SD 12)		
Sex (n male)	Dichotomous	83	47	(56.6%)	92	50	(54.3%)		
Duration of diabetes (yrs)	Continuous	83		2.4 (SD 3.2)	92		2.5 (SD 3.7)		
Ethnicity-White	Dichotomous	83	44	(53.0%)	92	47	(51.1%)		
Ethnicity-Black	Dichotomous	83	5	(6.0%)	92	12	(13.0%)		
Ethnicity-Asian (Indian subcontinent)	Dichotomous	83	15	(18.1%)	92	15	(16.3%)		
Ethnicity-Asian (non-Indian subcontinent)	Dichotomous	83	1	(1.2%)	92	1	(1.1%)		
Blood glucose: Hba1c <=8%	Dichotomous	83	38	(45.8%)	92	38	(41.3%)		

Hba1c >8%	Dichotomous	83	45	(54.2%)	92	54	(58.7%)		
Fasting plasma glucose (mmol/l) – 0wka	Continuous	79		10.9 (SD 3.56)	88		10.7 (SD 2.81)		
Body weight:									
BMI (kg/m2)	Continuous	83		32.2 (SD 6)	92		32.7 (SD 6.4)		
Weight (kg) – 0wka	Continuous	79		90.4 (SD 18.7)	88		92.6 (SD 23.5)		
Height (cm)	Continuous	83		167 (SD 9.2)	92		168.1 (SD 10.8)		
ITT									
Blood glucose:									
HbA1c (%) – 0wka	Continuous	79		8.4 (SD 0.9)	88		8.5 (SD 0.8)		

[a] SD calculated from reported SE

		Vildagliptin (50mg b.i.d)			Vildagliptin 50 mg qd				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Demographics:									
Age (years)	Continuous	83		50.2 (SD 12.7)	88		50.6 (SD 10.4)		
Sex (n male)	Dichotomous	83	47	(56.6%)	88	49	(55.7%)		
Duration of diabetes (yrs)	Continuous	83		2.4 (SD 3.2)	88		1.8 (SD 2.7)		
Ethnicity-White	Dichotomous	83	44	(53.0%)	88	48	(54.5%)		
Ethnicity-Black	Dichotomous	83	5	(6.0%)	88	7	(8.0%)		
Ethnicity-Asian (Indian subcontinent)	Dichotomous	83	15	(18.1%)	88	14	(15.9%)		
Ethnicity-Asian (non-Indian subcontinent)	Dichotomous	83	1	(1.2%)	88	3	(3.4%)		
Blood glucose:									
Hba1c <=8%	Dichotomous	83	38	(45.8%)	88	35	(39.8%)		
Hba1c >8%	Dichotomous	83	45	(54.2%)	88	53	(60.2%)		
Fasting plasma glucose (mmol/l) – 0wka	Continuous	79		10.9 (SD 3.56)	84		10.4 (SD 2.75)		
Body weight:									
BMI (kg/m2)	Continuous	83		32.2 (SD 6)	88		31.9 (SD 5.4)		
Weight (kg) – 0wka	Continuous	79		90.4 (SD 18.7)	84		90.4 (SD 22)		
Height (cm)	Continuous	83		167 (SD 9.2)	88		167.5 (SD 11.9)		
ITT									
Blood glucose:									
HbA1c (%) – 0wka	Continuous	79		8.4 (SD 0.9)	84		8.3 (SD 0.917)		

[a] SD calculated from reported SE

		Vildagliptin (100 mg qd)			Placebo				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Demographics:									
Age (years)	Continuous	91		52 (SD 11.7)	92		52 (SD 12)		
Sex (n male)	Dichotomous	91	49	(53.8%)	92	50	(54.3%)		
Duration of diabetes (yrs)	Continuous	91		2.1 (SD 2.9)	92		2.5 (SD 3.7)		
Ethnicity-White	Dichotomous	91	53	(58.2%)	92	47	(51.1%)		
Ethnicity-Black	Dichotomous	91	11	(12.1%)	92	12	(13.0%)		
Ethnicity-Asian (Indian subcontinent)	Dichotomous	91	15	(16.5%)	92	15	(16.3%)		
Ethnicity-Asian (non-Indian subcontinent)	Dichotomous	91	1	(1.1%)	92	1	(1.1%)		
Blood glucose:									
Hba1c <=8%	Dichotomous	91	33	(36.3%)	92	38	(41.3%)		

Hba1c >8%	Dichotomous	91	58	(63.7%)	92	54	(58.7%)		
Fasting plasma glucose (mmol/l) – 0wka	Continuous	89		10 (SD 2.83)	88		10.7 (SD 2.81)		
Body weight:									
BMI (kg/m2)	Continuous	91		31.9 (SD 5)	92		32.7 (SD 6.4)		
Weight (kg) – 0wka	Continuous	89		90.5 (SD 19.8)	88		92.6 (SD 23.5)		
Height (cm)	Continuous	91		168 (SD 10.5)	92		168.1 (SD 10.8)		
ITT									
Blood glucose:									
HbA1c (%) – 0wka	Continuous	89		8.3 (SD 0.8)	88		8.5 (SD 0.8)		

[a] SD calculated from reported SE

		Vildagliptin (100 mg qd)			Vildagliptin 50 mg qd				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Demographics:									
Age (years)	Continuous	91		52 (SD 11.7)	88		50.6 (SD 10.4)		
Sex (n male)	Dichotomous	91	49	(53.8%)	88	49	(55.7%)		
Duration of diabetes (yrs)	Continuous	91		2.1 (SD 2.9)	88		1.8 (SD 2.7)		
Ethnicity-White	Dichotomous	91	53	(58.2%)	88	48	(54.5%)		
Ethnicity-Black	Dichotomous	91	11	(12.1%)	88	7	(8.0%)		
Ethnicity-Asian (Indian subcontinent)	Dichotomous	91	15	(16.5%)	88	14	(15.9%)		
Ethnicity-Asian (non-Indian subcontinent)	Dichotomous	91	1	(1.1%)	88	3	(3.4%)		
Blood glucose:									
Hba1c <=8%	Dichotomous	91	33	(36.3%)	88	35	(39.8%)		
Hba1c >8%	Dichotomous	91	58	(63.7%)	88	53	(60.2%)		
Fasting plasma glucose (mmol/l) – 0wka	Continuous	89		10 (SD 2.83)	84		10.4 (SD 2.75)		
Body weight:									
BMI (kg/m2)	Continuous	91		31.9 (SD 5)	88		31.9 (SD 5.4)		
Weight (kg) – 0wka	Continuous	89		90.5 (SD 19.8)	84		90.4 (SD 22)		
Height (cm)	Continuous	91		168 (SD 10.5)	88		167.5 (SD 11.9)		
ITT									
Blood glucose:									
HbA1c (%) – 0wka	Continuous	89		8.3 (SD 0.8)	84		8.3 (SD 0.917)		

[a] SD calculated from reported SE

		Placebo			Vildagliptin 50 mg qd				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Demographics:									
Age (years)	Continuous	92		52 (SD 12)	88		50.6 (SD 10.4)		
Sex (n male)	Dichotomous	92	50	(54.3%)	88	49	(55.7%)		
Duration of diabetes (yrs)	Continuous	92		2.5 (SD 3.7)	88		1.8 (SD 2.7)		
Ethnicity-White	Dichotomous	92	47	(51.1%)	88	48	(54.5%)		
Ethnicity-Black	Dichotomous	92	12	(13.0%)	88	7	(8.0%)		
Ethnicity-Asian (Indian subcontinent)	Dichotomous	92	15	(16.3%)	88	14	(15.9%)		
Ethnicity-Asian (non-Indian subcontinent)	Dichotomous	92	1	(1.1%)	88	3	(3.4%)		
Blood glucose:									
Hba1c <=8%	Dichotomous	92	38	(41.3%)	88	35	(39.8%)		

Hba1c >8%	Dichotomous	92	54	(58.7%)	88	53	(60.2%)		
Fasting plasma glucose (mmol/l) – 0wka	Continuous	88		10.7 (SD 2.81)	84		10.4 (SD 2.75)		
Body weight:									
BMI (kg/m2)	Continuous	92		32.7 (SD 6.4)	88		31.9 (SD 5.4)		
Weight (kg) – 0wka	Continuous	88		92.6 (SD 23.5)	84		90.4 (SD 22)		
Height (cm)	Continuous	92		168.1 (SD 10.8)	88		167.5 (SD 11.9)		
ITT									
Blood glucose:									
HbA1c (%) – 0wka	Continuous	88		8.5 (SD 0.8)	84		8.3 (SD 0.917)		

[a] SD calculated from reported SE

Results

		Vildagliptin (50mg b.i.d)			Vildagliptin (100 mg qd)				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Blood glucose:									
HbA1c < 7% or <=7% – 24wka	Dichotomous	79	24	(30.4%)	89	35	(39.3%)		
Hypoglycaemic events:									
symptomatic (confirmed) – 24wk	Dichotomous	83	0	(0.0%)	91	0	(0.0%)		
asymptomatic (confirmed) – 24wk	Dichotomous	83	0	(0.0%)	91	0	(0.0%)		
Adverse events:									
Any adverse event(s) – 24wk	Dichotomous	83	48	(57.8%)	91	54	(59.3%)		
Any serious adverse event(s) – 24wk	Dichotomous	83	3	(3.6%)	91	7	(7.7%)		
Headache – 24wk	Dichotomous	83	4	(4.8%)	91	5	(5.5%)		
Hypertension – 24wk	Dichotomous	83	6	(7.2%)	91	1	(1.1%)		
Infection (upper airway or other common) – 24wk	Dichotomous	83	8	(9.6%)	91	10	(11.0%)		
Nasopharyngitis – 24wk	Dichotomous	83	4	(4.8%)	91	12	(13.2%)		
Pain (extremity) – 24wk	Dichotomous	83	2	(2.4%)	91	5	(5.5%)		
Dropouts:									
Total dropouts – 24wk	Dichotomous	83	16	(19.3%)	91	15	(16.5%)		
Dropout due to AEs – 24wk	Dichotomous	83	0	(0.0%)	91	1	(1.1%)		
Drop out due to unsatisfactory effect – 24wk	Dichotomous	83	3	(3.6%)	91	5	(5.5%)		
ITT									
Blood glucose:									
HbA1c (%) – 16wkb	Continuous	79		7.4 (SD 0.889)	89		7.35 (SD 0.943)		
HbA1c (%) – 24wkc	Mean change	79		-0.7 (SD 0.911)	89		-0.8 (SD 0.954)		
HbA1c (%) – 24wkd	Continuous	79		7.7 (SD 1.78)	89		7.5 (SD 0.943)		
Fasting plasma glucose (mmol/l) – 24wkd	Continuous	79		9.6 (SD 2.67)	89		9 (SD 2.83)		
Fasting plasma glucose (mmol/l) – 24wkc	Mean change	79		-1.2 (SD 2.67)	89		-1.1 (SD 2.83)		
Body weight:									
Weight (kg) – 24wkd	Continuous	79		90.5 (SD 18.7)	89		90.2 (SD 20.8)		
Weight (kg) – 24wkc	Mean change	79		0 (SD 3.56)	89		-0.4 (SD 2.83)		
Baseline Hba1c <=8%									
Blood glucose:									
HbA1c < 7% or <=7% – 24wk	Dichotomous	38	e		33	19a			

[a] approximated to nearest integer (percentages only presented in text)
[b] estimated from graph
[c] adjusted mean change; SD calculated from reported SE
[d] SD calculated from reported SE
[e] not reported

		Vildagliptin (50mg b.i.d)			Placebo				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 24wk	Mean change	79			88			MD=-0.700 (CI: -1.092, -0.308)	<0.001
HbA1c < 7% or <=7% – 24wk	Dichotomous	79	24a	(30.4%)	88	12	(13.6%)		<0.01b
Fasting plasma glucose (mmol/l) – 24wk	Mean change	79			88			MD=-1.300 (CI: -2.084, -0.516)	0.001
Body weight: Weight (kg) – 24wk	Mean change	79			88			MD=1.400 (CI: 0.420, 2.380)	0.005
Hypoglycaemic events: symptomatic (confirmed) – 24wk	Dichotomous	83	0	(0.0%)	92	0	(0.0%)		
asymptomatic (confirmed) – 24wk	Dichotomous	83	0	(0.0%)	92	0	(0.0%)		
Adverse events: Any adverse event(s) – 24wk	Dichotomous	83	48	(57.8%)	92	53	(57.6%)		
Any serious adverse event(s) – 24wk	Dichotomous	83	3	(3.6%)	92	1	(1.1%)		
Headache – 24wk	Dichotomous	83	4	(4.8%)	92	2	(2.2%)		
Hypertension – 24wk	Dichotomous	83	6	(7.2%)	92	2	(2.2%)		
Infection (upper airway or other common) – 24wk	Dichotomous	83	8	(9.6%)	92	9	(9.8%)		
Nasopharyngitis – 24wk	Dichotomous	83	4	(4.8%)	92	3	(3.3%)		
Pain (extremity) – 24wk	Dichotomous	83	2	(2.4%)	92	8	(8.7%)		
Dropouts: Total dropouts – 24wk	Dichotomous	83	16	(19.3%)	92	29	(31.5%)		
Dropout due to AEs – 24wk	Dichotomous	83	0	(0.0%)	92	3	(3.3%)		
Drop out due to unsatisfactory effect – 24wk	Dichotomous	83	3	(3.6%)	92	14	(15.2%)		
ITT Blood glucose: HbA1c (%) – 16wkc	Continuous	79		7.4 (SD 0.889)	88		8.08 (SD 1.13)		
HbA1c (%) – 24wkd	Mean change	79		-0.7 (SD 0.911)	88		0 (SD 0.959)		
HbA1c (%) – 24wke	Continuous	79		7.7 (SD 1.78)	88		8.4 (SD 1.88)		
Fasting plasma glucose (mmol/l) – 24wkd	Mean change	79		-1.2 (SD 2.67)	88		0.1 (SD 2.81)		
Fasting plasma glucose (mmol/l) – 24wke	Continuous	79		9.6 (SD 2.67)	88		10.7 (SD 3.75)		
Body weight: Weight (kg) – 24wke	Continuous	79		90.5 (SD 18.7)	88		91.1 (SD 22.5)		
Weight (kg) – 24wkd	Mean change	79		0 (SD 3.56)	88		-1.4 (SD 3.75)		
Baseline Hba1c <=8% Blood glucose: HbA1c (%) – 24wk	Mean change	0			0			MD=-0.700	
HbA1c < 7% or <=7% – 24wk	Dichotomous	38	f		38	7a			

[a] approximated to nearest integer (percentages only presented in text)
[b] No further details reported

[c] estimated from graph
[d] adjusted mean change; SD calculated from reported SE
[e] SD calculated from reported SE
[f] not reported

		Vildagliptin (50mg b.i.d)			Vildagliptin 50 mg qd			Δ	p
		N	k	mean	N	k	mean		
Blood glucose: HbA1c < 7% or <=7% – 24wk	Dichotomous	79	24a		88	b			
Hypoglycaemic events: symptomatic (confirmed) – 24wk	Dichotomous	83	0	(0.0%)	86	0	(0.0%)		
asymptomatic (confirmed) – 24wk	Dichotomous	83	0	(0.0%)	86	0	(0.0%)		
Adverse events: Any adverse event(s) – 24wk	Dichotomous	83	48	(57.8%)	86	48	(55.8%)		
Any serious adverse event(s) – 24wk	Dichotomous	83	3	(3.6%)	88	0	(0.0%)		
Headache – 24wk	Dichotomous	83	4	(4.8%)	86	8	(9.3%)		
Hypertension – 24wk	Dichotomous	83	6	(7.2%)	86	1	(1.2%)		
Infection (upper airway or other common) – 24wk	Dichotomous	83	8	(9.6%)	86	5	(5.8%)		
Nasopharyngitis – 24wk	Dichotomous	83	4	(4.8%)	86	3	(3.5%)		
Pain (extremity) – 24wk	Dichotomous	83	2	(2.4%)	86	4	(4.7%)		
Dropouts: Total dropouts – 24wk	Dichotomous	83	16	(19.3%)	88	21	(23.9%)		
Dropout due to AEs – 24wk	Dichotomous	83	0	(0.0%)	88	1	(1.1%)		
Drop out due to unsatisfactory effect – 24wk	Dichotomous	83	3	(3.6%)	88	9	(10.2%)		
ITT Blood glucose: HbA1c (%) – 16wkc	Continuous	79		7.4 (SD 0.889)	84		7.6 (SD 1.1)		
HbA1c (%) – 24wkd	Mean change	79		-0.7 (SD 0.911)	88		-0.5 (SD 0.938)		
HbA1c (%) – 24wke	Continuous	79		7.7 (SD 1.78)	84		7.9 (SD 1.83)		
Fasting plasma glucose (mmol/l) – 24wke	Continuous	79		9.6 (SD 2.67)	84		9.9 (SD 3.67)		
Fasting plasma glucose (mmol/l) – 24wkd	Mean change	79		-1.2 (SD 2.67)	88		-0.5 (SD 2.81)		
Body weight: Weight (kg) – 24wke	Continuous	79		90.5 (SD 18.7)	84		90.1 (SD 22)		
Weight (kg) – 24wkd	Mean change	79		0 (SD 3.56)	84		-0.4 (SD 3.75)		
Baseline Hba1c <=8% Blood glucose: HbA1c < 7% or <=7% – 24wkb	Dichotomous	38			35				

[a] approximated to nearest integer (percentages only presented in text)
[b] not reported
[c] estimated from graph
[d] adjusted mean change; SD calculated from reported SE
[e] SD calculated from reported SE

		Vildagliptin (100 mg qd)			Placebo			Δ	p
		N	k	mean	N	k	mean		
Blood glucose: HbA1c (%) – 24wk	Mean change	89			88			MD=-0.900 (CI: -1.292, -0.508)	<0.001
HbA1c < 7% or <=7% – 24wk	Dichotomous	89	35a	(39.3%)	88	12	(13.6%)		<0.001b

Fasting plasma glucose (mmol/l) – 24wk	Mean change	89			88			MD=-1.300 (CI: -2.084, -0.516)	0.001
Body weight: Weight (kg) – 24wk	Mean change	89			88			MD=1.000 (CI: 0.020, 1.980)	0.033
Hypoglycaemic events: symptomatic (confirmed) – 24wk	Dichotomous	91	0	(0.0%)	92	0	(0.0%)		
asymptomatic (confirmed) – 24wk	Dichotomous	91	0	(0.0%)	92	0	(0.0%)		
Adverse events: GI: nausea – 24wkc	Dichotomous	91	1	(1.1%)	92	0	(0.0%)		
Any adverse event(s) – 24wk	Dichotomous	91	54	(59.3%)	92	53	(57.6%)		
Any serious adverse event(s) – 24wk	Dichotomous	91	7	(7.7%)	92	1	(1.1%)		
Headache – 24wk	Dichotomous	91	5	(5.5%)	92	2	(2.2%)		
Hypertension – 24wk	Dichotomous	91	1	(1.1%)	92	2	(2.2%)		
Infection (upper airway or other common) – 24wk	Dichotomous	91	10	(11.0%)	92	9	(9.8%)		
Nasopharyngitis – 24wk	Dichotomous	91	12	(13.2%)	92	3	(3.3%)		
Pain (extremity) – 24wk	Dichotomous	91	5	(5.5%)	92	8	(8.7%)		
Dropouts: Total dropouts – 24wk	Dichotomous	91	15	(16.5%)	92	29	(31.5%)		
Dropout due to AEs – 24wk	Dichotomous	91	1	(1.1%)	92	3	(3.3%)		
Drop out due to unsatisfactory effect – 24wk	Dichotomous	91	5	(5.5%)	92	14	(15.2%)		
ITT Blood glucose: HbA1c (%) – 16wkd	Continuous	89		7.35 (SD 0.943)	88		8.08 (SD 1.13)		
HbA1c (%) – 24wke	Mean change	89		-0.8 (SD 0.954)	88		0 (SD 0.959)		
HbA1c (%) – 24wkf	Continuous	89		7.5 (SD 0.943)	88		8.4 (SD 1.88)		
Fasting plasma glucose (mmol/l) – 24wke	Mean change	89		-1.1 (SD 2.83)	88		0.1 (SD 2.81)		
Fasting plasma glucose (mmol/l) – 24wkf	Continuous	89		9 (SD 2.83)	88		10.7 (SD 3.75)		
Body weight: Weight (kg) – 24wkf	Continuous	89		90.2 (SD 20.8)	88		91.1 (SD 22.5)		
Weight (kg) – 24wke	Mean change	89		-0.4 (SD 2.83)	88		-1.4 (SD 3.75)		
Baseline Hba1c <=8% Blood glucose: HbA1c (%) – 24wk	Mean change	89			88			MD=-0.900	
HbA1c < 7% or <=7% – 24wka	Dichotomous	33	19	(57.6%)	38	7	(18.4%)		

[a] approximated to nearest integer (percentages only presented in text)
[b] No further details reported
[c] Estimated from reported percentages
[d] estimated from graph
[e] adjusted mean change; SD calculated from reported SE
[f] SD calculated from reported SE

	Vildagliptin (100 mg qd)	Vildagliptin 50 mg qd	Δ	p

		N	k	mean	N	k	mean		
Blood glucose: HbA1c < 7% or <=7% – 24wk	Dichotomous	89	35a		88	b			
Hypoglycaemic events: symptomatic (confirmed) – 24wk	Dichotomous	91	0	(0.0%)	86	0	(0.0%)		
asymptomatic (confirmed) – 24wk	Dichotomous	91	0	(0.0%)	86	0	(0.0%)		
Adverse events: Any adverse event(s) – 24wk	Dichotomous	91	54	(59.3%)	86	48	(55.8%)		
Any serious adverse event(s) – 24wk	Dichotomous	91	7	(7.7%)	88	0	(0.0%)		
Headache – 24wk	Dichotomous	91	5	(5.5%)	86	8	(9.3%)		
Hypertension – 24wk	Dichotomous	91	1	(1.1%)	86	1	(1.2%)		
Infection (upper airway or other common) – 24wk	Dichotomous	91	10	(11.0%)	86	5	(5.8%)		
Nasopharyngitis – 24wk	Dichotomous	91	12	(13.2%)	86	3	(3.5%)		
Pain (extremity) – 24wk	Dichotomous	91	5	(5.5%)	86	4	(4.7%)		
Dropouts: Total dropouts – 24wk	Dichotomous	91	15	(16.5%)	88	21	(23.9%)		
Dropout due to AEs – 24wk	Dichotomous	91	1	(1.1%)	88	1	(1.1%)		
Drop out due to unsatisfactory effect – 24wk	Dichotomous	91	5	(5.5%)	88	9	(10.2%)		
ITT									
Blood glucose: HbA1c (%) – 16wkc	Continuous	89		7.35 (SD 0.943)	84		7.6 (SD 1.1)		
HbA1c (%) – 24wkd	Mean change	89		-0.8 (SD 0.954)	88		-0.5 (SD 0.938)		
HbA1c (%) – 24wke	Continuous	89		7.5 (SD 0.943)	84		7.9 (SD 1.83)		
Fasting plasma glucose (mmol/l) – 24wke	Continuous	89		9 (SD 2.83)	84		9.9 (SD 3.67)		
Fasting plasma glucose (mmol/l) – 24wkd	Mean change	89		-1.1 (SD 2.83)	88		-0.5 (SD 2.81)		
Body weight: Weight (kg) – 24wke	Continuous	89		90.2 (SD 20.8)	84		90.1 (SD 22)		
Weight (kg) – 24wkd	Mean change	89		-0.4 (SD 2.83)	84		-0.4 (SD 3.75)		
Baseline Hba1c <=8%									
Blood glucose: HbA1c < 7% or <=7% – 24wk	Dichotomous	33	19a		35	b			

[a] approximated to nearest integer (percentages only presented in text)
[b] not reported
[c] estimated from graph
[d] adjusted mean change; SD calculated from reported SE
[e] SD calculated from reported SE

		Placebo			Vildagliptin 50 mg qd			Δ	p
		N	k	mean	N	k	mean		
Blood glucose: HbA1c < 7% or <=7% – 24wk	Dichotomous	88	12		88	a			
Hypoglycaemic events: symptomatic (confirmed) – 24wk	Dichotomous	92	0	(0.0%)	86	0	(0.0%)		
asymptomatic (confirmed) – 24wk	Dichotomous	92	0	(0.0%)	86	0	(0.0%)		
Adverse events: Any adverse event(s) – 24wk	Dichotomous	92	53	(57.6%)	86	48	(55.8%)		
Any serious adverse event(s) – 24wk	Dichotomous	92	1	(1.1%)	88	0	(0.0%)		

	Headache – 24wk	Dichotomous	92	2	(2.2%)	86	8	(9.3%)		
	Hypertension – 24wk	Dichotomous	92	2	(2.2%)	86	1	(1.2%)		
	Infection (upper airway or other common) – 24wk	Dichotomous	92	9	(9.8%)	86	5	(5.8%)		
	Nasopharyngitis – 24wk	Dichotomous	92	3	(3.3%)	86	3	(3.5%)		
	Pain (extremity) – 24wk	Dichotomous	92	8	(8.7%)	86	4	(4.7%)		
	Dropouts:									
	Total dropouts – 24wk	Dichotomous	92	29	(31.5%)	88	21	(23.9%)		
	Dropout due to AEs – 24wk	Dichotomous	92	3	(3.3%)	88	1	(1.1%)		
	Drop out due to unsatisfactory effect – 24wk	Dichotomous	92	14	(15.2%)	88	9	(10.2%)		
	ITT									
	Blood glucose:									
	HbA1c (%) – 16wkb	Continuous	88		8.08 (SD 1.13)	84		7.6 (SD 1.1)		
	HbA1c (%) – 24wkc	Mean change	88		0 (SD 0.959)	88		-0.5 (SD 0.938)		
	HbA1c (%) – 24wkd	Continuous	88		8.4 (SD 1.88)	84		7.9 (SD 1.83)		
	Fasting plasma glucose (mmol/l) – 24wkc	Mean change	88		0.1 (SD 2.81)	88		-0.5 (SD 2.81)		
	Fasting plasma glucose (mmol/l) – 24wkd	Continuous	88		10.7 (SD 3.75)	84		9.9 (SD 3.67)		
	Body weight:									
	Weight (kg) – 24wkc	Mean change	88		-1.4 (SD 3.75)	84		-0.4 (SD 3.75)		
	Weight (kg) – 24wkd	Continuous	88		91.1 (SD 22.5)	84		90.1 (SD 22)		
	Baseline Hba1c <=8%									
	Blood glucose:									
	HbA1c < 7% or <=7% – 24wk	Dichotomous	38	7e		35	a			
	Blood glucose:									
	HbA1c (%) – 24wk	Mean change	88			88				0.011
	Fasting plasma glucose (mmol/l) – 24wk	Mean change	88			88				0.101
	Body weight:									
	Weight (kg) – 24wk	Mean change	88			88			MD=1.100 (CI: 0.120, 2.080)	0.027
	Baseline Hba1c <=8%									
	Blood glucose:									
	HbA1c (%) – 24wk	Mean change	84			88			MD=-0.800	

[a] not reported
[b] estimated from graph
[c] adjusted mean change; SD calculated from reported SE
[d] SD calculated from reported SE
[e] approximated to nearest integer (percentages only presented in text)

	Changes from baseline in primary and secondary variables were analysed using an ANCOVA model with traetment and pooled centre as the classification variables and baseline as the covariate. Multiple testing was adjusted for using Hochberg's multiple testing step-up procedure.

Table 81: Pratley et al. (2006)

General	**Phase:** ☑ monotherapy ☐ dual therapy

	☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** The study was conducted in fifteen centers in South America and Mexico. **Authors' conclusions:** monotherapy with vildagliptin is well tolerated and improves glycemic control in diet-treated subjects with type 2 diabetes. Concomitant improvements in beta-cell function were also observed. Subjects with higher baseline HbA1c levels showed greater response. **Source of funding:** supported by a grant from Novartis Pharmaceuticals **Comments:** Report double-blind, randomised trial but no details of randomisation, blinding or allocation concealment reported.
Number and characteristics of patients	**Total number of patients:** 100 **Inclusion criteria:** Subjects were aged at least 30 years and had a BMI between 20 and 40 kg/m2 inclusive, type 2 diabetes that had been treated with diet only for at least eight weeks prior to enrolment, and agreed to maintain prior diet and exercise habits for the duration of the study **Exclusion criteria:** Subjects with a history of type 1 or secondary forms of diabetes, significant diabetic complications, clinically significant cardiovascular abnormalities, liver disease, acromegaly, asthma, major gastrointestinal surgery, or major skin allergies were excluded from the study. Subjects with fasting triglyceride levels above 4.5 mmol/l were excluded, as were those treated with corticosteroids or sodium channel blockers within the previous three months, or any investigational drug within the previous four weeks. Subjects receiving treatment with warfarin or dicoumarin derivatives or digoxin were also excluded; subjects receiving thyroid hormone replacement could only be included if the dose had remained stable for at least three months prior to entry Subjects were excluded if fasting plasma glucose (FPG) was less than 6.1 mmol/l or more than 15 mmol/l at week -4 or week -2, if ALT, AST or alkaline phosphatase was more than twice the upper limit of normal (ULN), bilirubin was more than 1.3 times the ULN, hematocrit was less than 37% or serum creatinine was more than 220 mol/l, or if TSH was abnorm Any clinically significant laboratory abnormalities or physical exam findings precluded randomization, as did any change of body weight of more than 5% between week -4 and week 0. Pre-randomisation phase: A four-week placebo run-in period preceded randomization during which the following inclusion/exclusion criteria were assessed. The mean (week ± 4 and week ± 2) HbA1c was to lie between 6.8 and 11.0 %. Also see exclusion criteria for exclusions during placebo run-in period
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** some on oral hypoglycaemic drugs and/or insulin **Details of washout period:** Treated with diet only for at least 8 weeks prior to enrolment
Lifestyle advice	prior diet and exercise habits were maintained for the duration of the study
Follow-up	**Total follow-up (wks):** 16 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 12 **Frequency of monitoring appointments:** Fasting plasma levels of glucose and lipids were measured at weeks 1, 2, 4, 8, and 12
Arms	**(1) Vildagliptin** N: 72 Treatment duration (wks): 12 Washout period (d): 0 Treatment(s): Vildagliptin (Oral) – fixed-dose Set dose (mg/d):50 Frequency of dosing: twice a day Details of dosing regimen: Vildagliptin 25 mg bid. Both study drugs were taken 30 minutes before breakfast and dinner **(2) Placebo** N: 28 Treatment duration (wks): 12 Washout period (d): 0 Treatment(s): Placebo (Oral) – fixed-dose Frequency of dosing: twice a day Details of dosing regimen: placebo bid. Both study drugs were taken 30 minutes before breakfast and dinner
Outcomes	**General** 7 (10%) patients in the vildagliptin group and 2 (7%) in placebo group discontinued the study Outcomes not reported in this evidence table include insulin profiles, measures of insulin resistence such as HOMA-B, c-peptides

The ITT population was used to analyse the primary outcome variable with the last observation carried forward

Hypoglycaemic events

symptomatic (confirmed) (An episode of hypoglycemia was defined as symptoms consistent with hypoglycemia accompanied by a glucose measurement less than or equal to 3.1 mmol/)

Baseline characteristics

		Vildagliptin			Placebo				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	70		56.9 (SD 9.4)	28		52.8 (SD 10)		
Sex (n male)	Dichotomous	70	28	(40.0%)	28	14	(50.0%)		
Duration of diabetes (yrs)	Continuous	70		4.6 (SD 5.6)	28		3.5 (SD 5.7)		
Ethnicity-White	Dichotomous	70	33	(47.1%)	28	13	(46.4%)		
Ethnicity-Black	Dichotomous	70	2	(2.9%)	28	0	(0.0%)		
Ethnicity-Oriental	Dichotomous	70	1	(1.4%)	28	0	(0.0%)		
Ethnicity-Other	Dichotomous	70	34	(48.6%)	28	15	(53.6%)		
Blood glucose: HbA1c (%) – 0wk	Continuous	70		8 (SD 0.9)	28		8.1 (SD 1.2)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	70		9.4 (SD 1.8)	28		10.1 (SD 3.2)		
Body weight: BMI (kg/m2)	Continuous	70		30 (SD 4.5)	28		29.9 (SD 4.1)		
Weight (kg) – 0wka	Continuous	70		84.672 (SD 12.7)	28		84.38976 (SD 11.6)		

[a] estimated from BMI assuming mean height of 1.68m

Results

		Vildagliptin			Placebo				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 12wka	Mean change	70		-0.6 (SD 0.837)	28		0 (SD 1.06)	MD=-0.600 (CI: -0.992, -0.208)	0.0012
Fasting plasma glucose (mmol/l) – 12wka	Mean change	70		-0.9 (SD 1.67)	28		0.2 (SD 1.59)	MD=-1.100 (CI: -1.884, -0.316)	0.0043
4h-post prandial glucose (mmol/l) – 12wkb	Mean change	63		-1.7 (SD 2.38)	26		0.2 (SD 2.04)	MD=-1.910 (CI: -2.890, -0.930)	<0.0001
Body weight: Weight (kg) – 12wk	Mean change	70			28			MD=0.500 (CI: -0.480, 1.480)	NS
Hypoglycaemic events: symptomatic (confirmed) – 12wk	Dichotomous	70	1	(1.4%)	28	0	(0.0%)		c
Adverse events: GI: nausea – 12wk	Dichotomous	70	1	(1.4%)	28	1	(3.6%)		
Any adverse event(s) – 12wkd	Dichotomous	70	39	(55.7%)	28	20	(71.4%)		c
Any serious adverse event(s) – 12wk	Dichotomous	70	0	(0.0%)	28	0	(0.0%)		c
Anxiety – 12wk	Dichotomous	70	1	(1.4%)	28	2	(7.1%)		c
Chest pain – 12wk	Dichotomous	70	1	(1.4%)	28	3	(10.7%)		c
Death – 12wk	Dichotomous	70	0	(0.0%)	28	0	(0.0%)		c
Dizziness – 12wk	Dichotomous	70	6	(8.6%)	28	0	(0.0%)		c
Fatigue – 12wk	Dichotomous	70	0	(0.0%)	28	0	(0.0%)		c
GI: abdominal pain – 12wk	Dichotomous	70	3	(4.3%)	28	2	(7.1%)		c
Headache – 12wk	Dichotomous	70	5	(7.1%)	28	1	(3.6%)		c

	Dropouts: Total dropouts – 12wk	Dichotomous	72	7	(9.7%)	28	2	(7.1%)		
	Dropout due to AEs – 12wk	Dichotomous	72	2	(2.8%)	28	0	(0.0%)		c
	Drop out due to unsatisfactory effect – 12wk	Dichotomous	72	2	(2.8%)	28	0	(SD 0.529)		
	baseline Hba1c between 7 and 8% Blood glucose: HbA1c (%) – 12wkb	Mean change	35		-0.5 (SD 0.592)	9		0.2 (SD 0.6)	MD=-0.700	e
	baseline Hba1c between 8 and 9.5% Blood glucose: HbA1c (%) – 12wkb	Mean change	24		-1 (SD 0.98)	11		0.1 (SD 0.995)	MD=-1.200	e

[a] adjusted mean change from baseline; SD calculated from reported SE
[b] adjusted mean change from baseline
[c] not reported
[d] at least one AE
[e] Other details not reported

	baseline characteristics of ITT population. Data were analyzed using an ANCOVA model including terms for treatment, baseline value, pooled center, and treatment by baseline interaction.

Table 82: Raz et al. (2006)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** Multinational (including Canada, Germany, Israel, New Zealand, Hungary, Poland, USA) **Authors' conclusions:** sitagliptin significantly improved glycaemic control and was well tolerated in patients with type 2 diabetes who had inadeqaute glycaemci control on exercise and diet **Source of funding:** Merck Research Laboratories **Comments:** Double-blind
Number and characteristics of patients	**Total number of patients:** 521 **Inclusion criteria:** patients with type 2 diabetes, aged 18-75 years, who were either treatment naïve or were taking monotherapy or low dose combination therapy and could be taken off their OHAs during the run-in period were eligible **Exclusion criteria:** type 1 diabetes, insulin therapy, significant hepatic or renal disease, BMI <20 kg/m2 or >43 kg/m2 Pre-randomisation phase: There was a run-in period of diet and exercise for up to 12 weeks based on prior therapy and Hba1c at study start (patients who were not current taking an OHA directly entered the 2 week placebo run-in period
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** some on oral hypoglycaemic drugs and/or insulin **Details of washout period:** patients discontinued OHA therapy and underwent a 12 week washout period
Lifestyle advice	patients received counselling on a diet consistent with ADA recommendations
Follow-up	**Total follow-up (wks):** 30 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 18 **Frequency of monitoring appointments:** Up to 12 week wash out period (including 2 week single blind placebo run in)
Arms	**(1) Sitagliptin (100 mg)**

N: 205
Treatment duration (wks): 18
Washout period (d): 84
Comments: There was a washout period of up to 12 weeks
Treatment(s): Sitagliptin (Oral) – fixed-dose
Set dose (mg/d):100
Frequency of dosing: once a day
Details of dosing regimen: sitagliptin 100 mg. Patients not meeting target glycaemic limits were provided with rescue therapy (metformin) if FBG>15 mmol/l until week 6, FBG>13.3 mmol/l from week 6-12 or FBG >11.1 mmol/l week 12-18.

(2) Placebo
N: 110
Treatment duration (wks): 18
Washout period (d): 84
Comments: There was a washout period of up to 12 weeks
Treatment(s): Placebo (Oral)

Outcomes

General
Data from 2/3 arms were exatrcted in this evidence table (sitagliptin 200 mg is over the licensed recommended dose in the SPC and was not included).
Analysis of efficacy data was conducted on data collected prior to rescue therapy.

Baseline characteristics

		Sitagliptin (100 mg)			Placebo				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	205		54.5 (SD 10)	110		55.5 (SD 10.1)		
Sex (n male)	Dichotomous	205	110	(53.7%)	110	69	(62.7%)		
Duration of diabetes (yrs)	Continuous	205		4.5 (SD 4.3)	110		4.7 (SD 5)		
Blood glucose: HbA1c (%) – 0wk	Continuous	205		8 (SD 0.8)	110		8 (SD 0.9)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	205		10 (SD 2.4)	110		10.2 (SD 2.7)		
Body weight: BMI (kg/m2)	Continuous	205		31.8 (SD 5.3)	110		32.5 (SD 5.2)		
Weight (kg) – 0wk	Continuous	205		89.7 (SD 19.1)	110		92.8 (SD 18.8)		
Previous blood glucose lowering drugs: Diet alone (i.e. drug naïve)	Dichotomous	205	87	(42.4%)	110	40	(36.4%)		

Results

		Sitagliptin (100 mg)			Placebo				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 12wk	Continuous	205		7.58 (SD 1)	110		8.17 (SD 1.26)		
HbA1c (%) – 18wka	Continuous	205		7.58 (SD 1.15)	110		8.21 (SD 1.35)		
HbA1c (%) – 18wka	Mean change	193		-0.48 (SD 0.92)	103		0.12 (SD 0.91)		
Fasting plasma glucose (mmol/l) – 12wk	Continuous	205		9.3 (SD 1.72)	110		10.72 (SD 2.52)		
Fasting plasma glucose (mmol/l) – 18wka	Continuous	205		9.3 (SD 3)	110		10.6 (SD 3.3)		
Fasting plasma glucose (mmol/l) – 18wka	Mean change	205		-0.7 (SD 2.93)	110		0.4 (SD 7.49)		
Body weight: Weight (kg) – 18wka	Mean change	193		-0.6 (SD 2.8)	103		-0.7 (SD 3.1)		

	Hypoglycaemic events: All hypoglycaemic events (no patients) – 18wk	Dichotomous	205	3	(1.5%)	110	0	(0.0%)		
	Adverse events: GI: nausea – 18wk	Dichotomous	205	2	(1.0%)	110	0	(0.0%)		
	Dropouts: Total dropouts – 18wkb	Dichotomous	205	17	(8.3%)	110	19	(17.3%)		
	Dropout due to AEs – 18wkc	Dichotomous	205	1	(0.5%)	110	4	(3.6%)		

[a] [DO NOT USE - OUTSIDE TIME RANGE]
[b] Data extracted from online supplement trial flow diagram
[c] Data extracted from online supplement trial flow diagram rather than Table

Safety data from Raz (2006) were not extracted as this may have included patients on metformin rescue therapy

Table 83: Ristic et al. (2005)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** conducted in 86 centres in USA and 5 centres in Russia **Authors' conclusions:** Vildagliptin at 50 and 100 mg (qd) was effective in reducing Hba1c levels compared with placebo in patients with type 2 diabetes. Vildagliptin at doses up to 100 mg (qd) appeared safe and well tolerated **Source of funding:** Not reported bu author works at Novartis Pharmaceuticals **Comments:** Double-blind randomised trial, details of randomisation, blinding and allocation concelament not reported
Number and characteristics of patients	**Total number of patients:** 279 **Inclusion criteria:** male and female patients with type 2 diabetes. During the run in phase, inclusion criteria were evaluated for mean Hba1c levels between 6.8% and 10%, FPG between 6.1 and 15 mmol/l, serum creatinine <220 µmol/l, bilirubin < 1.3 times the upper limit of normal (ULN), serum levels of liver enzymes <2 times the ULN and BMI of 20-42 kg/m2 **Exclusion criteria:** patients with abnormal thyroid stimulating hormone, type 1 diabetes, acute metabolic diabetic complications, history of myocardial infarction, clinically significant cardiovascular abnormalities, pancreatitis, parotitis, acromegaly, asthma or major skin allergies, liver disease or previous gastrointestinal surgery were excluded. Additional exclusion criteria were traetment with oral antidiabetic drugs or sodium channel blockers within the previous 12 weeks, combination oral oral antidiabetic therapy or insulin treatment within 6 months prior to study and treatment with systemic corticosteroids, throid hormone replacement, warfarin, dicoumarin or digoxin Pre-randomisation phase: there was a 4 week placebo run-in period followed by a 12 week maintenance phase (when randomisation occurs)
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** All treatment naive/ no OADs at screening **Details of washout period:** not reported
Lifestyle advice	No details were reported
Follow-up	**Total follow-up (wks):** 16 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 12 **Frequency of monitoring appointments:** patients were treated on an outpatient basis and attended clinic visits at screening, at baseline when they were randomised to treatment groups and at the 12 week endpoint
Arms	**(1) Vildagliptin 100mg qd** N: 63 Treatment duration (wks): 12

Washout period (d): 28
Comments: No explicit details on proportion of people with history of AHAs

Treatment(s): Vildagliptin (Oral) – fixed-dose
Set dose (mg/d):100
Frequency of dosing: once a day
Details of dosing regimen: For all patients treated once daily, the study drug was taken 30 mins prior to breakfast

(2) placebo

N: 58

Treatment duration (wks): 12
Washout period (d): 28
Comments: No explicit details on proportion of people with history of AHAs

Treatment(s): Placebo (Oral)
Details of dosing regimen: Details not reported but for those treated once daily, drug was taken was taken 30 mins prior to breakfast. For those treated twice daily, drug was taken at breakfast and dinner

(3) Vildagliptin 25 mg bid

N: 51

Treatment duration (wks): 12
Washout period (d): 28
Comments: No explicit details on proportion of people with history of AHAs

Treatment(s): Vildagliptin (Oral) – fixed-dose
Set dose (mg/d):50
Frequency of dosing: twice a day
Details of dosing regimen: For all patients treated once daily, the study drug was taken 30 mins prior to breakfast. 25 mg given bid

(4) Vildagliptin 25 mg qd

N: 54

Treatment duration (wks): 12
Washout period (d): 28
Comments: No explicit details on proportion of people with history of AHAs

Treatment(s): Vildagliptin (Oral) – fixed-dose
Set dose (mg/d):25
Frequency of dosing: once a day
Details of dosing regimen: For all patients treated once daily, the study drug was taken 30 mins prior to breakfast. Vildagliptin was given 25 mg qd.

(5) Vildagliptin 50 mg qd

N: 53

Treatment duration (wks): 12
Washout period (d): 28
Comments: No explicit details on proportion of people with history of AHAs

Treatment(s): Vildagliptin (Oral) – fixed-dose
Set dose (mg/d):50
Frequency of dosing: once a day
Details of dosing regimen: For all patients treated once daily, the study drug was taken 30 mins prior to breakfast. Vildagliptin was given 50 mg qd.

Outcomes

General

NB: 50 mg vildalgiptin daily are only recommended when used with sulfonylurea or in patients with end-stage renal disease. Outcomes not reported include postprandial insulin, HOMA-B and HOMA-R

Details of drop outs not reported

All analyses performed using ITT population

Hypoglycaemic events

symptomatic (confirmed) (plasma glucose <3.7 mmol/l)

Baseline characteristics

		Vildagliptin 100mg qd			placebo				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Demographics: Age (years)	Continuous	63		56.2 (SD 10.1)	58		54.6 (SD 10.6)		
Sex (n male)	Dichotomous	63	35	(55.6%)	58	33	(56.9%)		
Duration of diabetes (yrs)	Continuous	63		3.03 (SD 4.22)	58		2.28 (SD 2.99)		
Ethnicity-White	Dichotomous	63	47	(74.6%)	58	51	(87.9%)		

Blood glucose: HbA1c (%) – 0wk	Continuous	63		7.64 (SD 0.75)	58		7.76 (SD 0.83)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	63		9.25 (SD 1.85)	58		9.23 (SD 1.94)		
Body weight: BMI (kg/m2)	Continuous	63		31.1 (SD 4.01)	58		31.6 (SD 4.41)		
Weight (kg) – 0wka	Continuous	63		91.5 (SD 17.5)	58		92 (SD 16)		

[a] SD calculated from reported SE

		Vildagliptin 100mg qd			Vildagliptin 25 mg bid			Δ	p
		N	k	mean	N	k	mean		
Demographics: Age (years)	Continuous	63		56.2 (SD 10.1)	51		55.6 (SD 10.9)		
Sex (n male)	Dichotomous	63	35	(55.6%)	51	24	(47.1%)		
Duration of diabetes (yrs)	Continuous	63		3.03 (SD 4.22)	51		3.28 (SD 3.81)		
Ethnicity-White	Dichotomous	63	47	(74.6%)	51	41	(80.4%)		
Blood glucose: HbA1c (%) – 0wk	Continuous	63		7.64 (SD 0.75)	51		7.64 (SD 0.69)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	63		9.25 (SD 1.85)	51		9.18 (SD 2.07)		
Body weight: BMI (kg/m2)	Continuous	63		31.1 (SD 4.01)	51		30.9 (SD 5.23)		
Weight (kg) – 0wka	Continuous	63		91.5 (SD 17.5)	51		89.4 (SD 20)		

[a] SD calculated from reported SE

		Vildagliptin 100mg qd			Vildagliptin 25 mg qd			Δ	p
		N	k	mean	N	k	mean		
Demographics: Age (years)	Continuous	63		56.2 (SD 10.1)	54		57.4 (SD 10.2)		
Sex (n male)	Dichotomous	63	35	(55.6%)	54	34	(63.0%)		
Duration of diabetes (yrs)	Continuous	63		3.03 (SD 4.22)	54		3.1 (SD 5.16)		
Ethnicity-White	Dichotomous	63	47	(74.6%)	54	43	(79.6%)		
Blood glucose: HbA1c (%) – 0wk	Continuous	63		7.64 (SD 0.75)	54		7.73 (SD 0.8)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	63		9.25 (SD 1.85)	54		9.43 (SD 2.29)		
Body weight: BMI (kg/m2)	Continuous	63		31.1 (SD 4.01)	54		31.1 (SD 3.89)		
Weight (kg) – 0wka	Continuous	63		91.5 (SD 17.5)	54		91.1 (SD 14.7)		

[a] SD calculated from reported SE

		placebo			Vildagliptin 25 mg bid			Δ	p
		N	k	mean	N	k	mean		
Demographics: Age (years)	Continuous	58		54.6 (SD 10.6)	51		55.6 (SD 10.9)		
Sex (n male)	Dichotomous	58	33	(56.9%)	51	24	(47.1%)		
Duration of diabetes (yrs)	Continuous	58		2.28 (SD 2.99)	51		3.28 (SD 3.81)		

Ethnicity-White	Dichotomous	58	51	(87.9%)	51	41	(80.4%)		
Blood glucose: HbA1c (%) – 0wk	Continuous	58		7.76 (SD 0.83)	51		7.64 (SD 0.69)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	58		9.23 (SD 1.94)	51		9.18 (SD 2.07)		
Body weight: BMI (kg/m2)	Continuous	58		31.6 (SD 4.41)	51		30.9 (SD 5.23)		
Weight (kg) – 0wka	Continuous	58		92 (SD 16)	51		89.4 (SD 20)		

[a] SD calculated from reported SE

		placebo			Vildagliptin 25 mg qd				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	58		54.6 (SD 10.6)	54		57.4 (SD 10.2)		
Sex (n male)	Dichotomous	58	33	(56.9%)	54	34	(63.0%)		
Duration of diabetes (yrs)	Continuous	58		2.28 (SD 2.99)	54		3.1 (SD 5.16)		
Ethnicity-White	Dichotomous	58	51	(87.9%)	54	43	(79.6%)		
Blood glucose: HbA1c (%) – 0wk	Continuous	58		7.76 (SD 0.83)	54		7.73 (SD 0.8)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	58		9.23 (SD 1.94)	54		9.43 (SD 2.29)		
Body weight: BMI (kg/m2)	Continuous	58		31.6 (SD 4.41)	54		31.1 (SD 3.89)		
Weight (kg) – 0wka	Continuous	58		92 (SD 16)	54		91.1 (SD 14.7)		

[a] SD calculated from reported SE

		placebo			Vildagliptin 50 mg qd				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	58		54.6 (SD 10.6)	53		57 (SD 10.2)		
Sex (n male)	Dichotomous	58	33	(56.9%)	53	26	(49.1%)		
Duration of diabetes (yrs)	Continuous	58		2.28 (SD 2.99)	53		2.71 (SD 3.24)		
Ethnicity-White	Dichotomous	58	51	(87.9%)	53	41	(77.4%)		
Blood glucose: HbA1c (%) – 0wk	Continuous	58		7.76 (SD 0.83)	53		7.7 (SD 0.82)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	58		9.23 (SD 1.94)	53		9.22 (SD 2.09)		
Body weight: BMI (kg/m2)	Continuous	58		31.6 (SD 4.41)	53		31 (SD 3.9)		
Weight (kg) – 0wka	Continuous	58		92 (SD 16)	53		87.9 (SD 16.7)		

[a] SD calculated from reported SE

		Vildagliptin 25 mg bid			Vildagliptin 25 mg qd				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	51		55.6 (SD 10.9)	54		57.4 (SD 10.2)		
Sex (n male)	Dichotomous	51	24	(47.1%)	54	34	(63.0%)		

Duration of diabetes (yrs)	Continuous	51		3.28 (SD 3.81)	54		3.1 (SD 5.16)			
Ethnicity-White	Dichotomous	51	41	(80.4%)	54	43	(79.6%)			
Blood glucose: HbA1c (%) – 0wk	Continuous	51		7.64 (SD 0.69)	54		7.73 (SD 0.8)			
Fasting plasma glucose (mmol/l) – 0wk	Continuous	51		9.18 (SD 2.07)	54		9.43 (SD 2.29)			
Body weight: BMI (kg/m2)	Continuous	51		30.9 (SD 5.23)	54		31.1 (SD 3.89)			
Weight (kg) – 0wka	Continuous	51		89.4 (SD 20)	54		91.1 (SD 14.7)			

[a] SD calculated from reported SE

		Vildagliptin 25 mg qd			Vildagliptin 50 mg qd				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	54		57.4 (SD 10.2)	53		57 (SD 10.2)		
Sex (n male)	Dichotomous	54	34	(63.0%)	53	26	(49.1%)		
Duration of diabetes (yrs)	Continuous	54		3.1 (SD 5.16)	53		2.71 (SD 3.24)		
Ethnicity-White	Dichotomous	54	43	(79.6%)	53	41	(77.4%)		
Blood glucose: HbA1c (%) – 0wk	Continuous	54		7.73 (SD 0.8)	53		7.7 (SD 0.82)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	54		9.43 (SD 2.29)	53		9.22 (SD 2.09)		
Body weight: BMI (kg/m2)	Continuous	54		31.1 (SD 3.89)	53		31 (SD 3.9)		
Weight (kg) – 0wka	Continuous	54		91.1 (SD 14.7)	53		87.9 (SD 16.7)		

[a] SD calculated from reported SE

Results

		Vildagliptin 100mg qd			placebo				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 12wka	Mean change	60		-0.53 (SD 0.775)	55		-0.13 (SD 0.742)	MD=-0.400 (CI: -0.674, -0.126)	0.004b
HbA1c reduction >=1% – 12wk	Dichotomous	60	12	(20.0%)	55	6	(10.9%)		NR
HbA1c reduction >=0.5% – 12wk	Dichotomous	60	32	(53.3%)	55	15	(27.3%)		NR
Fasting plasma glucose (mmol/l) – 12wka	Mean change	62		-0.95 (SD 1.81)	55		-0.41 (SD 1.78)	MD=-0.540 (CI: -1.187, 0.107)	0.099b
4h-post prandial glucose (mmol/l) – 12wk	Mean change	33		-1.5 (SD 3.02)	25		-0.61 (SD 3.2)	MD=-0.890 (CI: -1.929, 0.149)	0.095b
Body weight: Weight (kg) – 12wka	Mean change	61		-0.07 (SD 2.42)	55		-0.73 (SD 2.45)	MD=0.670 (CI: -0.192, 1.532)	0.132b
Hypoglycaemic events: All hypoglycaemic events (no patients) – 12wk	Dichotomous	63	5	(8.1%)	58	3	(5.4%)		NR
All hypoglycaemic events (no patients) – 12wk	Dichotomous	62	5	(8.1%)	56	3	(5.4%)		NR
Major/severe hypoglycaemic event – 12wk	Dichotomous	62	0	(0.0%)	56	0	(0.0%)		NR

symptomatic (confirmed) – 12wk	Dichotomous	63	1	(1.6%)	58	0	(0.0%)		NR
Adverse events:									
GI: nausea – 12wk	Dichotomous	62	2	(3.2%)	56	3	(5.4%)		NR
Any adverse event(s) – 12wk	Dichotomous	62	35	(56.5%)	56	33	(58.9%)		NR
Any serious adverse event(s) – 12wk	Dichotomous	62	1	(1.6%)	56	3	(5.4%)		NR
Cough – 12wk	Dichotomous	63	0	(0.0%)	58	1	(1.7%)		NR
Dizziness – 12wk	Dichotomous	62	4	(6.5%)	56	2	(3.6%)		NR
Dyspepsia – 12wk	Dichotomous	62	4	(6.5%)	56	2	(3.6%)		NR
Edema peripheral – 12wk	Dichotomous	62	3	(4.8%)	56	2	(3.6%)		NR
GI: diarrhoea – 12wk	Dichotomous	62	0	(0.0%)	56	3	(5.4%)		NR
GI: constipation – 12wk	Dichotomous	62	2	(3.2%)	56	0	(0.0%)		NR
Headache – 12wk	Dichotomous	62	8	(12.9%)	56	4	(7.1%)		NR
Nasopharyngitis – 12wk	Dichotomous	62	5	(8.1%)	56	5	(8.9%)		NR
Sinusitis or sinus abnormality – 12wk	Dichotomous	63	0	(0.0%)	58	3	(5.2%)		NR
Temperature/influenza – 12wk	Dichotomous	63	0	(0.0%)	58	2	(3.4%)		NR
Dropouts:									
Dropout due to AEs – 12wk	Dichotomous	62	2	(3.2%)	56	3	(5.4%)		NR
Lipids:									
HDL cholesterol (mmol/l) – 12wk	Mean change	0			0			MD=-0.040	0.004c
HDL cholesterol (mmol/l) – 12wkd	Mean change							MD=-0.040	0.004c
HDL cholesterol (mmol/l) – 12wkd	Mean change	0			0			MD=-0.040	0.004c
Baseline Hba1c >=7%									
Blood glucose:									
HbA1c < 7% or <=7% – 12wke	Dichotomous	48	22	(45.8%)	48	11	(22.9%)		NR

[a] SD calculated from reported SE
[b] ANCOVA
[c] no other details reported
[d] not reported
[e] in patients with baseline Hba1c >=7% and endpoint measurement

		Vildagliptin 100mg qd			Vildagliptin 25 mg bid				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Blood glucose:									
HbA1c (%) – 12wka	Mean change	60		-0.53 (SD 0.775)	51		-0.31 (SD 0.786)		
HbA1c reduction >=1% – 12wk	Dichotomous	60	12	(20.0%)	51	6	(11.8%)		
HbA1c reduction >=0.5% – 12wk	Dichotomous	60	32	(53.3%)	51	18	(35.3%)		
Fasting plasma glucose (mmol/l) – 12wka	Mean change	62		-0.95 (SD 1.81)	51		-0.44 (SD 1.79)		
4h-post prandial glucose (mmol/l) – 12wk	Mean change	33		-1.5 (SD 3.02)	51		-1.03 (SD 2.86)		
Body weight:									
Weight (kg) – 12wka	Mean change	61		-0.07 (SD 2.42)	51		0.06 (SD 2.36)		
Hypoglycaemic events:									
All hypoglycaemic events (no patients) – 12wk	Dichotomous	62	5	(8.1%)	51	3	(5.9%)		
Major/severe hypoglycaemic event – 12wk	Dichotomous	62	0	(0.0%)	51	0	(0.0%)		
symptomatic (confirmed) – 12wk	Dichotomous	63	1	(1.6%)	51	1	(2.0%)		

Adverse events:									
GI: nausea – 12wk	Dichotomous	62	2	(3.2%)	51	0	(0.0%)		
Any adverse event(s) – 12wk	Dichotomous	62	35	(56.5%)	51	28	(54.9%)		
Any serious adverse event(s) – 12wk	Dichotomous	62	1	(1.6%)	51	1	(2.0%)		
Cough – 12wk	Dichotomous	63	0	(0.0%)	51	2	(3.9%)		
Dizziness – 12wk	Dichotomous	62	4	(6.5%)	51	2	(3.9%)		
Dyspepsia – 12wk	Dichotomous	62	4	(6.5%)	51	1	(2.0%)		
Edema peripheral – 12wk	Dichotomous	62	3	(4.8%)	51	3	(5.9%)		
GI: diarrhoea – 12wk	Dichotomous	62	0	(0.0%)	51	2	(3.9%)		
GI: constipation – 12wk	Dichotomous	62	2	(3.2%)	51	1	(2.0%)		
Headache – 12wk	Dichotomous	62	8	(12.9%)	51	3	(5.9%)		
Nasopharyngitis – 12wk	Dichotomous	62	5	(8.1%)	51	4	(7.8%)		
Sinusitis or sinus abnormality – 12wk	Dichotomous	63	0	(0.0%)	51	1	(2.0%)		
Temperature/influenza – 12wk	Dichotomous	63	0	(0.0%)	51	4	(7.8%)		
Dropouts:									
Dropout due to AEs – 12wk	Dichotomous	62	2	(3.2%)	51	4	(7.8%)		
Lipids:									
HDL cholesterol (mmol/l) – 12wk[b]	Mean change								
Baseline Hba1c >=7%									
Blood glucose:									
HbA1c < 7% or <=7% – 12wk[c]	Dichotomous	48	22	(45.8%)	51	18	(35.3%)		

[a] SD calculated from reported SE
[b] not reported
[c] in patients with baseline Hba1c >=7% and endpoint measurement

		Vildagliptin 100mg qd			Vildagliptin 25 mg qd				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Blood glucose:									
HbA1c (%) – 12wk[a]	Mean change	60		-0.53 (SD 0.775)	54		-0.27 (SD 0.735)		
HbA1c reduction >=1% – 12wk	Dichotomous	60	12	(20.0%)	54	6	(11.1%)		
HbA1c reduction >=0.5% – 12wk	Dichotomous	60	32	(53.3%)	54	17	(31.5%)		
Fasting plasma glucose (mmol/l) – 12wk[a]	Mean change	62		-0.95 (SD 1.81)	54		-0.3 (SD 1.76)		
4h-post prandial glucose (mmol/l) – 12wk	Mean change	33		-1.5 (SD 3.02)	54		-1.5 (SD 2.94)		
Body weight:									
Weight (kg) – 12wk[a]	Mean change	61		-0.07 (SD 2.42)	54		-0.55 (SD 2.35)		
Hypoglycaemic events:									
All hypoglycaemic events (no patients) – 12wk	Dichotomous	62	5	(8.1%)	54	4	(7.4%)		
Major/severe hypoglycaemic event – 12wk	Dichotomous	62	0	(0.0%)	54	0	(0.0%)		
symptomatic (confirmed) – 12wk	Dichotomous	63	1	(1.6%)	54	0	(0.0%)		
Adverse events:									
GI: nausea – 12wk	Dichotomous	62	2	(3.2%)	54	1	(1.9%)		
Any adverse event(s) – 12wk	Dichotomous	62	35	(56.5%)	54	32	(59.3%)		
Any serious adverse event(s) – 12wk	Dichotomous	62	1	(1.6%)	54	0	(0.0%)		
Cough – 12wk	Dichotomous	63	0	(0.0%)	54	4	(7.4%)		
Dizziness – 12wk	Dichotomous	62	4	(6.5%)	54	1	(1.9%)		
Dyspepsia – 12wk	Dichotomous	62	4	(6.5%)	54	0	(0.0%)		
Edema peripheral – 12wk	Dichotomous	62	3	(4.8%)	54	0	(0.0%)		
GI: diarrhoea – 12wk	Dichotomous	62	0	(0.0%)	54	3	(5.6%)		
GI: constipation – 12wk	Dichotomous	62	2	(3.2%)	54	0	(0.0%)		
Headache – 12wk	Dichotomous	62	8	(12.9%)	54	3	(5.6%)		
Nasopharyngitis – 12wk	Dichotomous	62	5	(8.1%)	54	3	(5.6%)		

Sinusitis or sinus abnormality – 12wk	Dichotomous	63	0	(0.0%)	54	0	(0.0%)		
Temperature/influenza – 12wk	Dichotomous	63	0	(0.0%)	54	0	(0.0%)		
Dropouts: Dropout due to AEs – 12wk	Dichotomous	62	2	(3.2%)	54	2	(3.7%)		
Lipids: HDL cholesterol (mmol/l) – 12wkb	Mean change								
Baseline Hba1c >=7% Blood glucose: HbA1c < 7% or <=7% – 12wkc	Dichotomous	48	22	(45.8%)	54	13	(24.1%)		

[a] SD calculated from reported SE
[b] not reported
[c] in patients with baseline Hba1c >=7% and endpoint measurement

		placebo			Vildagliptin 25 mg bid				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 12wka	Mean change	55		-0.13 (SD 0.742)	51		-0.31 (SD 0.786)	MD=-0.180 (CI: -0.474, 0.114)	0.216
HbA1c reduction >=1% – 12wk	Dichotomous	55	6	(10.9%)	51	6	(11.8%)		NR
HbA1c reduction >=0.5% – 12wk	Dichotomous	55	15	(27.3%)	51	18	(35.3%)		NR
Fasting plasma glucose (mmol/l) – 12wka	Mean change	55		-0.41 (SD 1.78)	51		-0.44 (SD 1.79)	MD=-0.330 (CI: -1.016, 0.356)	0.919
4h-post prandial glucose (mmol/l) – 12wk	Mean change	25		-0.61 (SD 3.2)	51		-1.03 (SD 2.86)		
Body weight: Weight (kg) – 12wka	Mean change	55		-0.73 (SD 2.45)	51		0.06 (SD 2.36)	MD=0.790 (CI: -0.112, 1.692)	0.088
Weight (kg) – 12wka	Mean change	58		-0.73 (SD 2.45)	51		0.06 (SD 2.36)	MD=0.790 (CI: -0.112, 1.692)	0.088
Hypoglycaemic events: All hypoglycaemic events (no patients) – 12wk	Dichotomous	58	3	(5.4%)	51	3	(5.9%)		NR
All hypoglycaemic events (no patients) – 12wk	Dichotomous	56	3	(5.4%)	51	3	(5.9%)		NR
Major/severe hypoglycaemic event – 12wk	Dichotomous	56	0	(0.0%)	51	0	(0.0%)		NR
symptomatic (confirmed) – 12wk	Dichotomous	58	0	(0.0%)	51	1	(2.0%)		NR
Adverse events: GI: nausea – 12wk	Dichotomous	56	3	(5.4%)	51	0	(0.0%)		NR
Any adverse event(s) – 12wk	Dichotomous	56	33	(58.9%)	51	28	(54.9%)		NR
Any serious adverse event(s) – 12wk	Dichotomous	56	3	(5.4%)	51	1	(2.0%)		NR
Cough – 12wk	Dichotomous	58	1	(1.7%)	51	2	(3.9%)		NR
Dizziness – 12wk	Dichotomous	56	2	(3.6%)	51	2	(3.9%)		NR
Dyspepsia – 12wk	Dichotomous	56	2	(3.6%)	51	1	(2.0%)		NR
Edema peripheral – 12wk	Dichotomous	56	2	(3.6%)	51	3	(5.9%)		NR
GI: diarrhoea – 12wk	Dichotomous	56	3	(5.4%)	51	2	(3.9%)		NR
GI: constipation – 12wk	Dichotomous	56	0	(0.0%)	51	1	(2.0%)		NR
Headache – 12wk	Dichotomous	56	4	(7.1%)	51	3	(5.9%)		NR
Nasopharyngitis – 12wk	Dichotomous	56	5	(8.9%)	51	4	(7.8%)		NR

Sinusitis or sinus abnormality – 12wk	Dichotomous	58	3	(5.2%)	51	1	(2.0%)		NR
Temperature/influenza – 12wk	Dichotomous	58	2	(3.4%)	51	4	(7.8%)		NR
Dropouts:									
Dropout due to AEs – 12wk	Dichotomous	56	3	(5.4%)	51	4	(7.8%)		NR
Lipids:									
HDL cholesterol (mmol/l) – 12wk	Mean change	58			51				NS
HDL cholesterol (mmol/l) – 12wkb	Mean change								NS
HDL cholesterol (mmol/l) – 12wkb	Mean change	58			51				NS
Baseline Hba1c >=7%									
Blood glucose:									
HbA1c < 7% or <=7% – 12wkc	Dichotomous	48	11	(22.9%)	51	18	(35.3%)		NR
Blood glucose:									
4h-post prandial glucose (mmol/l) – 12wk	Mean change	51			25			MD=-0.420 (CI: -1.518, 0.678)	0.459

[a] SD calculated from reported SE
[b] not reported
[c] in patients with baseline Hba1c >=7% and endpoint measurement

		placebo			Vildagliptin 25 mg qd				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Blood glucose:									
HbA1c (%) – 12wka	Mean change	55		-0.13 (SD 0.742)	54		-0.27 (SD 0.735)	MD=-0.420 (CI: -0.714, -0.126)	0.337
HbA1c reduction >=1% – 12wk	Dichotomous	55	6	(10.9%)	54	6	(11.1%)		NR
HbA1c reduction >=0.5% – 12wk	Dichotomous	55	15	(27.3%)	54	17	(31.5%)		NR
Fasting plasma glucose (mmol/l) – 12wka	Mean change	55		-0.41 (SD 1.78)	54		-0.3 (SD 1.76)	MD=0.110 (CI: -0.556, 0.776)	0.759
4h-post prandial glucose (mmol/l) – 12wk	Mean change	25		-0.61 (SD 3.2)	54		-1.5 (SD 2.94)		
Body weight:									
Weight (kg) – 12wka	Mean change	55		-0.73 (SD 2.45)	54		-0.55 (SD 2.35)	MD=0.180 (CI: -0.722, 1.082)	0.696
Weight (kg) – 12wka	Mean change	58		-0.73 (SD 2.45)	54		-0.55 (SD 2.35)	MD=0.180 (CI: -0.722, 1.082)	0.696
Hypoglycaemic events:									
All hypoglycaemic events (no patients) – 12wk	Dichotomous	58	3	(5.4%)	54	4	(7.4%)		NR
All hypoglycaemic events (no patients) – 12wk	Dichotomous	56	3	(5.4%)	54	4	(7.4%)		NR
Major/severe hypoglycaemic event – 12wk	Dichotomous	56	0	(0.0%)	54	0	(0.0%)		NR
symptomatic (confirmed) – 12wk	Dichotomous	58	0	(0.0%)	54	0	(0.0%)		NR
Adverse events:									
GI: nausea – 12wk	Dichotomous	56	3	(5.4%)	54	1	(1.9%)		NR
Any adverse event(s) – 12wk	Dichotomous	56	33	(58.9%)	54	32	(59.3%)		NR
Any serious adverse event(s) – 12wk	Dichotomous	56	3	(5.4%)	54	0	(0.0%)		NR
Cough – 12wk	Dichotomous	58	1	(1.7%)	54	4	(7.4%)		NR

Dizziness – 12wk	Dichotomous	56	2	(3.6%)	54	1	(1.9%)		NR
Dyspepsia – 12wk	Dichotomous	56	2	(3.6%)	54	0	(0.0%)		NR
Edema peripheral – 12wk	Dichotomous	56	2	(3.6%)	54	0	(0.0%)		NR
GI: diarrhoea – 12wk	Dichotomous	56	3	(5.4%)	54	3	(5.6%)		NR
GI: constipation – 12wk	Dichotomous	56	0	(0.0%)	54	0	(0.0%)		NR
Headache – 12wk	Dichotomous	56	4	(7.1%)	54	3	(5.6%)		NR
Nasopharyngitis – 12wk	Dichotomous	56	5	(8.9%)	54	3	(5.6%)		NR
Sinusitis or sinus abnormality – 12wk	Dichotomous	58	3	(5.2%)	54	0	(0.0%)		NR
Temperature/influenza – 12wk	Dichotomous	58	2	(3.4%)	54	0	(0.0%)		NR
Dropouts:									
Dropout due to AEs – 12wk	Dichotomous	56	3	(5.4%)	54	2	(3.7%)		NR
Lipids:									
HDL cholesterol (mmol/l) – 12wk	Mean change	58			54				NS
HDL cholesterol (mmol/l) – 12wkb	Mean change								NS
HDL cholesterol (mmol/l) – 12wkb	Mean change	58			54				NS
Baseline Hba1c >=7%									
Blood glucose:									
HbA1c < 7% or <=7% – 12wkc	Dichotomous	48	11	(22.9%)	54	13	(24.1%)		NR
Blood glucose:									
4h-post prandial glucose (mmol/l) – 12wk	Mean change	54			25			MD=-0.890 (CI: -1.988, 0.208)	0.116

[a] SD calculated from reported SE
[b] not reported
[c] in patients with baseline Hba1c >=7% and endpoint measurement

		placebo			Vildagliptin 50 mg qd				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Blood glucose: HbA1c (%) – 12wka	Mean change	55		-0.13 (SD 0.742)	52		-0.56 (SD 0.728)	MD=-0.430 (CI: -0.704, -0.156)	0.003
HbA1c reduction >=1% – 12wk	Dichotomous	55	6	(10.9%)	52	13	(25.0%)		NR
HbA1c reduction >=0.5% – 12wk	Dichotomous	55	15	(27.3%)	52	27	(51.9%)		NR
Fasting plasma glucose (mmol/l) – 12wka	Mean change	55		-0.41 (SD 1.78)	53		-0.97 (SD 1.82)	MD=-0.570 (CI: -1.236, 0.096)	0.103
4h-post prandial glucose (mmol/l) – 12wk	Mean change	25		-0.61 (SD 3.2)	53		-2 (SD 2.91)		
Body weight: Weight (kg) – 12wka	Mean change	55		-0.73 (SD 2.45)	53		0.04 (SD 2.4)	MD=0.770 (CI: -0.132, 1.672)	0.094
Weight (kg) – 12wka	Mean change	58		-0.73 (SD 2.45)	53		0.04 (SD 2.4)	MD=0.770 (CI: -0.132, 1.672)	0.094
Hypoglycaemic events:									
All hypoglycaemic events (no patients) – 12wk	Dichotomous	58	3	(5.4%)	53	2	(3.8%)		NR
All hypoglycaemic events (no patients) – 12wk	Dichotomous	56	3	(5.4%)	53	2	(3.8%)		NR
Major/severe hypoglycaemic event – 12wk	Dichotomous	56	0	(0.0%)	53	0	(0.0%)		NR

symptomatic (confirmed) – 12wk	Dichotomous	58	0	(0.0%)	53	0	(0.0%)		NR
Adverse events: GI: nausea – 12wk	Dichotomous	56	3	(5.4%)	53	2	(3.8%)		NR
Any adverse event(s) – 12wk	Dichotomous	56	33	(58.9%)	53	31	(58.5%)		NR
Any serious adverse event(s) – 12wk	Dichotomous	56	3	(5.4%)	53	0	(0.0%)		NR
Cough – 12wk	Dichotomous	58	1	(1.7%)	53	0	(0.0%)		NR
Dizziness – 12wk	Dichotomous	56	2	(3.6%)	53	1	(1.9%)		NR
Dyspepsia – 12wk	Dichotomous	56	2	(3.6%)	53	1	(1.9%)		NR
Edema peripheral – 12wk	Dichotomous	56	2	(3.6%)	53	2	(3.8%)		NR
GI: diarrhoea – 12wk	Dichotomous	56	3	(5.4%)	53	0	(0.0%)		NR
GI: constipation – 12wk	Dichotomous	56	0	(0.0%)	53	3	(5.7%)		NR
Headache – 12wk	Dichotomous	56	4	(7.1%)	53	1	(1.9%)		NR
Nasopharyngitis – 12wk	Dichotomous	56	5	(8.9%)	53	3	(5.7%)		NR
Sinusitis or sinus abnormality – 12wk	Dichotomous	58	3	(5.2%)	53	0	(0.0%)		NR
Temperature/influenza – 12wk	Dichotomous	58	2	(3.4%)	53	0	(0.0%)		NR
Dropouts: Dropout due to AEs – 12wk	Dichotomous	56	3	(5.4%)	53	3	(5.7%)		NR
Lipids: HDL cholesterol (mmol/l) – 12wk	Mean change	58			53				NS
HDL cholesterol (mmol/l) – 12wkb	Mean change								NS
HDL cholesterol (mmol/l) – 12wkb	Mean change	58			53				NS
Baseline Hba1c >=7% Blood glucose: HbA1c < 7% or <=7% – 12wkc	Dichotomous	48	11	(22.9%)	53	16	(30.2%)		NR
Blood glucose: 4h-post prandial glucose (mmol/l) – 12wk	Mean change	53			25			MD=-1.390 (CI: -2.448, -0.332)	0.012

[a] SD calculated from reported SE
[b] not reported
[c] in patients with baseline Hba1c >=7% and endpoint measurement

		Vildagliptin 25 mg bid			Vildagliptin 25 mg qd				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 12wka	Mean change	51		-0.31 (SD 0.786)	54		-0.27 (SD 0.735)		
HbA1c reduction >=1% – 12wk	Dichotomous	51	6	(11.8%)	54	6	(11.1%)		
HbA1c reduction >=0.5% – 12wk	Dichotomous	51	18	(35.3%)	54	17	(31.5%)		
Fasting plasma glucose (mmol/l) – 12wka	Mean change	51		-0.44 (SD 1.79)	54		-0.3 (SD 1.76)		
4h-post prandial glucose (mmol/l) – 12wk	Mean change	51		-1.03 (SD 2.86)	54		-1.5 (SD 2.94)		
Body weight: Weight (kg) – 12wka	Mean change	51		0.06 (SD 2.36)	54		-0.55 (SD 2.35)		
Hypoglycaemic events: All hypoglycaemic events (no patients) – 12wk	Dichotomous	51	3	(5.9%)	54	4	(7.4%)		
Major/severe hypoglycaemic event – 12wk	Dichotomous	51	0	(0.0%)	54	0	(0.0%)		
symptomatic (confirmed) – 12wk	Dichotomous	51	1	(2.0%)	54	0	(0.0%)		

Adverse events:									
GI: nausea – 12wk	Dichotomous	51	0	(0.0%)	54	1	(1.9%)		
Any adverse event(s) – 12wk	Dichotomous	51	28	(54.9%)	54	32	(59.3%)		
Any serious adverse event(s) – 12wk	Dichotomous	51	1	(2.0%)	54	0	(0.0%)		
Cough – 12wk	Dichotomous	51	2	(3.9%)	54	4	(7.4%)		
Dizziness – 12wk	Dichotomous	51	2	(3.9%)	54	1	(1.9%)		
Dyspepsia – 12wk	Dichotomous	51	1	(2.0%)	54	0	(0.0%)		
Edema peripheral – 12wk	Dichotomous	51	3	(5.9%)	54	0	(0.0%)		
GI: diarrhoea – 12wk	Dichotomous	51	2	(3.9%)	54	3	(5.6%)		
GI: constipation – 12wk	Dichotomous	51	1	(2.0%)	54	0	(0.0%)		
Headache – 12wk	Dichotomous	51	3	(5.9%)	54	3	(5.6%)		
Nasopharyngitis – 12wk	Dichotomous	51	4	(7.8%)	54	3	(5.6%)		
Sinusitis or sinus abnormality – 12wk	Dichotomous	51	1	(2.0%)	54	0	(0.0%)		
Temperature/influenza – 12wk	Dichotomous	51	4	(7.8%)	54	0	(0.0%)		
Dropouts:									
Dropout due to AEs – 12wk	Dichotomous	51	4	(7.8%)	54	2	(3.7%)		
Lipids:									
HDL cholesterol (mmol/l) – 12wkb	Mean change								
Baseline Hba1c >=7%									
Blood glucose:									
HbA1c < 7% or <=7% – 12wkc	Dichotomous	51	18	(35.3%)	54	13	(24.1%)		

[a] SD calculated from reported SE
[b] not reported
[c] in patients with baseline Hba1c >=7% and endpoint measurement

		Vildagliptin 25 mg qd			Vildagliptin 50 mg qd			Δ	p
		N	k	mean	N	k	mean		
Blood glucose:									
HbA1c (%) – 12wka	Mean change	54		-0.27 (SD 0.735)	52		-0.56 (SD 0.728)		
HbA1c reduction >=1% – 12wk	Dichotomous	54	6	(11.1%)	52	13	(25.0%)		
HbA1c reduction >=0.5% – 12wk	Dichotomous	54	17	(31.5%)	52	27	(51.9%)		
Fasting plasma glucose (mmol/l) – 12wka	Mean change	54		-0.3 (SD 1.76)	53		-0.97 (SD 1.82)		
4h-post prandial glucose (mmol/l) – 12wk	Mean change	54		-1.5 (SD 2.94)	53		-2 (SD 2.91)		
Body weight:									
Weight (kg) – 12wka	Mean change	54		-0.55 (SD 2.35)	53		0.04 (SD 2.4)		
Hypoglycaemic events:									
All hypoglycaemic events (no patients) – 12wk	Dichotomous	54	4	(7.4%)	53	2	(3.8%)		
Major/severe hypoglycaemic event – 12wk	Dichotomous	54	0	(0.0%)	53	0	(0.0%)		
symptomatic (confirmed) – 12wk	Dichotomous	54	0	(0.0%)	53	0	(0.0%)		
Adverse events:									
GI: nausea – 12wk	Dichotomous	54	1	(1.9%)	53	2	(3.8%)		
Any adverse event(s) – 12wk	Dichotomous	54	32	(59.3%)	53	31	(58.5%)		
Any serious adverse event(s) – 12wk	Dichotomous	54	0	(0.0%)	53	0	(0.0%)		
Cough – 12wk	Dichotomous	54	4	(7.4%)	53	0	(0.0%)		
Dizziness – 12wk	Dichotomous	54	1	(1.9%)	53	1	(1.9%)		
Dyspepsia – 12wk	Dichotomous	54	0	(0.0%)	53	1	(1.9%)		
Edema peripheral – 12wk	Dichotomous	54	0	(0.0%)	53	2	(3.8%)		
GI: diarrhoea – 12wk	Dichotomous	54	3	(5.6%)	53	0	(0.0%)		
GI: constipation – 12wk	Dichotomous	54	0	(0.0%)	53	3	(5.7%)		
Headache – 12wk	Dichotomous	54	3	(5.6%)	53	1	(1.9%)		
Nasopharyngitis – 12wk	Dichotomous	54	3	(5.6%)	53	3	(5.7%)		

	Sinusitis or sinus abnormality – 12wk	Dichotomous	54	0	(0.0%)	53	0	(0.0%)		
	Temperature/influenza – 12wk	Dichotomous	54	0	(0.0%)	53	0	(0.0%)		
	Dropouts: Dropout due to AEs – 12wk	Dichotomous	54	2	(3.7%)	53	3	(5.7%)		
	Lipids: HDL cholesterol (mmol/l) – 12wkb	Mean change								
	Baseline Hba1c >=7% Blood glucose: HbA1c < 7% or <=7% – 12wkc	Dichotomous	54	13	(24.1%)	53	16	(30.2%)		

[a] SD calculated from reported SE
[b] not reported
[c] in patients with baseline Hba1c >=7% and endpoint measurement

ANCOVA model inclusing terms for treatment, baseline Hba1c, pooled centre and treatment by baseline Hba1c interaction was used to compare the change from baseline of each parameter between vildagliptin and placebo treatment groups

Table 84: Roden et al. (2013)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** Belgium, Canada, China, Germany, India, Ireland, Japan, Switzerland, USA **Authors' conclusions:** - **Source of funding:** Boehringer Ingelheim, Eli Lilly **Comments:** -
Number and characteristics of patients	**Total number of patients:** 899 **Inclusion criteria:** Adults with T2DM, BMI <=45kg/m2 not on AHA at least 12 weeks prior to enrollment, HbA1c between 7 and 10%, despite diet and exercise regimen **Exclusion criteria:** - Pre-randomisation phase: 2 week open label placebo run in
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** some on oral hypoglycaemic drugs and/or insulin **Details of washout period:** 2 weeks open label placebo run in. Unclear what proportion of participants were truly AHA naïve but no AHA was allowed at least 12 weeks prior to enrollment
Lifestyle advice	Diet and exercise local recommendations
Follow-up	**Total follow-up (wks):** 26 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 24 **Frequency of monitoring appointments:** 2 week open label placebo run in phase followed by 24 week treatment period
Arms	**(1) Placebo** N: 228 Treatment duration (wks): 24 Washout period (d): 14 Comments: Patients were not on AHA at least 12 weeks prior to enrollment Treatment(s): Placebo (Oral) **(2) Sitagliptin 100mg** N: 223 Treatment duration (wks): 24 Washout period (d): 14 Comments: Patients were not on AHA at least 12 weeks prior to enrollment Treatment(s): Sitagliptin (Oral) – fixed-dose

Set dose (mg/d):100
Frequency of dosing: once a day
Details of dosing regimen: 100mg once a day

Outcomes

General

33/228 on placebo and 8/223 on sitagliptin received rescue medication.

Efficacy data after the start of rescue medication was excluded and missing data were imputed using LOCF. However, safety data included all patients receiving at least one dose of the study drug. Data from empagliflozin groups were not extracted as this drug is outside the scope of the review.

Data on dropouts (total and due to adverse events), nausea and hypoglycaemia were not extracted as these populations included those on rescue medication.

Baseline characteristics

		Placebo		
		N	**k**	**mean**
Demographics:				
Age (years)	Continuous	228		54.9 (SD 10.9)
Sex (n male)	Dichotomous	228	123	(53.9%)
Blood glucose:				
HbA1c (%) – 24wk	Continuous	228		7.91 (SD 0.78)
HbA1c (%) – 24wk	Continuous	228		7.91 (SD 0.78)
Fasting plasma glucose (mmol/l) – 24wk	Continuous	228		8.59 (SD 1.99)
Fasting plasma glucose (mmol/l) – 24wk	Continuous	228		8.59 (SD 1.99)
Body weight:				
BMI (kg/m2)	Continuous	228		28.7 (SD 6.2)
Weight (kg) – 0wk	Continuous	228		81.00288 (SD 17.49888) a
Weight (kg) – 0wk	Continuous	228		81.00288 (SD 17.49888) a
Weight (kg) – 24wk	Continuous	228		78.2 (SD 19.9)
Weight (kg) – 24wk	Continuous	228		78.2 (SD 19.9)

[a] estimated from BMI assuming mean height of 1.68m

		Sitagliptin 100mg		
		N	**k**	**mean**
Demographics:				
Age (years)	Continuous	223		55.1 (SD 9.9)
Sex (n male)	Dichotomous	223	141	(63.2%)
Blood glucose:				
HbA1c (%) – 24wk	Continuous	223		7.85 (SD 0.79)
HbA1c (%) – 24wk	Continuous	223		7.85 (SD 0.79)
Fasting plasma glucose (mmol/l) – 24wk	Continuous	223		8.16 (SD 1.6)
Fasting plasma glucose (mmol/l) – 24wk	Continuous	223		8.16 (SD 1.6)
Body weight:				
BMI (kg/m2)	Continuous	223		28.2 (SD 5.2)
Weight (kg) – 0wk	Continuous	223		79.59168 (SD 14.67648) a
Weight (kg) – 0wk	Continuous	223		79.59168 (SD 14.67648) a
Weight (kg) – 24wk	Continuous	223		79.3 (SD 20.4)
Weight (kg) – 24wk	Continuous	223		79.3 (SD 20.4)

[a] estimated from BMI assuming mean height of 1.68m

Results

		Placebo		
		N	**k**	**mean**
Blood glucose:				
HbA1c (%) – 12wk	Continuous	186		7.8857 (SD 0.662646892110492) a
HbA1c (%) – 12wk	Continuous	186		7.8857 (SD 0.662646892110492) a

HbA1c (%) – 24wk	Mean change	228		0.08 (SD 0.847445967814222) b
HbA1c (%) – 24wk	Mean change	228		0.08 (SD 0.847445967814222) b
HbA1c (%) – 24wk	Continuous	228		7.98 (SD 1.07856759539992) b
HbA1c (%) – 24wk	Continuous	228		7.98 (SD 1.07856759539992) b
Fasting plasma glucose (mmol/l) – 24wk	Mean change	228		0.65 (SD 1.61785139309988) b
Fasting plasma glucose (mmol/l) – 24wk	Mean change	228		0.65 (SD 1.61785139309988) b
Body weight:				
Weight (kg) – 24wk	Mean change	228		-0.33 (SD 2.61937844597123) b
Weight (kg) – 24wk	Mean change	228		-0.33 (SD 2.61937844597123) b
Weight (kg) – 24wk	Continuous	228		77.9 (SD 19.6453383447843) b
Weight (kg) – 24wk	Continuous	228		77.9 (SD 19.6453383447843) b

[a] Estimated from graph, SD calculated from 95% CI
[b] SD calculated from reported 95% CI

		Sitagliptin 100mg		
		N	**k**	**mean**
Blood glucose:				
HbA1c (%) – 12wk	Continuous	213		7.219 (SD 0.567335140313015) a
HbA1c (%) – 12wk	Continuous	213		7.219 (SD 0.567335140313015) a
HbA1c (%) – 24wk	Mean change	223		-0.66 (SD 0.76191116984083) b
HbA1c (%) – 24wk	Mean change	223		-0.66 (SD 0.76191116984083) b
HbA1c (%) – 24wk	Continuous	223		7.2 (SD 0.914293403808997) b
HbA1c (%) – 24wk	Continuous	223		7.2 (SD 0.914293403808997) b
Fasting plasma glucose (mmol/l) – 24wk	Mean change	223		-0.38 (SD 1.67620457364983) b
Fasting plasma glucose (mmol/l) – 24wk	Mean change	223		-0.38 (SD 1.67620457364983) b
Body weight:				
Weight (kg) – 24wk	Mean change	223		0.18 (SD 2.59049797745882) b
Weight (kg) – 24wk	Mean change	223		0.18 (SD 2.59049797745882) b
Weight (kg) – 24wk	Continuous	223		79.48 (SD 20.5716015857024) b
Weight (kg) – 24wk	Continuous	223		79.48 (SD 20.5716015857024) b

[a] Estimated from graph, SD calculated from 95% CI
[b] SD calculated from reported 95% CI

Table 85: Rosenstock et al. (2007)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** USA, Europe and Asia **Authors' conclusions:** First-line treatment with vildagliptin/pioglitazone combination in patients with type 2 diabetes provides better glycaemic control than either monotherapy component yet has minimal risk of hypoglycaemia and a tolerability profile comparable with component monotherapy **Source of funding:** Funded by Novartis Pharmaceuticals Corporation **Comments:** 24 week, double-blind, randomised, active controlled, parallel group study. Treatment blinding was maintained with a double-dummy technique
Number and characteristics of patients	**Total number of patients:** 607 **Inclusion criteria:** enrolled patients diagnosed with type 2 diabetes with a Hba1c between 7.5 and 11% at screening while receiving no pharmacological treatment for at least 12 weeks prior to screening and no OAD

	for more than three consecutive months at any time in the past. Male and female patients aged 18-80 years, body mass index (BMI) range of 22–45 kg/m2 and with FPG <15 mmol/l were eligible to participate **Exclusion criteria:** Patients were excluded if they had a history of type 1 or secondary forms of diabetes, acute metabolic diabetic complications, myocardial infarction, unstable angina or coronary artery bypass surgery within the previous 6 months, congestive heart failure, liver disease such as cirrhosis or chronic active hepatitis, or any contraindications and warnings according to the country-specific label for pioglitazone. Patients with any of the following laboratory abnormalities were also excluded: alanine aminotransferase or aspartate aminotransferase >2.5 times the upper limit of normal (ULN); direct bilirubin >1.3 times the ULN; serum creatinine levels >220 mmol/l, clinically significant abnormal TSH or fasting triglycerides (TGs) >7.9 mmol/l.
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** some on oral hypoglycaemic drugs and/or insulin **Details of washout period:** patients had received no pharmacological treatment for at least 12 weeks prior to screening
Lifestyle advice	no details reported
Follow-up	**Total follow-up (wks):** 24 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 24 **Frequency of monitoring appointments:** no details reported
Arms	**(1) Vildagliptin (100 mg qd)** N: 154 Treatment duration (wks): 24 Washout period (d): 0 Treatment(s): Vildagliptin (Oral) – fixed-dose Set dose (mg/d):100 Frequency of dosing: once a day **(2) Pioglitazone (30 mg qd)** N: 161 Treatment duration (wks): 24 Washout period (d): 0 Treatment(s): Pioglitazone (Oral) – fixed-dose Set dose (mg/d):30 Frequency of dosing: once a day **(3) -** N: 0 Treatment duration (wks): - Washout period (d): - Treatment(s):
Outcomes	**General** The ITT population (n=592) comprised all patients who received at least one dose of study medication and for whom a baseline and at least one post baseline efficacy assessment was available. Outcomes not extracted in this evidence table include beta cell function. Data from 2 trial arms not extracted as they compare dosages for combination therapy (outside scope of review). 28 (17.4%) patients in the pioglitazone group, 19 (12.8%) in the vilda/pio (100/30 mg) group, 29 (20.1%) in the vilda/pio (50/15 mg) and 18 (11.7%) discontinued the study
Baseline characteristics	

		Vildagliptin (100 mg qd)			Pioglitazone (30 mg qd)				
		N	k	mean	N	k	mean	Δ	p
Demographics:									
Age (years)	Continuous	154		51.4 (SD 10.8)	161		52.4 (SD 10.3)		
Sex (n male)	Dichotomous	154	98	(63.6%)	161	103	(64.0%)		
Duration of diabetes (yrs)	Continuous	154		1.9 (SD 3.1)	161		2.2 (SD 3.3)		
Ethnicity-White	Dichotomous	154	60	(39.0%)	161	71	(44.1%)		
Ethnicity-Asian	Dichotomous	154	70	(45.5%)	161	69	(42.9%)		
Ethnicity-Hispanic	Dichotomous	154	17	(11.0%)	161	14	(8.7%)		
Ethnicity-Other	Dichotomous	154	7	(4.5%)	161	7	(4.3%)		

Blood glucose: HbA1c (%) – 0wk	Continuous	154		8.6 (SD 1)	161		8.7 (SD 1)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	154		10.6 (SD 2.7)	161		10.5 (SD 3.1)		
Body weight: BMI (kg/m2)	Continuous	154		29.4 (SD 5.8)	161		28.9 (SD 5.5)		
Weight (kg) – 0wka	Continuous	154		82.97856 (SD 16.4)	161		81.56736 (SD 15.5)		
Lipids: Total cholesterol (mmol/l) – 0wk	Mean change	154		5.4 (SD 0.1)	161		5.3 (SD 0.1)		
HDL cholesterol (mmol/l) – 0wk	Mean change	154		1.09 (SD 0.03)	161		1.13 (SD 0.03)		
Triglycerides (mmol/l) – 0wk	Mean change	154		2.5 (SD 0.1)	161		2.3 (SD 0.1)		
LDL cholesterol (mmol/l) – 0wk	Mean change	154		3.2 (SD 0.1)	161		3.2 (SD 0.1)		

[a] estimated from BMI assuming mean height of 1.68m

Results

		Vildagliptin (100 mg qd)			Pioglitazone (30 mg qd)				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: peak glucose excursion (mmol/l) – 24wk	Mean change			-1.9a			-1.2b		
Dropouts: Total dropouts – 24wk	Dichotomous	154	18	(11.7%)	161	28	(17.4%)		
Dropout due to AEs – 24wk	Dichotomous	154	4	(2.6%)	161	9	(5.6%)		
Drop out due to unsatisfactory effect – 24wk	Dichotomous	154	1	(0.6%)	161	4	(2.5%)		
Lipids: Total cholesterol (mmol/l) – 24wk	Mean change	146		-1.7 (SD 15.7)	155		2.5 (SD 14.9)		
HDL cholesterol (mmol/l) – 24wk	Mean change	147		7.7 (SD 21.8)	151		17.5 (SD 24.6)		
Triglycerides (mmol/l) – 24wk	Mean change	146		-5.8 (SD 37.5)	155		-13.4 (SD 34.9)		
LDL cholesterol (mmol/l) – 24wk	Mean change	138		-0.4 (SD 24.7)	146		9.1 (SD 41.1)		
ITT Blood glucose: HbA1c (%) – 16wkc	Continuous	150		7.45 (SD 0.98)	157		7.25 (SD 0.251)		
HbA1c (%) – 24wkc	Continuous	150		7.45 (SD 1.1)	157		7.15 (SD 0.376)		
HbA1c (%) – 24wkd	Mean change	150		-1.1 (SD 1.22)	157		-1.4 (SD 1.25)		
HbA1c < 7% or <=7% – 24wke	Dichotomous	150	64	(42.7%)	157	67	(42.7%)		
Fasting plasma glucose (mmol/l) – 16wkc	Continuous	150		9.5 (SD 2.33)	157		8.4 (SD 1.63)		
Fasting plasma glucose (mmol/l) – 24wkc	Continuous	150		9.2 (SD 1.84)	157		8.4 (SD 1.63)		
Fasting plasma glucose (mmol/l) – 24wkd	Mean change	150		-1.3 (SD 2.45)	157		-1.9 (SD 2.51)		
Body weight: Weight (kg) – 24wkd	Mean change	154		0.2 (SD 3.72)	161		1.5 (SD 3.81)		
Safety population Hypoglycaemic events: All hypoglycaemic events (no patients) – 24wk	Dichotomous	153	1f	(0.7%)	161	1	(0.6%)		
Adverse events: Any adverse event(s) – 24wk	Dichotomous	153	79	(51.6%)	161	83	(51.6%)		

Asthenia – 24wk	Dichotomous	153	3	(2.0%)	161	2	(1.2%)			
Dizziness – 24wk	Dichotomous	153	9	(5.9%)	161	8	(5.0%)			
Edema peripheral – 24wk	Dichotomous	153	8	(5.2%)	161	15	(9.3%)			
Headache – 24wk	Dichotomous	153	5	(3.3%)	161	5	(3.1%)			
Infection (upper airway or other common) – 24wk	Dichotomous	153	6	(3.9%)	161	7	(4.3%)			
Nasopharyngitis – 24wk	Dichotomous	153	4	(2.6%)	161	6	(3.7%)			
Hba1c>9.0%										
Blood glucose: HbA1c (%) – 24wk	Mean change	48		-1.5 (SD 1.39)	55		-1.8 (SD 1.48)			

[a] SE 0.4
[b] SE 0.3
[c] estimated from graph
[d] assumed SE reported in text and converted
[e] approximated to nearest integer (percentages only presented in text)
[f] mild event BG>2.8 mmol/l

		Vildagliptin (100 mg qd)							
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Blood glucose: HbA1c (%) – 24wk	Mean change	154			148				<0.001
HbA1c < 7% or <=7% – 24wk	Dichotomous	154			148				<0.001
Fasting plasma glucose (mmol/l) – 24wk	Mean change	154			148				>0.05a
Body weight: Weight (kg) – 24wk	Mean change	154			148				>0.05a
Lipids: Total cholesterol (mmol/l) – 24wk	Mean change	146			144				>0.05a
HDL cholesterol (mmol/l) – 24wk	Mean change	147			140				>0.05a
Triglycerides (mmol/l) – 24wk	Mean change	146			144				>0.05a
LDL cholesterol (mmol/l) – 24wk	Mean change	138			129				>0.05a
Hba1c>9.0% Blood glucose: HbA1c (%) – 24wk	Mean change	48			56				>0.05a

[a] assumed NS as not reported in text

		Vildagliptin (100 mg qd)							
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Blood glucose: HbA1c (%) – 24wk	Mean change	154			144				>0.05a
HbA1c < 7% or <=7% – 24wk	Dichotomous	154			144				>0.05a
Fasting plasma glucose (mmol/l) – 24wk	Mean change	154			144				>0.05a
Body weight: Weight (kg) – 24wk	Mean change	154			144				>0.05a
Lipids: Total cholesterol (mmol/l) – 24wk	Mean change	146			136				>0.05a
HDL cholesterol (mmol/l) – 24wk	Mean change	147			133				>0.05a
Triglycerides (mmol/l) – 24wk	Mean change	146			136				>0.05a
LDL cholesterol (mmol/l) – 24wk	Mean change	138			122				>0.05a

Hba1c>9.0%										
Blood glucose: HbA1c (%) – 24wk	Mean change	48			51					>0.05a

[a] assumed NS as not reported in text

		Pioglitazone (30 mg qd)							
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Blood glucose: HbA1c (%) – 24wk	Mean change	161			148				<0.001
HbA1c < 7% or <=7% – 24wk	Dichotomous	161			148				<0.001
Fasting plasma glucose (mmol/l) – 24wk	Mean change	161			148				<0.001
Body weight: Weight (kg) – 24wk	Mean change	161			148			MD=0.700 (CI: -0.280, 1.680)	>0.05
Lipids: Total cholesterol (mmol/l) – 24wk	Mean change	155			144				0.001
HDL cholesterol (mmol/l) – 24wk	Mean change	151			140				0.058
Triglycerides (mmol/l) – 24wk	Mean change	155			144				0.252
LDL cholesterol (mmol/l) – 24wk	Mean change	146			129				0.033
Hba1c>9.0% Blood glucose: HbA1c (%) – 24wk	Mean change	55			56				<0.001

		Pioglitazone (30 mg qd)							
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Blood glucose: HbA1c (%) – 24wk	Mean change	161			144				0.039
HbA1c < 7% or <=7% – 24wk	Dichotomous	161			144				>0.05a
Fasting plasma glucose (mmol/l) – 24wk	Mean change	161			144				0.022
Body weight: Weight (kg) – 24wk	Mean change	161			144				>0.05a
Lipids: Total cholesterol (mmol/l) – 24wk	Mean change	155			136				0.448
HDL cholesterol (mmol/l) – 24wk	Mean change	151			133				0.009
Triglycerides (mmol/l) – 24wk	Mean change	155			136				0.073
LDL cholesterol (mmol/l) – 24wk	Mean change	146			122				0.164
Hba1c>9.0% Blood glucose: HbA1c (%) – 24wk	Mean change	55			51				>0.05a

[a] assumed NS as not reported in text

Changes from baseline in primary and secondary endpoints were analysed using an analysis of variance (ANCOVA) model, with treatment and pooled centre as the classification variables and baseline value as the covariate. Chi-square tests were performed to compare the percentage of patients achieving ADA target HbA1c level at endpoint. Meal test was conducted in a subset of patients (approx 19%) but total number from

	each group not reported. The primary comparisons were made to test for superiority of the vildagliptin/pioglitazone combination (100/30 mg q.d.) to pioglitazone monotherapy. Secondary comparisons were made to test for superiority of the vildagliptin/pioglitazone combination (100/30 mg q.d.) to vildagliptin monotherapy and for superiority of the lowdose combination (50/15 mg q.d.) to pioglitazone (30 mg q.d.) monotherapy. It is assumed that other comparisons were not completed. Repeated measures ANCOVAs were performed to determine the significance of the between-group differences in HbA1c

Table 86: Rosenthal & (2002)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** Germany **Authors' conclusions:** Acarbose may be useful in lowering BP in ceratin patients with type 2 diabetes, particularly those with isolated systolic hypertension **Source of funding:** Bayer **Comments:** Unclear blinding
Number and characteristics of patients	**Total number of patients:** 76 **Inclusion criteria:** Patients aged 40-75 years with type 2 diabetes (included patients were obese with mild hypertension) **Exclusion criteria:** patients with myocardial infarction within the last 3 months, type 1 diabetes, severe liver disease, those with hyper or hypothyroidism Pre-randomisation phase: There was a 4 week washout phase where oral antidiabetics and antihypertensive agents were discontinued
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** some on oral hypoglycaemic drugs and/or insulin **Details of washout period:** Unclear what treatments patients were taking at baseline but OADs were washed off during a 4 week period
Lifestyle advice	Lifestyle modification was allowed (no further details reported)
Follow-up	**Total follow-up (wks):** 30 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 26 **Frequency of monitoring appointments:** Assessments undertaken at baseline, 3 and 6 months treatment
Arms	**(1) Glibenclamide** N: 37 Treatment duration (wks): 26 Washout period (d): 28 Comments: Unclear what treatments patients were taking at baseline but OADs were washed off during a 4 week period Treatment(s): Sulfonylurea (Oral) Mean dose (mg/d): 5.1 Minimum dose (mg/d): 1.75 Maximum dose (mg/d): 10.5 Details of dosing regimen: Glibenclamide was titrated from a starting dose of 1.75 mg/day od to a maximum of 10.5 mg/day **(2) Acarbose** N: 39 Treatment duration (wks): 26 Washout period (d): 28 Comments: Unclear what treatments patients were taking at baseline but OADs were washed off during a 4 week period Treatment(s): Acarbose (Oral) – fixed-dose Minimum dose (mg/d): 150 Maximum dose (mg/d): 300 Frequency of dosing: three times a day Details of dosing regimen: Acarbose 50 mg TID, uptitrated to 100 mg TID

Outcomes

General

Unclear if analysis conducted in ITT, analysis or completer set (no details reported).

Baseline characteristics

		Glibenclamide			Acarbose				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	37		57.7 (SD 10.5)	39		57.4 (SD 8.6)		
Blood glucose: Fasting plasma glucose (mmol/l) – 0wk	Continuous	37		8.6025 (SD 2.61)	39		7.548 (SD 2.44)		
Body weight: BMI (kg/m2)	Continuous	37		28.8 (SD 4.3)	39		29.1 (SD 4.3)		
Weight (kg) – 0wk	Continuous	37		82.8 (SD 13.8)	39		84.7 (SD 15.1)		
Height (cm)	Continuous	37		169.5 (SD 10.6)	39		170.4 (SD 10)		
Blood pressure: Systolic blood pressure (mmHg)	Continuous	31		138.5 (SD 14.1)	32		134.9 (SD 11.6)		
Diastolic blood pressure (mmHg)	Continuous	37		85.9 (SD 6.2)	39		84.2 (SD 6.2)		
Lipids: Total cholesterol (mmol/l) – 0wk	Continuous	31		5.717646 (SD 0.959)	32		5.965902 (SD 1.2)		
HDL cholesterol (mmol/l) – 0wk	Continuous	31		1.205076 (SD 0.322)	32		1.20249 (SD 0.438)		
Triglycerides (mmol/l) – 0wk	Continuous	31		1.972363 (SD 1.41)	32		2.171067 (SD 1.21)		
Full analysis set (FAS) or efficacy analysis pop Blood glucose: HbA1c (%) – 0wk	Continuous	31		7.2 (SD 1.7)	32		7 (SD 1.4)		

Results

		Glibenclamide			Acarbose				
		N	k	mean	N	k	mean	Δ	p
Hypoglycaemic events: All hypoglycaemic events (no patients) – 24wk	Dichotomous	37	0	(0.0%)	39	0	(0.0%)		
Adverse events: Any adverse event(s) – 24wka	Dichotomous	37	2	(5.4%)	39	8	(20.5%)		
Full analysis set (FAS) or efficacy analysis pop Blood glucose: HbA1c (%) – 24wk	Continuous	31		7.2 (SD 1.7)	32		7 (SD 1.4)		
Fasting plasma glucose (mmol/l) – 24wk	Continuous	31		7.7145 (SD 1.94)	32		6.8265 (SD 1.83)		
Fasting plasma glucose (mmol/l) – 24wk	Mean change	31		-0.9 (SD 2.5)	32		-0.7 (SD 2.4)		
Body weight: Weight (kg) – 24wk	Continuous	31		83 (SD 12.6)	32		82.2 (SD 13.5)		
Lipids: Total cholesterol (mmol/l) – 24wkb	Mean change	31		-0.001293	32		-0.00059478		
HDL cholesterol (mmol/l) – 24wkb	Mean change	31		0.00152574	32		-0.02205858		

[a] No of patients
[b] SD not reported

Table 87: Saleem et al. (2011)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** Pakistan **Authors' conclusions:** - **Source of funding:** - **Comments:** -
Number and characteristics of patients	**Total number of patients:** 100 **Inclusion criteria:** Adults (30-70 years) newly diagnosed with T2DM, uncontrolled after diet and exercise and on no other treatment **Exclusion criteria:** -
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** All treatment naive/ no OADs at screening **Details of washout period:** None reported. All patients not on any treatment
Lifestyle advice	Not reported
Follow-up	**Total follow-up (wks):** 52 **Length of titration period (wks):** - **Length of maintenance period (wks):** 52 **Frequency of monitoring appointments:** Follow up visits every 2 weeks. Assessments at baseline, 6 and 12 months for HbA1c
Arms	**(1) Repaglinide** N: 50 Treatment duration (wks): 52 Washout period (d): 0 Comments: Repaglinide up to three timees a day before meals adjusted to blood glucose level (mean dose = 4.27mg/day) Treatment(s): repaglinide (Oral) – flexible-dose (dose-adjusted) Mean dose (mg/d): 4.27 Frequency of dosing: variable Details of dosing regimen: given preprandially up to 3 times per day, dosage was adjusted according to blood glucose level. **(2) Glibenclamide** N: 50 Treatment duration (wks): 52 Washout period (d): - Comments: Glibenclamide given once or twice daily adjusted for blood glucose level (Mean dose = 8.8mg/day) Treatment(s): Sulfonylurea (Oral) – flexible-dose (dose-adjusted) Mean dose (mg/d): 8.8 Frequency of dosing: variable Details of dosing regimen: administered once or twice per day (unclear if given preprandially or not). Dose was adjusted according to blood glucose level.
Outcomes	
Baseline characteristics	

		Repaglinide			Glibenclamide				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Demographics:									
Age (years)	Continuous	50		46.6 (SD 10.5)	50		45.8 (SD 8.8)		
Sex (n male)	Dichotomous	50	16	(32.0%)	50	10	(20.0%)		

Blood glucose: HbA1c (%) – 0wk	Continuous	50		9.9 (SD 1.6)	50		10.2 (SD 1.6)		
Fasting plasma glucose (mg/dl) – 26wk	Continuous	50		171 (SD 53)	50		140 (SD 56)		
Fasting plasma glucose (mg/dl) – 26wk	Continuous	50		171 (SD 53)	50		116 (SD 18)		
Fasting plasma glucose (mg/dl) – 26wk	Continuous	50		124 (SD 26)	50		140 (SD 56)		
Fasting plasma glucose (mg/dl) – 26wk	Continuous	50		124 (SD 26)	50		116 (SD 18)		
Body weight: BMI (kg/m2)	Continuous	50		27.1 (SD 3.5)	50		30.4 (SD 5.6)		
Weight (kg) – 0wka	Continuous	50		76.48704 (SD 9.88)	50		85.80096 (SD 15.8)		
Weight (kg) – 26wk	Continuous	50		66 (SD 9.4)	50		72.7 (SD 17.4)		
Weight (kg) – 26wk	Continuous	50		66 (SD 9.4)	50		72.2 (SD 16.5)		
Weight (kg) – 26wk	Continuous	50		65.8 (SD 9.4)	50		72.7 (SD 17.4)		
Weight (kg) – 26wk	Continuous	50		65.8 (SD 9.4)	50		72.2 (SD 16.5)		
Height (cm)	Continuous	50		154 (SD 50)	50		160 (SD 50)		

[a] estimated from BMI assuming mean height of 1.68m

Results

		Repaglinide			Glibenclamide				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Blood glucose: HbA1c (%) – 26wk	Continuous	50		9.3 (SD 1.6)	50		9.8 (SD 1.6)		
HbA1c (%) – 52wk	Continuous	50		8.8 (SD 1.7)	50		9.4 (SD 1.5)		
Fasting plasma glucose (mg/dl) – 26wk	Continuous	50		171 (SD 53)	50		140 (SD 56)		
Fasting plasma glucose (mg/dl) – 26wk	Continuous	50		171 (SD 53)	50		116 (SD 18)		
Fasting plasma glucose (mg/dl) – 26wk	Continuous	50		124 (SD 26)	50		140 (SD 56)		
Fasting plasma glucose (mg/dl) – 26wk	Continuous	50		124 (SD 26)	50		116 (SD 18)		
Fasting plasma glucose (mg/dl) – 52wk	Continuous	50		106 (SD 11)	50		105 (SD 12.7)		
Body weight: Weight (kg) – 26wk	Continuous	50		66 (SD 9.4)	50		72.7 (SD 17.4)		
Weight (kg) – 26wk	Continuous	50		66 (SD 9.4)	50		72.2 (SD 16.5)		
Weight (kg) – 26wk	Continuous	50		65.8 (SD 9.4)	50		72.7 (SD 17.4)		
Weight (kg) – 26wk	Continuous	50		65.8 (SD 9.4)	50		72.2 (SD 16.5)		
Weight (kg) – 52wk	Continuous	50		66 (SD 8.8)	50		71.7 (SD 15.2)		

Table 88: Salman S,Salman F,Satman I,Yilmaz Y,Ozer E,Sengul (2001)

General

Phase:
☑ monotherapy
☐ dual therapy
☐ triple therapy
☐ insulin monotherapy
☐ insulin+oral

Parallel / crossover: Parallel

Country: Turkey

Authors' conclusions: The results of the study demonstrate that acarbose and gliclazide were reasonably effective in improving metabolic control in patients insufficiently controlled with diet alone, and both

	treatments were well tolerated **Source of funding:** Bayer **Comments:** Open trial
Number and characteristics of patients	**Total number of patients:** 72 **Inclusion criteria:** patients with type 2 diabetes for at least 3 months, aged 35-70 years, previously treated with diet alone, BMI <=35 kg/m2, stable body weight, Hba1c 8-10% **Exclusion criteria:** hypersensitivity to acarbose or gliclazide, significant disease or condition, ketonuria or other indication of severe and poorly controlled diabetes, impaired liver or kidney function Pre-randomisation phase: There was a 4 week, placebo controlled run-in period
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** All treatment naive/ no OADs at screening **Details of washout period:** 4 week placebo run in
Lifestyle advice	No details provided
Follow-up	**Total follow-up (wks):** 28 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 24 **Frequency of monitoring appointments:** 4 week placebo run in. Patients attended the clinic at weeks 0, 4, 8, 12, 18 and 24
Arms	**(1) Gliclazide** N: 30 Treatment duration (wks): 24 Washout period (d): 28 Comments: AHA naïve Treatment(s): Sulfonylurea (Oral) – flexible-dose (dose-adjusted) Minimum dose (mg/d): 80 Maximum dose (mg/d): 160 Details of dosing regimen: Gliclazide was started with doses of 40 mg bid until week 4. After this dose was increased up to 80 mg bid depending on metabolic control **(2) Acarbose** N: 27 Treatment duration (wks): 24 Washout period (d): 28 Comments: AHA naïve Treatment(s): Acarbose (Oral) – fixed-dose Minimum dose (mg/d): 50 Maximum dose (mg/d): 300 Frequency of dosing: three times a day Details of dosing regimen: Acarbose, week 1 to 4 every week 50 mg increase to 100 mg BID, week 4-24 100 mg TID, dose reduced to 100 mg BID in case of adverse events
Outcomes	
Baseline characteristics	

		Gliclazide			Acarbose				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	30		56.1 (SD 8.7)	27		52.6 (SD 9.1)		
Sex (n male)	Dichotomous	30	16	(53.3%)	27	17	(63.0%)		
Duration of diabetes (yrs)	Continuous	30		4.7 (SD 5.6)	27		4.2 (SD 3.4)		
Blood glucose: HbA1c (%) – 0wk	Continuous	30		8.7 (SD 0.6)	27		8.9 (SD 0.7)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	30		9.66 (SD 2)	27		9.88 (SD 2.39)		
Body weight: BMI (kg/m2) – 0wk	Continuous	30		29.2 (SD 2.8)	27		30.2 (SD 3.8)		
Blood pressure: Systolic blood pressure (mmHg) – 0wk	Continuous	30		141 (SD 23)	27		144 (SD 24)		
Diastolic blood pressure (mmHg) – 0wk	Continuous	30		84 (SD 12)	27		86 (SD 12)		

	Lipids: Total cholesterol (mmol/l) – 0wk	Continuous	30		5.9 (SD 1.06)	27		5.74 (SD 1.24)		
	HDL cholesterol (mmol/l) – 0wk	Continuous	30		1.09 (SD 0.31)	27		1.11 (SD 0.23)		
	Triglycerides (mmol/l) – 0wk	Continuous	30		2.33 (SD 1.09)	27		2.31 (SD 1.7)		
	LDL cholesterol (mmol/l) – 0wk	Continuous	30		3.81 (SD 0.86)	27		3.68 (SD 1.22)		

Results

		Gliclazide			Acarbose				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Blood glucose: HbA1c (%) – 24wk	Continuous	30		6.5 (SD 0.9)	27		7.1 (SD 1.6)		
Fasting plasma glucose (mmol/l) – 24wk	Continuous	30		7.04 (SD 1.33)	27		7.88 (SD 1.89)		
Body weight: BMI (kg/m2) – 24wk	Continuous	30		29.4 (SD 2.8)	27		29.7 (SD 4)		
Hypoglycaemic events: All hypoglycaemic events (no patients) – 24wk	Dichotomous	30	3	(10.0%)	27	0	(0.0%)		
Adverse events: GI: nausea – 24wk	Dichotomous	30	0	(0.0%)	27	1	(3.7%)		
Any adverse event(s) – 24wk	Dichotomous	30	6	(20.0%)	27	9	(33.3%)		
Blood pressure: Systolic blood pressure (mmHg) – 24wk	Continuous	30		138 (SD 18)	27		144 (SD 17)		
Diastolic blood pressure (mmHg) – 24wk	Continuous	30		82 (SD 9)	27		85 (SD 9)		
Lipids: Total cholesterol (mmol/l) – 24wk	Continuous	30		5.59 (SD 1.03)	27		5.33 (SD 1.03)		
Total cholesterol (mmol/l) – 24wk	Mean change	30		-0.31 (SD 1.13)	27		-0.4 (SD 0.8)		
HDL cholesterol (mmol/l) – 24wk	Mean change	30		0.04 (SD 0.28)	27		0.06 (SD 0.3)		
HDL cholesterol (mmol/l) – 24wk	Continuous	30		1.14 (SD 0.28)	27		1.16 (SD 0.26)		
Triglycerides (mmol/l) – 24wk	Mean change	30		-0.12 (SD 0.83)	27		-0.43 (SD 1.22)		
Triglycerides (mmol/l) – 24wk	Continuous	30		2.21 (SD 0.92)	27		1.88 (SD 0.88)		
LDL cholesterol (mmol/l) – 24wk	Continuous	30		3.4 (SD 0.86)	27		3.37 (SD 0.96)		
LDL cholesterol (mmol/l) – 24wk	Mean change	30		-0.42 (SD 0.94)	27		-0.33 (SD 0.78)		

Table 89: Santeusanio F,Ventura MM,Contadini S,Compagnucci P,Moriconi V,Zaccarini (1993)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy

	☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** Unclear but assumed Italy **Authors' conclusions:** The results of the study confirm that acarbose is effective in NIDDM patients treated with diet alone, even at doses of 50 mg tid. Furthermore the low dose of acarbose was able to minimise gastrointestinal effects **Source of funding:** Unclear **Comments:** Double-blind
Number and characteristics of patients	**Total number of patients:** 84 **Inclusion criteria:** patients with NIDDM for at least 6 months, who no longer had satisfactory metabolic control (Hba1c between 6 and 11%, BMI <35 kg/m2, FBG>140 mg/dl, stable body weight in the previous 3 months, treatment with diet alone for at least 2 months and no previous treatment with insulin or oral agents **Exclusion criteria:** existing gastrointestinal disease, severe or poorly controlled diabetes Pre-randomisation phase: There was a 4 week placebo controlled run-in period
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** All treatment naive/ no OADs at screening **Details of washout period:** AHA naïve, 4 week placebo run-in period
Lifestyle advice	an isocaloric diet was received during the run-in period to maintain a stable body weight
Follow-up	**Total follow-up (wks):** 20 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 16 **Frequency of monitoring appointments:** Hba1c was measured at week 0, 8 and 16
Arms	**(1) Acarbose (50mg TID)** N: 28 Treatment duration (wks): 16 Washout period (d): 28 Comments: AHA naïve Treatment(s): Acarbose (Oral) – fixed-dose Set dose (mg/d):150 Frequency of dosing: three times a day Details of dosing regimen: Acarbose was given 50 mg tid **(2) Placebo** N: 29 Treatment duration (wks): 16 Washout period (d): 28 Comments: AHA naïve Treatment(s): Placebo (Oral) **(3) Acarbose (100 mg tid)** N: 27 Treatment duration (wks): 16 Washout period (d): 28 Comments: AHA naïve Treatment(s): Acarbose (Oral) – fixed-dose Set dose (mg/d):300 Frequency of dosing: three times a day Details of dosing regimen: Acarbose 100 mg TID
Outcomes	
Baseline characteristics	

		Acarbose (50mg TID)			Placebo				
		N	k	mean	N	k	mean	Δ	p
Full analysis set (FAS) or efficacy analysis pop									
Demographics:									
Age (years) a	Continuous	18		58.9 (SD 9.76)	23		55.5 (SD 2.4)		
Sex (n male)	Dichotomous	18	10	(55.6%)	23	16	(69.6%)		
Duration of diabetes (yrs) a	Continuous	18		3.85 (SD 2.97)	23		3.87 (SD 4.32)		

Blood glucose: HbA1c (%) – 0wka	Continuous	18		7.07 (SD 0.849)	23		7.22 (SD 0.911)
Fasting plasma glucose (mmol/l) – 0wka	Continuous	18		9.6015 (SD 1.98)	23		10.0455 (SD 0.494)
Body weight: BMI (kg/m2) – 16wka	Continuous	18		27.8 (SD 2.97)	23		29.4 (SD 3.36)

[a] SD calculated from reported SE

		Acarbose (50mg TID)			Acarbose (100 mg tid)				
		N	k	mean	N	k	mean	Δ	p
Full analysis set (FAS) or efficacy analysis pop									
Demographics: Age (years) a	Continuous	18		58.9 (SD 9.76)	23		53.8 (SD 11)		
Sex (n male)	Dichotomous	18	10	(55.6%)	23	15	(65.2%)		
Duration of diabetes (yrs) a	Continuous	18		3.85 (SD 2.97)	23		5.05 (SD 4.8)		
Blood glucose: HbA1c (%) – 0wka	Continuous	18		7.07 (SD 0.849)	23		7.15 (SD 0.844)		
Fasting plasma glucose (mmol/l) – 0wka	Continuous	18		9.6015 (SD 1.98)	23		10.3785 (SD 2.26)		
Body weight: BMI (kg/m2) – 16wk	Continuous	18		27.8 (SD 2.97) a	23		28.6 (SD 3.8) b		

[a] SD calculated from reported SE
[b] Assumed SD reported

		Placebo			Acarbose (100 mg tid)				
		N	k	mean	N	k	mean	Δ	p
Full analysis set (FAS) or efficacy analysis pop									
Demographics: Age (years) a	Continuous	23		55.5 (SD 2.4)	23		53.8 (SD 11)		
Sex (n male)	Dichotomous	23	16	(69.6%)	23	15	(65.2%)		
Duration of diabetes (yrs) a	Continuous	23		3.87 (SD 4.32)	23		5.05 (SD 4.8)		
Blood glucose: HbA1c (%) – 0wka	Continuous	23		7.22 (SD 0.911)	23		7.15 (SD 0.844)		
Fasting plasma glucose (mmol/l) – 0wka	Continuous	23		10.0455 (SD 0.494)	23		10.3785 (SD 2.26)		
Body weight: BMI (kg/m2) – 16wk	Continuous	23		29.4 (SD 3.36) a	23		28.6 (SD 3.8) b		

[a] SD calculated from reported SE
[b] Assumed SD reported

Results

		Acarbose (50mg TID)			Placebo				
		N	k	mean	N	k	mean	Δ	p
Adverse events: Any adverse event(s) – 16wk	Dichotomous	18	9	(50.0%)	23	9	(39.1%)		
Flatulence – 16wk	Dichotomous	18	8	(44.4%)	23	7	(30.4%)		
GI: diarrhoea – 16wk	Dichotomous	18	0	(0.0%)	23	0	(0.0%)		
GI: abdominal pain – 16wk	Dichotomous	18	4	(22.2%)	23	0	(0.0%)		
Dropouts: Dropout due to AEs – 16wk	Dichotomous	28	2	(7.1%)	29	1	(3.4%)		

Lipids: Total cholesterol (mmol/l) – 16wk	Mean change	18		-0.03 (SD 0.81)	22		0.06 (SD 0.91)		
HDL cholesterol (mmol/l) – 16wk	Mean change	17		-0.05 (SD 0.31)	21		0.04 (SD 0.29)		
Triglycerides (mmol/l) – 16wk	Mean change	17		0.09 (SD 1)	20		-0.04 (SD 1.4)		
Full analysis set (FAS) or efficacy analysis pop Blood glucose: HbA1c (%) – 16wk	Continuous	18		6.47 (SD 0.933)	23		7.52 (SD 1.1)		
Fasting plasma glucose (mmol/l) – 16wk	Continuous	18		8.3805 (SD 2.52)	23		10.4007 (SD 2.26)		

		Acarbose (50mg TID)			Acarbose (100 mg tid)				
		N	k	mean	N	k	mean	Δ	p
Adverse events: Any adverse event(s) – 16wk	Dichotomous	18	9	(50.0%)	23	17	(73.9%)		
Flatulence – 16wk	Dichotomous	18	8	(44.4%)	23	14	(60.9%)		
GI: diarrhoea – 16wk	Dichotomous	18	0	(0.0%)	23	1	(4.3%)		
GI: abdominal pain – 16wk	Dichotomous	18	4	(22.2%)	23	3	(13.0%)		
Dropouts: Dropout due to AEs – 16wk	Dichotomous	28	2	(7.1%)	27	4	(14.8%)		
Lipids: Total cholesterol (mmol/l) – 16wk	Mean change	18		-0.03 (SD 0.81)	22		0.05 (SD 1.01)		
HDL cholesterol (mmol/l) – 16wk	Mean change	17		-0.05 (SD 0.31)	22		0.02 (SD 0.3)		
Triglycerides (mmol/l) – 16wk	Mean change	17		0.09 (SD 1)	21		0.22 (SD 1.03)		
Full analysis set (FAS) or efficacy analysis pop Blood glucose: HbA1c (%) – 16wk	Continuous	18		6.47 (SD 0.933)	23		6.41 (SD 1.15)		
Fasting plasma glucose (mmol/l) – 16wk	Continuous	18		8.3805 (SD 2.52)	23		9.0798 (SD 1.81)		

		Placebo			Acarbose (100 mg tid)				
		N	k	mean	N	k	mean	Δ	p
Adverse events: Any adverse event(s) – 16wk	Dichotomous	23	9	(39.1%)	23	17	(73.9%)		
Flatulence – 16wk	Dichotomous	23	7	(30.4%)	23	14	(60.9%)		
GI: diarrhoea – 16wk	Dichotomous	23	0	(0.0%)	23	1	(4.3%)		
GI: abdominal pain – 16wk	Dichotomous	23	0	(0.0%)	23	3	(13.0%)		
Dropouts: Dropout due to AEs – 16wk	Dichotomous	29	1	(3.4%)	27	4	(14.8%)		
Lipids: Total cholesterol (mmol/l) – 16wk	Mean change	22		0.06 (SD 0.91)	22		0.05 (SD 1.01)		
HDL cholesterol (mmol/l) – 16wk	Mean change	21		0.04 (SD 0.29)	22		0.02 (SD 0.3)		
Triglycerides (mmol/l) – 16wk	Mean change	20		-0.04 (SD 1.4)	21		0.22 (SD 1.03)		

	Full analysis set (FAS) or efficacy analysis pop									
	Blood glucose:									
	HbA1c (%) – 16wk	Continuous	23		7.52 (SD 1.1)	23		6.41 (SD 1.15)		
	Fasting plasma glucose (mmol/l) – 16wk	Continuous	23		10.4007 (SD 2.26)	23		9.0798 (SD 1.81)		

Table 90: Santilli et al. (2010)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** Italy **Authors' conclusions:** Postprandial hyperglycaemia is associated with enhanced lipid peroxidation and platelet activation in early type 2 diabetes. A moderate decrease in PPG achieved with acarbose causes time-dependent downregulation of these phenomena, suggesting a causal link between early metabolic abnormalities and platelet activation in this setting **Source of funding:** supported by an unrestricted grant from Bayer (the funding source had no role in design, conduct, data analysis or reporting of the study **Comments:** Double-blind randomised trial. Randomisation list was generated by the trial statistician with blocks of 6 participants and number were stored in opaque envelopes and opened by the enrolling clinic staff at the time of enrollment. Patients and all investigators were blind to treatment allocation
Number and characteristics of patients	**Total number of patients:** 48 **Inclusion criteria:** patients with type 2 diabetes (according to ADA criteria), in an early stage as defined by a known disease suration <=6 months, presenting at the time of recruitment with Hba1c values <=7% in the absence of any treatment affecting glycaemic control, no previous AHA **Exclusion criteria:** smoking, evidence of clinically significant hepatic, renal, cardiac or pulmonary insufficiency, history of malignant neoplasms (diagnosed and treated within the last 5 years), type 1 diabetes, microvasular complications (nephropathy, detected by persistent microalbuminuria between 30 and 300 mg/24 hour in at least two of three consecutive 24 hour urine collections), macrovasular complications, pregnancy or lactation, history of malabsorption or regular daily consumption of alchohol. Patients requiring chronic non-steroidal anti-inflammatory drug therapy or low dose aspirin were also excluded. All patients with documented gastrointestinal disease and those taking medications likely to alter gut motility or absoption were also excluded. Patents with arterial hypertension or hypercholesterolemia were included if well controlled with stable drug therapy Pre-randomisation phase: The study included a 3 week baseline period during which patients were not treated with any drugs that could interfere with glucose metabolism. 3 week baseline period followed by 4 week titration (assumed to be part of treatment period)
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** All treatment naive/ no OADs at screening **Details of washout period:** All AHA naïve, 3 week run in
Lifestyle advice	At randomisation, patients were instructed to follow a low-fat and low-caloric diet (-20% of estimated daily energyexpenditure) and were encouraged to exercise regularly. These instructions were reinforced at each visit
Follow-up	**Total follow-up (wks):** 23 **Length of titration period (wks):** 4 **Length of maintenance period (wks):** 16 **Frequency of monitoring appointments:** No details reported
Arms	**(1) Acarbose** N: 27 Treatment duration (wks): 20

Washout period (d): 21
Comments: Drug naïve

Treatment(s): Acarbose (Oral) – forced titration
Set dose (mg/d):300
Minimum dose (mg/d): 50
Maximum dose (mg/d): 300
Participants achieving full dose (n): 23
Frequency of dosing: three times a day
Compliance: drug compliance was verified by pill counts
Details of dosing regimen: Acarbose was titrated over a period of 4 weeks according to the following schedule: 50 mg once daily for the first 7 days (at dinner time), 50 mg twice daily (lunch and dinner) for the following 7 days, 50 mg three times daily (at breakfast, lunch and dinner) for another week and finally 100 mg three times daily. Down titration to 50 mg three times daily for those who could not tolerate 100 mg three times daily was allowed in order to minimise the rate of drop out. During the treatment period, each subject received the randomised treatment every day with the first bite of each meal. After titration 94% of subjects receiveing acarbose had received the full dose of 100 mg three times daily. In 3 patients, the drug was down-titrated to 50 mg twice daily during the last 4 weeks due to gastrointestinal intolerance.

(2) Placebo

N: 27

Treatment duration (wks): 20
Washout period (d): 21
Comments: Drug naïve

Treatment(s): Placebo
Compliance: drug compliance was verified by pill counts
Details of dosing regimen: No details reported

Outcomes

General

The primary endpoint in this study was urinary 11-dehydro-TXB2 excretion rate at 20 weeks (not extracted in this evidence table). Other outcomes not extracted in this table include MAGE, plasma P-selectin, urinary 8-iso-PGF, plasma CD40L, serum CRP and plasma ADMA.

4 (15%) patients in the acarbose and 2 patients (7%) in the placebo group did not complete the study.

Data collected from samples on the first and third weeks before randomisation were averaged to obtain baseline values

Baseline characteristics

		Acarbose			Placebo				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	25		med: 62 [rng 51–68]	23		med: 61 [rng 54–65]		
Sex (n male)	Dichotomous	25	14	(56.0%)	23	12	(52.2%)		
Blood glucose: HbA1c (%) – 0wk	Continuous	25		med: 6.7 [rng 6.5–7]	23		med: 6.5 [rng 6.1–6.8]		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	25		med: 6.985785 [rng 6.4269–7.5924]	23		med: 7.0374 [rng 6.7599–7.8144]		
Postprandial plasma glucose (mmol/l) – 0wk	Continuous	25		med: 9.9234 [rng 6.82095–11.5329]	23		med: 8.9244 [rng 7.04295–10.0344]		
Body weight: BMI (kg/m2) – 0wk	Continuous	25		med: 27 [rng 24.6–31.2]	23		med: 26.7 [rng 23.7–30.1]		
Waist/hip ratio	Continuous	25		med: 0.98 [rng 0.94–1.03]	23		med: 0.96 [rng 0.88–0.99]		
Blood pressure: Diagnosis of hypertension	Dichotomous	25	15	(60.0%)	23	13	(56.5%)		
Systolic blood pressure (mmHg)	Continuous	25		med: 130 [rng 120–135]	23		med: 130 [rng 120–146]		
Diastolic blood pressure (mmHg)	Continuous	25		med: 80 [rng 71–87]	23		med: 79 [rng 70–80]		
Lipids: Total cholesterol (mmol/l)	Continuous	25		med: 4.962534 [rng 3.928134–5.841774]	23		med: 5.531454 [rng 4.497054–5.738334]		

HDL cholesterol (mmol/l)	Continuous	25		med: 1.290414 [rng 1.135254–1.497294]	23		med: 1.393854 [rng 1.212834–1.600734]			
Triglycerides (mmol/l)	Continuous	25		med: 1.220449 [rng 0.949489–1.718338]	23		med: 1.231739 [rng 1.028519–1.695758]			
Other medication: Anti-hypertensive	Dichotomous	25	15	(60.0%)	23	13	(56.5%)			

Results

		Acarbose			Placebo				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 8wka	Mean change	25		-0.018 (SD 0.125)	23		-0.002 (SD 0.115)	MD=-0.016 (CI: -0.030, -0.002)	0.027b
HbA1c (%) – 20wka	Mean change	25		-0.026 (SD 0.15)	23		0.02 (SD 0.134)	MD=-0.028 (CI: -0.044, -0.012)	0.027c
Fasting plasma glucose (mmol/l) – 4wka	Mean change	25		-0.0002775 (SD 0.0139)	23		-0.0004995 (SD 0.0138)	MD=0.000 (CI: -0.001, 0.002)	0.80d
Fasting plasma glucose (mmol/l) – 8wka	Mean change	25		-0.0012765 (SD 0.0139)	23		-0.0000555 (SD 0.0138)	MD=-0.001 (CI: -0.003, 0.000)	0.15e
Fasting plasma glucose (mmol/l) – 12wkf	Mean change	25		-0.0008325 (SD 0.0153)	23		-0.0002775 (SD 0.0149)	MD=-0.001 (CI: -0.002, 0.001)	0.53g
Fasting plasma glucose (mmol/l) – 16wkf	Mean change	25		-0.0019425 (SD 0.0153)	23		0.0000555 (SD 0.0149)	MD=-0.002 (CI: -0.004, 0.000)	0.028h
Fasting plasma glucose (mmol/l) – 20wka	Mean change	25		-0.0018315 (SD 0.0153)	23		-0.0001665 (SD 0.0149)	MD=-0.002 (CI: -0.003, 0.000)	0.058i
Postprandial plasma glucose (mmol/l) – 4wka	Mean change	25		-0.0049395 (SD 0.0272)	23		-0.0012765 (SD 0.0266)	MD=-0.004 (CI: -0.007, -0.001)	0.021j
Postprandial plasma glucose (mmol/l) – 8wka	Mean change	25		-0.003996 (SD 0.0275)	23		-0.001443 (SD 0.0266)	MD=-0.003 (CI: -0.006, 0.000)	0.011k
Postprandial plasma glucose (mmol/l) – 12wkf	Mean change	25		-0.0053835 (SD 0.0275)	23		-0.0030525 (SD 0.0266)	MD=-0.002 (CI: -0.005, 0.001)	0.15l
Postprandial plasma glucose (mmol/l) – 16wkf	Mean change	25		-0.003885 (SD 0.0272)	23		-0.0030525 (SD 0.0266)	MD=-0.001 (CI: -0.004, 0.002)	0.62m
Postprandial plasma glucose (mmol/l) – 20wka	Mean change	25		-0.00555 (SD 0.0272)	23		-0.000222 (SD 0.024)	MD=-0.005 (CI: -0.008, -0.003)	0.001n
Body weight: BMI (kg/m2) – 20wka	Mean change	25		-0.003 (SD 0.15)	23		-0.007 (SD 0.0959)	MD=0.004 (CI: -0.120, 0.128)	0.60o
Dropouts: Total dropouts – 20wk	Dichotomous	27	2	(7.4%)	27	4	(14.8%)		
Dropout due to AEs – 20wk	Dichotomous	27	2	(7.4%)	27	2	(7.4%)		

[a] [DO NOT USE - OUTSIDE TIME RANGE]
[b] 95% CI -0.03 to -0.02
[c] 95% CI -0.044 to -0.011
[d] 95% CI -0.026 to 0.033
[e] 95% CI -0.052 to 0.008
[f] Log-transformed mean change
[g] 95% CI -0.041 to 0.021
[h] 95% CI -0.067 to -0.004
[i] 95% CI -0.062 to 0.001
[j] 95% CI -0.12 to -0.01
[k] 95% CI -0.1 to 0.01
[l] 95% CI -0.099 to 0.015
[m] 95% CI -0.073 to 0.44
[n] 95% CI -0.15 to -0.043

	[o] 95% CI -0.12 to 0.21
	Comparisons of baseline data between the groups were performed by chi-squared statistics, Fisher exact tests, unpaired Student's t-tests or Mann-Whitney U-tests. Linear mixed-effects model for repeated measures over time was used for the primary analysis (and other continuous variables) with 11-dehdro-TXB2 excretion rate as the dependent variable, week of visit, study groupand time-by-group interaction as fixed effects, and patients and error as random effects. Least-sqaures estimates of treatment differences and standard errors were obtained from the mixed effect model

Table 91: Scherbaum et al. (2002)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** Germany **Authors' conclusions:** The results indicate that pioglitazone monotherapy together with dietary control is both effective and safe in patients with type 2 diabetes **Source of funding:** Takeda **Comments:** Double-blind
Number and characteristics of patients	**Total number of patients:** 233 **Inclusion criteria:** Patients with type 2 diabetes, aged 35 to 70 years, BMI between 25 and 35 kg/m2, Hba1c between 7.5 and 12% and FBG between 140 and 300 mg/dl (<=250 mg/dl at end of washout period) **Exclusion criteria:** patients with type 1 diabetes, secondary failure to treatment with sulfonylurea or requirement for other antidiabetic treatment, history of ketoacidosis, pancreatitis, liver disease, heart failure, myocardial infarction Pre-randomisation phase: There was a 10 week placebo washout phase
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** some on oral hypoglycaemic drugs and/or insulin **Details of washout period:** Unclear previous OAD therapy but there was a 10 week placebo washout where previous therapy was discontinued
Lifestyle advice	Patients were required to follow a disease and bodyweight oriented diet throughout the study period
Follow-up	**Total follow-up (wks):** 26 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 26 **Frequency of monitoring appointments:** Hba1c values were obtained at weeks 4,8,12,18,22 and 26
Arms	**(1) Pioglitazone (15 mg)** N: 83 Treatment duration (wks): 26 Washout period (d): 70 Comments: Unclear previous OAD therapy but there was a 10 week placebo washout where previous therapy was discontinued Treatment(s): Pioglitazone (Oral) – fixed-dose Set dose (mg/d):15 Frequency of dosing: once a day Details of dosing regimen: 15 mg/day od **(2) Pioglitazone (30 mg)** N: 72 Treatment duration (wks): 26 Washout period (d): 70 Comments: Unclear previous OAD therapy but there was a 10 week placebo washout where previous therapy was discontinued Treatment(s): Pioglitazone (Oral) – fixed-dose Set dose (mg/d):30 Frequency of dosing: once a day Details of dosing regimen: 30 mg/day od

(3) Placebo
N: 78
Treatment duration (wks): 26
Washout period (d): 70
Comments: Unclear previous OAD therapy but there was a 10 week placebo washout where previous therapy was discontinued
Treatment(s): Placebo (Oral)

Outcomes

Baseline characteristics

		Pioglitazone (15 mg)			Pioglitazone (30 mg)				
		N	k	mean	N	k	mean	Δ	p
Demographics:									
Age (years)	Continuous	89		58	78		59.6		
Sex (n male)	Dichotomous	89	56	(62.9%)	78	32	(41.0%)		
Duration of diabetes (yrs)	Continuous	89		5.4	78		4.6		
Blood glucose:									
HbA1c (%) – 0wk	Continuous	89		9.33 (SD 1.18)	78		9.06 (SD 1.2)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	89		13.02585 (SD 2.31)	78		12.32655 (SD 3.61)		
Body weight:									
BMI (kg/m2)	Continuous	89		29.9	78		29.3		
Weight (kg) – 0wka	Continuous	89		84.38976	78		82.69632		

[a] estimated from BMI assuming mean height of 1.68m

		Pioglitazone (15 mg)			Placebo				
		N	k	mean	N	k	mean	Δ	p
Demographics:									
Age (years)	Continuous	89		58	84		59.1		
Sex (n male)	Dichotomous	89	56	(62.9%)	84	47	(56.0%)		
Duration of diabetes (yrs)	Continuous	89		5.4	84		5.6		
Blood glucose:									
HbA1c (%) – 0wk	Continuous	89		9.33 (SD 1.18)	84		8.75 (SD 1.06)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	89		13.02585 (SD 2.31)	84		11.4774 (SD 2.57)		
Body weight:									
BMI (kg/m2)	Continuous	89		29.9	84		29.2		
Weight (kg) – 0wka	Continuous	89		84.38976	84		82.41408		

[a] estimated from BMI assuming mean height of 1.68m

		Pioglitazone (30 mg)			Placebo				
		N	k	mean	N	k	mean	Δ	p
Demographics:									
Age (years)	Continuous	78		59.6	84		59.1		
Sex (n male)	Dichotomous	78	32	(41.0%)	84	47	(56.0%)		
Duration of diabetes (yrs)	Continuous	78		4.6	84		5.6		
Blood glucose:									
HbA1c (%) – 0wk	Continuous	78		9.06 (SD 1.2)	84		8.75 (SD 1.06)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	78		12.32655 (SD 3.61)	84		11.4774 (SD 2.57)		
Body weight:									
BMI (kg/m2)	Continuous	78		29.3	84		29.2		
Weight (kg) – 0wka	Continuous	78		82.69632	84		82.41408		

[a] estimated from BMI assuming mean height of 1.68m

Results

		Pioglitazone (15 mg)			Pioglitazone (30 mg)			Δ	p
		N	k	mean	N	k	mean		
Blood glucose: HbA1c (%) – 26wk	Continuous	89		7.99 (SD 0.95)	78		7.78 (SD 1.18)		
HbA1c (%) – 26wk	Mean change	89		-0.92 (SD 1.5)	78		-1.05 (SD 1.25)		
Fasting plasma glucose (mmol/l) – 26wk	Continuous	89		10.5783 (SD 2.36)	78		9.97335 (SD 2.81)		
Fasting plasma glucose (mmol/l) – 26wk	Mean change	89		-1.90365 (SD 2.82)	78		-1.998 (SD 3.47)		
Body weight: Weight (kg) – 26wk	Mean change	89		0.3	78		0.8		
Adverse events: Any serious adverse event(s) – 26wk	Dichotomous	89	1	(1.1%)	78	0	(0.0%)		
Back pain – 26wk	Dichotomous	89	0	(0.0%)	78	3	(3.8%)		
Bronchitis – 26wk	Dichotomous	89	3	(3.4%)	78	3	(3.8%)		
Edema peripheral – 26wk	Dichotomous	89	0	(0.0%)	78	2	(2.6%)		
Liver enzymes: AST (U/l) – 26wka	Continuous	89		0	78		1		
Temperature/influenza – 26wk	Dichotomous	89	2	(2.2%)	78	7	(9.0%)		
UTI – 26wk	Dichotomous	89	2	(2.2%)	78	2	(2.6%)		
Dropouts: Total dropouts – 26wk	Dichotomous	83	22	(26.5%)	72	8	(11.1%)		
Dropout due to AEs – 26wkb	Dichotomous	89	2	(2.2%)	78	0	(0.0%)		

[a] >3 times ULN
[b] Inconsistent with information provided in Study population

		Pioglitazone (15 mg)			Placebo			Δ	p
		N	k	mean	N	k	mean		
Blood glucose: HbA1c (%) – 26wk	Continuous	89		7.99 (SD 0.95)	84		8.29 (SD 1.05)		
HbA1c (%) – 26wk	Mean change	89		-0.92 (SD 1.5)	84		-0.34 (SD 0.98)		
Fasting plasma glucose (mmol/l) – 26wk	Continuous	89		10.5783 (SD 2.36)	84		11.1444 (SD 2.12)		
Fasting plasma glucose (mmol/l) – 26wk	Mean change	89		-1.90365 (SD 2.82)	84		0.1332 (SD 2.57)		
Body weight: Weight (kg) – 26wk	Mean change	89		0.3	84		-1.1		
Adverse events: Any serious adverse event(s) – 26wk	Dichotomous	89	1	(1.1%)	84	4	(4.8%)		
Back pain – 26wk	Dichotomous	89	0	(0.0%)	84	4	(4.8%)		
Bronchitis – 26wk	Dichotomous	89	3	(3.4%)	84	5	(6.0%)		
Edema peripheral – 26wk	Dichotomous	89	0	(0.0%)	84	0	(0.0%)		
Liver enzymes: AST (U/l) – 26wka	Continuous	89		0	84		1		
Temperature/influenza – 26wk	Dichotomous	89	2	(2.2%)	84	7	(8.3%)		
UTI – 26wk	Dichotomous	89	2	(2.2%)	84	4	(4.8%)		
Dropouts: Total dropouts – 26wk	Dichotomous	83	22	(26.5%)	78	19	(24.4%)		
Dropout due to AEs – 26wkb	Dichotomous	89	2	(2.2%)	84	2	(2.4%)		

[a] >3 times ULN
[b] Inconsistent with information provided in Study population

	Pioglitazone (30 mg)	Placebo	Δ	p

		N	k	mean	N	k	mean
Blood glucose: HbA1c (%) – 26wk	Continuous	78		7.78 (SD 1.18)	84		8.29 (SD 1.05)
HbA1c (%) – 26wk	Mean change	78		-1.05 (SD 1.25)	84		-0.34 (SD 0.98)
Fasting plasma glucose (mmol/l) – 26wk	Continuous	78		9.97335 (SD 2.81)	84		11.1444 (SD 2.12)
Fasting plasma glucose (mmol/l) – 26wk	Mean change	78		-1.998 (SD 3.47)	84		0.1332 (SD 2.57)
Body weight: Weight (kg) – 26wk	Mean change	78		0.8	84		-1.1
Adverse events: Any serious adverse event(s) – 26wk	Dichotomous	78	0	(0.0%)	84	4	(4.8%)
Back pain – 26wk	Dichotomous	78	3	(3.8%)	84	4	(4.8%)
Bronchitis – 26wk	Dichotomous	78	3	(3.8%)	84	5	(6.0%)
Edema peripheral – 26wk	Dichotomous	78	2	(2.6%)	84	0	(0.0%)
Liver enzymes: AST (U/l) – 26wka	Continuous	78		1	84		1
Temperature/influenza – 26wk	Dichotomous	78	7	(9.0%)	84	7	(8.3%)
UTI – 26wk	Dichotomous	78	2	(2.6%)	84	4	(4.8%)
Dropouts: Total dropouts – 26wk	Dichotomous	72	8	(11.1%)	78	19	(24.4%)
Dropout due to AEs – 26wkb	Dichotomous	78	0	(0.0%)	84	2	(2.4%)

[a] >3 times ULN
[b] Inconsistent with information provided in Study population

Table 92: Scherbaum et al. (2008)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** 69 sites in Finland (3), France (4), Germany (42), Romania (5), Spain (7) and Sweden (8) **Authors' conclusions:** In drug naïve patients with mild hyperglycaemia, relative to placebo, 52 week treatment with vildagliptin 50 mg (q.d) significantly decreases Hba1c, FPG and PPG and improved beta cell function without weight gain or hypoglycaemia **Source of funding:** Funded by Novartis Pharmaceticals **Comments:** Multicentre, double-blind, randomised placebo controlled trial but no details reported about method of randomisation, blinding and allocation concealment
Number and characteristics of patients	**Total number of patients:** 306 **Inclusion criteria:** drug naïve patients aged 18 years and over who were diagnosed with type 2 diabetes at least 8 weeks previously and who had a Hba1c between 6.2 and 7.5% at the screening visit (upper limit of 7% for centres in Finland and Spain). Patients who had taken no oral antidiabetic drug (OAD) for at least 12 weeks prior to screening and no OAD for more than three consecutive months at any time in the past was considered to be representative of a drug naïve population. Male and female (non-fertile or of child-bearing potential using a medically approved birth control method) patients with a BMI of 22-45 kg/m2 inclusive, were eligble to participate **Exclusion criteria:** history of type 1 diabetes or secondary forms of diabetes, acute metabolic diabetic complications within the past 6 months or evidence of significant diabetic complications. A history of cardiac arrhythmia, congestive heart failure or liver disease also precluded participation, as did any significant laboratory abnormalities Pre-randomisation phase: Each patient attended one screening visit (week 2) during which inclusion/exclusion criteria were assessed. Eligible patients were randomised at visit 2 (baseline)

Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** some on oral hypoglycaemic drugs and/or insulin **Details of washout period:** Drug naïve defined as those not taking any OADs at least 12 weeks prior to screening and no history of 3 consecutive months of OADs
Lifestyle advice	Patients received individualised lifestyle counselling (recommendations to reduce weight by decreasing fat and total colric intake, follow a healthy diet and increase physical activity) at each study visit
Follow-up	**Total follow-up (wks):** 58 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 52 **Frequency of monitoring appointments:** Efficacy and tolerability were assessed during seven additional visits at weeks 4, 12, 16, 24, 32, 40 and 52 weeks of active treatment and at week 56 after a 4 week active treatment-free period (i.e. washout)
Arms	**(1) Vildagliptin** N: 156 Treatment duration (wks): 52 Washout period (d): 0 Comments: There was a post intervention washout. No washout was necessary pre-intervention as patients were drug naïve Treatment(s): Vildagliptin (Oral) – fixed-dose Set dose (mg/d):50 Frequency of dosing: once a day Details of dosing regimen: No further details reported **(2) Placebo** N: 150 Treatment duration (wks): 52 Washout period (d): 0 Comments: There was a post intervention washout. No washout was necessary pre-intervention as patients were drug naïve Treatment(s): Placebo (Oral) Details of dosing regimen: No further details reported-assumed oral to maintain blinding
Outcomes	**General** Outcomes not extracted in this evidence table include beta cell function. In addition analysis by baseline Hba1c >6.5% were not extracted as numbers of patients in each arm were not reported in the full paper and glycaemic measures following the 4-week washout period at 56 weeks were not extracted. There were 23 (15%) drop outs in the vildagliptin group and 19 (13%) in the placebo group Not reported that ITT analysis was carried out

Baseline characteristics

		Vildagliptin			Placebo				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	156		63.3 (SD 10.2)	150		62.8 (SD 11)		
Sex (n male)	Dichotomous	156	93	(59.6%)	150	89	(59.3%)		
Duration of diabetes (yrs)	Continuous	156		2.5 (SD 2.9)	150		2.7 (SD 3.2)		
Ethnicity-White	Dichotomous	156	155	(99.4%)	150	149	(99.3%)		
Ethnicity-Other	Dichotomous	156	1	(0.6%)	150	1	(0.7%)		
Blood glucose: HbA1c (%) – 0wk	Continuous	156		6.7 (SD 0.4)	150		6.8 (SD 0.4)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	156		7.1 (SD 1.2)	150		7.2 (SD 1.2)		
2-h post prandial glucose (mmol/l) – 0wka	Continuous	153		9 (SD 2.47)	149		9.3 (SD 2.44)		
Body weight: BMI (kg/m2)	Continuous	156		30.4 (SD 4.9)	150		30 (SD 4.9)		
Weight (kg) – 0wk	Continuous	156		86 (SD 1.2)	150		85 (SD 1.4)		

[a] SE assumed to be reported in text

Results

		Vildagliptin			Placebo				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 16wka	Continuous	138		6.45 (SD 0.47)	131		6.82 (SD 0.687)		
HbA1c (%) – 24wka	Continuous	138		6.37 (SD 0.47)	131		6.75 (SD 0.572)		
HbA1c (%) – 52wka	Continuous	138		6.48 (SD 0.587)	131		6.86 (SD 0.88)		
HbA1c (%) – 52wkb	Mean change	138		-0.2 (SD 1.25)	131		0.1 (SD 1.22)	MD=-0.300 (CI: -0.496, -0.104)	<0.001
Fasting plasma glucose (mmol/l) – 52wk	Continuous	156			150			MD=-0.400 (CI: -0.792, -0.008)	0.032
Fasting plasma glucose (mmol/l) – 52wkb	Mean change	153		0.2 (SD 1.25)	149		0.5 (SD 1.22)		
Peak prandial glucose excursion – 52wk	Mean change	156			150			MD=-0.500 (CI: -0.892, -0.108)	0.016
2-h post prandial glucose (mmol/l) – 52wka	Mean change	137		-0.49 (SD 3.28)	133		0.45 (SD 3.23)	MD=-0.900 (CI: -1.684, -0.116)	0.012
Body weight: Weight (kg) – 52wkc	Mean change	153		-0.5 (SD 3.75)	149		-0.2 (SD 3.67)	MD=-0.300 (CI: -1.084, 0.484)	0.444
Hypoglycaemic events: symptomatic (confirmed) – 52wkd	Dichotomous	156	0	(0.0%)	150	1	(0.7%)		
Adverse events: Any adverse event(s) – 56wke	Dichotomous	156	114	(73.1%)	150	109	(72.7%)		
Any serious adverse event(s) – 56wkd	Dichotomous	156	13	(8.3%)	150	13	(8.7%)		
Any serious adverse event(s) – 56wkd	Dichotomous	156	13	(8.3%)	150	9	(6.0%)		
Any serious adverse event(s) – 56wkd	Dichotomous	156	10	(6.4%)	150	13	(8.7%)		
Any serious adverse event(s) – 56wkd	Dichotomous	156	10	(6.4%)	150	9	(6.0%)		
Back pain – 56wkd	Dichotomous	156	9	(5.8%)	150	6	(4.0%)		
Bronchitis – 56wkd	Dichotomous	156	5	(3.2%)	150	11	(7.3%)		
Dizziness – 56wkd	Dichotomous	156	8	(5.1%)	150	5	(3.3%)		
Headache – 56wkd	Dichotomous	156	9	(5.8%)	150	6	(4.0%)		
Nasopharyngitis – 56wkd	Dichotomous	156	16	(10.3%)	150	13	(8.7%)		
Osteoarthritis – 56wkd	Dichotomous	156	8	(5.1%)	150	2	(1.3%)		
Dropouts: Total dropouts – 108wk	Dichotomous	156	98	(62.8%)	150	100	(66.7%)		
Dropout due to AEs – 56wkd	Dichotomous	156	14	(9.0%)	150	6	(4.0%)		0.0789f
BMI >=30kg/m2 Blood glucose: HbA1c (%) – 52wk	Mean change	72			70			MD=-0.300 (CI: -0.496, -0.104)	0.044

BMI <30.0 kg/m2 Blood glucose: HbA1c (%) – 52wk	Mean change	84			80			MD=-0.300 (CI: -0.496, -0.104)	0.002
Age >=65 years Blood glucose: HbA1c (%) – 52wk	Mean change	71			73			MD=-0.400 (CI: -0.596, -0.204)	0.005
Age <65 years Blood glucose: HbA1c (%) – 52wk	Mean change	85			77			MD=-0.300 (CI: -0.496, -0.104)	0.009
2-year follow-up (reported in Scherbaum et al. 2008a) Blood glucose: HbA1c (%) – 52wk	Mean change	153			149				<0.001g
HbA1c (%) – 108wkh	Mean change	67		-0.1 (SD 0.819)	61		0.5 (SD 0.781)		
HbA1c (%) – 108wka	Continuous	67		6.54 (SD 0.491)	61		7.05 (SD 0.859)		
Fasting plasma glucose (mmol/l) – 52wk	Mean change	153			149				0.227g
Fasting plasma glucose (mmol/l) – 108wka	Continuous	67		6.9 (SD 1.64)	61		7.8 (SD 1.8)		
Fasting plasma glucose (mmol/l) – 108wkh	Mean change	67		0.6 (SD 2.46)	61		1.2 (SD 2.34)		0.181g
2-h post prandial glucose (mmol/l) – 0wk	Continuous	68			63				NR
2-h post prandial glucose (mmol/l) – 108wka	Continuous	68		8.55 (SD 2.47)	63		10.7 (SD 3.17)		
Body weight: Weight (kg) – 108wkh	Mean change	68		-1.1 (SD 4.12)	63		-0.3 (SD 3.17)	MD=-0.800 (CI: -2.172, 0.572)	0.203
Hypoglycaemic events: symptomatic (confirmed) – 108wk	Dichotomous	156	0	(0.0%)	150	2	(1.3%)		
Adverse events: Any adverse event(s) – 108wk	Dichotomous	68	57	(83.8%)	63	56	(88.9%)		
Any serious adverse event(s) – 108wk	Dichotomous	68	14	(20.6%)	63	12	(19.0%)		
Study drug-related adverse event – 108wk	Dichotomous	68	6	(8.8%)	63	4	(6.3%)		
Arthralgia – 108wk	Dichotomous	68	9	(13.2%)	63	4	(6.3%)		
Back pain – 108wk	Dichotomous	68	11	(16.2%)	63	3	(4.8%)		
Bronchitis – 108wk	Dichotomous	68	8	(11.8%)	63	11	(17.5%)		
Death – 108wk	Dichotomous	68	0	(0.0%)	63	0	(0.0%)		
GI: gastritis – 108wk	Dichotomous	68	5	(7.4%)	63	2	(3.2%)		
GI: gatroenteritis – 108wk	Dichotomous	68	2	(2.9%)	63	4	(6.3%)		
Headache – 108wk	Dichotomous	68	5	(7.4%)	63	1	(1.6%)		
Hypertension – 108wk	Dichotomous	68	6	(8.8%)	63	2	(3.2%)		
Musculoskeletal and connective tissue disorders – 108wk	Dichotomous	68	4	(5.9%)	63	4	(6.3%)		
Nasopharyngitis – 108wk	Dichotomous	68	8	(11.8%)	63	6	(9.5%)		
Osteoarthritis – 108wk	Dichotomous	68	9	(13.2%)	63	2	(3.2%)		
Skin reaction – 108wk	Dichotomous	68	5	(7.4%)	63	3	(4.8%)		

Dropouts: Dropout due to AEs – 108wk	Dichotomous	156	18	(11.5%)	150	10	(6.7%)		
Drop out due to unsatisfactory effect – 108wk	Dichotomous	68	3	(4.4%)	63	14	(22.2%)		

[a] estimated from graph
[b] SE assumed to be reported in text as in graph
[c] SE assumed to be reported (assume ITT population)
[d] (assume ITT population)
[e] number of patients experiencing one or more AE
[f] No further details reported assume ANCOVA
[g] No other details reported
[h] assumed ITT population and SE reported in text

	Last observation carried forward was used to assess change from baseline in Hba1c for patients who discontinued early. Adjusted mean changes reported. Change from baseline in primary and secondary variables were analysed using ANCOVA model with treatment and pooled centre as classification variables and baseline as the covariate. P-values for between group comparisons of adverse events were not reported

Table 93: Schernthaner et al. (2004)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** European countries (France, Latvia, Romania, Germany, Sweden, Lithuania, Hungary, Austria, Bulgaria, Ireland, Greece, Czech Republic) **Authors' conclusions:** Hba1c reduction is similar after pioglitazone and metformin monotherapies, but differences in FPG, plasma lipids and adverse effects between the two compounds may influence decision-making in individual prescribers **Source of funding:** not reported **Comments:** parallel group, double-blind study. Patients randomised centrally using block randomisation. A computer-generated list was administered centrally via a telephone randomisation and resupply service. The study medication was identified by pack numbers.
Number and characteristics of patients	**Total number of patients:** 1199 **Inclusion criteria:** patients aged 35-75 years, with type 2 diabetes inadequately treated with diet alone were randomised. Male and female patients were eligible if they had a Hba1c between 7.5% and 11% with stable or worsening glycaemic control for at least 3 months **Exclusion criteria:** prior use of glucose-lowering pharamcotherapy and specific contraindications to either drug. Corticosteroids and beta-blockers were permitted if treatment commenced at least 4 weeks before screening. At study entry, antihypertensive agents, except thiazides, were allowed dependent on clinical need
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** All treatment naive/ no OADs at screening **Details of washout period:** N/A (treatment naïve)
Lifestyle advice	patients were instructed to adhere to a disease and weight-oriented diet throughout the study. Dietary advice was given at baseline with the target of body weight normalisation and supply of individually appropraite calories and nutrients. If body weight increased by more than 5% at any stage or Hba1c increased to greater than 9% after completed dose titration, patients were given additional intensive dietary counseling
Follow-up	**Total follow-up (wks):** 52 **Length of titration period (wks):** 12 **Length of maintenance period (wks):** 40 **Frequency of monitoring appointments:** Hba1c was measured at baseline and every 4-8 weeks up to week 52. Mean Hba1c values at week 0 (or last available pretreatment value within the previous 2 weeks) were taken as baseline.
Arms	**(1) Pioglitazone**

N: 597

Treatment duration (wks): 52
Washout period (d): 0

Treatment(s): Pioglitazone (Oral) – forced titration

Mean dose (mg/d): 43
Minimum dose (mg/d): 30
Maximum dose (mg/d): 45
Participants achieving full dose (n): 475
Frequency of dosing: variable
Details of dosing regimen: up to 45 mg pioglitazone with metformin placebo once daily. Patients started with 30 mg and doses were increased, maintained or decreased at 4, 8 and 12 weeks according to tolerability. The dose reached at week 12 was fixed for the rest of the study. The goal of forced titration was to reach the individual maximum tolerated dose as quickly as possible.

85.9% of patients reached the maximum dose of pioglitazone.

(2) Metformin

N: 597

Treatment duration (wks): 52
Washout period (d): 0

Treatment(s): Metformin (Oral) – forced titration

Mean dose (mg/d): 2124
Minimum dose (mg/d): 850
Maximum dose (mg/d): 2550
Participants achieving full dose (n): 339
Frequency of dosing: variable
Details of dosing regimen: 850 mg metformin with pioglitazone placebo. Patients started with 850 mg and doses were increased, maintained or decreased at 4, 8 and 12 weeks according to tolerability. The dose reached at week 12 was fixed for the rest of the study. The goal of forced titration was to reach the individual maximum tolerated dose as quickly as possible.

61.6% of patients reached the maximum dose of metformin.

Outcomes

General

Analysis of the primary efficacy end point was performed on an intention to treat (ITT) last observation carried forward basis using an analysis of covariance model with the factor treatment group and the covariant baseline HbA1c (single slope model).

98 (16%) in pioglitazone and 96 (16%) of patients in metformin group withdrew from the study.

Outcomes not extracted in this evidence table include fasting insulin, c-peptide, split proinsulin, blood pressure (not enough data to extract)

Baseline characteristics

		Pioglitazone			Metformin				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Demographics:									
Age (years)	Continuous	597		57 (SD 9.4)	597		56 (SD 9.3)		
Sex (n male)	Dichotomous	597	314	(52.6%)	597	345	(57.8%)		
Duration of diabetes (yrs)	Continuous	597		3.4 (SD 4.3)	597		3.1 (SD 3.8)		
Blood glucose:									
Fasting plasma glucose (mmol/l) – 0wk	Continuous	597		11.3997 (SD 2.71)	597		11.2998 (SD 2.78)		
Body weight:									
BMI (kg/m2)	Continuous	597		31.2 (SD 4.9)	597		31.4 (SD 5.2)		
Weight (kg) – 0wk	Continuous	597		88.2 (SD 15.5)	597		89.7 (SD 16.6)		
Lipids:									
HDL cholesterol (mmol/l) – 0wka	Continuous	588		1.13	588		1.13		
Triglycerides (mmol/l) – 0wka	Continuous	588		2.64	588		2.61		
LDL cholesterol (mmol/l) – 0wka	Continuous	588		3.56	588		3.56		
TC/HDL ratio – 0wka	Continuous	588		5.34	588		5.34		
ITT									
Blood glucose:									
HbA1c (%) – 0wk	Continuous	597		8.7 (SD 1)	597		8.7 (SD 1)		

[a] no SD reported

Results

		Pioglitazone			Metformin				
		N	k	mean	N	k	mean	Δ	p
Body weight: Weight (kg) – 0wk	Continuous	597			597				a
Adverse events: GI: nausea – 0wk	Dichotomous	597			597				a
GI: nausea – 52wk	Dichotomous	597	14	(2.3%)	597	25	(4.2%)		
Any adverse event(s) – 0wk	Dichotomous	597			597				a
Any adverse event(s) – 52wk	Dichotomous	597	316	(52.9%)	597	346	(58.0%)		
Any serious adverse event(s) – 0wk	Dichotomous	597			597				a
Any serious adverse event(s) – 52wkb	Dichotomous	597	29	(4.9%)	597	44	(7.4%)		
Arthralgia – 0wk	Dichotomous	597			597				a
Arthralgia – 52wk	Dichotomous	597	9	(1.5%)	597	12	(2.0%)		
Back pain – 0wk	Dichotomous	597			597				a
Back pain – 52wk	Dichotomous	597	14	(2.3%)	597	17	(2.8%)		
Bronchitis – 0wk	Dichotomous	597			597				a
Bronchitis – 52wk	Dichotomous	597	11	(1.8%)	597	14	(2.3%)		
cardiovascular AE – 0wk	Dichotomous	597			597				a
cardiovascular AE – 52wk	Dichotomous	597	22	(3.7%)	597	23b	(3.9%)		
Death – 0wk	Dichotomous	597			597				a
Death – 52wk	Dichotomous	597	3	(0.5%)	597	2	(0.3%)		
Dizziness – 0wk	Dichotomous	597			597				a
Dizziness – 52wk	Dichotomous	597	14	(2.3%)	597	11	(1.8%)		
Edema peripheral – 0wk	Dichotomous	597			597				a
Edema peripheral – 52wk	Dichotomous	597	27	(4.5%)	597	10	(1.7%)		
Fatigue – 0wk	Dichotomous	597			597				a
Fatigue – 52wk	Dichotomous	597	8	(1.3%)	597	12	(2.0%)		
GI: diarrhoea – 0wk	Dichotomous	597			597				a
GI: diarrhoea – 52wk	Dichotomous	597	19	(3.2%)	597	66	(11.1%)		
Headache – 0wk	Dichotomous	597			597				a
Headache – 52wk	Dichotomous	597	26	(4.4%)	597	14	(2.3%)		
Hypertension – 0wk	Dichotomous	597			597				a
Hypertension – 52wk	Dichotomous	597	15	(2.5%)	597	17	(2.8%)		
liver function/liver enzymes – 0wk	Dichotomous	597			597				a
liver function/liver enzymes – 52wk	Dichotomous	597	0	(0.0%)	597	9	(1.5%)		
Nasopharyngitis – 0wk	Dichotomous	597			597				a
Nasopharyngitis – 52wk	Dichotomous	597	25	(4.2%)	597	19	(3.2%)		
pharyngitis – 0wk	Dichotomous	597			597				a
pharyngitis – 52wk	Dichotomous	597	15	(2.5%)	597	9	(1.5%)		
Temperature/influenza – 0wk	Dichotomous	597			597				a
Temperature/influenza – 52wk	Dichotomous	597	14	(2.3%)	597	22	(3.7%)		
Dropouts: Total dropouts – 52wk	Dichotomous	597	98	(16.4%)	597	96	(16.1%)		
Dropout due to AEs – 0wk	Dichotomous	597			597				a

Dropout due to AEs – 52wk	Dichotomous	597	42	(7.0%)	597	39	(6.5%)		
Drop out due to unsatisfactory effect – 0wk	Dichotomous	597			597				a
Drop out due to unsatisfactory effect – 52wk	Dichotomous	597	15	(2.5%)	597	10	(1.7%)		
ITT									
Blood glucose:									
HbA1c (%) – 12wkc	Continuous	588		7.7 (SD 1.05)	588		7.45 (SD 1)		
HbA1c (%) – 24wkc	Continuous	588		7.15 (SD 1.1)	588		7 (SD 0.9)		
HbA1c (%) – 52wk	Continuous	588		7.28	588		7.18		
HbA1c (%) – 52wkd	Mean change	588		-1.41 (SD 0.97)	588		-1.5 (SD 0.97)		e
Fasting plasma glucose (mmol/l) – 12wkc	Continuous	588		9.102984 (SD 2.5)	588		9.15849 (SD 2.22)		
Fasting plasma glucose (mmol/l) – 24wkc	Continuous	588		8.88096 (SD 2.22)	588		8.769948 (SD 2.22)		
Fasting plasma glucose (mmol/l) – 52wk	Mean change	588		-2.4975 (SD 0.899)	588		-2.1978 (SD 0.899)	MD=-0.300	0.016
Body weight:									
Weight (kg) – 52wkf	Mean change	588		1.9	588		-2.5		
Lipids:									
HDL cholesterol (mmol/l) – 52wkg	Continuous	588		1.29	588		1.21		
HDL cholesterol (mmol/l) – 52wkf	Mean change	588		0.16	588		0.08		
HDL cholesterol (mmol/l) – 52wk	Percentage change from baseline	597			597				<0.001
Triglycerides (mmol/l) – 52wkg	Continuous	588		2.03	588		2.31		
Triglycerides (mmol/l) – 52wkf	Mean change	588		-0.61	588		-0.3		
Triglycerides (mmol/l) – 52wk	Percentage change from baseline	597			597				<0.001
LDL cholesterol (mmol/l) – 52wk	Percentage change from baseline	597			597				<0.001
LDL cholesterol (mmol/l) – 52wkg	Continuous	588		3.83	588		3.44		
LDL cholesterol (mmol/l) – 52wkf	Mean change	588		0.27	588		-0.12		
TC/HDL ratio – 52wk	Percentage change from baseline	597			597				0.98
TC/HDL ratio – 52wkg	Continuous	588		4.92	588		4.92		
PP									
Blood glucose:									
HbA1c (%) – 52wk	Mean change	506		-1.55 (SD 0.9)	516		-1.63 (SD 0.909)		
Fasting plasma glucose (mmol/l) – 52wk	Mean change	506		-2.5974 (SD 0.899)	516		-2.3199 (SD 0.899)		

[a] not reported
[b] approximated to nearest integer (percentages only presented in text)
[c] estimated from graph
[d] SD calculated from reported SE
[e] 90% CI -0.01 to 0.19 at week 52
[f] No SDs reported
[g] SD not reported

	The primary variable, HbA1c, was analyzed by a one-sided t test. Treatment effects on secondary efficacy parameters were analyzed using an analysis of covariance model similar to the primary model for HbA1c, with baseline as covariate. Two-sided t tests were used to compare treatments using 95% CIs and alpha set at 5%. Descriptive statistics were used to summarize changes in body weight, demographics, baseline characteristics, and AEs

Table 94: Schernthaner et al. (2004)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** Austria, Belgium, the Czech Republic, France, Germany, Hungary, Italy, the Netherlands, Poland, Slovakia, Spain, and the United Kingdom were involved. **Authors' conclusions:** This study provides new insights into therapeutic strategies using sulphonylureas. It shows that gliclazide MR is at least as effective as limepiride, either as monotherapy or in combination. The safety of gliclazide MR was significantly better, demonstrating approximately 50% fewer confirmed hypoglycaemic episodes in comparison with glimepiride. **Source of funding:** supported by a grant from the Institut de Recherches Internationales Servier **Comments:** Double-blind trial. Tablets were masked in capsules. It was checked that the blinding method used capsules did not modify the dissolution kinetics of the tablets.
Number and characteristics of patients	**Total number of patients:** 845 **Inclusion criteria:** type 2 diabetic patients (according to World Health Organization criteria), >35 years old, treated for at least 3 months with diet alone or in combination with metformin or an a-glucosidase inhibitor (acarbose or miglitol), with glycated haemoglobin (HbA1c) between 6·9% to 11·5%, and able to perform home blood glucose monitoring. **Exclusion criteria:** current treatment with insulin-secreting agents or thiazolidinediones, contraindication to study drugs, no effective contraception in women with child-bearing potential, elevated transaminases more than threefold the upper normal range or calculated creatinine clearance (CCl) using the Cockroft formula Pre-randomisation phase: titration period assumed to form part of the maintenance period
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** some on oral hypoglycaemic drugs and/or insulin **Details of washout period:** Those on current treatment (metformin or alpha glucosidase inhibitor) continued taking medications at a stable dose and were not washed off (subgroup analyses were reported by baseline OAD). Combinations with alpha glucosidase inhibitor were not extracted
Lifestyle advice	no details reported
Follow-up	**Total follow-up (wks):** 27 **Length of titration period (wks):** 9 **Length of maintenance period (wks):** 18 **Frequency of monitoring appointments:** Visits were scheduled every 9 weeks following titration
Arms	**(1) Gliclazide MR** N: 129 Treatment duration (wks): 27 Washout period (d): 0 Treatment(s): Sulfonylurea (modified release) (Oral) – flexible-dose (dose-adjusted) Mean dose (mg/d): 76.2 Minimum dose (mg/d): 30 Maximum dose (mg/d): 120 Frequency of dosing: once a day Details of dosing regimen: The four dosages of gliclazide MR, from 30 to 120 mg daily currently recommended in European countries were used. Capsules were taken once daily, just before or during breakfast as follows (gliclazide MR/glimepiride): dose 1 (30 mg or 1 mg); dose 2 (60 mg or 2 mg); dose 3 (90 mg or 3 mg); dose 4 (120 mg or 4 mg); and dose 5 (120 mg or 6 mg). Patients started double-blind medication with the lowest dose of gliclazide MR 30 mg. During the titration period, the dose of study medication could be increased every 3 weeks up to dose 4 until metabolic control was achieved [therapeutic

goal defined as fasting plasma glucose (FPG) between 5 and 7·8 mmol/l].

Throughout the study, the dose could be decreased in case of hypoglycaemia according to the investigator's judgement or more than 3 episodes within 1 month.

The method in which the final doses were distributed was similar in the gliclazide MR/glimepiride groups: dose 1 (32%/32·8%); dose 2 18%/19·2%); dose 3 (14·2%/16·9%); dose 4 (15·5%/14·3%), and dose 5 (20·3%/16·8%). Mean (± SD) final daily dosages were 76·2 (38·1) mg for gliclazide MR and 2·9 (1·8) mg for glimepiride for the whole study population (these data do not refer to monotherapy or dual therapy specifically)

(2) Glimepiride

N: 150

Treatment duration (wks): 27
Washout period (d): 0

Treatment(s): Sulfonylurea (Oral) – flexible-dose (dose-adjusted)

Mean dose (mg/d): 2.9
Minimum dose (mg/d): 1
Maximum dose (mg/d): 6
Frequency of dosing: once a day
Details of dosing regimen: The five dosages of glimepiride, from 1 to 6 mg daily, currently recommended in European countries were used. Capsules were taken once

daily, just before or during breakfast as follows (gliclazide MR/glimepiride): dose 1 (30 mg or 1 mg); dose 2 (60 mg or 2 mg); dose 3 (90 mg or 3 mg); dose 4 (120 mg or 4 mg); and dose 5 (120 mg or 6 mg). Patients started double-blind medication with the lowest dose of glimepiride 1 mg. During the titration period, the dose of study medication could be increased every 3 weeks up to dose 4 until metabolic control was achieved [therapeutic goal defined as fasting plasma glucose (FPG) between 5 and 7·8 mmol/l].

Throughout the study, the dose could be decreased in case of hypoglycaemia according to the investigator's judgement or more than 3 pisodes within 1 month.

The method in which the final doses were distributed was similar in the gliclazide MR/glimepiride groups: dose 1 (32%/32·8%); dose 2 18%/19·2%); dose 3 (14·2%/16·9%); dose 4 (15·5%/14·3%), and dose 5 (20·3%/16·8%). Mean (± SD) final daily dosages were 76·2 (38·1) mg for gliclazide MR and 2·9 (1·8) mg for glimepiride for the whole study population (these data do not refer to monotherapy or dual therapy specifically)

(3) Any gliclazide MR

N: 405

Treatment duration (wks): -
Washout period (d): -

Treatment(s): Sulfonylurea (modified release) (Oral)

(4) Any Glimepiride

N: 440

Treatment duration (wks): -
Washout period (d): -

Treatment(s): Sulfonylurea (Oral)

Outcomes

General

Only pre-specified subgroup analyses by treatment regimen (i.e. monotherapy or in combination with metformin) were extracted in this evidence table. Data relating to alpha-glucosidase inhibitor + study drug were not extracted as this included either acarbose or miglitol. Therefore outcomes not extracted included FPG.

All efficacy analyses were performed on the intention-totreat population, defined as all patients exposed to study medication with one baseline and at least one postbaseline efficacy evaluation on treatment, and the per-protocol population defined as completed patients without deviation

interfering with primary efficacy criterion. Safety analyses were performed on all patients who were exposed to at least one dose of study medication. Final values for withdrawn patients corresponded to the final values on treatment (final observation on treatment carried forward).

67 patients withdrew from the study (35 gliclazide MR/32 glimepiride)

Data from 2 trial arms not extracted (dual therapy for first intensification, as patients were on monotherapy and there was no washout period)

Baseline characteristics

		Any Glimepiride		
		N	**k**	**mean**
Demographics:				
Age (years)	Continuous	440		60.6 (SD 10.5)
Sex (n male)	Dichotomous	440	52	(11.8%)
Duration of diabetes (yrs)	Continuous	440		5.8 (SD 5.8)

Blood glucose: Fasting plasma glucose (mmol/l)	Continuous	440		10.1 (SD 2.6)
Body weight: BMI (kg/m2)	Continuous	440		30.6 (SD 4.9)
Weight (kg)	Continuous	440		83.8 (SD 16)
Blood pressure: Systolic blood pressure (mmHg)	Continuous	440		137 (SD 14)
Diastolic blood pressure (mmHg)	Continuous	440		81 (SD 8)
Diabetic complications: Microvascular	Dichotomous	440	11	(2.5%)
Macrovascular	Dichotomous	440	21	(4.8%)
Other medication: Anti-hypertensive	Dichotomous	440	62	(14.1%)
Lipid-lowering medication	Dichotomous	440	33	(7.5%)
ITT Blood glucose: HbA1c (%) – 0wk	Continuous	440		8.2 (SD 1)
HbA1c (%) – 0wk	Continuous	440		8.2 (SD 1)

Results

		Gliclazide MR			Glimepiride				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Blood glucose: HbA1c (%) – 27wk	Continuous	129			150				a
Hypoglycaemic events: confirmed hypoglycaemia – 27wk	Dichotomous	129			150				NS
ITT Blood glucose: HbA1c (%) – 27wk	Mean change	129		-1.3 (SD 1.1)	150		-1.2 (SD 1)		
Safety population Hypoglycaemic events: confirmed hypoglycaemia – 27wk	Dichotomous	133	7	(5.3%)	156	15	(9.6%)		

[a] not reported for subgroups

For efficacy analyses, covariance analysis on the last value including the baseline value as covariate and country and concomitant antidiabetic treatment as factors was used. Changes from baseline to last value were analyzed in each treatment group using a paired Student's t-test. Changes from baseline were tested in each treatment group using one-way analysis of variance for repeated measures on time factor and completed by a Dunnett t-test (baseline as reference). For hypoglycaemic episodes, the percentage of patients reporting at least one episode and the distribution of the number of episodes were compared between treatment groups using Fisher's exact test. The time of occurrence of the first event was compared between the two treatment groups using a model for survival curves (Kaplan–Meier estimator) and Wilcoxon test. Baseline characteristics refer to the whole study population which includes patients on both monotherapy and combination therapyFor efficacy analyses, covariance analysis on the last value including the baseline value as covariate and country and concomitant antidiabetic treatment as factors was used

Table 95: Schwartz et al. (2006)

General

Phase:
☑ monotherapy
☐ dual therapy
☐ triple therapy
☐ insulin monotherapy
☐ insulin+oral

Parallel / crossover: Parallel

	Country: USA **Authors' conclusions:** Once- or twice-daily extended-release metformin was as safe and effective as twice-daily immediate-release metformin and provided continued glycemic control for up to 24 weeks of treatment. **Source of funding:** Financial support provided by Depomed **Comments:** A randomized, doubleblind, active-controlled, fixed-dose trial
Number and characteristics of patients	**Total number of patients:** 750 **Inclusion criteria:** The trial enrolled male and female outpatients, 18–79 years of age, with type 2 diabetes. Patients were either drug naïve (with newly diagnosed diabetes or treated with diet and exercise only) or had received prior drug therapy (monotherapy with oral hypoglycemic agents ther than metformin up to the maximum dose allowed, metformin monotherapy up to 2,000 mg/day, or metformin up to 1,500 mg/day with sulfonylurea up to one-half the maximum allowed dose). Inclusion criteria (determined at the screening visit) included HbA1c levels 7.0–12.0% (drugnaive patients) or 6.5–10.0% (prior drug therapy patients), fasting plasma glucose (FPG) levels 120–400 mg/dl (drug-naive patients) or 120–250 mg/dl (prior drug therapy patients), C-peptide levels >1.0 ng/ml, BMI 22–50 kg/m2, and a negative pregnancy test for female patients. **Exclusion criteria:** Patients were excluded from the study if they were receiving insulin, systemic corticosteroids, nicotinic acid, or isoniazid; had a history of background retinopathy, symptomatic autonomic neuropathy, or unstable angina; had chronic gastroparesis or chronic severe gastrointestinal symptoms, a history of gastric or duodenal ulcers, abdominal surgery within 1 year, or active gastrointestinal disease within 2 years; had any uncontrolled or untreated cardiovascular, hepatic, pulmonary, renal, or neurological system conditions; or had serum creatinine >1.5 mg/dl (male patients) or >1.4 mg/dl (female patients) or proteinuria. Patients were also excluded for lack of efficacy (defined as fasting blood glucose >250 mg/dl for 1 week or >300 mg/dl for 3 days) Pre-randomisation phase: there was a washout period (of current OHAs) of 6 weeks followed by titrtaion of 2-3 weeks (this was assumed to form part of the total treatment duration of 24 weeks)
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** some on oral hypoglycaemic drugs and/or insulin **Details of washout period:** Patients were either drug naïve (with newly diagnosed diabetes or treated with diet and exercise only) or had received prior drug therapy (monotherapy with oral hypoglycemic agents other than metformin up to the maximum dose allowed, metformin monotherapy up to 2,000 mg/day, or metformin up to 1,500 mg/day with sulfonylurea up to one-half the maximum allowed dose). There was a 6 week washout period
Lifestyle advice	no details reported
Follow-up	**Total follow-up (wks):** 30 **Length of titration period (wks):** 3 **Length of maintenance period (wks):** 24 **Frequency of monitoring appointments:** There was a 6 week washout period in this trial. Patients were evaluated every 1–2 weeks during the screening and washout periods, weekly for the first 4 weeks of treatment and then every 4 weeks until the end of study.
Arms	**(1) Extended release metformin 1500mg (qd)** N: 178 Treatment duration (wks): 24 Washout period (d): 42 Treatment(s): Metformin (modified release) (Oral) – fixed-dose Set dose (mg/d):1500 Frequency of dosing: once a day Details of dosing regimen: all patients began metformin dosing at 1,000 mg q.d., which was titrated to their assigned dose over 2–3 weeks and continued at that dose for a total treatment duration of 24 weeks. All study drugs and placebos were taken after a meal. 1500mg was given once daily. **(2) Extended release metformin 1500mg (twice daily)** N: 182 Treatment duration (wks): 24 Washout period (d): 42 Treatment(s): Metformin (modified release) (Oral) – fixed-dose Set dose (mg/d):1500 Frequency of dosing: twice a day Details of dosing regimen: all patients began metformin dosing at 1,000 mg q.d., which was titrated to their assigned dose over 2–3 weeks and continued at that dose for a total treatment duration of 24 weeks. All study drugs and placebos were taken after a meal. 1500 mg was given twice daily (500 mg in morning and 1000 mg in the evening) **(3) Extended release metformin 2000mg (qd)** N: 172 Treatment duration (wks): 24 Washout period (d): 42

Treatment(s): Metformin (modified release) (Oral) – fixed-dose
Set dose (mg/d):2000
Frequency of dosing: once a day
Details of dosing regimen: all patients began metformin dosing at 1,000 mg q.d., which was titrated to their assigned dose over 2–3 weeks and continued at that dose for a total treatment duration of 24 weeks. All study drugs and placebos were taken after a meal. 2000 mg was given once daily.

(4) Immediate release metformin 1500 mg (twice daily)

N: 174

Treatment duration (wks): 24
Washout period (d): 42

Treatment(s): Metformin (Oral) – fixed-dose
Set dose (mg/d):1500
Frequency of dosing: twice a day
Details of dosing regimen: all patients began metformin dosing at 1,000 mg q.d., which was titrated to their assigned dose over 2–3 weeks and continued at that dose for a total treatment duration of 24 weeks. All study drugs and placebos were taken after a meal. 1500 mg of immediate release metformin was given twice daily (500 mg in the morning and 1000 mg in the evening)

(5) Any extended release

N: 532

Treatment duration (wks): 24
Washout period (d): 42

Treatment(s): Metformin (modified release)

Outcomes

General

Efficacy and safety analyses were performed using an intent-to-treat population (n=706), defined as all randomly assigned patients who received a study drug and had available efficacy data. Adverse event analyses included all patients who received at least one dose of study drug.

Outcomes not extracted in this evidence table include fructosamine. Data for Hba1c levels from subgroup analyses were not extracted as no baseline measurements or SDs were reported.

The paper reports that 706/750 randomly assigned were included in ITT population and 529 patients completed the study per protocol. No further details relating to drop outs per trial arm are reported.

Baseline characteristics

		All study participants		
		N	k	mean
Demographics:				
Age (years)	Continuous	706		54 (SD 11.8)
Sex (n male)	Dichotomous	706	380	(53.8%)
Duration of diabetes (yrs)	Continuous	706		4.2 (SD 4.8)
Ethnicity-White	Dichotomous	706	441	(62.5%)
Ethnicity-Black	Dichotomous	706	93	(13.2%)
Ethnicity-Asian	Dichotomous	706	16	(2.3%)
Ethnicity-Hispanic	Dichotomous	706	143	(20.3%)
Ethnicity-Other	Dichotomous	706	13	(1.8%)
Body weight:				
BMI (kg/m2)	Continuous	706		33.5 (SD 6.6)
Weight (kg)	Continuous	706		94.5504 (SD 18.62784) a
Previous blood glucose lowering drugs:				
Diet alone (i.e. drug naïve)	Dichotomous	706	338	(47.9%)
Metformin	Dichotomous	706	175	(24.8%)
Sulfonylurea	Dichotomous	706	111	(15.7%)
Metformin + Sulfonylurea	Dichotomous	706	59	(8.4%)
Other	Dichotomous	706	4	(0.6%)

[a] estimated from BMI assuming mean height of 1.68m

	Extended release metformin 1500mg (qd)	Extended release metformin 1500mg (twice daily)	Δ	p

		N	k	mean	N	k	mean		
Demographics: Age (years)	Continuous	178		54 (SD 11.4)	182		54 (SD 11.8)		
Sex (n male)	Dichotomous	178	83	(46.6%)	182	111	(61.0%)		
Duration of diabetes (yrs)	Continuous	178		3.9 (SD 4.5)	182		4.5 (SD 4.9)		
Ethnicity-White	Dichotomous	178	107	(60.1%)	182	116	(63.7%)		
Ethnicity-Black	Dichotomous	178	30	(16.9%)	182	18	(9.9%)		
Ethnicity-Asian	Dichotomous	178	5	(2.8%)	182	5	(2.7%)		
Ethnicity-Hispanic	Dichotomous	178	32	(18.0%)	182	38	(20.9%)		
Ethnicity-Other	Dichotomous	178	4	(2.2%)	182	5	(2.7%)		
Blood glucose: Fasting plasma glucose (mmol/l) – 0wk	Continuous	178		10.545 (SD 7.33)	172		10.68375 (SD 7.21)		
Body weight: BMI (kg/m2)	Continuous	178		33.4 (SD 6.6)	182		33 (SD 6.3)		
Lipids: Total cholesterol (mmol/l) – 0wk	Continuous	178		5.368536 (SD 2.52)	182		5.293542 (SD 2.41)		
HDL cholesterol (mmol/l) – 0wk	Continuous	178		1.17663 (SD 0.656)	182		1.17663 (SD 0.628)		
Triglycerides (mmol/l) – 0wk	Continuous	178		2.244452 (SD 4.41)	182		2.24671 (SD 4.22)		
LDL cholesterol (mmol/l) – 0wk	Continuous	178		3.188538 (SD 2.17)	182		3.16785 (SD 2.06)		
Previous blood glucose lowering drugs: Diet alone (i.e. drug naïve)	Dichotomous	178	81	(45.5%)	182	86	(47.3%)		
Metformin	Dichotomous	178	43	(24.2%)	182	44	(24.2%)		
Sulfonylurea	Dichotomous	178	29	(16.3%)	182	30	(16.5%)		
Metformin + Sulfonylurea	Dichotomous	178	20	(11.2%)	182	12	(6.6%)		
Other	Dichotomous	178	1	(0.6%)	182	2	(1.1%)		
ITT Blood glucose: HbA1c (%) – 0wka	Continuous	178		8.22 (SD 3.34)	182		8.5 (SD 3.24)		

[a] SD calculated from reported SE

		Extended release metformin 1500mg (qd)			Extended release metformin 2000mg (qd)				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	178		54 (SD 11.4)	172		55 (SD 11.7)		
Sex (n male)	Dichotomous	178	83	(46.6%)	172	91	(52.9%)		
Duration of diabetes (yrs)	Continuous	178		3.9 (SD 4.5)	172		3.9 (SD 4.3)		
Ethnicity-White	Dichotomous	178	107	(60.1%)	172	107	(62.2%)		
Ethnicity-Black	Dichotomous	178	30	(16.9%)	172	23	(13.4%)		
Ethnicity-Asian	Dichotomous	178	5	(2.8%)	172	3	(1.7%)		
Ethnicity-Hispanic	Dichotomous	178	32	(18.0%)	172	36	(20.9%)		
Ethnicity-Other	Dichotomous	178	4	(2.2%)	172	3	(1.7%)		
Blood glucose: Fasting plasma glucose (mmol/l) – 0wk	Continuous	178		10.545 (SD 7.33)	172		10.20645 (SD 7.21)		
Body weight: BMI (kg/m2)	Continuous	178		33.4 (SD 6.6)	172		33.7 (SD 6.6)		

Lipids: Total cholesterol (mmol/l) – 0wk	Continuous	178		5.368536 (SD 2.52)	172		5.373708 (SD 2.44)		
HDL cholesterol (mmol/l) – 0wk	Continuous	178		1.17663 (SD 0.656)	172		1.153356 (SD 0.644)		
Triglycerides (mmol/l) – 0wk	Continuous	178		2.244452 (SD 4.41)	172		2.440898 (SD 4.34)		
LDL cholesterol (mmol/l) – 0wk	Continuous	178		3.188538 (SD 2.17)	172		3.222156 (SD 2)		
Previous blood glucose lowering drugs: Diet alone (i.e. drug naïve)	Dichotomous	178	81	(45.5%)	172	84	(48.8%)		
Metformin	Dichotomous	178	43	(24.2%)	172	45	(26.2%)		
Sulfonylurea	Dichotomous	178	29	(16.3%)	172	22	(12.8%)		
Metformin + Sulfonylurea	Dichotomous	178	20	(11.2%)	172	17	(9.9%)		
Other	Dichotomous	178	1	(0.6%)	172	0	(0.0%)		
ITT Blood glucose: HbA1c (%) – 0wk[a]	Continuous	178		8.22 (SD 3.34)	172		8.26 (SD 3.15)		

[a] SD calculated from reported SE

		Extended release metformin 1500mg (qd)			Immediate release metformin 1500 mg (twice daily)			Δ	p
		N	k	mean	N	k	mean		
Demographics: Age (years)	Continuous	178		54 (SD 11.4)	174		54 (SD 12.5)		
Sex (n male)	Dichotomous	178	83	(46.6%)	174	95	(54.6%)		
Duration of diabetes (yrs)	Continuous	178		3.9 (SD 4.5)	174		4.4 (SD 5.4)		
Ethnicity-White	Dichotomous	178	107	(60.1%)	174	111	(63.8%)		
Ethnicity-Black	Dichotomous	178	30	(16.9%)	174	22	(12.6%)		
Ethnicity-Asian	Dichotomous	178	5	(2.8%)	174	3	(1.7%)		
Ethnicity-Hispanic	Dichotomous	178	32	(18.0%)	174	37	(21.3%)		
Ethnicity-Other	Dichotomous	178	4	(2.2%)	174	1	(0.6%)		
Blood glucose: Fasting plasma glucose (mmol/l) – 0wk	Continuous	178		10.545 (SD 7.33)	174		10.90575 (SD 8.2)		
Body weight: BMI (kg/m2)	Continuous	178		33.4 (SD 6.6)	174		33.8 (SD 6.8)		
Lipids: Total cholesterol (mmol/l) – 0wk	Continuous	178		5.368536 (SD 2.52)	174		5.241822 (SD 2.49)		
HDL cholesterol (mmol/l) – 0wk	Continuous	178		1.17663 (SD 0.656)	174		1.140426 (SD 0.648)		
Triglycerides (mmol/l) – 0wk	Continuous	178		2.244452 (SD 4.41)	174		2.09994 (SD 4.36)		
LDL cholesterol (mmol/l) – 0wk	Continuous	178		3.188538 (SD 2.17)	174		3.165264 (SD 2.01)		
Previous blood glucose lowering drugs: Diet alone (i.e. drug naïve)	Dichotomous	178	81	(45.5%)	174	87	(50.0%)		
Metformin	Dichotomous	178	43	(24.2%)	174	43	(24.7%)		
Sulfonylurea	Dichotomous	178	29	(16.3%)	174	30	(17.2%)		
Metformin + Sulfonylurea	Dichotomous	178	20	(11.2%)	174	10	(5.7%)		

Other	Dichotomous	178	1	(0.6%)	174	1	(0.6%)		
ITT									
Blood glucose:									
HbA1c (%) – 0wka	Continuous	178		8.22 (SD 3.34)	174		8.7 (SD 3.3)		

[a] SD calculated from reported SE

		Extended release metformin 1500mg (twice daily)			Extended release metformin 2000mg (qd)				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Demographics:									
Age (years)	Continuous	182		54 (SD 11.8)	172		55 (SD 11.7)		
Sex (n male)	Dichotomous	182	111	(61.0%)	172	91	(52.9%)		
Duration of diabetes (yrs)	Continuous	182		4.5 (SD 4.9)	172		3.9 (SD 4.3)		
Ethnicity-White	Dichotomous	182	116	(63.7%)	172	107	(62.2%)		
Ethnicity-Black	Dichotomous	182	18	(9.9%)	172	23	(13.4%)		
Ethnicity-Asian	Dichotomous	182	5	(2.7%)	172	3	(1.7%)		
Ethnicity-Hispanic	Dichotomous	182	38	(20.9%)	172	36	(20.9%)		
Ethnicity-Other	Dichotomous	182	5	(2.7%)	172	3	(1.7%)		
Blood glucose:									
Fasting plasma glucose (mmol/l) – 0wk	Continuous	172		10.68375 (SD 7.21)	172		10.20645 (SD 7.21)		
Body weight:									
BMI (kg/m2)	Continuous	182		33 (SD 6.3)	172		33.7 (SD 6.6)		
Lipids:									
Total cholesterol (mmol/l) – 0wk	Continuous	182		5.293542 (SD 2.41)	172		5.373708 (SD 2.44)		
HDL cholesterol (mmol/l) – 0wk	Continuous	182		1.17663 (SD 0.628)	172		1.153356 (SD 0.644)		
Triglycerides (mmol/l) – 0wk	Continuous	182		2.24671 (SD 4.22)	172		2.440898 (SD 4.34)		
LDL cholesterol (mmol/l) – 0wk	Continuous	182		3.16785 (SD 2.06)	172		3.222156 (SD 2)		
Previous blood glucose lowering drugs:									
Diet alone (i.e. drug naïve)	Dichotomous	182	86	(47.3%)	172	84	(48.8%)		
Metformin	Dichotomous	182	44	(24.2%)	172	45	(26.2%)		
Sulfonylurea	Dichotomous	182	30	(16.5%)	172	22	(12.8%)		
Metformin + Sulfonylurea	Dichotomous	182	12	(6.6%)	172	17	(9.9%)		
Other	Dichotomous	182	2	(1.1%)	172	0	(0.0%)		
ITT									
Blood glucose:									
HbA1c (%) – 0wka	Continuous	182		8.5 (SD 3.24)	172		8.26 (SD 3.15)		

[a] SD calculated from reported SE

		Extended release metformin 1500mg (twice daily)			Immediate release metformin 1500 mg (twice daily)				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Demographics:									
Age (years)	Continuous	182		54 (SD 11.8)	174		54 (SD 12.5)		
Sex (n male)	Dichotomous	182	111	(61.0%)	174	95	(54.6%)		
Duration of diabetes (yrs)	Continuous	182		4.5 (SD 4.9)	174		4.4 (SD 5.4)		

Ethnicity-White	Dichotomous	182	116	(63.7%)	174	111	(63.8%)		
Ethnicity-Black	Dichotomous	182	18	(9.9%)	174	22	(12.6%)		
Ethnicity-Asian	Dichotomous	182	5	(2.7%)	174	3	(1.7%)		
Ethnicity-Hispanic	Dichotomous	182	38	(20.9%)	174	37	(21.3%)		
Ethnicity-Other	Dichotomous	182	5	(2.7%)	174	1	(0.6%)		
Blood glucose: Fasting plasma glucose (mmol/l) – 0wk	Continuous	172		10.68375 (SD 7.21)	174		10.90575 (SD 8.2)		
Body weight: BMI (kg/m2)	Continuous	182		33 (SD 6.3)	174		33.8 (SD 6.8)		
Lipids: Total cholesterol (mmol/l) – 0wk	Continuous	182		5.293542 (SD 2.41)	174		5.241822 (SD 2.49)		
HDL cholesterol (mmol/l) – 0wk	Continuous	182		1.17663 (SD 0.628)	174		1.140426 (SD 0.648)		
Triglycerides (mmol/l) – 0wk	Continuous	182		2.24671 (SD 4.22)	174		2.09994 (SD 4.36)		
LDL cholesterol (mmol/l) – 0wk	Continuous	182		3.16785 (SD 2.06)	174		3.165264 (SD 2.01)		
Previous blood glucose lowering drugs: Diet alone (i.e. drug naïve)	Dichotomous	182	86	(47.3%)	174	87	(50.0%)		
Metformin	Dichotomous	182	44	(24.2%)	174	43	(24.7%)		
Sulfonylurea	Dichotomous	182	30	(16.5%)	174	30	(17.2%)		
Metformin + Sulfonylurea	Dichotomous	182	12	(6.6%)	174	10	(5.7%)		
Other	Dichotomous	182	2	(1.1%)	174	1	(0.6%)		
ITT Blood glucose: HbA1c (%) – 0wka	Continuous	182		8.5 (SD 3.24)	174		8.7 (SD 3.3)		

[a] SD calculated from reported SE

		Extended release metformin 2000mg (qd)			Immediate release metformin 1500 mg (twice daily)			Δ	p
		N	k	mean	N	k	mean		
Demographics: Age (years)	Continuous	172		55 (SD 11.7)	174		54 (SD 12.5)		
Sex (n male)	Dichotomous	172	91	(52.9%)	174	95	(54.6%)		
Duration of diabetes (yrs)	Continuous	172		3.9 (SD 4.3)	174		4.4 (SD 5.4)		
Ethnicity-White	Dichotomous	172	107	(62.2%)	174	111	(63.8%)		
Ethnicity-Black	Dichotomous	172	23	(13.4%)	174	22	(12.6%)		
Ethnicity-Asian	Dichotomous	172	3	(1.7%)	174	3	(1.7%)		
Ethnicity-Hispanic	Dichotomous	172	36	(20.9%)	174	37	(21.3%)		
Ethnicity-Other	Dichotomous	172	3	(1.7%)	174	1	(0.6%)		
Blood glucose: Fasting plasma glucose (mmol/l) – 0wk	Continuous	172		10.20645 (SD 7.21)	174		10.90575 (SD 8.2)		
Body weight: BMI (kg/m2)	Continuous	172		33.7 (SD 6.6)	174		33.8 (SD 6.8)		
Lipids: Total cholesterol (mmol/l) – 0wk	Continuous	172		5.373708 (SD 2.44)	174		5.241822 (SD 2.49)		
HDL cholesterol (mmol/l) – 0wk	Continuous	172		1.153356 (SD 0.644)	174		1.140426 (SD 0.648)		

Triglycerides (mmol/l) – 0wk	Continuous	172		2.440898 (SD 4.34)	174		2.09994 (SD 4.36)		
LDL cholesterol (mmol/l) – 0wk	Continuous	172		3.222156 (SD 2)	174		3.165264 (SD 2.01)		
Previous blood glucose lowering drugs: Diet alone (i.e. drug naïve)	Dichotomous	172	84	(48.8%)	174	87	(50.0%)		
Metformin	Dichotomous	172	45	(26.2%)	174	43	(24.7%)		
Sulfonylurea	Dichotomous	172	22	(12.8%)	174	30	(17.2%)		
Metformin + Sulfonylurea	Dichotomous	172	17	(9.9%)	174	10	(5.7%)		
Other	Dichotomous	172	0	(0.0%)	174	1	(0.6%)		
ITT Blood glucose: HbA1c (%) – 0wka	Continuous	172		8.26 (SD 3.15)	174		8.7 (SD 3.3)		

[a] SD calculated from reported SE

Results

		Extended release metformin 1500mg (qd)			Extended release metformin 1500mg (twice daily)			Δ	p
		N	k	mean	N	k	mean		
Adverse events: GI: nausea – 24wk	Dichotomous	178	17	(9.6%)	182	14	(7.7%)		
Dyspepsia – 24wk	Dichotomous	178	9	(5.1%)	182	5	(2.7%)		
Gastrointestinal disorders (any) – 24wka	Dichotomous	178	33	(18.5%)	182	28	(15.4%)		
GI: diarrhoea – 24wk	Dichotomous	178	12a	(6.7%)	182	33	(18.1%)		
GI: diarrhoea – 24wk	Dichotomous	178	25	(14.0%)	182	15a	(8.2%)		
GI: diarrhoea – 24wk	Dichotomous	178	25	(14.0%)	182	33	(18.1%)		
GI: diarrhoea – 24wka	Dichotomous	178	12	(6.7%)	182	15	(8.2%)		
GI: abdominal pain – 24wk	Dichotomous	178	9	(5.1%)	182	6	(3.3%)		
Dropouts: drop out due to diarrhoea – 24wk	Dichotomous	178	1b	(0.6%)	182	0	(0.0%)		
drop out due to nausea – 24wk	Dichotomous	178	0	(0.0%)	182	0	(0.0%)		
drop out due to other GI event – 24wk	Dichotomous	178	1	(0.6%)	182	1	(0.5%)		
ITT Blood glucose: HbA1c (%) – 24wkc	Continuous	178		7.62 (SD 1.6)	182		7.6 (SD 1.62)		
Fasting plasma glucose (mmol/l) – 24wkd	Continuous	178		8.5692 (SD 3.26)	182		8.94105 (SD 3.29)		
Dropouts: Drop out due to unsatisfactory effect – 24wke	Dichotomous	178			182				
Lipids: Total cholesterol (mmol/l) – 24wkf	Continuous	178		5.435772 (SD 1.59)	182		5.089248 (SD 1.5)		
HDL cholesterol (mmol/l) – 24wkg	Continuous	178		1.230936 (SD 0.242)	182		1.210248 (SD 0.244)		
Triglycerides (mmol/l) – 24wkg	Continuous	178		2.29187 (SD 1.84)	182		2.271548 (SD 1.84)		
LDL cholesterol (mmol/l) – 24wkh	Continuous	178		2.904078 (SD 0.863)	182		2.901492 (SD 0.872)		

[a] during dosing at 1000 mg qd
[b] Overall Dropouts due to AE not reported
[c] SD calculated from reported SE; total N=673

[d] total N=686
[e] not reported
[f] total N=645
[g] total N=642
[h] total N=594

		Extended release metformin 1500mg (qd)			Extended release metformin 2000mg (qd)				
		N	k	mean	N	k	mean	Δ	p
Adverse events:									
GI: nausea – 24wk	Dichotomous	178	17	(9.6%)	172	14	(8.1%)		
Dyspepsia – 24wk	Dichotomous	178	9	(5.1%)	172	8	(4.7%)		
Gastrointestinal disorders (any) – 24wka	Dichotomous	178	33	(18.5%)	172	35	(20.3%)		
GI: diarrhoea – 24wk	Dichotomous	178	12a	(6.7%)	172	27	(15.7%)		
GI: diarrhoea – 24wk	Dichotomous	178	25	(14.0%)	172	15a	(8.7%)		
GI: diarrhoea – 24wk	Dichotomous	178	25	(14.0%)	172	27	(15.7%)		
GI: diarrhoea – 24wka	Dichotomous	178	12	(6.7%)	172	15	(8.7%)		
GI: abdominal pain – 24wk	Dichotomous	178	9	(5.1%)	172	4	(2.3%)		
Dropouts:									
drop out due to diarrhoea – 24wk	Dichotomous	178	1b	(0.6%)	172	0	(0.0%)		
drop out due to nausea – 24wk	Dichotomous	178	0	(0.0%)	172	0	(0.0%)		
drop out due to other GI event – 24wk	Dichotomous	178	1	(0.6%)	172	0	(0.0%)		
ITT									
Blood glucose:									
HbA1c (%) – 24wkc	Continuous	178		7.62 (SD 1.6)	172		7.29 (SD 1.57)		
Fasting plasma glucose (mmol/l) – 24wkd	Continuous	178		8.5692 (SD 3.26)	172		8.3805 (SD 3.28)		
Dropouts:									
Drop out due to unsatisfactory effect – 24wk	Dichotomous	178	e		172	3			
Lipids:									
Total cholesterol (mmol/l) – 24wkf	Continuous	178		5.435772 (SD 1.59)	172		4.838406 (SD 1.53)		
HDL cholesterol (mmol/l) – 24wkg	Continuous	178		1.230936 (SD 0.242)	172		1.225764 (SD 0.237)		
Triglycerides (mmol/l) – 24wkg	Continuous	178		2.29187 (SD 1.84)	172		2.334772 (SD 1.82)		
LDL cholesterol (mmol/l) – 24wkh	Continuous	178		2.904078 (SD 0.863)	172		2.854944 (SD 0.848)		

[a] during dosing at 1000 mg qd
[b] Overall Dropouts due to AE not reported
[c] SD calculated from reported SE; total N=673
[d] total N=686
[e] not reported
[f] total N=645
[g] total N=642
[h] total N=594

		Extended release metformin 1500mg (qd)			Immediate release metformin 1500 mg (twice daily)				
		N	k	mean	N	k	mean	Δ	p
Adverse events:									
GI: nausea – 24wk	Dichotomous	178	17	(9.6%)	174	19	(10.9%)		

Dyspepsia – 24wk	Dichotomous	178	9	(5.1%)	174	10	(5.7%)
Gastrointestinal disorders (any) – 24wka	Dichotomous	178	33	(18.5%)	174	33	(19.0%)
GI: diarrhoea – 24wk	Dichotomous	178	12a	(6.7%)	174	25	(14.4%)
GI: diarrhoea – 24wk	Dichotomous	178	25	(14.0%)	174	18a	(10.3%)
GI: diarrhoea – 24wk	Dichotomous	178	25	(14.0%)	174	25	(14.4%)
GI: diarrhoea – 24wka	Dichotomous	178	12	(6.7%)	174	18	(10.3%)
GI: abdominal pain – 24wk	Dichotomous	178	9	(5.1%)	174	4	(2.3%)
Dropouts:							
drop out due to diarrhoea – 24wk	Dichotomous	178	1b	(0.6%)	174	2	(1.1%)
drop out due to nausea – 24wk	Dichotomous	178	0	(0.0%)	174	3	(1.7%)
drop out due to other GI event – 24wk	Dichotomous	178	1	(0.6%)	174	2	(1.1%)
ITT							
Blood glucose:							
HbA1c (%) – 24wkc	Continuous	178		7.62 (SD 1.6)	174		7.65 (SD 1.58)
Fasting plasma glucose (mmol/l) – 24wkd	Continuous	178		8.5692 (SD 3.26)	174		8.92995 (SD 3.29)
Dropouts:							
Drop out due to unsatisfactory effect – 24wk	Dichotomous	178	e		174	14	
Lipids:							
Total cholesterol (mmol/l) – 24wkf	Continuous	178		5.435772 (SD 1.59)	174		5.09442 (SD 1.54)
HDL cholesterol (mmol/l) – 24wkg	Continuous	178		1.230936 (SD 0.242)	174		1.210248 (SD 0.239)
Triglycerides (mmol/l) – 24wkg	Continuous	178		2.29187 (SD 1.84)	174		2.051393 (SD 1.82)
LDL cholesterol (mmol/l) – 24wkh	Continuous	178		2.904078 (SD 0.863)	174		3.048894 (SD 0.853)

[a] during dosing at 1000 mg qd
[b] Overall Dropouts due to AE not reported
[c] SD calculated from reported SE; total N=673
[d] total N=686
[e] not reported
[f] total N=645
[g] total N=642
[h] total N=594

		Extended release metformin 1500mg (twice daily)			Extended release metformin 2000mg (qd)				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Adverse events:									
GI: nausea – 24wk	Dichotomous	182	14	(7.7%)	172	14	(8.1%)		
Dyspepsia – 24wk	Dichotomous	182	5	(2.7%)	172	8	(4.7%)		
Gastrointestinal disorders (any) – 24wka	Dichotomous	182	28	(15.4%)	172	35	(20.3%)		
GI: diarrhoea – 24wk	Dichotomous	182	15a	(8.2%)	172	27	(15.7%)		
GI: diarrhoea – 24wk	Dichotomous	182	33	(18.1%)	172	15a	(8.7%)		
GI: diarrhoea – 24wk	Dichotomous	182	33	(18.1%)	172	27	(15.7%)		
GI: diarrhoea – 24wka	Dichotomous	182	15	(8.2%)	172	15	(8.7%)		
GI: abdominal pain – 24wk	Dichotomous	182	6	(3.3%)	172	4	(2.3%)		
Dropouts:									
drop out due to diarrhoea – 24wk	Dichotomous	182	0	(0.0%)	172	0	(0.0%)		

drop out due to nausea – 24wk	Dichotomous	182	0	(0.0%)	172	0	(0.0%)		
drop out due to other GI event – 24wk	Dichotomous	182	1	(0.5%)	172	0	(0.0%)		
ITT									
Blood glucose:									
HbA1c (%) – 24wkb	Continuous	182		7.6 (SD 1.62)	172		7.29 (SD 1.57)		
Fasting plasma glucose (mmol/l) – 24wkc	Continuous	182		8.94105 (SD 3.29)	172		8.3805 (SD 3.28)		
Dropouts:									
Drop out due to unsatisfactory effect – 24wk	Dichotomous	182	d		172	3			
Lipids:									
Total cholesterol (mmol/l) – 24wke	Continuous	182		5.089248 (SD 1.5)	172		4.838406 (SD 1.53)		
HDL cholesterol (mmol/l) – 24wkf	Continuous	182		1.210248 (SD 0.244)	172		1.225764 (SD 0.237)		
Triglycerides (mmol/l) – 24wkf	Continuous	182		2.271548 (SD 1.84)	172		2.334772 (SD 1.82)		
LDL cholesterol (mmol/l) – 24wkg	Continuous	182		2.901492 (SD 0.872)	172		2.854944 (SD 0.848)		

[a] during dosing at 1000 mg qd
[b] SD calculated from reported SE; total N=673
[c] total N=686
[d] not reported
[e] total N=645
[f] total N=642
[g] total N=594

		Extended release metformin 1500mg (twice daily)			Immediate release metformin 1500 mg (twice daily)			Δ	p
		N	k	mean	N	k	mean		
Adverse events:									
GI: nausea – 24wk	Dichotomous	182	14	(7.7%)	174	19	(10.9%)		
Dyspepsia – 24wk	Dichotomous	182	5	(2.7%)	174	10	(5.7%)		
Gastrointestinal disorders (any) – 24wka	Dichotomous	182	28	(15.4%)	174	33	(19.0%)		
GI: diarrhoea – 24wk	Dichotomous	182	15a	(8.2%)	174	25	(14.4%)		
GI: diarrhoea – 24wk	Dichotomous	182	33	(18.1%)	174	18a	(10.3%)		
GI: diarrhoea – 24wk	Dichotomous	182	33	(18.1%)	174	25	(14.4%)		
GI: diarrhoea – 24wka	Dichotomous	182	15	(8.2%)	174	18	(10.3%)		
GI: abdominal pain – 24wk	Dichotomous	182	6	(3.3%)	174	4	(2.3%)		
Dropouts:									
drop out due to diarrhoea – 24wk	Dichotomous	182	0	(0.0%)	174	2	(1.1%)		
drop out due to nausea – 24wk	Dichotomous	182	0	(0.0%)	174	3	(1.7%)		
drop out due to other GI event – 24wk	Dichotomous	182	1	(0.5%)	174	2	(1.1%)		
ITT									
Blood glucose:									
HbA1c (%) – 24wkb	Continuous	182		7.6 (SD 1.62)	174		7.65 (SD 1.58)		
Fasting plasma glucose (mmol/l) – 24wkc	Continuous	182		8.94105 (SD 3.29)	174		8.92995 (SD 3.29)		
Dropouts:									
Drop out due to unsatisfactory effect – 24wk	Dichotomous	182	d		174	14			

Lipids: Total cholesterol (mmol/l) – 24wke	Continuous	182		5.089248 (SD 1.5)	174		5.09442 (SD 1.54)		
HDL cholesterol (mmol/l) – 24wkf	Continuous	182		1.210248 (SD 0.244)	174		1.210248 (SD 0.239)		
Triglycerides (mmol/l) – 24wkf	Continuous	182		2.271548 (SD 1.84)	174		2.051393 (SD 1.82)		
LDL cholesterol (mmol/l) – 24wkg	Continuous	182		2.901492 (SD 0.872)	174		3.048894 (SD 0.853)		

[a] during dosing at 1000 mg qd
[b] SD calculated from reported SE; total N=673
[c] total N=686
[d] not reported
[e] total N=645
[f] total N=642
[g] total N=594

		Extended release metformin 2000mg (qd)			Immediate release metformin 1500 mg (twice daily)			Δ	p
		N	k	mean	N	k	mean		
Adverse events: GI: nausea – 24wk	Dichotomous	172	14	(8.1%)	174	19	(10.9%)		
Dyspepsia – 24wk	Dichotomous	172	8	(4.7%)	174	10	(5.7%)		
Gastrointestinal disorders (any) – 24wka	Dichotomous	172	35	(20.3%)	174	33	(19.0%)		
GI: diarrhoea – 24wk	Dichotomous	172	15a	(8.7%)	174	25	(14.4%)		
GI: diarrhoea – 24wk	Dichotomous	172	27	(15.7%)	174	18a	(10.3%)		
GI: diarrhoea – 24wk	Dichotomous	172	27	(15.7%)	174	25	(14.4%)		
GI: diarrhoea – 24wka	Dichotomous	172	15	(8.7%)	174	18	(10.3%)		
GI: abdominal pain – 24wk	Dichotomous	172	4	(2.3%)	174	4	(2.3%)		
Dropouts: Drop out due to unsatisfactory effect – 0wk	Dichotomous	178			174				0.007
drop out due to diarrhoea – 24wk	Dichotomous	172	0	(0.0%)	174	2	(1.1%)		
drop out due to nausea – 24wk	Dichotomous	172	0	(0.0%)	174	3	(1.7%)		
drop out due to other GI event – 24wk	Dichotomous	172	0	(0.0%)	174	2	(1.1%)		
ITT									
Blood glucose: HbA1c (%) – 24wkb	Continuous	172		7.29 (SD 1.57)	174		7.65 (SD 1.58)		
Fasting plasma glucose (mmol/l) – 24wkc	Continuous	172		8.3805 (SD 3.28)	174		8.92995 (SD 3.29)		
Dropouts: Drop out due to unsatisfactory effect – 24wk	Dichotomous	172	3	(1.7%)	174	14	(8.0%)		
Lipids: Total cholesterol (mmol/l) – 24wkd	Continuous	172		4.838406 (SD 1.53)	174		5.09442 (SD 1.54)		
HDL cholesterol (mmol/l) – 24wke	Continuous	172		1.225764 (SD 0.237)	174		1.210248 (SD 0.239)		
Triglycerides (mmol/l) – 24wke	Continuous	172		2.334772 (SD 1.82)	174		2.051393 (SD 1.82)		
LDL cholesterol (mmol/l) – 24wkf	Continuous	172		2.854944 (SD 0.848)	174		3.048894 (SD 0.853)		

[a] during dosing at 1000 mg qd
[b] SD calculated from reported SE; total N=673
[c] total N=686
[d] total N=645
[e] total N=642
[f] total N=594

		Immediate release metformin 1500 mg (twice daily)			Any extended release				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 0wk	Mean change	178			174				0.013a
HbA1c (%) – 0wk	Continuous	178			174				0.013a
Fasting plasma glucose (mmol/l) – 0wk	Continuous	178			174				0.051a
Adverse events: GI: nausea – 0wk	Dichotomous	178			174				0.050b
Dyspepsia – 0wk	Dichotomous	178			174				>0.05a
Gastrointestinal disorders (any) – 0wk	Dichotomous	178			174				>0.05a
Gastrointestinal disorders (any) – 0wk	Dichotomous	178			174				>0.05b
GI: diarrhoea – 0wk	Dichotomous	178			174				>0.05a
GI: diarrhoea – 0wk	Dichotomous	178			174				>0.05b
GI: abdominal pain – 0wk	Dichotomous	172			174				>0.05a
Dropouts: drop out due to diarrhoea – 0wk	Dichotomous	178			174				>0.05a
drop out due to diarrhoea – 0wk	Dichotomous	178			174				>0.05a
drop out due to nausea – 0wk	Dichotomous	178			174				>0.05a
drop out due to nausea – 0wk	Dichotomous	178			174				>0.05a
drop out due to other GI event – 0wk	Dichotomous	178			174				>0.05a
drop out due to other GI event – 0wk	Dichotomous	178			174				>0.05a
Lipids: Total cholesterol (mmol/l) – 0wk	Continuous	178			174				0.005a
HDL cholesterol (mmol/l) – 0wk	Continuous	178			174				0.506a
Triglycerides (mmol/l) – 0wk	Continuous	178			174				0.030a
LDL cholesterol (mmol/l) – 0wk	Continuous	178			174				0.015a

[a] p-value relates to overall comparisons among treatment groups
[b] during dosing at 1000 mg qd, p-value relates to overall comparisons among treatment groups

The primary efficacy parameter, mean change in A1C concentration from baseline to end point, was analyzed using an ANCOVA parallel model that included treatment, center, and stratification factor as fixed factors and baseline A1C as a covariate. The least squares estimate of the mean change from baseline for each treatment and its 95% CI were calculated. Continuous secondary efficacy parameters were analyzed using an ANCOVA model that included treatment, center, treatment-by-center interaction, and stratification factor as fixed factors and the baseline measurement as a covariate.Data for continuous variables are from ANOVA or ANCOVA (see intra-arm data for more details). For the primary efficacy parameter a two-sided 98.4% CI of the pairwise mean difference between each extended-release metformin treatment and immediate-release metformin (extended-release metformin - immediate- release metformin) in mean change from baseline to end point for A1C levels was constructed. Fisher's exact test was used to compare the incidence of adverse events among treatment groups. Categorical secondary efficacy parameters were analyzed using a two-sided Fisher's exact test for overall comparison among treatment groups. In addition, a

	two-sample Z test on proportions was performed. The difference between a proportion and its 95% CI was determined. NB: overall comparisons among treatment groups have been extracted as relating to extended release vs. immediate release as reported in the statistical methods section. However these p-values may relate to trend effects across treatment groups.

Table 96: Schweizer et al. (2007)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** 183 centres in 10 countries in the Americas and Europe **Authors' conclusions:** A clinically meaningful decrease in HbA1c that was sustained throughout a 1-year treatment in drug-naïve patients with Type 2 DM was seen with both metformin and vildagliptin monotherapy **Source of funding:** Funded by Novartis. The concept, design, data analysis and writeup of this study were by Novartis **Comments:** double-blind, randomised trial but no details reported relating to methods of randomisation, allocation concealment and blinding
Number and characteristics of patients	**Total number of patients:** 780 **Inclusion criteria:** The study enrolled patients with Type 2 DM and who had an HbA1c of 7.5–11.0% at the screening visit while receiving no drug treatment. Patients who had taken no oral glucose-lowering agents for at least 12 weeks prior to screening and no oral glucose lowering agents for more than three consecutive months at any time in the past were considered to be drug naïve. Male and female patients (non-fertile or of childbearing potential using a medically approved birth control method) aged 18–78 years, inclusive, with fasting plasma glucose (FPG) < 15 mmol/l were eligible to participate. **Exclusion criteria:** history of Type 1 or secondary forms of diabetes, acute metabolic diabetic complications within the past 6 months, congestive heart failure requiring pharmacological pharmacological treatment, or myocardial infarction, unstable angina, or coronary artery bypass surgery within the previous 6 months. Liver disease such as cirrhosis or chronic active hepatitis also precluded participation, as did renal disease or renal dysfunction suggested by elevated serum creatinine levels, in accordance with prescribing guidelines for metformin. Patients with any of the following laboratory abnormalities were also excluded: ALT or AST greater than three times the upper limit of normal (ULN), direct bilirubin greater than 1.3 times the ULN, clinically significant abnormal TSH or fasting triglycerides > 7.9 mmol/l. During the study, patients discontinued due to 'unsatisfactory therapeutic effect' if FPG > 15 mmol/l (or 13.3 mmol/l in Argentina) confirmed by a repeat measurement in the absence of intercurrent illness, or they had symptoms of worsening hyperglycaemia in the absence of intercurrent illness or other incidental circumstances potentially causing deterioration of glucose control. A patient could also be withdrawn as a result of an unsatisfactory therapeutic effect solely on the investigator's judgement Pre-randomisation phase: Each patient attended one screening visit (week –2), during which inclusion/exclusion criteria were assessed. Eligible patients were randomized at visit 2 (baseline)
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** All treatment naive/ no OADs at screening **Details of washout period:** N/A
Lifestyle advice	No details reported
Follow-up	**Total follow-up (wks):** 52 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 52 **Frequency of monitoring appointments:** Efficacy and tolerability were assessed during seven additional visits, at weeks 4, 12, 16, 24, 32, 40 and 52 of active treatment
Arms	**(1) Vildagliptin** N: 526 Treatment duration (wks): 52 Washout period (d): 0 Comments: Drug naïve (no OADs for at least 12 weeks prior to screening) Treatment(s): Vildagliptin (Oral) – fixed-dose Set dose (mg/d):100

Frequency of dosing: variable
Compliance: no details reported
Details of dosing regimen: dose was given as equally divided doses

(2) Metformin

N: 254

Treatment duration (wks): 52
Washout period (d): 0
Comments: Drug naïve (no OADs for at least 12 weeks prior to screening)

Treatment(s): Metformin (Oral) – fixed-dose
Set dose (mg/d):2000
Mean dose (mg/d): 1988
Frequency of dosing: variable
Compliance: no details reported
Details of dosing regimen: dose was given as equally divided doses

Outcomes

General

The randomized population comprised all patients randomized (n=780). The safety population consisted of all patients who received at least one dose of study medication and who had at least one post-baseline safety assessment (n=771). The intent-totreat (ITT) population comprised all patients who received at least one dose of study medication and had at least one postbaseline HbA1c assessment (n=760). The primary efficacy variable was the change from baseline in HbA1c at study end point in the ITT population using last observation carried forward for patients who discontinued early.

All outcomes were extracted in this evidence table.

148 (28%) in vildagliptin group and 63 (25%) in metformin group did not complete the study.

Hypoglycaemic events

Major/severe hypoglycaemic event (Severe hypoglycaemia was defined as any episode requiring the assistance of another party.)

symptomatic (confirmed) (Hypoglycaemia was defined as symptoms suggestive of low blood glucose confirmed by self-monitored blood glucose measurement < 3.1 mmol/l plasma glucose equivalent)

Baseline characteristics

		All study participants		
		N	k	mean
2-year follow-up (reported in Goke et al. 2005)				
Demographics:				
Age (years)	Continuous	463		54 (SD 11)
Duration of diabetes (yrs)	Continuous	463		2.4 (SD 3.4)
Body weight:				
BMI (kg/m2)	Continuous	463		32.7 (SD 5.7)
Weight (kg) – 0wk	Continuous	463		92.29248 (SD 16.08768) a
Weight (kg) – 0wk	Continuous	463		92.29248 (SD 16.08768) a

[a] estimated from BMI assuming mean height of 1.68m

		Vildagliptin			Metformin				
		N	k	mean	N	k	mean	Δ	p
Demographics:									
Age (years)	Continuous	526		52.8 (SD 11.7)	254		53.6 (SD 10.2)		
Sex (n male)	Dichotomous	526	278	(52.9%)	254	146	(57.5%)		
Duration of diabetes (yrs)	Continuous	526		med: 1.05a	254		med: 1.03b		
Ethnicity-White	Dichotomous	526	357	(67.9%)	254	177	(69.7%)		
Ethnicity-Black	Dichotomous	526	42	(8.0%)	254	13	(5.1%)		
Ethnicity-Hispanic	Dichotomous	526	104	(19.8%)	254	55	(21.7%)		
Ethnicity-Other	Dichotomous	526	23	(4.4%)	254	9	(3.5%)		
Blood glucose:									
Fasting plasma glucose (mmol/l) – 0wk	Continuous	526		10.5 (SD 2.9)	254		10.5 (SD 2.9)		
Body weight:									
BMI (kg/m2)	Continuous	526		32.4 (SD 5.7)	254		32.5 (SD 5.7)		
Weight (kg) – 0wkc	Continuous	526		91.44576 (SD 16.1)	254		91.728 (SD 16.1)		

Blood pressure: Systolic blood pressure (mmHg)	Continuous	526		133 (SD 14)	254		133 (SD 16)		
Diastolic blood pressure (mmHg)	Continuous	526		82 (SD 8)	254		82 (SD 9)		
Lipids: Total cholesterol (mmol/l) – 0wk	Mean change	526		5.3 (SD 1.1)	254		5.2 (SD 1.1)		
HDL cholesterol (mmol/l) – 0wk	Mean change	526		1.2 (SD 0.2)	254		1.2 (SD 0.3)		
Triglycerides (mmol/l) – 0wk	Mean change	526		2.4 (SD 1.8)	254		2.4 (SD 1.6)		
LDL cholesterol (mmol/l) – 0wk	Mean change	526		3.1 (SD 0.9)	254		3.1 (SD 0.9)		
ITT Blood glucose: HbA1c (%) – 0wk	Continuous	526		8.7 (SD 1.1)	254		8.7 (SD 1.1)		
2-year follow-up (reported in Goke et al. 2005) Body weight: Weight (kg) – 0wk	Continuous	305		93.1 (SD 1.3)	158		95.7 (SD 1.6)		

[a] IQR 3.54
[b] 3.28
[c] estimated from BMI assuming mean height of 1.68m

Results

		Vildagliptin			Metformin				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Blood glucose: HbA1c (%) – 16wka	Continuous	511		7.5 (SD 0.904)	249		7.25 (SD 0.316)		
HbA1c (%) – 24wka	Continuous	511		7.35 (SD 0.904)	249		7.2 (SD 0.158)		
HbA1c (%) – 52wkb	Continuous	511		7.5 (SD 1.33)	249		7.14 (SD 1.26)		
HbA1c (%) – 52wk	Mean change	526			254				<0.001c
HbA1c < 7% or <=7% – 52wk	Dichotomous	526			254				d
Fasting plasma glucose (mmol/l) – 52wk	Mean change	526			254				<0.001e
Body weight: Weight (kg) – 52wk	Mean change	526			254				<0.001e
Hypoglycaemic events: Major/severe hypoglycaemic event – 52wk	Dichotomous	526			254				d
symptomatic (confirmed) – 52wk	Dichotomous	526			254				d
Adverse events: GI: nausea – 52wk	Dichotomous	526			254				f
Any adverse event(s) – 52wk	Dichotomous	526			254				<0.001
Any serious adverse event(s) – 52wk	Dichotomous	526			254				d
Back pain – 52wk	Dichotomous	526			254				d
Death – 52wk	Dichotomous	526			254				d
Dizziness – 52wk	Dichotomous	526			254				d
Dyspepsia – 52wk	Dichotomous	526			254				d
Flatulence – 52wk	Dichotomous	526			254				f
Gastrointestinal disorders (any) – 52wk	Dichotomous	526			254				<0.001

	GI: diarrhoea – 52wk	Dichotomous	526			254				f
	GI: vomiting – 52wk	Dichotomous	526			254				f
	GI: abdominal pain – 52wk	Dichotomous	526			254				f
	GI: constipation – 52wk	Dichotomous	526			254				f
	Headache – 52wk	Dichotomous	526			254				d
	Infection (upper airway or other common) – 52wk	Dichotomous	526			254				d
	Nasopharyngitis – 52wk	Dichotomous	526			254				d
	Dropouts:									
	Dropout due to AEs – 52wk	Dichotomous	526	19	(3.6%)	254	16	(6.3%)		d
	Drop out due to unsatisfactory effect – 52wk	Dichotomous	526	35	(6.7%)	254	3	(1.2%)		d
	drop out due to other GI event – 52wkg	Dichotomous	526	4	(0.8%)	254	11	(4.3%)		d
	Lipids:									
	Total cholesterol (mmol/l) – 52wk	Mean change	526			254				>0.05h
	HDL cholesterol (mmol/l) – 52wk	Mean change	526			254				>0.05i
	Triglycerides (mmol/l) – 52wk	Mean change	526			254				>0.05h
	LDL cholesterol (mmol/l) – 52wk	Mean change	526			254				>0.05h
	ITT									
	Blood glucose:									
	HbA1c (%) – 52wkj	Mean change	511		-1 (SD 2.26)	249		-1.4 (SD 1.58)		
	HbA1c < 7% or <=7% – 52wk	Dichotomous	511	179g	(35.0%)	249	112	(45.0%)		
	Fasting plasma glucose (mmol/l) – 52wk	Mean change	511		-0.9 (SD 2.29)	249		-1.9 (SD 3.19)		
	Body weight:									
	Weight (kg) – 52wkj	Mean change	511		0.3 (SD 4.59)	249		-1.9 (SD 4.78)		
	Lipids:									
	Total cholesterol (mmol/l) – 52wkk	Mean change	526		-2.4 (SD 18.3)	254		-2.7 (SD 17.5)		
	HDL cholesterol (mmol/l) – 52wkk	Mean change	511		2.6 (SD 18.3)	249		4.6 (SD 17.5)		
	Triglycerides (mmol/l) – 52wkk	Mean change	511		5.3 (SD 57.3)	249		3.9 (SD 54.2)		
	LDL cholesterol (mmol/l) – 52wkk	Mean change	511		-2.8 (SD 27.1)	249		-4.4 (SD 26.8)		
	Safety population									
	Hypoglycaemic events:									
	Major/severe hypoglycaemic event – 52wk	Dichotomous	519	0	(0.0%)	252	0	(0.0%)		
	symptomatic (confirmed) – 52wk	Dichotomous	519	3l	(0.6%)	252	1g	(0.4%)		
	symptomatic (confirmed) – 52wk	Dichotomous	519	3g	(0.6%)	252	1	(0.4%)		
	symptomatic (confirmed) – 52wk	Dichotomous	519	3l	(0.6%)	252	1	(0.4%)		
	symptomatic (confirmed) – 52wkg	Dichotomous	519	3	(0.6%)	252	1	(0.4%)		
	Adverse events:									
	GI: nausea – 52wk	Dichotomous	519	17g	(3.3%)	252	26m	(10.3%)		

Any adverse event(s) – 52wk	Dichotomous	519	364	(70.1%)	252	190	(75.4%)		
Any serious adverse event(s) – 52wkg	Dichotomous	519	35	(6.7%)	252	13	(5.2%)		
Back pain – 52wk	Dichotomous	519	27	(5.2%)	252	9	(3.6%)		
Death – 52wk	Dichotomous	519	2	(0.4%)	252	2	(0.8%)		
Dizziness – 52wk	Dichotomous	519	25	(4.8%)	252	15	(6.0%)		
Dyspepsia – 52wk	Dichotomous	519	6	(1.2%)	252	12	(4.8%)		
Flatulence – 52wk	Dichotomous	519	5	(1.0%)	252	10	(4.0%)		
Gastrointestinal disorders (any) – 52wk	Dichotomous	519	113	(21.8%)	252	110	(43.7%)		
GI: diarrhoea – 52wk	Dichotomous	519	31	(6.0%)	252	66	(26.2%)		
GI: vomiting – 52wk	Dichotomous	519	11	(2.1%)	252	11	(4.4%)		
GI: abdominal pain – 52wk	Dichotomous	519	12	(2.3%)	252	18	(7.1%)		
GI: constipation – 52wk	Dichotomous	519	25	(4.8%)	252	5	(2.0%)		
Headache – 52wk	Dichotomous	519	52	(10.0%)	252	18	(7.1%)		
Infection (upper airway or other common) – 52wk	Dichotomous	519	27	(5.2%)	252	15	(6.0%)		
Nasopharyngitis – 52wk	Dichotomous	519	50	(9.6%)	252	24	(9.5%)		
Baseline Hba1c <=8% Blood glucose: HbA1c (%) – 52wkn	Mean change	180		-0.6	79		-0.7		
Baseline Hba1c >8% Blood glucose: HbA1c (%) – 52wkn	Mean change	331		-1.1	170		-1.7		
2-year follow-up (reported in Goke et al. 2005) Blood glucose: HbA1c (%) – 104wk	Mean change	305			158			MD=0.510 (CI: 0.250, 0.770)	<0.001
Body weight: Weight (kg) – 104wk	Mean change	305			158				<0.001
Adverse events: Any adverse event(s) – 104wk	Dichotomous	305			158				NR
Serious AE drug related – 104wk	Dichotomous	305			158				NR
Study drug-related adverse event – 104wk	Dichotomous	305			158				NR
Death – 104wk	Dichotomous	305			158				NR
Gastrointestinal disorders (any) – 104wk	Dichotomous	305			158				<0.001
Dropouts: Total dropouts – 104wk	Dichotomous	526	266	(50.6%)	254	112	(44.1%)		
Dropout due to AEs – 104wk	Dichotomous	305			158				NR
Drop out due to unsatisfactory effect – 104wk	Dichotomous	305			158				NR
Other medication: Taking rescue medication – 104wk	Dichotomous	305	116	(38.0%)	158	43g	(27.2%)		NR
2-year follow-up (reported in Goke et al. 2005) - ITT Blood glucose: HbA1c (%) – 104wko	Mean change	305		-1.5 (SD 1.75)	158		-1 (SD 1.26)		
Body weight: Weight (kg) – 104wkp	Mean change	305		0.5 (SD 6.99)	158		-2.5 (SD 6.28)		

	2-year follow-up (reported in Goke et al. 2005) - Safety population									
	Hypoglycaemic events: symptomatic (confirmed) – 104wk	Dichotomous	304	1	(0.3%)	158	0	(0.0%)		
	Adverse events: GI: nausea – 104wk	Dichotomous	304	9q	(3.0%)	158	15r	(9.5%)		
	Any adverse event(s) – 104wk	Dichotomous	305	250	(82.0%)	158	138	(87.3%)		
	Serious AE drug related – 104wk	Dichotomous	305	27	(8.9%)	158	11	(7.0%)		
	Study drug-related adverse event – 104wk	Dichotomous	305	42	(13.8%)	158	42	(26.6%)		
	Death – 104wk	Dichotomous	305	1	(0.3%)	158	1	(0.6%)		
	Flatulence – 104wk	Dichotomous	305	3	(1.0%)	158	8	(5.1%)		
	Gastrointestinal disorders (any) – 104wk	Dichotomous	305	76	(24.9%)	158	72	(45.6%)		
	GI: diarrhoea – 104wk	Dichotomous	305	19g	(6.2%)	158	45	(28.5%)		
	GI: abdominal pain – 104wk	Dichotomous	305	7	(2.3%)	158	11	(7.0%)		
	Nasopharyngitis – 104wk	Dichotomous	305	48g	(15.7%)	158	19	(12.0%)		
	Dropouts: Dropout due to AEs – 104wk	Dichotomous	304	5	(1.6%)	158	3	(1.9%)		

[a] estimated from graph
[b] estimated from graph; SD calculated from SE
[c] mean difference not reported 95% CI 0.28 to 0.65
[d] not reported
[e] mean difference not reported
[f] no statistical comparison
[g] approximated to nearest integer (percentages only presented in text)
[h] assumed p>0.05 as no significant differences in lipid parameters
[i] assumed p>0.05 as no significant differences in lipid parameter
[j] SD calculated from reported assumed SE
[k] adjusted mean change from baseline (%)
[l] approximated to nearest integer (percentages only presented in text); approximated to nearest integer (percentages only presented in text)
[m] calculated from reported percentages
[n] no SD reported
[o] assumed SE reported for mean change, although paper reports as SD
[p] assumed SE reported for mean change
[q] (used in analysis) approximated to nearest integer (percentages only presented in text); approximated to nearest integer (percentages only presented in text)
[r] (used in analysis) calculated from reported percentages

Changes from baseline in primary and secondary end points were analysed using an ANCOVA model, with treatment and pooled centre as the classification variables, and baseline HbA1c as the covariate. SE's assumed to be reported and have been converted to SDs. Adverse events relate to number of people.

Table 97: Schweizer et al. (2009)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** conducted in 113 centres in 14 countries in Europe, the Americas and Asia **Authors' conclusions:** Vildagliptin is as effective and well-tolerated treatment option in elderly patients with type 2 diabetes, demonstrating similar improvement in glycaemic control as metformin, with superior GI

	tolerability **Source of funding:** funded by Norvartis Pharmaceutical Corporation **Comments:** Independent cardiovascular and cerebrovascular committee reviewed all occurences of CCV events in a blinded fashion. Report double-blind, randomised active-controlled, parallel group trial but no details of randomisation methods, allocation concelament and blinding.
Number and characteristics of patients	**Total number of patients:** 335 **Inclusion criteria:** patients with type 2 diabetes aged >=65 years with a Hba1c of 7-9% at screening. Patients who had taken no oral blood glucose lowering agnets for at least 12 weeks prior to screening and no oral glucose-lowering agents for more than three consecutive months at any time in the past were considered to be drug naïve. Male and female patients with FPG<15 mmol/l and with BMI 22-40 kg/m2 were eligible to participate. **Exclusion criteria:** history of type 1 or secondary forms of diabetes, acute metabolic diabetic complications within the past 6 months, congestive heart failure requiring pharmacological treatment or myocardial infarction, unstable angina or stroke or coronary artery bypass surgery within the past 6 months. Liver disease such as cirrhosis or chronic active hepatitis also precluded participation, as did renal disease or renal dysfunction suggested by elevated serum sreatinine levels, in accordance with country-specific prescribing guidelines for metformin Pre-randomisation phase: 2 week screening phase, titration phase not explicitly reported apart from information in arm details, unclear if this is before and separate from the 24 week active treatment (assumed to be included in maintenance phase)
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** All treatment naive/ no OADs at screening **Details of washout period:** N/A (drug naïve-see inclusion criteria for definition)
Lifestyle advice	No details reported
Follow-up	**Total follow-up (wks):** 24 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 24 **Frequency of monitoring appointments:** Hba1c, FPG and body weight were measured at screening and at weeks 0 (baseline), 4, 12, 16 and 24
Arms	**(1) Vildagliptin** N: 169 Treatment duration (wks): 24 Washout period (d): 0 Treatment(s): Vildagliptin (Oral) – fixed-dose Set dose (mg/d):100 Frequency of dosing: once a day Details of dosing regimen: Dose adjustments of study medication were not allowed **(2) Metformin** N: 166 Treatment duration (wks): 24 Washout period (d): 0 Treatment(s): Metformin (Oral) – forced titration Set dose (mg/d):1500 Frequency of dosing: twice a day Details of dosing regimen: metformin was titrated (started at 500 mg/day with weekly increase of 500 mg) to 1500 mg daily (given as divided doses 1000 mg in morning and 500 mg in evening) for 24 weeks of active treatment. Dose adjustments were not alllowed; patients who were unable to tolerate 1500 mg daily metformin were to be discontinued from the study
Outcomes	**General** The safety population consisted of all patients who received at least one dose of study medication and who had at least one post baseline safety assessment (n=332). The ITT population comprised all patients who received at least one dose of study medication and had at least one post-baseline Hba1c assessment (n=323). Outcomes relating to ALT and AST and bilirubin (liver function) have not been extracted in this evidence table. 27 (16%) in vildagliptin group and 26 (15.7%) in metformin group discontinued the study **Hypoglycaemic events** Major/severe hypoglycaemic event (severe hypoglycaemia was defined as any episode requiring the assistance by another party) symptomatic (confirmed) (hypoglycaemia was defined as symptoms suggestive of low blood glucose confirmed by self-monitored blood glucose measurement <3.1 mmol/l plasma equivalent)

Baseline characteristics

		Vildagliptin			Metformin				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	169		71.6 (SD 5.2)	166		70.2 (SD 5.1)		
Sex (n male)	Dichotomous	169	75	(44.4%)	166	88	(53.0%)		
Duration of diabetes (yrs)	Continuous	169		2.9 (SD 4.2)	166		3 (SD 4.7)		
Ethnicity-White	Dichotomous	169	123	(72.8%)	166	117	(70.5%)		
Ethnicity-Asian	Dichotomous	169	32	(18.9%)	166	36	(21.7%)		
Ethnicity-Hispanic	Dichotomous	169	13	(7.7%)	166	10	(6.0%)		
Ethnicity-Other	Dichotomous	169	1	(0.6%)	166	3	(1.8%)		
Blood glucose: Fasting plasma glucose (mmol/l) – 0wk	Continuous	169		9.2 (SD 2.2)	166		9.2 (SD 2.2)		
Body weight: BMI (kg/m2)	Continuous	169		29.8 (SD 4.4)	166		29.4 (SD 4.6)		
Weight (kg) – 0wka	Continuous	169		84.10752 (SD 12.4)	166		82.97856 (SD 13)		
Renal function: normalb	Dichotomous	169	65	(38.5%)	166	72	(43.4%)		
mild renal insufficiencyc	Dichotomous	169	102	(60.4%)	166	90	(54.2%)		
moderate renal insufficiencyd	Dichotomous	169	2	(1.2%)	166	4	(2.4%)		
ITT Blood glucose: HbA1c (%) – 0wk	Continuous	169		7.8 (SD 0.6)	166		7.7 (SD 0.6)		

[a] estimated from BMI assuming mean height of 1.68m
[b] GFR >80
[c] GFR >=50 to <80
[d] GFR >=30 to <50

Results

		Vildagliptin			Metformin				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 24wk	Mean change	169			166			MD=0.110 (CI: 0.080, 0.140)	0.258a
HbA1c < 7% or <=7% – 24wkb	Dichotomous	167	82	(49.1%)	165	101	(61.2%)		0.036c
HbA1c <= 6.5% – 24wkb	Dichotomous	167	47	(28.1%)	165	50	(30.3%)		0.649c
Fasting plasma glucose (mmol/l) – 24wk	Mean change	167		-0.78 (SD 1.55)	165		-1.27 (SD 1.54)		0.006c
Body weight: Weight (kg) – 24wk	Mean change	167		-0.45 (SD 2.58)	165		-1.25 (SD 2.44)		0.004c
Weight (kg) – 24wk	Mean change	169		-0.45 (SD 2.58)	166		-1.25 (SD 2.44)		0.004c
Hypoglycaemic events: Major/severe hypoglycaemic event – 24wk	Dichotomous	169			166				NR
symptomatic (confirmed) – 24wk	Dichotomous	169			166				NS
Adverse events: GI: nausea – 24wk	Dichotomous	169			166				NS
Any adverse event(s) – 24wk	Dichotomous	169			166				NS
Any serious adverse event(s) – 24wk	Dichotomous	169			166				NS
Study drug-related adverse event – 24wk	Dichotomous	169			166				NS

Death – 24wk	Dichotomous	169			166				NR
Dizziness – 24wk	Dichotomous	169			166				NS
Gastrointestinal disorders (any) – 24wk	Dichotomous	169			166				0.028c
GI: diarrhoea – 24wk	Dichotomous	169			166				NS
Headache – 24wk	Dichotomous	169			166				NS
Hypertension – 24wk	Dichotomous	169			166				NS
Nasopharyngitis – 24wk	Dichotomous	169			166				NS
Dropouts:									
Total dropouts – 24wk	Dichotomous	169	27	(16.0%)	166	26	(15.7%)		
Dropout due to AEs – 24wk	Dichotomous	169			166				NS
Drop out due to unsatisfactory effect – 24wk	Dichotomous	169			166				NR
Diabetic complications:									
cardiovascular or cerebrovascular – 24wk	Dichotomous	169			166				NR
ITT									
Blood glucose:									
HbA1c (%) – 24wk	Mean change	159		-0.64 (SD 0.91)	161		-0.75 (SD 0.902)		
Safety population									
Hypoglycaemic events:									
Major/severe hypoglycaemic event – 24wk	Dichotomous	167	0	(0.0%)	165	0	(0.0%)		
symptomatic (confirmed) – 24wk	Dichotomous	167	0	(0.0%)	165	2	(1.2%)		
Adverse events:									
GI: nausea – 24wk	Dichotomous	167	5	(3.0%)	165	9	(5.5%)		
Any adverse event(s) – 24wk	Dichotomous	167	74	(44.3%)	165	83	(50.3%)		
Any serious adverse event(s) – 24wk	Dichotomous	167	5	(3.0%)	165	6	(3.6%)		
Study drug-related adverse event – 24wk	Dichotomous	167	14	(8.4%)	165	33	(20.0%)		
Death – 24wk	Dichotomous	167	1d	(0.6%)	165	0	(0.0%)		
Dizziness – 24wk	Dichotomous	167	7	(4.2%)	165	4	(2.4%)		
Gastrointestinal disorders (any) – 24wk	Dichotomous	167	25	(15.0%)	165	41	(24.8%)		
GI: diarrhoea – 24wk	Dichotomous	167	5	(3.0%)	165	22	(13.3%)		
Headache – 24wk	Dichotomous	167	6	(3.6%)	165	3	(1.8%)		
Hypertension – 24wk	Dichotomous	167	6	(3.6%)	165	7	(4.2%)		
Nasopharyngitis – 24wk	Dichotomous	167	8	(4.8%)	165	9	(5.5%)		
Dropouts:									
Dropout due to AEs – 24wk	Dichotomous	169	6	(3.6%)	166	13	(7.8%)		
Drop out due to unsatisfactory effect – 24wk	Dichotomous	169	1	(0.6%)	166	2	(1.2%)		
Diabetic complications:									
cardiovascular or cerebrovascular – 24wk	Dichotomous	167	2	(1.2%)	165	2	(1.2%)		
Baseline Hba1c >8%									
Blood glucose:									
HbA1c (%) – 24wke	Mean change	55		-0.93	45		-1.02		

[a] 95% CI -0.08 to 0.29
[b] approximated to nearest integer (percentages only presented in text)
[c] no other details reported
[d] not thought to be study drug related
[e] No SD reported

	The last observation carried forward method was used for patients who discontinued early. Adjusted mean changes from baseline in primary and secondary end-points were analysed using ANCOVA model with treatment and pooled centre as the classification variables and baseline Hba1c as the covariate. Adverse events relate to the number of people. The primary efficacy variable was assessed using the ITT population-assumed that all analyses were carried out on ITT population. Assumed SEs reported in text which have been converted to SD in this evidence table

Table 98: Scott et al. (1999)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** Australia and New Zealand **Authors' conclusions:** These data show that acarbose reduces FBG and triglyceride levels, lowers Hba1c and limits the glycaemic and insulin response to food. **Source of funding:** Unclear **Comments:** Double-blind
Number and characteristics of patients	**Total number of patients:** 105 **Inclusion criteria:** patients with type 2 diabetes, <70 years of age, with diabetes duration between 3-60 months, BMI between 25-35 kg/m2, FBG <10 mmol/l and Hba1c >6% but not >11% **Exclusion criteria:** No details reported Pre-randomisation phase: There was a 6 week run-in period
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** some on oral hypoglycaemic drugs and/or insulin **Details of washout period:** If used these were withdrawn
Lifestyle advice	All patients received diet instructions conforming to current recommendations for type 2 diabetes
Follow-up	**Total follow-up (wks):** 16 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 16 **Frequency of monitoring appointments:** Patients were seen at weeks 4,8,12 and 16
Arms	**(1) Placebo** N: 52 Treatment duration (wks): 16 Washout period (d): 42 Comments: There was a 6 week placebo run-in Treatment(s): Placebo (Oral) **(2) Acarbose** N: 53 Treatment duration (wks): 16 Washout period (d): 42 Comments: There was a 6 week placebo run-in Treatment(s): Acarbose (Oral) – fixed-dose Set dose (mg/d):300 Frequency of dosing: three times a day Details of dosing regimen: Acarbose, week 1-2 50 mg TID, wk 3-16 100 mg TID, dose reduced to 50 mg TID in case of adverse events
Outcomes	
Baseline characteristics	

	Placebo			Acarbose				
	N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**

Demographics: Age (years)	Continuous	52		57 (SD 8)	53		56 (SD 9)		
Sex (n male) a	Dichotomous	52	34	(65.4%)	53	33	(62.3%)		
Duration of diabetes (months)	Continuous	52		26 (SD 17)	53		21 (SD 15)		
Blood glucose: HbA1c (%) – 0wk	Continuous	52		6.89 (SD 0.85)	53		7 (SD 0.87)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	52		7.71 (SD 1.46)	53		8.32 (SD 1.78)		
Body weight: Weight (kg)	Continuous	52		84 (SD 12)	53		91 (SD 13)		
Lipids: Total cholesterol (mmol/l) – 0wk	Mean change	52		5.86 (SD 1.21)	53		5.8 (SD 1.37)		
HDL cholesterol (mmol/l) – 0wk	Mean change	52		0.99 (SD 0.31)	53		1.05 (SD 0.26)		
Triglycerides (mmol/l) – 0wk	Mean change	52		2.08 (SD 1.53)	53		1.83 (SD 1.73)		

[a] approximated to nearest integer (percentages only presented in text)

Results

		Placebo			Acarbose				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Blood glucose: HbA1c (%) – 16wk	Continuous	52		7.14 (SD 1.19)	53		6.86 (SD 0.79)		
Fasting plasma glucose (mmol/l) – 16wk	Continuous	52		8.61 (SD 2.32)	53		7.86 (SD 1.83)		
Adverse events: Any adverse event(s) – 16wk	Dichotomous	52	49	(94.2%)	53	51	(96.2%)		
Flatulence – 16wk	Dichotomous	52	19	(36.5%)	53	49	(92.5%)		
Dropouts: Dropout due to AEs – 16wk	Dichotomous	52	4	(7.7%)	53	4	(7.5%)		
Lipids: Total cholesterol (mmol/l) – 16wk	Continuous	52		6.14 (SD 1.17)	53		5.76 (SD 1.17)		
HDL cholesterol (mmol/l) – 16wk	Continuous	52		1.05 (SD 0.32)	53		1.05 (SD 0.25)		
Triglycerides (mmol/l) – 16wk	Continuous	52		2.23 (SD 1.6)	53		1.68 (SD 1.71)		
PP Blood glucose: HbA1c (%) – 16wk	Mean change	42		0.25 (SD 1.2)	41		-0.14 (SD 0.9)		
Fasting plasma glucose (mmol/l) – 16wk	Mean change	42		0.9 (SD 2.2)	41		-0.46 (SD 2)		

Table 99: Scott et al. (2007)

General

Phase:
☑ monotherapy
☐ dual therapy
☐ triple therapy
☐ insulin monotherapy
☐ insulin+oral

Parallel / crossover: Parallel

Country: multinational

	Authors' conclusions: In summary, in this study sitaglitptin improved glycaemic control, with 50 mg bid being the most effective dose, and was generally well tolerated in patients with type 2 diabetes **Source of funding:** sponsored by Merck & Co **Comments:** Multinational, double-blind, randomised placebo and active controlled parallel group dose range finding study. Randomised based on computer generated random allocation schedule, and study medication described as matching (no other details relating to blinding or allocation concealment).
Number and characteristics of patients	**Total number of patients:** 743 **Inclusion criteria:** male and female patients 21-75 years of age with type 2 diabetes, either currently on OHA monotherapy (except thiazolidinediones) with Hba1c >=6% and <=9% or not currently on an OHA with Hba1c >=6.5% and <10% were eligible to participate. **Exclusion criteria:** type 1 diabetes, unstable cardiac disease, active liver or gall blader disease, creatinine clearance <60ml/min or elevated ALT, AST or creatinine phosphokinase Pre-randomisation phase: patients not on an OHA with a Hba1c >=6.5% to <10% entered a diet and exercise period of 2-6 weeks. Patients on OHA monotherapy with Hba1c >=6% to <=9% had their OHA discontinued and enetered a diet and exercise period of 6 weeks. If Hba1c was >=6.5 and <10% and FPG was >=7.22 mmol/l and <=13.32 mmol/l after the exercise and diet run-in period, patients were eligible to be randomised after completing a 2 week single blind placebo run-in period. Tittration period for glipizide formed part of the maintenance period
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** some on oral hypoglycaemic drugs and/or insulin **Details of washout period:** diet and exercise period 2-6 weeks followed by a 2 week single blind, placebo run-in period (see pre-randomisation phase for more details)
Lifestyle advice	patients received counselling on diet and exercise consistent with ADA recommendations
Follow-up	**Total follow-up (wks):** 20 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 12 **Frequency of monitoring appointments:** -
Arms	**(1) sitagliptin (5mg bid)** N: 125 Treatment duration (wks): 12 Washout period (d): 56 Treatment(s): Sitagliptin (Oral) – fixed-dose Frequency of dosing: twice a day Details of dosing regimen: patients were instructed to take their study medication (sitagliptin or matching placebo and glipizide or matching placebo) twice daily, prior to the morning and evening meals **(2) Sitagliptin (12.5 mg bid)** N: 123 Treatment duration (wks): 12 Washout period (d): 56 Treatment(s): Sitagliptin (Oral) – fixed-dose Frequency of dosing: twice a day Details of dosing regimen: patients were instructed to take their study medication (sitagliptin or matching placebo and glipizide or matching placebo) twice daily, prior to the morning and evening meals **(3) Sitagliptin (25 mg bid)** N: 123 Treatment duration (wks): 12 Washout period (d): 56 Treatment(s): Sitagliptin (Oral) – fixed-dose Frequency of dosing: twice a day Details of dosing regimen: patients were instructed to take their study medication (sitagliptin or matching placebo and glipizide or matching placebo) twice daily, prior to the morning and evening meals **(4) Sitagliptin (50 mg bid)** N: 124 Treatment duration (wks): 12 Washout period (d): 56 Treatment(s): Sitagliptin (Oral) – fixed-dose Frequency of dosing: twice a day Details of dosing regimen: patients were instructed to take their study medication (sitagliptin or matching placebo and glipizide or matching placebo) twice daily, prior to the morning and evening meals **(5) glipizide**

N: 123
Treatment duration (wks): 12
Washout period (d): 56
Treatment(s): Sulfonylurea (Oral) – flexible-dose (dose-adjusted)
Minimum dose (mg/d): 5
Maximum dose (mg/d): 20
Frequency of dosing: twice a day
Details of dosing regimen: the mean daily glucose (MDG) was used to determine whether the glipizide dose was to be uptitrated. At 2 week intervals over the first 6 weeks of treatment, glipizide was uptitrated by 5 mg/day if all the following criteria were met: if MDG >8.88 mmol/l, all fingerstick glucose from the week prior were >5.55 mmol/l and there were no episodes of hypoglycaemia prior to the visit. If patients experienced unexplained hypoglycaemia at any time during the study, glipizide was downtitrated to 5 mg/day and held there for the remainder of the study. If patients continue to experience hypoglycaemic episodes following down titration to 5 mg/day they were discontinued from the study

(6) placebo

N: 125
Treatment duration (wks): 12
Washout period (d): 56
Treatment(s): Placebo (Oral)
Frequency of dosing: twice a day
Details of dosing regimen: patients were instructed to take their study medication (sitagliptin or matching placebo and glipizide or matching placebo) twice daily, prior to the morning and evening meals

Outcomes

General

Effiicacy analyses were based on the all-patients treated population, consisting of all randomiosed patients who received at least one dose of study drug and who had both a baseline (randomisation visit) and at least one post-randomisation measurement. Missing data were handles using the last observation carried forward method.

17 (13.6%) patients in the placebo group, 18 (14.4%) in 5mg, 7 (5.7%) in 12.5mg, 15 (12.2%) in 25mg, 12 (9.7%) in 50mg and 23 (18.7%) in glipizide groups discontinued the study.

Outcomes not reported in this evidence table include mean daily glucose, fasting insulin, HOMA-beta, HOMA-IR, QUICKI, area under the curve measures, FFA

Hypoglycaemic events

All hypoglycaemic events (no patients) (hypoglycaemia was assessed by investigators through reviewing daily glucose logs and patient reported self-report signs an symptoms of hypoglycaemia)

Baseline characteristics

		sitagliptin (5mg bid)			Sitagliptin (12.5 mg bid)			Δ	p
		N	k	mean	N	k	mean		
Demographics: Age (years)	Continuous	125		55.1 (SD 9.5)	123		56.2 (SD 9)		
Sex (n male)	Dichotomous	125	62	(49.6%)	123	59	(48.0%)		
Duration of diabetes (yrs)	Continuous	125		4.3 (SD 4.1)	123		4.9 (SD 5)		
Ethnicity-White	Dichotomous	125	86	(68.8%)	123	78	(63.4%)		
Ethnicity-Black	Dichotomous	125	8	(6.4%)	123	6	(4.9%)		
Ethnicity-Asian	Dichotomous	125	7	(5.6%)	123	6	(4.9%)		
Ethnicity-Other	Dichotomous	125	24	(19.2%)	123	33	(26.8%)		
Blood glucose: HbA1c (%) – 0wk	Continuous	125		7.9 (SD 1)	123		7.9 (SD 0.9)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	125		9.5 (SD 2.2)	123		9.4 (SD 2)		
Body weight: BMI (kg/m2)	Continuous	125		30.8 (SD 5.1)	123		30.5 (SD 5)		
Weight (kg) – 0wka	Continuous	125		86.92992 (SD 14.4)	123		86.0832 (SD 14.1)		

[a] estimated from BMI assuming mean height of 1.68m

	sitagliptin (5mg bid)			Sitagliptin (25 mg bid)			Δ	p
	N	k	mean	N	k	mean		

Demographics: Age (years)	Continuous	125		55.1 (SD 9.5)	123		55.6 (SD 9)		
Sex (n male)	Dichotomous	125	62	(49.6%)	123	71	(57.7%)		
Duration of diabetes (yrs)	Continuous	125		4.3 (SD 4.1)	123		5 (SD 5.2)		
Ethnicity-White	Dichotomous	125	86	(68.8%)	123	75	(61.0%)		
Ethnicity-Black	Dichotomous	125	8	(6.4%)	123	11	(8.9%)		
Ethnicity-Asian	Dichotomous	125	7	(5.6%)	123	6	(4.9%)		
Ethnicity-Other	Dichotomous	125	24	(19.2%)	123	31	(25.2%)		
Blood glucose: HbA1c (%) – 0wk	Continuous	125		7.9 (SD 1)	123		7.9 (SD 0.9)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	125		9.5 (SD 2.2)	123		9.6 (SD 2.2)		
Body weight: BMI (kg/m2)	Continuous	125		30.8 (SD 5.1)	123		31.4 (SD 6.9)		
Weight (kg) – 0wka	Continuous	125		86.92992 (SD 14.4)	123		88.62336 (SD 19.5)		

[a] estimated from BMI assuming mean height of 1.68m

		sitagliptin (5mg bid)			Sitagliptin (50 mg bid)				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	125		55.1 (SD 9.5)	124		55.1 (SD 9.8)		
Sex (n male)	Dichotomous	125	62	(49.6%)	124	65	(52.4%)		
Duration of diabetes (yrs)	Continuous	125		4.3 (SD 4.1)	124		4.2 (SD 4)		
Ethnicity-White	Dichotomous	125	86	(68.8%)	124	86	(69.4%)		
Ethnicity-Black	Dichotomous	125	8	(6.4%)	124	6	(4.8%)		
Ethnicity-Asian	Dichotomous	125	7	(5.6%)	124	3	(2.4%)		
Ethnicity-Other	Dichotomous	125	24	(19.2%)	124	29	(23.4%)		
Blood glucose: HbA1c (%) – 0wk	Continuous	125		7.9 (SD 1)	124		7.8 (SD 1)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	125		9.5 (SD 2.2)	124		9.4 (SD 2.2)		
Body weight: BMI (kg/m2)	Continuous	125		30.8 (SD 5.1)	124		30.4 (SD 4.9)		
Weight (kg) – 0wka	Continuous	125		86.92992 (SD 14.4)	124		85.80096 (SD 13.8)		

[a] estimated from BMI assuming mean height of 1.68m

		sitagliptin (5mg bid)			placebo				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	125		55.1 (SD 9.5)	125		55.3 (SD 9.7)		
Sex (n male)	Dichotomous	125	62	(49.6%)	125	78	(62.4%)		
Duration of diabetes (yrs)	Continuous	125		4.3 (SD 4.1)	125		4.8 (SD 4.7)		
Ethnicity-White	Dichotomous	125	86	(68.8%)	125	83	(66.4%)		
Ethnicity-Black	Dichotomous	125	8	(6.4%)	125	10	(8.0%)		
Ethnicity-Asian	Dichotomous	125	7	(5.6%)	125	3	(2.4%)		
Ethnicity-Other	Dichotomous	125	24	(19.2%)	125	29	(23.2%)		
Blood glucose: HbA1c (%) – 0wk	Continuous	125		7.9 (SD 1)	125		7.9 (SD 1)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	125		9.5 (SD 2.2)	125		9.6 (SD 2.5)		
Body weight: BMI (kg/m2)	Continuous	125		30.8 (SD 5.1)	125		31.6 (SD 5.8)		

Weight (kg) – 0wka	Continuous	125		86.92992 (SD 14.4)	125		89.18784 (SD 16.4)		

[a] estimated from BMI assuming mean height of 1.68m

		Sitagliptin (12.5 mg bid)			Sitagliptin (25 mg bid)			Δ	p
		N	k	mean	N	k	mean		
Demographics:									
Age (years)	Continuous	123		56.2 (SD 9)	123		55.6 (SD 9)		
Sex (n male)	Dichotomous	123	59	(48.0%)	123	71	(57.7%)		
Duration of diabetes (yrs)	Continuous	123		4.9 (SD 5)	123		5 (SD 5.2)		
Ethnicity-White	Dichotomous	123	78	(63.4%)	123	75	(61.0%)		
Ethnicity-Black	Dichotomous	123	6	(4.9%)	123	11	(8.9%)		
Ethnicity-Asian	Dichotomous	123	6	(4.9%)	123	6	(4.9%)		
Ethnicity-Other	Dichotomous	123	33	(26.8%)	123	31	(25.2%)		
Blood glucose:									
HbA1c (%) – 0wk	Continuous	123		7.9 (SD 0.9)	123		7.9 (SD 0.9)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	123		9.4 (SD 2)	123		9.6 (SD 2.2)		
Body weight:									
BMI (kg/m2)	Continuous	123		30.5 (SD 5)	123		31.4 (SD 6.9)		
Weight (kg) – 0wka	Continuous	123		86.0832 (SD 14.1)	123		88.62336 (SD 19.5)		

[a] estimated from BMI assuming mean height of 1.68m

		Sitagliptin (12.5 mg bid)			Sitagliptin (50 mg bid)			Δ	p
		N	k	mean	N	k	mean		
Demographics:									
Age (years)	Continuous	123		56.2 (SD 9)	124		55.1 (SD 9.8)		
Sex (n male)	Dichotomous	123	59	(48.0%)	124	65	(52.4%)		
Duration of diabetes (yrs)	Continuous	123		4.9 (SD 5)	124		4.2 (SD 4)		
Ethnicity-White	Dichotomous	123	78	(63.4%)	124	86	(69.4%)		
Ethnicity-Black	Dichotomous	123	6	(4.9%)	124	6	(4.8%)		
Ethnicity-Asian	Dichotomous	123	6	(4.9%)	124	3	(2.4%)		
Ethnicity-Other	Dichotomous	123	33	(26.8%)	124	29	(23.4%)		
Blood glucose:									
HbA1c (%) – 0wk	Continuous	123		7.9 (SD 0.9)	124		7.8 (SD 1)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	123		9.4 (SD 2)	124		9.4 (SD 2.2)		
Body weight:									
BMI (kg/m2)	Continuous	123		30.5 (SD 5)	124		30.4 (SD 4.9)		
Weight (kg) – 0wka	Continuous	123		86.0832 (SD 14.1)	124		85.80096 (SD 13.8)		

[a] estimated from BMI assuming mean height of 1.68m

		Sitagliptin (12.5 mg bid)			glipizide			Δ	p
		N	k	mean	N	k	mean		
Demographics:									
Age (years)	Continuous	123		56.2 (SD 9)	123		54.7 (SD 10.7)		
Sex (n male)	Dichotomous	123	59	(48.0%)	123	70	(56.9%)		
Duration of diabetes (yrs)	Continuous	123		4.9 (SD 5)	123		4.7 (SD 4.2)		
Ethnicity-White	Dichotomous	123	78	(63.4%)	123	75	(61.0%)		

Ethnicity-Black	Dichotomous	123	6	(4.9%)	123	4	(3.3%)		
Ethnicity-Asian	Dichotomous	123	6	(4.9%)	123	6	(4.9%)		
Ethnicity-Other	Dichotomous	123	33	(26.8%)	123	38	(30.9%)		
Blood glucose: HbA1c (%) – 0wk	Continuous	123		7.9 (SD 0.9)	123		7.9 (SD 1)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	123		9.4 (SD 2)	123		9.5 (SD 2.2)		
Body weight: BMI (kg/m2)	Continuous	123		30.5 (SD 5)	123		30.6 (SD 5.3)		
Weight (kg) – 0wka	Continuous	123		86.0832 (SD 14.1)	123		86.36544 (SD 15)		

[a] estimated from BMI assuming mean height of 1.68m

		Sitagliptin (12.5 mg bid)			placebo				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	123		56.2 (SD 9)	125		55.3 (SD 9.7)		
Sex (n male)	Dichotomous	123	59	(48.0%)	125	78	(62.4%)		
Duration of diabetes (yrs)	Continuous	123		4.9 (SD 5)	125		4.8 (SD 4.7)		
Ethnicity-White	Dichotomous	123	78	(63.4%)	125	83	(66.4%)		
Ethnicity-Black	Dichotomous	123	6	(4.9%)	125	10	(8.0%)		
Ethnicity-Asian	Dichotomous	123	6	(4.9%)	125	3	(2.4%)		
Ethnicity-Other	Dichotomous	123	33	(26.8%)	125	29	(23.2%)		
Blood glucose: HbA1c (%) – 0wk	Continuous	123		7.9 (SD 0.9)	125		7.9 (SD 1)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	123		9.4 (SD 2)	125		9.6 (SD 2.5)		
Body weight: BMI (kg/m2)	Continuous	123		30.5 (SD 5)	125		31.6 (SD 5.8)		
Weight (kg) – 0wka	Continuous	123		86.0832 (SD 14.1)	125		89.18784 (SD 16.4)		

[a] estimated from BMI assuming mean height of 1.68m

		Sitagliptin (25 mg bid)			Sitagliptin (50 mg bid)				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	123		55.6 (SD 9)	124		55.1 (SD 9.8)		
Sex (n male)	Dichotomous	123	71	(57.7%)	124	65	(52.4%)		
Duration of diabetes (yrs)	Continuous	123		5 (SD 5.2)	124		4.2 (SD 4)		
Ethnicity-White	Dichotomous	123	75	(61.0%)	124	86	(69.4%)		
Ethnicity-Black	Dichotomous	123	11	(8.9%)	124	6	(4.8%)		
Ethnicity-Asian	Dichotomous	123	6	(4.9%)	124	3	(2.4%)		
Ethnicity-Other	Dichotomous	123	31	(25.2%)	124	29	(23.4%)		
Blood glucose: HbA1c (%) – 0wk	Continuous	123		7.9 (SD 0.9)	124		7.8 (SD 1)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	123		9.6 (SD 2.2)	124		9.4 (SD 2.2)		
Body weight: BMI (kg/m2)	Continuous	123		31.4 (SD 6.9)	124		30.4 (SD 4.9)		
Weight (kg) – 0wka	Continuous	123		88.62336 (SD 19.5)	124		85.80096 (SD 13.8)		

[a] estimated from BMI assuming mean height of 1.68m

		Sitagliptin (25 mg bid)			placebo			Δ	p
		N	k	mean	N	k	mean		
Demographics: Age (years)	Continuous	123		55.6 (SD 9)	125		55.3 (SD 9.7)		
Sex (n male)	Dichotomous	123	71	(57.7%)	125	78	(62.4%)		
Duration of diabetes (yrs)	Continuous	123		5 (SD 5.2)	125		4.8 (SD 4.7)		
Ethnicity-White	Dichotomous	123	75	(61.0%)	125	83	(66.4%)		
Ethnicity-Black	Dichotomous	123	11	(8.9%)	125	10	(8.0%)		
Ethnicity-Asian	Dichotomous	123	6	(4.9%)	125	3	(2.4%)		
Ethnicity-Other	Dichotomous	123	31	(25.2%)	125	29	(23.2%)		
Blood glucose: HbA1c (%) – 0wk	Continuous	123		7.9 (SD 0.9)	125		7.9 (SD 1)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	123		9.6 (SD 2.2)	125		9.6 (SD 2.5)		
Body weight: BMI (kg/m2)	Continuous	123		31.4 (SD 6.9)	125		31.6 (SD 5.8)		
Weight (kg) – 0wka	Continuous	123		88.62336 (SD 19.5)	125		89.18784 (SD 16.4)		

[a] estimated from BMI assuming mean height of 1.68m

		Sitagliptin (50 mg bid)			glipizide			Δ	p
		N	k	mean	N	k	mean		
Demographics: Age (years)	Continuous	124		55.1 (SD 9.8)	123		54.7 (SD 10.7)		
Sex (n male)	Dichotomous	124	65	(52.4%)	123	70	(56.9%)		
Duration of diabetes (yrs)	Continuous	124		4.2 (SD 4)	123		4.7 (SD 4.2)		
Ethnicity-White	Dichotomous	124	86	(69.4%)	123	75	(61.0%)		
Ethnicity-Black	Dichotomous	124	6	(4.8%)	123	4	(3.3%)		
Ethnicity-Asian	Dichotomous	124	3	(2.4%)	123	6	(4.9%)		
Ethnicity-Other	Dichotomous	124	29	(23.4%)	123	38	(30.9%)		
Blood glucose: HbA1c (%) – 0wk	Continuous	124		7.8 (SD 1)	123		7.9 (SD 1)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	124		9.4 (SD 2.2)	123		9.5 (SD 2.2)		
Body weight: BMI (kg/m2)	Continuous	124		30.4 (SD 4.9)	123		30.6 (SD 5.3)		
Weight (kg) – 0wka	Continuous	124		85.80096 (SD 13.8)	123		86.36544 (SD 15)		

[a] estimated from BMI assuming mean height of 1.68m

		Sitagliptin (50 mg bid)			placebo			Δ	p
		N	k	mean	N	k	mean		
Demographics: Age (years)	Continuous	124		55.1 (SD 9.8)	125		55.3 (SD 9.7)		
Sex (n male)	Dichotomous	124	65	(52.4%)	125	78	(62.4%)		
Duration of diabetes (yrs)	Continuous	124		4.2 (SD 4)	125		4.8 (SD 4.7)		
Ethnicity-White	Dichotomous	124	86	(69.4%)	125	83	(66.4%)		
Ethnicity-Black	Dichotomous	124	6	(4.8%)	125	10	(8.0%)		
Ethnicity-Asian	Dichotomous	124	3	(2.4%)	125	3	(2.4%)		
Ethnicity-Other	Dichotomous	124	29	(23.4%)	125	29	(23.2%)		
Blood glucose: HbA1c (%) – 0wk	Continuous	124		7.8 (SD 1)	125		7.9 (SD 1)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	124		9.4 (SD 2.2)	125		9.6 (SD 2.5)		

Body weight: BMI (kg/m2)	Continuous	124		30.4 (SD 4.9)	125		31.6 (SD 5.8)		
Weight (kg) – 0wka	Continuous	124		85.80096 (SD 13.8)	125		89.18784 (SD 16.4)		

[a] estimated from BMI assuming mean height of 1.68m

		glipizide			placebo				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	123		54.7 (SD 10.7)	125		55.3 (SD 9.7)		
Sex (n male)	Dichotomous	123	70	(56.9%)	125	78	(62.4%)		
Duration of diabetes (yrs)	Continuous	123		4.7 (SD 4.2)	125		4.8 (SD 4.7)		
Ethnicity-White	Dichotomous	123	75	(61.0%)	125	83	(66.4%)		
Ethnicity-Black	Dichotomous	123	4	(3.3%)	125	10	(8.0%)		
Ethnicity-Asian	Dichotomous	123	6	(4.9%)	125	3	(2.4%)		
Ethnicity-Other	Dichotomous	123	38	(30.9%)	125	29	(23.2%)		
Blood glucose: HbA1c (%) – 0wk	Continuous	123		7.9 (SD 1)	125		7.9 (SD 1)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	123		9.5 (SD 2.2)	125		9.6 (SD 2.5)		
Body weight: BMI (kg/m2)	Continuous	123		30.6 (SD 5.3)	125		31.6 (SD 5.8)		
Weight (kg) – 0wka	Continuous	123		86.36544 (SD 15)	125		89.18784 (SD 16.4)		

[a] estimated from BMI assuming mean height of 1.68m

Results

		sitagliptin (5mg bid)			Sitagliptin (12.5 mg bid)				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 12wk	Mean change	122		-0.15 (SD 0.789)	122		-0.41 (SD 0.789)		
Fasting plasma glucose (mmol/l) – 12wk	Mean change	124		-0.04 (SD 1.99)	123		-0.72 (SD 1.98)		
2-h post prandial glucose (mmol/l) – 12wk	Mean change	44		-1.63 (SD 3.22)	39		-1.83 (SD 3.22)		
Hypoglycaemic events: All hypoglycaemic events (no patients) – 12wk	Dichotomous	125	0	(0.0%)	123	5	(4.1%)		
Adverse events: Any adverse event(s) – 12wk	Dichotomous	125	68	(54.4%)	123	67	(54.5%)		
Any serious adverse event(s) – 12wk	Dichotomous	125	4	(3.2%)	123	2	(1.6%)		
Serious AE drug related – 12wk	Dichotomous	125	0	(0.0%)	123	0	(0.0%)		
Study drug-related adverse event – 12wk	Dichotomous	124	11	(8.9%)	123	20	(16.3%)		
Dropouts: Total dropouts – 12wk	Dichotomous	125	18	(14.4%)	123	7	(5.7%)		
Dropout due to AEs – 12wk	Dichotomous	125	2	(1.6%)	123	3	(2.4%)		
drop out due to drug related AE – 12wk	Dichotomous	125	1	(0.8%)	123	3	(2.4%)		
drop out due to SAE – 12wk	Dichotomous	125	0	(0.0%)	123	0	(0.0%)		
drop out due to drug related SAE – 12wk	Dichotomous	125	0	(0.0%)	123	0	(0.0%)		
Drop out due to unsatisfactory effect – 12wk	Dichotomous	125	7	(5.6%)	123	2	(1.6%)		
Lipids: Total cholesterol (mmol/l) – 12wk	Mean change	120		1.9 (SD 13.4)	121		1 (SD 12.9)		

HDL cholesterol (mmol/l) – 12wk	Mean change	120		1.1 (SD 12.3)	121		3 (SD 12.3)		
Triglycerides (mmol/l) – 12wk	Mean change	120		9.8 (SD 38.6)	121		-0.5 (SD 38.2)		
LDL cholesterol (mmol/l) – 12wk	Mean change	120		1.7 (SD 20.5)	121		3 (SD 20.9)		

		sitagliptin (5mg bid)			Sitagliptin (25 mg bid)			Δ	p
		N	k	mean	N	k	mean		
Blood glucose: HbA1c (%) – 12wk	Mean change	122		-0.15 (SD 0.789)	120		-0.43 (SD 0.727)		
Fasting plasma glucose (mmol/l) – 12wk	Mean change	124		-0.04 (SD 1.99)	121		-0.72 (SD 2.02)		
2-h post prandial glucose (mmol/l) – 12wk	Mean change	44		-1.63 (SD 3.22)	28		-2.2 (SD 4.4)		
Hypoglycaemic events: All hypoglycaemic events (no patients) – 12wk	Dichotomous	125	0	(0.0%)	123	5	(4.1%)		
Adverse events: Any adverse event(s) – 12wk	Dichotomous	125	68	(54.4%)	123	76	(61.8%)		
Any serious adverse event(s) – 12wk	Dichotomous	125	4	(3.2%)	123	1	(0.8%)		
Serious AE drug related – 12wk	Dichotomous	125	0	(0.0%)	123	0	(0.0%)		
Study drug-related adverse event – 12wk	Dichotomous	124	11	(8.9%)	123	17	(13.8%)		
Dropouts: Total dropouts – 12wk	Dichotomous	125	18	(14.4%)	123	15	(12.2%)		
Dropout due to AEs – 12wk	Dichotomous	125	2	(1.6%)	123	1	(0.8%)		
drop out due to drug related AE – 12wk	Dichotomous	125	1	(0.8%)	123	1	(0.8%)		
drop out due to SAE – 12wk	Dichotomous	125	0	(0.0%)	123	0	(0.0%)		
drop out due to drug related SAE – 12wk	Dichotomous	125	0	(0.0%)	123	0	(0.0%)		
Drop out due to unsatisfactory effect – 12wk	Dichotomous	125	7	(5.6%)	123	8	(6.5%)		
Lipids: Total cholesterol (mmol/l) – 12wk	Mean change	120		1.9 (SD 13.4)	117		1.2 (SD 13.2)		
HDL cholesterol (mmol/l) – 12wk	Mean change	120		1.1 (SD 12.3)	117		4.1 (SD 12.7)		
Triglycerides (mmol/l) – 12wk	Mean change	120		9.8 (SD 38.6)	117		4.9 (SD 38.6)		
LDL cholesterol (mmol/l) – 12wk	Mean change	120		1.7 (SD 20.5)	117		1.9 (SD 20.9)		

		sitagliptin (5mg bid)			Sitagliptin (50 mg bid)			Δ	p
		N	k	mean	N	k	mean		
Blood glucose: HbA1c (%) – 12wk	Mean change	122		-0.15 (SD 0.789)	121		-0.54 (SD 0.786)		
Fasting plasma glucose (mmol/l) – 12wk	Mean change	124		-0.04 (SD 1.99)	122		-1.01 (SD 1.97)		
2-h post prandial glucose (mmol/l) – 12wk	Mean change	44		-1.63 (SD 3.22)	40		-2.69 (SD 3.23)		

Hypoglycaemic events: All hypoglycaemic events (no patients) – 12wk	Dichotomous	125	0	(0.0%)	124	2	(1.6%)		
Adverse events: Any adverse event(s) – 12wk	Dichotomous	125	68	(54.4%)	124	73	(58.9%)		
Any serious adverse event(s) – 12wk	Dichotomous	125	4	(3.2%)	124	3	(2.4%)		
Serious AE drug related – 12wk	Dichotomous	125	0	(0.0%)	124	0	(0.0%)		
Study drug-related adverse event – 12wk	Dichotomous	124	11	(8.9%)	122	15	(12.3%)		
Dropouts: Total dropouts – 12wk	Dichotomous	125	18	(14.4%)	124	12	(9.7%)		
Dropout due to AEs – 12wk	Dichotomous	125	2	(1.6%)	124	3	(2.4%)		
drop out due to drug related AE – 12wk	Dichotomous	125	1	(0.8%)	124	1	(0.8%)		
drop out due to SAE – 12wk	Dichotomous	125	0	(0.0%)	124	0	(0.0%)		
drop out due to drug related SAE – 12wk	Dichotomous	125	0	(0.0%)	124	0	(0.0%)		
Drop out due to unsatisfactory effect – 12wk	Dichotomous	125	7	(5.6%)	124	1	(0.8%)		
Lipids: Total cholesterol (mmol/l) – 12wk	Mean change	120		1.9 (SD 13.4)	119		3.4 (SD 13.4)		
HDL cholesterol (mmol/l) – 12wk	Mean change	120		1.1 (SD 12.3)	119		4.6 (SD 12.8)		
Triglycerides (mmol/l) – 12wk	Mean change	120		9.8 (SD 38.6)	119		3.6 (SD 38.4)		
LDL cholesterol (mmol/l) – 12wk	Mean change	120		1.7 (SD 20.5)	119		5.5 (SD 21)		

		sitagliptin (5mg bid)			**placebo**				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Blood glucose: HbA1c (%) – 12wk	Mean change	122		-0.15 (SD 0.789)	121		0.23 (SD 0.73)	MD=-0.380 (CI: -0.580, -0.180)	<0.001a
Fasting plasma glucose (mmol/l) – 12wk	Mean change	124		-0.04 (SD 1.99)	123		0.44 (SD 1.98)	MD=-0.480 (CI: -0.970, 0.010)	0.051a
2-h post prandial glucose (mmol/l) – 12wk	Continuous	125			125				b
2-h post prandial glucose (mmol/l) – 12wk	Mean change	44		-1.63 (SD 3.22)	38		0.31 (SD 3.21)		
Body weight: Weight (kg) – 12wk	Mean change	125			125			MD=0.100 (CI: -0.500, 0.700)	>0.1
Hypoglycaemic events: All hypoglycaemic events (no patients) – 12wk	Dichotomous	125	0	(0.0%)	125	3	(2.4%)		b
Adverse events: Any adverse event(s) – 12wk	Dichotomous	125	68	(54.4%)	125	67	(53.6%)		b
Any serious adverse event(s) – 12wk	Dichotomous	125	4	(3.2%)	125	4	(3.2%)		b
Serious AE drug related – 12wk	Dichotomous	125	0	(0.0%)	125	0	(0.0%)		b
Study drug-related adverse event – 12wk	Dichotomous	124	11	(8.9%)	125	12	(9.6%)		
Dropouts: Total dropouts – 12wk	Dichotomous	125	18	(14.4%)	125	17	(13.6%)		

Dropout due to AEs – 12wk	Dichotomous	125	2	(1.6%)	125	1	(0.8%)		b
drop out due to drug related AE – 12wk	Dichotomous	125	1	(0.8%)	125	0	(0.0%)		b
drop out due to SAE – 12wk	Dichotomous	125	0	(0.0%)	125	0	(0.0%)		b
drop out due to drug related SAE – 12wk	Dichotomous	125	0	(0.0%)	125	0	(0.0%)		b
Drop out due to unsatisfactory effect – 12wk	Dichotomous	125	7	(5.6%)	125	9	(7.2%)		b
Lipids: Total cholesterol (mmol/l) – 12wk	Mean change	120		1.9 (SD 13.4)	117		1.6 (SD 12.7)	MD=0.200 (CI: -3.900, 4.300)	NS
HDL cholesterol (mmol/l) – 12wk	Mean change	120		1.1 (SD 12.3)	117		0.6 (SD 12.7)	MD=0.500 (CI: -2.700, 3.700)	NS
Triglycerides (mmol/l) – 12wk	Mean change	120		9.8 (SD 38.6)	117		13.9 (SD 38.6)	MD=-4.100 (CI: -13.800, 5.600)	NS
LDL cholesterol (mmol/l) – 12wk	Mean change	120		1.7 (SD 20.5)	117		0.9 (SD 21.7)	MD=0.900 (CI: -4.300, 6.100)	NS

[a] p-value is trend test for sitagliptin dose vs. placebo
[b] not reported

		Sitagliptin (12.5 mg bid)			Sitagliptin (25 mg bid)				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 12wk	Mean change	122		-0.41 (SD 0.789)	120		-0.43 (SD 0.727)		
Fasting plasma glucose (mmol/l) – 12wk	Mean change	123		-0.72 (SD 1.98)	121		-0.72 (SD 2.02)		
2-h post prandial glucose (mmol/l) – 12wk	Mean change	39		-1.83 (SD 3.22)	28		-2.2 (SD 4.4)		
Hypoglycaemic events: All hypoglycaemic events (no patients) – 12wk	Dichotomous	123	5	(4.1%)	123	5	(4.1%)		
Adverse events: Any adverse event(s) – 12wk	Dichotomous	123	67	(54.5%)	123	76	(61.8%)		
Any serious adverse event(s) – 12wk	Dichotomous	123	2	(1.6%)	123	1	(0.8%)		
Serious AE drug related – 12wk	Dichotomous	123	0	(0.0%)	123	0	(0.0%)		
Study drug-related adverse event – 12wk	Dichotomous	123	20	(16.3%)	123	17	(13.8%)		
Dropouts: Total dropouts – 12wk	Dichotomous	123	7	(5.7%)	123	15	(12.2%)		
Dropout due to AEs – 12wk	Dichotomous	123	3	(2.4%)	123	1	(0.8%)		
drop out due to drug related AE – 12wk	Dichotomous	123	3	(2.4%)	123	1	(0.8%)		
drop out due to SAE – 12wk	Dichotomous	123	0	(0.0%)	123	0	(0.0%)		
drop out due to drug related SAE – 12wk	Dichotomous	123	0	(0.0%)	123	0	(0.0%)		
Drop out due to unsatisfactory effect – 12wk	Dichotomous	123	2	(1.6%)	123	8	(6.5%)		
Lipids: Total cholesterol (mmol/l) – 12wk	Mean change	121		1 (SD 12.9)	117		1.2 (SD 13.2)		
HDL cholesterol (mmol/l) – 12wk	Mean change	121		3 (SD 12.3)	117		4.1 (SD 12.7)		
Triglycerides (mmol/l) – 12wk	Mean change	121		-0.5 (SD 38.2)	117		4.9 (SD 38.6)		
LDL cholesterol (mmol/l) – 12wk	Mean change	121		3 (SD 20.9)	117		1.9 (SD 20.9)		

		Sitagliptin (12.5 mg bid)			Sitagliptin (50 mg bid)			Δ	p
		N	k	mean	N	k	mean		
Blood glucose: HbA1c (%) – 12wk	Mean change	122		-0.41 (SD 0.789)	121		-0.54 (SD 0.786)		
Fasting plasma glucose (mmol/l) – 12wk	Mean change	123		-0.72 (SD 1.98)	122		-1.01 (SD 1.97)		
2-h post prandial glucose (mmol/l) – 12wk	Mean change	39		-1.83 (SD 3.22)	40		-2.69 (SD 3.23)		
Hypoglycaemic events: All hypoglycaemic events (no patients) – 12wk	Dichotomous	123	5	(4.1%)	124	2	(1.6%)		
Adverse events: Any adverse event(s) – 12wk	Dichotomous	123	67	(54.5%)	124	73	(58.9%)		
Any serious adverse event(s) – 12wk	Dichotomous	123	2	(1.6%)	124	3	(2.4%)		
Serious AE drug related – 12wk	Dichotomous	123	0	(0.0%)	124	0	(0.0%)		
Study drug-related adverse event – 12wk	Dichotomous	123	20	(16.3%)	122	15	(12.3%)		
Dropouts: Total dropouts – 12wk	Dichotomous	123	7	(5.7%)	124	12	(9.7%)		
Dropout due to AEs – 12wk	Dichotomous	123	3	(2.4%)	124	3	(2.4%)		
drop out due to drug related AE – 12wk	Dichotomous	123	3	(2.4%)	124	1	(0.8%)		
drop out due to SAE – 12wk	Dichotomous	123	0	(0.0%)	124	0	(0.0%)		
drop out due to drug related SAE – 12wk	Dichotomous	123	0	(0.0%)	124	0	(0.0%)		
Drop out due to unsatisfactory effect – 12wk	Dichotomous	123	2	(1.6%)	124	1	(0.8%)		
Lipids: Total cholesterol (mmol/l) – 12wk	Mean change	121		1 (SD 12.9)	119		3.4 (SD 13.4)		
HDL cholesterol (mmol/l) – 12wk	Mean change	121		3 (SD 12.3)	119		4.6 (SD 12.8)		
Triglycerides (mmol/l) – 12wk	Mean change	121		-0.5 (SD 38.2)	119		3.6 (SD 38.4)		
LDL cholesterol (mmol/l) – 12wk	Mean change	121		3 (SD 20.9)	119		5.5 (SD 21)		

		Sitagliptin (12.5 mg bid)			glipizide			Δ	p
		N	k	mean	N	k	mean		
Blood glucose: HbA1c (%) – 12wk	Mean change	122		-0.41 (SD 0.789)	119		-0.76 (SD 0.779)		
Fasting plasma glucose (mmol/l) – 12wk	Mean change	123		-0.72 (SD 1.98)	121		-1.38 (SD 1.96)		
2-h post prandial glucose (mmol/l) – 12wk	Mean change	39		-1.83 (SD 3.22)	32		-3.69 (SD 3.2)		
Hypoglycaemic events: All hypoglycaemic events (no patients) – 12wk	Dichotomous	123	5	(4.1%)	123	21	(17.1%)		
Adverse events: Any adverse event(s) – 12wk	Dichotomous	123	67	(54.5%)	123	77	(62.6%)		
Any serious adverse event(s) – 12wk	Dichotomous	123	2	(1.6%)	123	6	(4.9%)		
Serious AE drug related – 12wk	Dichotomous	123	0	(0.0%)	123	0	(0.0%)		

Study drug-related adverse event – 12wk	Dichotomous	123	20	(16.3%)	123	34	(27.6%)			
Dropouts:										
Total dropouts – 12wk	Dichotomous	123	7	(5.7%)	123	23	(18.7%)			
Dropout due to AEs – 12wk	Dichotomous	123	3	(2.4%)	123	7	(5.7%)			
drop out due to drug related AE – 12wk	Dichotomous	123	3	(2.4%)	123	4	(3.3%)			
drop out due to SAE – 12wk	Dichotomous	123	0	(0.0%)	123	3	(2.4%)			
drop out due to drug related SAE – 12wk	Dichotomous	123	0	(0.0%)	123	0	(0.0%)			
Drop out due to unsatisfactory effect – 12wk	Dichotomous	123	2	(1.6%)	123	2	(1.6%)			
Lipids:										
Total cholesterol (mmol/l) – 12wk	Mean change	121		1 (SD 12.9)	112		1.8 (SD 13.5)			
HDL cholesterol (mmol/l) – 12wk	Mean change	121		3 (SD 12.3)	112		2.8 (SD 13)			
Triglycerides (mmol/l) – 12wk	Mean change	121		-0.5 (SD 38.2)	112		7 (SD 38.3)			
LDL cholesterol (mmol/l) – 12wk	Mean change	121		3 (SD 20.9)	112		2 (SD 21.5)			

		Sitagliptin (12.5 mg bid)			**placebo**				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Blood glucose: HbA1c (%) – 12wk	Mean change	122		-0.41 (SD 0.789)	121		0.23 (SD 0.73)	MD=-0.640 (CI: -0.840, -0.440)	<0.001a
Fasting plasma glucose (mmol/l) – 12wk	Mean change	123		-0.72 (SD 1.98)	123		0.44 (SD 1.98)	MD=-1.160 (CI: -1.650, -0.670)	<0.001a
2-h post prandial glucose (mmol/l) – 12wk	Continuous	123			125				b
2-h post prandial glucose (mmol/l) – 12wk	Mean change	39		-1.83 (SD 3.22)	38		0.31 (SD 3.21)		
Body weight: Weight (kg) – 12wk	Mean change	123			125			MD=0.100 (CI: -0.500, 0.700)	>0.1
Hypoglycaemic events: All hypoglycaemic events (no patients) – 12wk	Dichotomous	123	5	(4.1%)	125	3	(2.4%)		b
Adverse events: Any adverse event(s) – 12wk	Dichotomous	123	67	(54.5%)	125	67	(53.6%)		b
Any serious adverse event(s) – 12wk	Dichotomous	123	2	(1.6%)	125	4	(3.2%)		b
Serious AE drug related – 12wk	Dichotomous	123	0	(0.0%)	125	0	(0.0%)		b
Study drug-related adverse event – 12wk	Dichotomous	123	20	(16.3%)	125	12	(9.6%)		
Dropouts: Total dropouts – 12wk	Dichotomous	123	7	(5.7%)	125	17	(13.6%)		
Dropout due to AEs – 12wk	Dichotomous	123	3	(2.4%)	125	1	(0.8%)		b
drop out due to drug related AE – 12wk	Dichotomous	123	3	(2.4%)	125	0	(0.0%)		b
drop out due to SAE – 12wk	Dichotomous	123	0	(0.0%)	125	0	(0.0%)		b

drop out due to drug related SAE – 12wk	Dichotomous	123	0	(0.0%)	125	0	(0.0%)		b
Drop out due to unsatisfactory effect – 12wk	Dichotomous	123	2	(1.6%)	125	9	(7.2%)		b
Lipids:									
Total cholesterol (mmol/l) – 12wk	Mean change	121		1 (SD 12.9)	117		1.6 (SD 12.7)	MD=-0.600 (CI: -3.900, 2.700)	NS
HDL cholesterol (mmol/l) – 12wk	Mean change	121		3 (SD 12.3)	117		0.6 (SD 12.7)	MD=2.400 (CI: -0.800, 5.600)	NS
Triglycerides (mmol/l) – 12wk	Mean change	121		-0.5 (SD 38.2)	117		13.9 (SD 38.6)	MD=-14.400 (CI: -24.100, -4.700)	<0.05
LDL cholesterol (mmol/l) – 12wk	Mean change	121		3 (SD 20.9)	117		0.9 (SD 21.7)	MD=2.100 (CI: -3.100, 7.300)	NS

[a] p-value is trend test for sitagliptin dose vs. placebo
[b] not reported

		Sitagliptin (25 mg bid)			Sitagliptin (50 mg bid)				
		N	k	mean	N	k	mean	Δ	p
Blood glucose:									
HbA1c (%) – 12wk	Mean change	120		-0.43 (SD 0.727)	121		-0.54 (SD 0.786)		
Fasting plasma glucose (mmol/l) – 12wk	Mean change	121		-0.72 (SD 2.02)	122		-1.01 (SD 1.97)		
2-h post prandial glucose (mmol/l) – 12wk	Mean change	28		-2.2 (SD 4.4)	40		-2.69 (SD 3.23)		
Hypoglycaemic events:									
All hypoglycaemic events (no patients) – 12wk	Dichotomous	123	5	(4.1%)	124	2	(1.6%)		
Adverse events:									
Any adverse event(s) – 12wk	Dichotomous	123	76	(61.8%)	124	73	(58.9%)		
Any serious adverse event(s) – 12wk	Dichotomous	123	1	(0.8%)	124	3	(2.4%)		
Serious AE drug related – 12wk	Dichotomous	123	0	(0.0%)	124	0	(0.0%)		
Study drug-related adverse event – 12wk	Dichotomous	123	17	(13.8%)	122	15	(12.3%)		
Dropouts:									
Total dropouts – 12wk	Dichotomous	123	15	(12.2%)	124	12	(9.7%)		
Dropout due to AEs – 12wk	Dichotomous	123	1	(0.8%)	124	3	(2.4%)		
drop out due to drug related AE – 12wk	Dichotomous	123	1	(0.8%)	124	1	(0.8%)		
drop out due to SAE – 12wk	Dichotomous	123	0	(0.0%)	124	0	(0.0%)		
drop out due to drug related SAE – 12wk	Dichotomous	123	0	(0.0%)	124	0	(0.0%)		
Drop out due to unsatisfactory effect – 12wk	Dichotomous	123	8	(6.5%)	124	1	(0.8%)		
Lipids:									
Total cholesterol (mmol/l) – 12wk	Mean change	117		1.2 (SD 13.2)	119		3.4 (SD 13.4)		
HDL cholesterol (mmol/l) – 12wk	Mean change	117		4.1 (SD 12.7)	119		4.6 (SD 12.8)		
Triglycerides (mmol/l) – 12wk	Mean change	117		4.9 (SD 38.6)	119		3.6 (SD 38.4)		
LDL cholesterol (mmol/l) – 12wk	Mean change	117		1.9 (SD 20.9)	119		5.5 (SD 21)		

	Sitagliptin (25 mg bid)	placebo	Δ	p

		N	k	mean	N	k	mean		
Blood glucose: HbA1c (%) – 12wk	Mean change	120		-0.43 (SD 0.727)	121		0.23 (SD 0.73)	MD=-0.660 (CI: -0.850, -0.470)	<0.001a
Fasting plasma glucose (mmol/l) – 12wk	Mean change	121		-0.72 (SD 2.02)	123		0.44 (SD 1.98)	MD=-1.160 (CI: -1.660, -0.660)	<0.001a
2-h post prandial glucose (mmol/l) – 12wk	Continuous	123			125				b
2-h post prandial glucose (mmol/l) – 12wk	Mean change	28		-2.2 (SD 4.4)	38		0.31 (SD 3.21)		
Body weight: Weight (kg) – 12wk	Mean change	123			125			MD=0.300 (CI: -0.200, 0.800)	>0.1
Hypoglycaemic events: All hypoglycaemic events (no patients) – 12wk	Dichotomous	123	5	(4.1%)	125	3	(2.4%)		b
Adverse events: Any adverse event(s) – 12wk	Dichotomous	123	76	(61.8%)	125	67	(53.6%)		b
Any serious adverse event(s) – 12wk	Dichotomous	123	1	(0.8%)	125	4	(3.2%)		b
Serious AE drug related – 12wk	Dichotomous	123	0	(0.0%)	125	0	(0.0%)		b
Study drug-related adverse event – 12wk	Dichotomous	123	17	(13.8%)	125	12	(9.6%)		
Dropouts: Total dropouts – 12wk	Dichotomous	123	15	(12.2%)	125	17	(13.6%)		
Dropout due to AEs – 12wk	Dichotomous	123	1	(0.8%)	125	1	(0.8%)		b
drop out due to drug related AE – 12wk	Dichotomous	123	1	(0.8%)	125	0	(0.0%)		b
drop out due to SAE – 12wk	Dichotomous	123	0	(0.0%)	125	0	(0.0%)		b
drop out due to drug related SAE – 12wk	Dichotomous	123	0	(0.0%)	125	0	(0.0%)		b
Drop out due to unsatisfactory effect – 12wk	Dichotomous	123	8	(6.5%)	125	9	(7.2%)		b
Lipids: Total cholesterol (mmol/l) – 12wk	Mean change	117		1.2 (SD 13.2)	117		1.6 (SD 12.7)	MD=-0.400 (CI: -3.800, 3.000)	NS
HDL cholesterol (mmol/l) – 12wk	Mean change	117		4.1 (SD 12.7)	117		0.6 (SD 12.7)	MD=3.500 (CI: 0.200, 6.800)	<0.05
Triglycerides (mmol/l) – 12wk	Mean change	117		4.9 (SD 38.6)	117		13.9 (SD 38.6)	MD=-9.000 (CI: -18.800, 0.800)	<0.05
LDL cholesterol (mmol/l) – 12wk	Mean change	117		1.9 (SD 20.9)	117		0.9 (SD 21.7)	MD=1.000 (CI: -4.200, 6.200)	NS

[a] p-value is trend test for sitagliptin dose vs. placebo
[b] not reported

		Sitagliptin (50 mg bid)			glipizide				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 12wk	Mean change	121		-0.54 (SD 0.786)	119		-0.76 (SD 0.779)		
Fasting plasma glucose (mmol/l) – 12wk	Mean change	122		-1.01 (SD 1.97)	121		-1.38 (SD 1.96)		

2-h post prandial glucose (mmol/l) – 12wk	Mean change	40		-2.69 (SD 3.23)	32		-3.69 (SD 3.2)		
Hypoglycaemic events: All hypoglycaemic events (no patients) – 12wk	Dichotomous	124	2	(1.6%)	123	21	(17.1%)		
Adverse events: Any adverse event(s) – 12wk	Dichotomous	124	73	(58.9%)	123	77	(62.6%)		
Any serious adverse event(s) – 12wk	Dichotomous	124	3	(2.4%)	123	6	(4.9%)		
Serious AE drug related – 12wk	Dichotomous	124	0	(0.0%)	123	0	(0.0%)		
Study drug-related adverse event – 12wk	Dichotomous	122	15	(12.3%)	123	34	(27.6%)		
Dropouts: Total dropouts – 12wk	Dichotomous	124	12	(9.7%)	123	23	(18.7%)		
Dropout due to AEs – 12wk	Dichotomous	124	3	(2.4%)	123	7	(5.7%)		
drop out due to drug related AE – 12wk	Dichotomous	124	1	(0.8%)	123	4	(3.3%)		
drop out due to SAE – 12wk	Dichotomous	124	0	(0.0%)	123	3	(2.4%)		
drop out due to drug related SAE – 12wk	Dichotomous	124	0	(0.0%)	123	0	(0.0%)		
Drop out due to unsatisfactory effect – 12wk	Dichotomous	124	1	(0.8%)	123	2	(1.6%)		
Lipids: Total cholesterol (mmol/l) – 12wk	Mean change	119		3.4 (SD 13.4)	112		1.8 (SD 13.5)		
HDL cholesterol (mmol/l) – 12wk	Mean change	119		4.6 (SD 12.8)	112		2.8 (SD 13)		
Triglycerides (mmol/l) – 12wk	Mean change	119		3.6 (SD 38.4)	112		7 (SD 38.3)		
LDL cholesterol (mmol/l) – 12wk	Mean change	119		5.5 (SD 21)	112		2 (SD 21.5)		

		Sitagliptin (50 mg bid)			**placebo**				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Blood glucose: HbA1c (%) – 12wk	Mean change	121		-0.54 (SD 0.786)	121		0.23 (SD 0.73)	MD=-0.770 (CI: -0.960, -0.580)	<0.001a
Fasting plasma glucose (mmol/l) – 12wk	Mean change	122		-1.01 (SD 1.97)	123		0.44 (SD 1.98)	MD=-1.450 (CI: -1.940, -0.960)	<0.001a
2-h post prandial glucose (mmol/l) – 12wk	Continuous	124			125				b
2-h post prandial glucose (mmol/l) – 12wk	Mean change	40		-2.69 (SD 3.23)	38		0.31 (SD 3.21)		
Body weight: Weight (kg) – 12wk	Mean change	124			125			MD=0.400 (CI: -0.200, 1.000)	>0.1
Hypoglycaemic events: All hypoglycaemic events (no patients) – 12wk	Dichotomous	124	2	(1.6%)	125	3	(2.4%)		b
Adverse events: Any adverse event(s) – 12wk	Dichotomous	124	73	(58.9%)	125	67	(53.6%)		b
Any serious adverse event(s) – 12wk	Dichotomous	124	3	(2.4%)	125	4	(3.2%)		b
Serious AE drug related – 12wk	Dichotomous	124	0	(0.0%)	125	0	(0.0%)		b
Study drug-related adverse event – 12wk	Dichotomous	122	15	(12.3%)	125	12	(9.6%)		

Dropouts: Total dropouts – 12wk	Dichotomous	124	12	(9.7%)	125	17	(13.6%)		
Dropout due to AEs – 12wk	Dichotomous	124	3	(2.4%)	125	1	(0.8%)		b
drop out due to drug related AE – 12wk	Dichotomous	124	1	(0.8%)	125	0	(0.0%)		b
drop out due to SAE – 12wk	Dichotomous	124	0	(0.0%)	125	0	(0.0%)		b
drop out due to drug related SAE – 12wk	Dichotomous	124	0	(0.0%)	125	0	(0.0%)		b
Drop out due to unsatisfactory effect – 12wk	Dichotomous	124	1	(0.8%)	125	9	(7.2%)		b
Lipids: Total cholesterol (mmol/l) – 12wk	Mean change	119		3.4 (SD 13.4)	117		1.6 (SD 12.7)	MD=1.700 (CI: -1.600, 5.000)	NS
HDL cholesterol (mmol/l) – 12wk	Mean change	119		4.6 (SD 12.8)	117		0.6 (SD 12.7)	MD=3.900 (CI: 0.700, 7.100)	<0.05
Triglycerides (mmol/l) – 12wk	Mean change	119		3.6 (SD 38.4)	117		13.9 (SD 38.6)	MD=-10.300 (CI: -20.100, -0.500)	<0.05
LDL cholesterol (mmol/l) – 12wk	Mean change	119		5.5 (SD 21)	117		0.9 (SD 21.7)	MD=4.700 (CI: -0.600, 10.000)	NS

[a] p-value is trend test for sitagliptin dose vs. placebo
[b] not reported

		glipizide			placebo				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Blood glucose: HbA1c (%) – 12wk	Mean change	119		-0.76 (SD 0.779)	121		0.23 (SD 0.73)	MD=-1.000 (CI: -1.190, -0.810)	
Fasting plasma glucose (mmol/l) – 12wk	Mean change	121		-1.38 (SD 1.96)	123		0.44 (SD 1.98)	MD=-1.820 (CI: -2.310, -1.330)	
2-h post prandial glucose (mmol/l) – 12wk	Continuous	123			125				a
2-h post prandial glucose (mmol/l) – 12wk	Mean change	32		-3.69 (SD 3.2)	38		0.31 (SD 3.21)		
Body weight: Weight (kg) – 12wk	Mean change	123			125			MD=1.300 (CI: 0.800, 1.800)	
Hypoglycaemic events: All hypoglycaemic events (no patients) – 12wk	Dichotomous	123	21	(17.1%)	125	3	(2.4%)		a
Adverse events: Any adverse event(s) – 12wk	Dichotomous	123	77	(62.6%)	125	67	(53.6%)		a
Any serious adverse event(s) – 12wk	Dichotomous	123	6	(4.9%)	125	4	(3.2%)		a
Serious AE drug related – 12wk	Dichotomous	123	0	(0.0%)	125	0	(0.0%)		a
Study drug-related adverse event – 12wk	Dichotomous	123	34	(27.6%)	125	12	(9.6%)		
Dropouts: Total dropouts – 12wk	Dichotomous	123	23	(18.7%)	125	17	(13.6%)		
Dropout due to AEs – 12wk	Dichotomous	123	7	(5.7%)	125	1	(0.8%)		a
drop out due to drug related AE – 12wk	Dichotomous	123	4	(3.3%)	125	0	(0.0%)		a
drop out due to SAE – 12wk	Dichotomous	123	3	(2.4%)	125	0	(0.0%)		a

	drop out due to drug related SAE – 12wk	Dichotomous	123	0	(0.0%)	125	0	(0.0%)		a
	Drop out due to unsatisfactory effect – 12wk	Dichotomous	123	2	(1.6%)	125	9	(7.2%)		a
	Lipids:									
	Total cholesterol (mmol/l) – 12wk	Mean change	112		1.8 (SD 13.5)	117		1.6 (SD 12.7)	MD=0.100 (CI: -3.300, 3.500)	NS
	HDL cholesterol (mmol/l) – 12wk	Mean change	112		2.8 (SD 13)	117		0.6 (SD 12.7)	MD=2.100 (CI: -1.100, 5.300)	NS
	Triglycerides (mmol/l) – 12wk	Mean change	112		7 (SD 38.3)	117		13.9 (SD 38.6)	MD=-6.900 (CI: -16.800, 3.000)	NS
	LDL cholesterol (mmol/l) – 12wk	Mean change	112		2 (SD 21.5)	117		0.9 (SD 21.7)	MD=1.100 (CI: -4.200, 6.400)	NS

[a] not reported

	LS mean change from baseline reported for continuous outcomes. ANCOVA model was used to compare treatment groups for continuous efficacy parameters, focusing on change from baseline at week 12, with baseline values and prior OHA status as covariates. The between group differences (relative to placebo) were assessed by testing the differnce in the least squares mean change from baseline to week 12.

Table 100: Segal et al. (1997)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** Austria, Germany, Israel and Czech Republic **Authors' conclusions:** Miglitol monotherapy is effective and safe in NIDDM patients. Compared with glibenclamide, it reduced Hba1c less effectively and caused moe gastrointestinal effects. On the other hand, glibenclamide tended to cause hypoglycaemia, hyperinsulinemia and weight gain, which are not desirable in patients with NIDDM **Source of funding:** Employees of Bayer were involved **Comments:** Double-blind
Number and characteristics of patients	**Total number of patients:** 79 **Inclusion criteria:** patients with NIDDM of at least 3 months duration, stable bodyweight on diet alone, no other diabetes medication in previous 3 months, hba1c between 7.5 and 9.5% **Exclusion criteria:** Major illness Pre-randomisation phase: there was a 4 week placebo run-in period
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** All treatment naive/ no OADs at screening **Details of washout period:** -
Lifestyle advice	-
Follow-up	**Total follow-up (wks):** 24 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 24 **Frequency of monitoring appointments:** outcomes were determined at the onset, middle and end of the treatment period
Arms	**(1) sulfonylurea (glibenclamide)** N: 37 Treatment duration (wks): 24 Washout period (d): 0 Comments: treatment naïve

Treatment(s): Sulfonylurea (Oral) – flexible-dose (dose-adjusted)
Mean dose (mg/d): 3.6
Details of dosing regimen: Glibenclamide 3.5 mg once or twice daily. The dose could be doubled after 4 weeks if hyperglycaemia was not acceptable, it did not allow dose lowering, therefore those with symptomatic hypoglycaemia had to drop out of the study. The mean daily dose in the last 3 months was 3.6 mg.

(2) Placebo

N: 42

Treatment duration (wks): 24
Washout period (d): 0
Comments: treatment naïve

Treatment(s): Placebo (Oral)

Outcomes

General

Data were extracted from 2/3 of the arms (data for miglitol were not extracted as this drug was not included as part of the scope)

Baseline characteristics

		sulfonylurea (glibenclamide)			Placebo			Δ	p
		N	k	mean	N	k	mean		
Demographics:									
Age (years)	Continuous	37		56	42		59		
Sex (n male)	Dichotomous	37	23	(62.2%)	42	24	(57.1%)		
Duration of diabetes (yrs) a	Continuous	37			42				
Blood glucose:									
HbA1c (%) – 0wk	Continuous	37		7.96	42		8.25		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	37		9.6015	42		9.546		

[a] NR

Results

		sulfonylurea (glibenclamide)			Placebo			Δ	p
		N	k	mean	N	k	mean		
Blood glucose:									
HbA1c (%) – 24wk	Mean change	37		-1.01a	42		b		
Fasting plasma glucose (mmol/l) – 24wka	Mean change	37		-0.777	42		0.7215		
Adverse events:									
Any adverse event(s) – 24wk	Dichotomous	69	13	(18.8%)	65	14	(21.5%)		
Flatulence – 24wk	Dichotomous	69	6	(8.7%)	65	3	(4.6%)		
GI: diarrhoea – 24wk	Dichotomous	69	2	(2.9%)	65	1	(1.5%)		
liver function/liver enzymes – 24wk	Dichotomous	69	1	(1.4%)	65	2	(3.1%)		
Dropouts:									
Total dropouts – 24wk	Dichotomous	61	11	(18.0%)	64	6	(9.4%)		
Dropout due to AEs – 24wk	Dichotomous	69	2	(2.9%)	65	1	(1.5%)		

[a] SD not reported
[b] NR

Table 101: Shah et al. (2011)

General

Phase:

☑ monotherapy

	☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** - **Authors' conclusions:** - **Source of funding:** - **Comments:** -
Number and characteristics of patients	**Total number of patients:** 200 **Inclusion criteria:** Adults (30 to 65 years) with newly diagnosed T2DM not on insulin, uncontrolled by diet and exercise **Exclusion criteria:** -
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** All treatment naive/ no OADs at screening **Details of washout period:** None. All patients were newly diagnosed and uncontrolled with diet and exercise
Lifestyle advice	Individualised diet to maintain weight (55-60% carbohydrates, 30% fat, 12-20% protein) and motivated to maintain dietary habits, physical activity and general life style constant
Follow-up	**Total follow-up (wks):** 52 **Length of titration period (wks):** - **Length of maintenance period (wks):** 52 **Frequency of monitoring appointments:** Every 2 week
Arms	**(1) Repaglinide** N: 100 Treatment duration (wks): 52 Washout period (d): 0 Comments: Repaglinide given up to three times/daily adjusted for blood glucose level (mean dose = 4.27 mg/day) Treatment(s): repaglinide (Oral) – flexible-dose (dose-adjusted) Minimum dose (mg/d): 1.5 Maximum dose (mg/d): 6 Frequency of dosing: three times a day Details of dosing regimen: Starting dose of 0.5mg 3 times per day before meals and uptitrated to a maximum of 2mg 3 times per day based on blood glucose levels **(2) Glibenclamide** N: 100 Treatment duration (wks): 52 Washout period (d): 0 Comments: Glibenclamide given once or twice adjusted for blood glucose level (mean dose = 8.8 mg/day) Treatment(s): Sulfonylurea (Oral) Minimum dose (mg/d): 5 Maximum dose (mg/d): 15 Details of dosing regimen: Administered 1 or 2 times per day, starting dose of 5mg/d, uptitrated to a maximum of 15mg/d
Outcomes	
Baseline characteristics	

		Repaglinide		
		N	**k**	**mean**
Demographics:				
Age (years)	Continuous	100		46 (SD 10.1)
Sex (n male)	Dichotomous	100	31	(31.0%)
Blood glucose:				
Fasting plasma glucose (mg/dl) – 52wk	Continuous	100		161 (SD 53)
Fasting plasma glucose (mg/dl) – 52wk	Continuous	100		161 (SD 53)
Body weight:				
BMI (kg/m2)	Continuous	100		27.2 (SD 3.2)
Weight (kg) – 52wk	Continuous	100		66.8 (SD 9.5)
Weight (kg) – 52wk	Continuous	100		66.8 (SD 9.5)

Height (cm)	Continuous	100		150 (SD 50)

		Glibenclamide		
		N	k	mean
Demographics:				
Age (years)	Continuous	100		45.2 (SD 8.2)
Sex (n male)	Dichotomous	100	20	(20.0%)
Blood glucose:				
Fasting plasma glucose (mg/dl) – 52wk	Continuous	100		140 (SD 50)
Fasting plasma glucose (mg/dl) – 52wk	Continuous	100		140 (SD 50)
Body weight:				
BMI (kg/m2)	Continuous	100		30.2 (SD 5.5)
Weight (kg) – 52wk	Continuous	100		72.5 (SD 17.3)
Weight (kg) – 52wk	Continuous	100		72.5 (SD 17.3)
Height (cm)	Continuous	100		150 (SD 50)

Results

		Repaglinide		
		N	k	mean
Blood glucose:				
Fasting plasma glucose (mg/dl) – 26wk	Continuous	100		120 (SD 26)
Fasting plasma glucose (mg/dl) – 26wk	Continuous	100		120 (SD 26)
Fasting plasma glucose (mg/dl) – 52wk	Continuous	100		105 (SD 11)
Fasting plasma glucose (mg/dl) – 52wk	Continuous	100		105 (SD 11)
Body weight:				
Weight (kg) – 26wk	Continuous	100		66 (SD 9.5)
Weight (kg) – 26wk	Continuous	100		66 (SD 9.5)
Weight (kg) – 52wk	Continuous	100		65 (SD 8.7)
Weight (kg) – 52wk	Continuous	100		65 (SD 8.7)

		Glibenclamide		
		N	k	mean
Blood glucose:				
Fasting plasma glucose (mg/dl) – 26wk	Continuous	100		110 (SD 18)
Fasting plasma glucose (mg/dl) – 26wk	Continuous	100		110 (SD 18)
Fasting plasma glucose (mg/dl) – 52wk	Continuous	100		103 (SD 12.7)
Fasting plasma glucose (mg/dl) – 52wk	Continuous	100		103 (SD 12.7)
Body weight:				
Weight (kg) – 26wk	Continuous	100		72.6 (SD 16.6)
Weight (kg) – 26wk	Continuous	100		72.6 (SD 16.6)
Weight (kg) – 52wk	Continuous	100		72.7 (SD 15.3)
Weight (kg) – 52wk	Continuous	100		72.7 (SD 15.3)

Table 102: Shihara et al. (2011)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** Japan **Authors' conclusions:** there was no statistically significant difference between glimepiride and pioglitazone with respect to glycaemic control and both agents were well tolerated. Glimepiride significantly lowered total cholesterol and LDL-cholesterol, whereas pioglitazone increased HDL-cholesterol **Source of funding:** Funded by a grant from Sanofi Aventis **Comments:** non-blinded, randomised parallel group trial. Randomisation was carried out by a central registration method but no further details of method of randomisation and allocation concealment reported
Number and characteristics of patients	**Total number of patients:** 191 **Inclusion criteria:** outpatients of either sex with type 2 diabetes aged 30-75 years who were committed to a stable dietary and exercise regimen for > 1 month before randomisation were eligible for recruitment. Hba1c had to be 6.9 to <10.4% 1 month before and at randomisation, with an absolute Hba1c differences <1% between these measurements **Exclusion criteria:** type 1 diabetes, use of insulin or any oral hypoglycaemic agent in the month before randomisation, heart failure or history of heart failure, any serious intercurrent complication involving the heart, kidney, liver, pancreas or other organs or haematological condition. All patients had to be suffciiently competent to give consent to participate in the study, and capable of reading, understanding and signing the informed consent form for study participation Pre-randomisation phase: Titration period not explicitly reported as separate from maintenance period therefore assumed no separate additional titration period
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** All treatment naive/ no OADs at screening **Details of washout period:** N/A (drug naïve)
Lifestyle advice	Patients continued their stable pre-enrollment dietary and exercise regimen throughout the study. Adherence to dietary and exercise therapy was categorised as 'strictly followed', 'sometimes followed' or 'not followed' at each monthly visit
Follow-up	**Total follow-up (wks):** 26 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 26 **Frequency of monitoring appointments:** 6 month follow up. Patients attended morning clinic visits at baseline (month 0), 2 weeks (month 0.5) and each month thereafter (months 1, 2, 3, 4, 5, 6)
Arms	**(1) Pioglitazone** N: 96 Treatment duration (wks): 26 Washout period (d): 0 Treatment(s): Pioglitazone (Oral) – flexible-dose (dose-adjusted) Mean dose (mg/d): 23.24 Minimum dose (mg/d): 15 Maximum dose (mg/d): 45 Compliance: adherence to test diabetic therapy was determined from returned tablet counts as 'excellent' (90-100% compliance), 'good' (70-89%), 'fair' (50-69%) and 'poor' (<50%) Details of dosing regimen: The starting dose of pioglitazone was 15 mg/day which could be increased to a maximum of 45 and 30 mg/day in men and women respectively, in order to achieve morning blood glucose level <120 mg/dl. The dosage of glimepiride or pioglitazone could be decreased according to the supervising physician's judgement if morning fasting blood glucose was < 80 mg/dl. Doses were titrated according to morning fasting blood glucose measured at scheduled clinic visits. The mean daily dose at month 6 was 23.24 ± 11.40 mg **(2) glimepiride** N: 95 Treatment duration (wks): 26 Washout period (d): 0 Treatment(s): Sulfonylurea (Oral) – flexible-dose (dose-adjusted) Mean dose (mg/d): 1.51

Minimum dose (mg/d): 0.5
Maximum dose (mg/d): 6
Details of dosing regimen: Patients could receive either glimepiride or gliclazide but in practice al patients received glimepiride. The starting dose was 0.5 mg/day for patients with Hba1c >=6.9 to <7.4% and 1 mg/day for those with Hba1c >=7.4 to <10.4%. The dose could be increased to a maximum of 6mg/day in order to achieve morning fasting blood glucose <120 mg/dl. At month 6 the mean daily dose was 1.51 ± 1.27 mg

Outcomes

General

Anaalyses were carried out using the safety population under the headings 'study population' and 'safety' in the results, whereas analyses under the other headings were carried out using the efficacy population. The safety population included all patients intially randomised to glimepiride (n=95) and pioglitazone (n=96), whereas the efficacy population included 86 in the glimpiride group and 91 in the pioglitazone group.

9 patients in glimpiride group and 5 in pioglitazone group did not complete the study.

Outcomes not extracted in this evidence table include brain natriuretic peptide, insulin resistance (HOMA-R), beta cell-function and fasting insulin.

Hypoglycaemic events

confirmed hypoglycaemia (Definitions of hypoglycaemia were not specifically reported or defined as an outcome but results of the number of patients experiencing blood glucose concentrations <60 mg/dl were presented as part of the safety analysis)

Baseline characteristics

		Pioglitazone			glimepiride				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	96		56.8 (SD 10.3)	95		57.7 (SD 10.4)		
Sex (n male)	Dichotomous	96	65	(67.7%)	95	62	(65.3%)		
Duration of diabetes (yrs)	Continuous	96		4.1 (SD 4.3)	95		6 (SD 8.2)		
Blood glucose: HbA1c (%) – 0wk	Continuous	96		7.8 (SD 0.9)	95		7.8 (SD 0.9)		
Body weight: BMI (kg/m2) – 0wk	Continuous	96		24.5 (SD 4.3)	95		24.6 (SD 3.8)		
Weight (kg) – 0wk	Continuous	96		65.5 (SD 14.6)	95		65.6 (SD 12.5)		
Lipids: Total cholesterol (mmol/l) – 0wk	Continuous	96		5.31423 (SD 0.988)	95		5.36595 (SD 1.01)		
HDL cholesterol (mmol/l) – 0wk	Continuous	96		1.365408 (SD 0.354)	95		1.533498 (SD 0.595)		
Triglycerides (mmol/l) – 0wk	Continuous	96		1.85156 (SD 1.27)	95		1.465442 (SD 0.772)		
LDL cholesterol (mmol/l) – 0wk	Continuous	96		3.185952 (SD 0.843)	95		3.27129 (SD 0.944)		

Results

		Pioglitazone			glimepiride				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 13wk	Mean change	83			80				0.022a
HbA1c (%) – 13wkb	Continuous	83		7.3 (SD 1)	80		6.9 (SD 0.7)		
HbA1c (%) – 26wkc	Mean change	88		-0.86 (SD 0.98)	85		-0.98 (SD 0.72)		0.31d
Hba1c <6.9% – 26wk	Dichotomous	88	50	(56.8%)	85	52	(61.2%)		0.64e
Fasting plasma glucose (mmol/l) – 26wk	Mean change	91		-0.69375 (SD 2.65)	86		-1.1766 (SD 1.87)		0.17d
Body weight: BMI (kg/m2) – 26wk	Continuous	91		24.9 (SD 4.3)	86		24.8 (SD 3.6)		
Weight (kg) – 26wk	Continuous	91		66.2 (SD 14.4)	86		66.4 (SD 11.7)		

Hypoglycaemic events: confirmed hypoglycaemia – 0wk	Dichotomous	96			95				NS
confirmed hypoglycaemia – 26wk	Dichotomous	96	5	(5.2%)	95	7	(7.4%)		
Adverse events: Any adverse event(s) – 26wk	Dichotomous	96	4	(4.2%)	95	1	(1.1%)		
Any serious adverse event(s) – 26wk	Dichotomous	96	0	(0.0%)	95	0	(0.0%)		
Dropouts: Total dropouts – 26wk	Dichotomous	96	5	(5.2%)	95	9	(9.5%)		
Lipids: Total cholesterol (mmol/l) – 26wk	Mean change	79		0.020688 (SD 0.851)	72		-0.299976 (SD 0.838)		0.022d
HDL cholesterol (mmol/l) – 26wk	Mean change	82		0.108612 (SD 0.225)	81		-0.100854 (SD 0.535)		0.0013d
Triglycerides (mmol/l) – 26wk	Mean change	84		-0.268702 (SD 0.84)	82		-0.059837 (SD 0.562)		0.063d
LDL cholesterol (mmol/l) – 26wk	Mean change	72		-0.018102 (SD 0.768)	70		-0.27153 (SD 0.786)		0.053d
Compliance: Compliance – 26wkf	Dichotomous	91	88	(96.7%)	86	82	(95.3%)		
adherence to diet – 26wk	Dichotomous	91	83f	(91.2%)	86	77g	(89.5%)		
adherence to exercise – 26wk	Dichotomous	91	76f	(83.5%)	86	74g	(86.0%)		

[a] ANOVA-no further details reported (glimepiride vs. pio)
[b] Hba1c at 3 months from text
[c] estimated from graph
[d] ANOVA-no further details reported
[e] chi-squared
[f] median %, approximated to nearest integer (percentages only presented in text)
[g] median %

Intra-group comparison of data over time vs. baseline was analysed by paired t-test. Inter- group comparisons were analysed by one-way ANOVA or chi-sqaured tests. P-values for between group comparisons of adverse events were not reported

Table 103: Taslimi et al. (2013)

General

Phase:
☑ monotherapy
☐ dual therapy
☐ triple therapy
☐ insulin monotherapy
☐ insulin+oral

Parallel / crossover: Parallel

Country: Iran

Authors' conclusions: -

Source of funding: -

Comments: -

Number and characteristics of patients

Total number of patients: 60

Inclusion criteria: 60 adults with established diagnosis of T2DM after the age of 30, all drug naïve and had not previously been treated with metformin or pioglitazone.

Exclusion criteria: -

Previous glucose-lowering therapy

Any participants previously taking glucose-lowering therapy? All treatment naive/ no OADs at screening

Details of washout period: All were drug naïve

Lifestyle advice	Not reported
Follow-up	**Total follow-up (wks):** 12 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 12 **Frequency of monitoring appointments:** Baseline and 3 months
Arms	**(1) Metformin** N: 30 Treatment duration (wks): 12 Washout period (d): 0 Comments: Meformin dose = 500mg twice daily Treatment(s): Metformin (Oral) – fixed-dose Set dose (mg/d):1000 Frequency of dosing: twice a day Details of dosing regimen: 500mg tablets twice daily **(2) Pioglitazone** N: 30 Treatment duration (wks): 12 Washout period (d): 0 Comments: Pioglitazone dose = 30mg daily Treatment(s): Pioglitazone (Oral) – fixed-dose Set dose (mg/d):30 Details of dosing regimen: 30mg daily - frequency of dosing not reported
Outcomes	
Baseline characteristics	

		Metformin		
		N	**k**	**mean**
Demographics:				
Age (years)	Continuous	30		51 (SD 10)
Sex (n male)	Dichotomous	30	15	(50.0%)
Duration of diabetes (months)	Continuous	30		24 (SD 18)
Blood glucose:				
HbA1c (%) – 3mo	Continuous	30		8.4 (SD 1.5)
HbA1c (%) – 3mo	Continuous	30		8.4 (SD 1.5)
Fasting plasma glucose (g/dl) – 3mo	Continuous	30		186 (SD 67)
Fasting plasma glucose (g/dl) – 3mo	Continuous	30		186 (SD 67)
Body weight:				
BMI (kg/m2) – 3mo	Continuous	30		28.7 (SD 5.6)
BMI (kg/m2) – 3mo	Continuous	30		28.7 (SD 5.6)
Weight (kg) – 3mo	Continuous	30		76.8 (SD 12.5)
Weight (kg) – 3mo	Continuous	30		76.8 (SD 12.5)

		Pioglitazone		
		N	**k**	**mean**
Demographics:				
Age (years)	Continuous	30		56 (SD 11)
Sex (n male)	Dichotomous	30	13	(43.3%)
Duration of diabetes (months)	Continuous	30		36 (SD 10)
Blood glucose:				
HbA1c (%) – 3mo	Continuous	30		8.2 (SD 1.8)
HbA1c (%) – 3mo	Continuous	30		8.2 (SD 1.8)
Fasting plasma glucose (g/dl) – 3mo	Continuous	30		178 (SD 65)
Fasting plasma glucose (g/dl) – 3mo	Continuous	30		178 (SD 65)

Body weight:				
BMI (kg/m2) – 3mo	Continuous	30		28.4 (SD 4)
BMI (kg/m2) – 3mo	Continuous	30		28.4 (SD 4)
Weight (kg) – 3mo	Continuous	30		73.8 (SD 13.1)
Weight (kg) – 3mo	Continuous	30		73.8 (SD 13.1)

Results

		Metformin		
		N	**k**	**mean**
Blood glucose:				
HbA1c (%) – 3mo	Continuous	30		7 (SD 1.4)
HbA1c (%) – 3mo	Continuous	30		7 (SD 1.4)
Fasting plasma glucose (g/dl) – 3mo	Continuous	30		135 (SD 48)
Fasting plasma glucose (g/dl) – 3mo	Continuous	30		135 (SD 48)
Body weight:				
BMI (kg/m2) – 3mo	Continuous	30		28.7 (SD 5.5)
BMI (kg/m2) – 3mo	Continuous	30		28.7 (SD 5.5)
Weight (kg) – 3mo	Continuous	30		76.5 (SD 12.3)
Weight (kg) – 3mo	Continuous	30		76.5 (SD 12.3)
Dropouts:				
Total dropouts – 3mo	Dichotomous	30	0	(0.0%)
Dropout due to AEs – 3mo	Dichotomous	30	0	(0.0%)

		Pioglitazone		
		N	**k**	**mean**
Blood glucose:				
HbA1c (%) – 3mo	Continuous	30		7.3 (SD 1.6)
HbA1c (%) – 3mo	Continuous	30		7.3 (SD 1.6)
Fasting plasma glucose (g/dl) – 3mo	Continuous	30		142 (SD 53)
Fasting plasma glucose (g/dl) – 3mo	Continuous	30		142 (SD 53)
Body weight:				
BMI (kg/m2) – 3mo	Continuous	30		29 (SD 4.1)
BMI (kg/m2) – 3mo	Continuous	30		29 (SD 4.1)
Weight (kg) – 3mo	Continuous	30		75.5 (SD 13.7)
Weight (kg) – 3mo	Continuous	30		75.5 (SD 13.7)
Dropouts:				
Total dropouts – 3mo	Dichotomous	30	0	(0.0%)
Dropout due to AEs – 3mo	Dichotomous	30	0	(0.0%)

Table 104: Teramoto et al. (2007)

General

Phase:
☑ monotherapy
☐ dual therapy

	☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** 18 centres in Japan **Authors' conclusions:** Glibenclamide reduced FPG levels through increased insulin secretion. Pioglitazone and glibenclamide are well tolerated. Pioglitazone improved dyslipidemia related to insulin resistance, whereas glibenclamide enhanced insulin secreation with only a minor effct on lipid control in Japanese patients with type 2 diabetes **Source of funding:** Unclear **Comments:** Report a randomised, multicentre, non-blinded parallel group study but no details of randomisation methods or allocation concelament reported
Number and characteristics of patients	**Total number of patients:** 92 **Inclusion criteria:** had received dietary and exercise instructions, without anti-diabetic and hypolipidemic agents, had FPG >= 140 mg/d, HDL levels <=80 mg/dl and tryglyceride levels between 150 and 500 mg/dl. **Exclusion criteria:** patients taking any medications known to affect glucose metabolism, history of ketoacidosis, unstable progressive diabetic coma or pre-coma condition, impaired liver function, kidney function, abnormal lipid metabolism, history of allergy to thiazolidinediones and/or sulfonylurea, tumor therapy, alcohol abuse, myocardial infarction or cerebrovascular dysfuction and those receiving insulin because of a severe infection Pre-randomisation phase: No details reported (titration relating to blood glucose levels were included as part of maintenance period)
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** All treatment naive/ no OADs at screening **Details of washout period:** N/A (drug naïve)
Lifestyle advice	No details reported
Follow-up	**Total follow-up (wks):** 24 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 24 **Frequency of monitoring appointments:** No details reported
Arms	**(1) Pioglitazone** N: 46 Treatment duration (wks): 24 Washout period (d): 0 Comments: drug naïve Treatment(s): Pioglitazone (Oral) – flexible-dose (dose-adjusted) Minimum dose (mg/d): 15 Maximum dose (mg/d): 30 Frequency of dosing: once a day Details of dosing regimen: 15 mg given once daily. When patients had FPG >=126 mg/dl after eight weeks of traetment, the dose was increased during weeks 9 to 24 to 30 mg (once daily) **(2) Glibenclamide** N: 46 Treatment duration (wks): 24 Washout period (d): 0 Comments: drug naïve Treatment(s): Sulfonylurea (Oral) – flexible-dose (dose-adjusted) Minimum dose (mg/d): 1.25 Maximum dose (mg/d): 2.5 Frequency of dosing: once a day Details of dosing regimen: Patients started on 1.25 mg in weeks 0-8. If patients had FPG >=126 mg/dl after 8 weeks of treatment, the dose was increased to 2.5 mg (once daily) in weeks 9 to 24
Outcomes	**General** The primary endpoint was a change from the baseline lipid parameters (TG and HDL cholesterol). Outcomes not reported in this evidence table include Lipoprotein lipase protein, ratio of visceral to subcutaneous fat volumes, Lipoprotein size, fasting insulin and HOMA resistance. 7 (15%) in pioglitazone and 5 (11%) in glibenclamide groups did not complete the study Use of ITT population not reported

Baseline characteristics

		Pioglitazone			Glibenclamide				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	46		57 (SD 10.7)	46		56.4 (SD 10.5)		
Sex (n male)	Dichotomous	46	33	(71.7%)	46	35	(76.1%)		
Blood glucose: HbA1c (%) – 0wk	Continuous	46		8.01 (SD 1.29)	45		8.36 (SD 1.29)		
Body weight: BMI (kg/m2)	Continuous	46		24.7 (SD 3.4)	46		25.2 (SD 4.8)		
Weight (kg)	Continuous	46		64.8 (SD 9.9)	46		67.7 (SD 14.5)		

Results

		Pioglitazone			Glibenclamide				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 0wk	Mean change	46			45				<0.05a
HbA1c (%) – 24wk	Mean change	46		-0.8 (SD 1.14)	45		-1.43 (SD 1.09)		
Fasting plasma glucose (mmol/l) – 24wk	Mean change	46		-2.12565 (SD 3.17)	45		-2.84715 (SD 2.58)		
Adverse events: Any adverse event(s) – 0wk	Dichotomous	46			46				NS
Any adverse event(s) – 24wk	Dichotomous	46	30	(65.2%)	46	32	(69.6%)		
Dropouts: Total dropouts – 24wk	Dichotomous	46	7	(15.2%)	46	5	(10.9%)		
Dropout due to AEs – 0wk	Dichotomous	46			46				b
Dropout due to AEs – 24wk	Dichotomous	46	1	(2.2%)	46	3	(6.5%)		
Lipids: HDL cholesterol (mmol/l) – 0wk	Mean change	46			45				<0.05a
HDL cholesterol (mmol/l) – 16wkc	Mean change	46		-0.01293 (SD 0.155)	45		0.100854 (SD 0.178)		
HDL cholesterol (mmol/l) – 24wk	Mean change	46		0.098268 (SD 0.212)	45		-0.031032 (SD 0.163)		
Triglycerides (mmol/l) – 0wk	Mean change	46			45				<0.05a
Triglycerides (mmol/l) – 16wkc	Mean change	46		-0.1129 (SD 1.69)	45		-0.4516 (SD 1.64)		
Triglycerides (mmol/l) – 24wk	Mean change	46		-0.651433 (SD 1.26)	45		0.082417 (SD 1.27)		
LDL cholesterol (mmol/l) – 0wk	Mean change	46			46				NS
LDL cholesterol (mmol/l) – 16wkc	Mean change	46		0.02586 (SD 0.465)	45		0.10344 (SD 0.453)		
LDL cholesterol (mmol/l) – 24wk	Mean change	46		0.223689 (SD 0.607)	45		-0.0338766 (SD 0.645)		

[a] no other details reported
[b] not reported
[c] extracted from graph

The difference of change values was compared using the two sample t-test

Table 105: Tessier et al. (1999)

General

Phase:
☑ monotherapy
☐ dual therapy
☐ triple therapy
☐ insulin monotherapy
☐ insulin+oral

Parallel / crossover: Parallel

Country: Canada

Authors' conclusions: Despite different mechanisms of action, gliclazide and metformin demonstrated comparable levels of efficacy and complementary effects on lipid peroxidation markers

Source of funding: Unclear

Comments: Open label

Number and characteristics of patients

Total number of patients: 36

Inclusion criteria: Patients with type 2 diabetes

Exclusion criteria: No acute cardiovascular or neurological events in prior 6 months. Patients treated with thiazide, beta-blockers, steroids or insulin or those previously exposed to gliclazide or metformin were excluded

Previous glucose-lowering therapy

Any participants previously taking glucose-lowering therapy? some on oral hypoglycaemic drugs and/or insulin

Details of washout period: Unclear if on therapy before study but oral hypoglycaemic medication was withdrawn at least 30 days before randomisation

Lifestyle advice

Patients met with a dietitian for assessment 28 days and 14 days before the baseline visit

Follow-up

Total follow-up (wks): 24

Length of titration period (wks): 0

Length of maintenance period (wks): 24

Frequency of monitoring appointments: patients were measured at weeks 6,12,18 and 24

Arms

(1) Metformin

N: 18

Treatment duration (wks): 26
Washout period (d): 0
Comments: Oral therapy was stopped

Treatment(s): Metformin (Oral)
Minimum dose (mg/d): 750
Maximum dose (mg/d): 2550
Details of dosing regimen: 750 to 2550 mg/day divided into 3 doses. The dose was gradually titrated to achieve acceptable glycaemic control.

(2) Gliclazide

N: 18

Treatment duration (wks): 26
Washout period (d): 0
Comments: Oral therapy was stopped

Treatment(s): Sulfonylurea (Oral)
Minimum dose (mg/d): 80
Maximum dose (mg/d): 320
Details of dosing regimen: Gliclazide 80 to 320 mg/day divided into 2 doses.

Outcomes

Baseline characteristics

		Metformin			Gliclazide				
		N	k	mean	N	k	mean	Δ	p
Demographics:									
Age (years)	Continuous	18		59.1 (SD 7.1)	18		59.3 (SD 7.3)		
Sex (n male)	Dichotomous	18	15	(83.3%)	18	10	(55.6%)		
Duration of diabetes (yrs)	Continuous	18		5.4 (SD 6.5)	18		4.7 (SD 6.1)		
Blood glucose:									
HbA1c (%) – 0wk	Continuous	18		7.1 (SD 1.7)	18		7.8 (SD 1.8)		
Fasting plasma glucose (mmol/l)	Continuous	18		9.1 (SD 3.5)	18		11.3 (SD 3.1)		
Body weight:									
BMI (kg/m2)	Continuous	18		29.3 (SD 3)	18		28.6 (SD 4)		

	Weight (kg) – 0wk	Continuous	18		84.9 (SD 11.1)	18		81.9 (SD 16.3)		
	Lipids:									
	Total cholesterol (mmol/l) – 0wk	Continuous	18		5.4 (SD 1.2)	18		4.8 (SD 0.8)		
	HDL cholesterol (mmol/l) – 0wk	Continuous	18		1 (SD 0.3)	18		1.3 (SD 0.7)		
	Triglycerides (mmol/l) – 0wk	Continuous	18		3.7 (SD 5.8)	18		1.9 (SD 0.9)		
	LDL cholesterol (mmol/l) – 0wk	Continuous	18		3.1 (SD 0.9)	18		2.8 (SD 0.7)		

Results

		Metformin			Gliclazide			Δ	p
		N	k	mean	N	k	mean		
Blood glucose:									
HbA1c (%) – 12wk	Continuous	18		6.3 (SD 1.1)	18		6.8 (SD 1.5)		
HbA1c (%) – 24wka	Continuous	18		6.1 (SD 0.7)	18		6.8 (SD 1.6)		
Fasting plasma glucose (any) – 24wka	Continuous	18		6.4 (SD 1.1)	18		8 (SD 3.1)		
Body weight:									
Weight (kg) – 12wk	Continuous	18		83 (SD 11.2)	18		80.9 (SD 17.1)		
Weight (kg) – 24wka	Continuous	18		82.3 (SD 11.6)	18		81.5 (SD 17.2)		
Hypoglycaemic events:									
All hypoglycaemic events (no patients) – 24wk	Dichotomous	18	3	(16.7%)	18	8	(44.4%)		
Dropouts:									
Total dropouts – 24wk	Dichotomous	20	2	(10.0%)	19	1	(5.3%)		
Dropout due to AEs – 24wk	Dichotomous	20	1	(5.0%)	19	1	(5.3%)		
Lipids:									
Total cholesterol (mmol/l) – 24wka	Continuous	18		5.3 (SD 1)	18		4.7 (SD 0.9)		
HDL cholesterol (mmol/l) – 24wka	Continuous	18		1.1 (SD 0.3)	18		1.2 (SD 0.4)		
Triglycerides (mmol/l) – 24wka	Continuous	18		2.3 (SD 1.3)	18		1.8 (SD 0.9)		
LDL cholesterol (mmol/l) – 24wka	Continuous	18		3.1 (SD 0.8)	18		2.7 (SD 0.9)		
LDL/HDL ratio – 24wk	Continuous	18		2.8 (SD 0.8)	18		2.25 (SD 1)		

[a] open label trial

Table 106: Tosi et al. (2003)

General

Phase:
☑ monotherapy
☐ dual therapy
☐ triple therapy
☐ insulin monotherapy
☐ insulin+oral

Parallel / crossover: Crossover

Country: Italy

Authors' conclusions: In conclusion, combination treatment with metformin and sulfonylurea is more effective than these drugs alone in improving glycaemic control in type 2 diabetes, while also allowing a reduced dosage of each drug

Source of funding: supported by a grant from Italian Ministry of University and Scientific and Technological Research

Comments: Double-blind

Number and characteristics of patients

Total number of patients: 88

Inclusion criteria: patients with type 2 diabetes, FBG>140mg/dl and Hba1c>=6.3%

Exclusion criteria: patients treated with insulin, ketonuria, concurrent medical illness, severe diabetic complications, severe cardiovasculat, hepatic, renal, respiratory or pancreatic diseases

	Pre-randomisation phase: 4 week run-in period
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** some on oral hypoglycaemic drugs and/or insulin **Details of washout period:** previous treatments were discontinued and there was a 4 week run-in period
Lifestyle advice	patients were instructed to follow a diet, which was individualised and kept constant
Follow-up	**Total follow-up (wks):** 26 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 26 **Frequency of monitoring appointments:** -
Arms	**(1) Glibenclamide** N: 20 Treatment duration (wks): 26 Washout period (d): 30 Comments: 4 week run-in period Treatment(s): Sulfonylurea (Oral) Mean dose (mg/d): 8.66 Minimum dose (mg/d): 5 Maximum dose (mg/d): 15 Details of dosing regimen: glibenclamide, po.The starting dosewas 1 tablet before lunch, consisting of glibenclamide 5 mg. The subsequent steps were 1 tablet twice daily (before breakfast and before dinner), 2 tablets twice daily (before breakfast and before dinner), and 2 tablets 3 times daily (before breakfast, before lunch and before dinner) For the group treated with glibenclamide alone, the last 2 steps were 1 tablet of active drug + 1 tablet of placebo. The mean dose was 8.66 (SD 2.4) mg/d and the max dose was reached in 25 patients (15 when they were on combination treatment). Doses were titrated to achieve Hba1c<=6% and FBG <140 mg/dl **(2) Metformin** N: 19 Treatment duration (wks): 26 Washout period (d): 30 Comments: 4 week run-in period Treatment(s): Metformin (Oral) – flexible-dose (dose-adjusted) Set dose (mg/d):1530 Minimum dose (mg/d): 500 Maximum dose (mg/d): 3000 Details of dosing regimen: Tosi (2003)-metformin, po. The starting dose was 1 tablet before lunch, consisting of metformin 500 mg. The subsequent steps were 1 tablet twice daily (before breakfast and before dinner), 2 tablets twice daily (before breakfast and before dinner), and 2 tablets 3 times daily (before breakfast, before lunch and before dinner).Therefore scheduled dose steps were 500, 1.000, 2.000, 3.000 mg/d for metformin. The mean dose was 1530 (SD 613) mg/d and the max dose was reached in 21 patients (8 when on combination therapy).
Outcomes	**General** First treatment period outcomes were extracted from this cross-over trial as there was an unclear washout period before cross-over.

Baseline characteristics

		Glibenclamide			Metformin				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	41		57.3 (SD 7.2)	39		57.8 (SD 7.4)		
Sex (n male)	Dichotomous	41	28	(68.3%)	39	23	(59.0%)		
Duration of diabetes (yrs)	Continuous	41		med: 10.4 [rng 3.7–15.5]	39		med: 9.9 [rng 4–14]		
Blood glucose: HbA1c (%) – 0wk	Continuous	41		med: 8.2 [rng 7.2–9.1]	39		med: 7.8 [rng 7–8.7]		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	41		med: 13.2645 [rng 10.2675–15.3735]	39		med: 12.2655 [rng 10.212–14.5965]		
Body weight: BMI (kg/m2) – 0wk	Continuous	41		26.9 (SD 2.5)	39		27 (SD 2.9)		

	Weight (kg) – 0wka	Continuous	41		75.92256 (SD 7.06)	39		76.2048 (SD 8.18)			

[a] estimated from BMI assuming mean height of 1.68m

Results

		Glibenclamide			Metformin				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 26wk	Mean change	20		-0.5 (SD 1.3)	19		-0.5 (SD 1.1)		
Fasting plasma glucose (mmol/l) – 26wk	Mean change	20		-3.1 (SD 2.4)	19		-2.8 (SD 2.9)		
Body weight: BMI (kg/m2) – 26wk	Mean change	20		0.27 (SD 0.88)	19		-0.51 (SD 0.83)		
Weight (kg) – 26wk	Mean change	20		0.8 (SD 2.7)	19		-2.3 (SD 2.4)		

Baseline characteristics are reported for patients who completed the study (including those on combination therapy). Data for adverse events were not extracted as these relate to study endpoint.Some efficacy outcomes were extracted from cochrane review

Table 107: Uehara et al. (2001)

General

Phase:
☑ monotherapy
☐ dual therapy
☐ triple therapy
☐ insulin monotherapy
☐ insulin+oral

Parallel / crossover: Parallel

Country: Brazil

Authors' conclusions: Reductions in both the insulin levels and the resistance index reinforced metformin capacity to improve the peripheral sensitivity. Moreover, suc benefits were not accompanied by any hypotensive effects. Since leptin levels were affected neither by metformin per se nor by the induced insulinaemia reduction, our data support the role of body weight as the major determinant of circulating leptin levels

Source of funding: Unclear

Comments: Double-blind, randomised, placebo controlled trial but no details of randomisation, allocation concealment or blinding

Number and characteristics of patients

Total number of patients: 26

Inclusion criteria: mild to moderate hypertensive patients aged 40-65 years, with BMI >27 kg/m2 and type 2 diabetes were initially recruited from the clinic of diabetes and hypertension of the federal university of Sao Paulo. Diabetic patients should be treated with diet alone or, if on a sulfonylurea, the agnet was discontinued at least 8 weeks before entering the study. Eligible patients were those with fasting glycaemia between 6.5 and 15.5 mmol/l and diastolic BP <105 mmHg.

Exclusion criteria: No patient suffered from any other disease apart from diabetes, hypertension and mild dyslipidemia: none took any medication other than calcuim channel blocker. 10 patients were not included due to contraindicated use of biguaindes (heart and peripheral vascular disease, renal and hepatic insufficencies, alcohol abuse and lactic acidosis history) or unstable glycaemic control or elevated BP despite the use of calcium channel blocker. Treatment was discontinued prematurely if FPG remained >15.5 mmol/l for two consecutive visits

Pre-randomisation phase: There was an initial 4 week placebo run-in period where compliance was assessed, followed by a 12 week treatment period. Patients received placebo twice a day until randomisation. It has been assumed there was no separate titration period and this was carried out during the 12 week maintenance period and baseline measurements carried out at beginning of maintenance (including titration).

Previous glucose-lowering

Any participants previously taking glucose-lowering therapy? All treatment naive/ no OADs at screening

Details of washout period: If on sulfonylurea, the agent was discontinued at least 8 weeks before entering the study

therapy	
Lifestyle advice	patients were all advised about normocaloric diet and exercise in compliance with ADA recommendations
Follow-up	**Total follow-up (wks):** 16 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 12 **Frequency of monitoring appointments:** No details reported
Arms	**(1) Metfomrin** N: 11 Treatment duration (wks): 12 Washout period (d): 30 Comments: 4 week placebo run-in Treatment(s): Metformin (Oral) – flexible-dose (dose-adjusted) Minimum dose (mg/d): 1000 Maximum dose (mg/d): 2000 Frequency of dosing: variable Compliance: Patient compliance was evaluated by tablet counting at each vist and considered adequate if >80% Details of dosing regimen: Metformin 500 mg twice daily. Patients were seen 4 and 8 weeks after randomisation for their medication dosage to be adjusted based on capillary glycaemia. Adjustments were done if glycaemic levels were >6.5 mmol/l until a maximum dose of four tablets a day (2 g daily, at week 8) **(2) Placebo** N: 11 Treatment duration (wks): 12 Washout period (d): 30 Comments: 4 week placebo run-in Treatment(s): Placebo (Oral) Details of dosing regimen: No details reported but assumed oral to maintain double-blinding
Outcomes	**General** Outcomes not extracted in this evidence table include insulin, proinsulin, leptin, aldosterone, noradrenaline, adrenaline, dopamine, heart rate and systolic load. 2 patients from placebo and 2 from metformin group did not complete the study No details reported about ITT analysis
Baseline characteristics	

		Metfomrin			Placebo				
		N	k	mean	N	k	mean	Δ	p
Demographics:									
Age (years)	Continuous	11		57.2 (SD 4.3)	11		57.5 (SD 6.7)		
Duration of diabetes (months)	Continuous	11		36.6 (SD 23.8)	11		45.5 (SD 43.1)		
Blood glucose:									
HbA1c (%) – 0wk	Continuous	11		5.3 (SD 1.5)	11		6.7 (SD 3)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	11		8.54 (SD 1.71)	11		11.1 (SD 4.2)		
Body weight:									
BMI (kg/m2) – 0wk	Continuous	11		29.2 (SD 2.1)	11		30.1 (SD 2.5)		
Weight (kg) – 0wka	Continuous	11		82.41408 (SD 5.93)	11		84.95424 (SD 7.06)		
Blood pressure:									
Duration of hypertension (months)	Continuous	11		85 (SD 70.7)	11		57.6 (SD 57.9)		
Office SBP – 0wk	Continuous	11		143.6 (SD 15.7)	11		142.3 (SD 14.7)		
Office DBP – 0wk	Continuous	11		86.8 (SD 8.1)	11		87.3 (SD 8.2)		
ambulatory SBP – 0wk	Continuous	11		131 (SD 15.6)	11		127.4 (SD 8)		
ambulatory DBP – 0wk	Continuous	11		79.8 (SD 7.4)	11		80.5 (SD 9.1)		
Nocturnal SBP – 0wk	Continuous	11		123 (SD 15.8)	11		119.8 (SD 13.1)		
Nocturnal DBP – 0wk	Continuous	11		71.1 (SD 9.7)	11		70.8 (SD 10)		
Lipids:									
Total cholesterol (mmol/l) – 0wk	Continuous	11		5.76 (SD 1.44)	11		5.97 (SD 0.9)		

	HDL cholesterol (mmol/l) – 0wk	Continuous	11		1.26 (SD 0.51)	11		1.15 (SD 0.32)		
	Triglycerides (mmol/l) – 0wk	Continuous	11		1.71 (SD 0.68)	11		2.06 (SD 1.35)		
	LDL cholesterol (mmol/l) – 0wk	Continuous	11		3.7 (SD 1.34)	11		3.96 (SD 0.81)		

[a] estimated from BMI assuming mean height of 1.68m

Results

		Metfomrin			Placebo				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 12wk	Continuous	11		4.6 (SD 0.9)	11		5.9 (SD 2.6)		a
Fasting plasma glucose (mmol/l) – 12wk	Continuous	11		7.54 (SD 1.33)	11		10.6 (SD 4.16)		a
Body weight: BMI (kg/m2) – 12wk	Continuous	11		29 (SD 2.5)	11		29.9 (SD 2.6)		a
Weight (kg) – 12wk	Continuous	11		69.5 (SD 10.9)	11		73 (SD 8.8)		a
Dropouts: Total dropouts – 12wk	Dichotomous	13	2	(15.4%)	13	2	(15.4%)		
Dropout due to AEs – 12wk	Dichotomous	11	0	(0.0%)	11	0	(0.0%)		a
Blood pressure: Office SBP – 12wk	Continuous	11		132.3 (SD 17.2)	11		133.6 (SD 14.3)		a
Office DBP – 12wk	Continuous	11		82.7 (SD 6.5)	11		87.3 (SD 6.5)		a
ambulatory SBP – 12wk	Continuous	11		130.4 (SD 16.6)	11		128.5 (SD 7.5)		a
ambulatory DBP – 12wk	Continuous	11		80.9 (SD 9.8)	11		80.8 (SD 8.4)		a
Nocturnal SBP – 12wk	Continuous	11		124 (SD 17.5)	11		123.4 (SD 12.2)		a
Nocturnal DBP – 12wk	Continuous	11		73.6 (SD 11.1)	11		73.4 (SD 9.5)		a
Lipids: Total cholesterol (mmol/l) – 12wk	Continuous	11		5.81 (SD 1)	11		5.76 (SD 0.67)		
Total cholesterol (mmol/l) – 12wk	Mean change	11			11				a
HDL cholesterol (mmol/l) – 12wk	Continuous	11		1.44 (SD 0.63)	11		1.3 (SD 0.36)		
HDL cholesterol (mmol/l) – 12wk	Mean change	11			11				a
Triglycerides (mmol/l) – 12wk	Continuous	11		1.7 (SD 0.82)	11		1.7 (SD 0.82)		
Triglycerides (mmol/l) – 12wk	Mean change	11			11				a
LDL cholesterol (mmol/l) – 12wk	Mean change	11			11				a
LDL cholesterol (mmol/l) – 12wk	Continuous	11		3.6 (SD 0.9)	11		3.67 (SD 0.89)		

[a] not reported

A parametric and non-parametric test were used to compare variables between groups (unpaired t-test or Mann-Whitney U-test) although results of between group differences were unclear

Table 108: Viberti et al. (2002)

General

Phase:
☑ monotherapy
☐ dual therapy
☐ triple therapy
☐ insulin monotherapy

	☐ insulin+oral **Parallel / crossover:** Parallel **Country:** North America, Canada and Europe **Authors' conclusions:** ADOPT will provide data on the effect of mechanistically differing treatment options on metabolic control, beta-cell function and markers of macrovascular disease risk in type 2 diabetes **Source of funding:** SmithKline Beecham **Comments:** Double-blind
Number and characteristics of patients	**Total number of patients:** 2895 **Inclusion criteria:** patients with type 2 diabetes, aged between 30 and 75 years, FBG 126 to 180 mg/dl on diet alone **Exclusion criteria:** clinically significant hepatic disease, renal impairement, history of lactic acidosis, unstable or severe angina, known congestive heart failure or uncontrolled hypertension Pre-randomisation phase: there was a 4 week placebo run-in phase
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** All treatment naive/ no OADs at screening **Details of washout period:** -
Lifestyle advice	During the run-in period diet and exercise recommendations were reinforced
Follow-up	**Total follow-up (wks):** 208 **Length of titration period (wks):** - **Length of maintenance period (wks):** - **Frequency of monitoring appointments:** -
Arms	**(1) Glyburide** N: 1441 Treatment duration (wks): 208 Washout period (d): 0 Comments: Treatment naïve Treatment(s): Sulfonylurea (Oral) – flexible-dose (dose-adjusted) Minimum dose (mg/d): 2.5 Maximum dose (mg/d): 15 Details of dosing regimen: glibenclamide was given initially as 2.5 mg, then up to 15 mg /day given as 7.5 mg twice daily if FPG>140 mg/dl **(2) Metformin** N: 1454 Treatment duration (wks): 208 Washout period (d): 0 Comments: Treatment naïve Treatment(s): Metformin (Oral) – flexible-dose (dose-adjusted) Minimum dose (mg/d): 500 Maximum dose (mg/d): 2000 Details of dosing regimen: metformin was given initially as 500 mg, then up to 2 g (1 g twice a day)
Outcomes	**General** Data from 2/3 arms were extracted (one arm related to rosiglitazone which is not included as part of the scope). Data from Khan (2006) is reported here.

Baseline characteristics

		Glyburide			Metformin				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	1441		56.4 (SD 10.2)	1454		57.9 (SD 9.9)		
Sex (n male)	Dichotomous	1441	836	(58.0%)	1454	864	(59.4%)		
Body weight: BMI (kg/m2)	Continuous	1441		32.2 (SD 6.3)	1454		32.1 (SD 6.1)		
Weight (kg) – 0wka	Continuous	1441		92 (SD 20)	1454		91.6 (SD 18.7)		
Blood pressure: Systolic blood pressure (mmHg)	Continuous	1441		133 (SD 15)	1454		133 (SD 15)		

	Diastolic blood pressure (mmHg)	Continuous	1441		79 (SD 9)	1454		80 (SD 9)		
	[a] wide SD reported									
Results			**Glyburide**			**Metformin**				
			N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
	Blood glucose: HbA1c (%) – 26wka	Continuous	1441		6.5 (SD 0.38)	1454		6.7 (SD 0.381)		
	HbA1c (%) – 26wka	Continuous	1441		6.5 (SD 0.38)	1454		7.1 (SD 0.381)		
	HbA1c (%) – 26wka	Continuous	1441		7.38 (SD 0.759)	1454		6.7 (SD 0.381)		
	HbA1c (%) – 26wka	Continuous	1441		7.38 (SD 0.759)	1454		7.1 (SD 0.381)		
	HbA1c (%) – 52wka	Continuous	1441		6.65 (SD 0.949)	1454		6.65 (SD 0.953)		
	HbA1c (%) – 104wka	Continuous	1441		6.88 (SD 0.949)	1454		6.8 (SD 0.953)		
	HbA1c (%) – 156wka	Continuous	1441		7.1 (SD 0.38)	1454		6.94 (SD 0.381)		
	HbA1c (%) – 208wk	Mean change	1310		0.07 (SD 1.1)	1352		-0.2 (SD 1.1)		
	Fasting plasma glucose (mmol/l) – 26wka	Continuous	1441		6.993756 (SD 2.11)	1454		7.382298 (SD 1.06)		
	Fasting plasma glucose (mmol/l) – 52wka	Continuous	1441		7.271286 (SD 1.05)	1454		7.326792 (SD 2.12)		
	Fasting plasma glucose (mmol/l) – 104wka	Continuous	1441		7.659828 (SD 2.11)	1454		7.49331 (SD 1.06)		
	Fasting plasma glucose (mmol/l) – 156wka	Continuous	1441		7.937358 (SD 2.11)	1454		7.659828 (SD 1.06)		
	Fasting plasma glucose (mmol/l) – 208wk	Mean change	1334		-0.09 (SD 2.3)	1394		-0.5 (SD 2)		
	Body weight: Weight (kg) – 26wka	Continuous	1441		93 (SD 3.8)	1454		89.9 (SD 3.81)		
	Weight (kg) – 52wka	Continuous	1441		93.3 (SD 6.33)	1454		89.33 (SD 6.36)		
	Weight (kg) – 104wka	Continuous	1441		93.3 (SD 6.34)	1454		89.167 (SD 6.37)		
	Weight (kg) – 156wka	Continuous	1441		93.2 (SD 3.8)	1454		89 (SD 3.81)		
	Weight (kg) – 208wka	Continuous	1441		93 (SD 3.8)	1454		88.8 (SD 3.81)		
	Weight (kg) – 208wk	Mean change	1441		1.6 (SD 11.6)	1454		-2.9 (SD 10.7)		
	Hypoglycaemic events: All hypoglycaemic events (no patients) – 208wk	Dichotomous	1441	557	(38.7%)	1454	168	(11.6%)		
	Major/severe hypoglycaemic event – 208wk	Dichotomous	1441	8	(0.6%)	1454	1	(0.1%)		
	Adverse events: GI: nausea – 208wk	Dichotomous	1441	99	(6.9%)	1454	170	(11.7%)		
	Any adverse event(s) – 208wk	Dichotomous	1441	1321	(91.7%)	1454	1341	(92.2%)		
	Any serious adverse event(s) – 208wk	Dichotomous	1441	308	(21.4%)	1454	331	(22.8%)		
	cardiovascular AE – 208wk	Dichotomous	1441	41	(2.8%)	1454	58	(4.0%)		
	cardiac: MI – 208wkb	Dichotomous	1441	15	(1.0%)	1454	21	(1.4%)		
	cancer – 208wk	Dichotomous	1441	55	(3.8%)	1454	50	(3.4%)		
	CV death – 208wk	Dichotomous	1441	8	(0.6%)	1454	4	(0.3%)		
	Death – 208wk	Dichotomous	1441	31	(2.2%)	1454	31	(2.1%)		
	Edema peripheral – 208wkc	Dichotomous	1441	123	(8.5%)	1454	104	(7.2%)		

	Gastrointestinal disorders (any) – 208wk	Dichotomous	1441	316	(21.9%)	1454	557	(38.3%)		
	GI: diarrhoea – 208wk	Dichotomous	1441	142	(9.9%)	1454	345	(23.7%)		
	GI: vomiting – 208wk	Dichotomous	1441	45	(3.1%)	1454	84	(5.8%)		
	GI: discomfort – 208wk	Dichotomous	1441	163	(11.3%)	1454	224	(15.4%)		
	Dropouts:									
	Total dropouts – 208wk	Dichotomous	1441	634	(44.0%)	1454	551	(37.9%)		
	Dropout due to AEs – 208wk	Dichotomous	1441	215	(14.9%)	1454	178	(12.2%)		
	Diabetic complications:									
	Peripheral revascularisation – 208wk	Dichotomous	1441	31	(2.2%)	1454	27	(1.9%)		

[a] estimated from graph; N included for analysis unclear
[b] non-fatal
[c] not specified as peripheral

Table 109: Wang et al. (2013)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** - **Country:** - **Authors' conclusions:** - **Source of funding:** - **Comments:** -
Number and characteristics of patients	**Total number of patients:** 90 **Inclusion criteria:** Drug naïve adults newly diagnosed with T2DM, HbA1c between 7 and 10% **Exclusion criteria:** BMI <18.5 or >35kg/m2, obvious dyslipidaemia, previous AHA or on medication known to affect carbohydrate homeostasis or lipid levels Pre-randomisation phase: 4 weeks of diet therapy (~30kcal/kg ideal body weight per day)
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** All treatment naive/ no OADs at screening **Details of washout period:** All were drug naïve
Lifestyle advice	-
Follow-up	**Total follow-up (wks):** - **Length of titration period (wks):** - **Length of maintenance period (wks):** - **Frequency of monitoring appointments:** -
Arms	**(1) Gliclazide** N: 30 Treatment duration (wks): 26 Washout period (d): 0 Comments: initiated dose according to blood glucose levels and maximum dose = 120mg/day Mean (SD) drug dose at baseline: 48 (14.9) Mean (SD) drug dose at 6 months: 61 (14.7) Treatment(s): Sulfonylurea (Oral) – flexible-dose (dose-adjusted) Maximum dose (mg/d): 120 Details of dosing regimen: The initiated dose of each drug was according to the level of blood glucose **(2) Metformin**

N: 29
Treatment duration (wks): 26
Washout period (d): 0
Comments: initiated dose according to blood glucose levels and maximum dose = 1700mg/day
Mean (SD) drug dose at baseline: 1000 (330)
Mean (SD) drug dose at 6 months: 1230 (430)
Treatment(s): Metformin (Oral) – flexible-dose (dose-adjusted)
Maximum dose (mg/d): 1700
Details of dosing regimen: The initiated dose was according to the level of blood glucose

(3) Acarbose
N: 27
Treatment duration (wks): 26
Washout period (d): -
Comments: initiated dose according to blood glucose levels and maximum dose = 300mg/day
Mean (SD) drug dose at baseline: 138 (23.4)
Mean (SD) drug dose at 6 months: 181.5 (73.6)
Treatment(s): Acarbose (Oral) – flexible-dose (dose-adjusted)
Maximum dose (mg/d): 300
Details of dosing regimen: The initiated dose was according to the level of blood glucose

Outcomes

Baseline characteristics

		Gliclazide			Metformin			Δ	p
		N	k	mean	N	k	mean		
Demographics: Age (years)	Continuous	30		55.89 (SD 10.2)	29		54 (SD 10.3)		
Sex (n male)	Dichotomous	30	21	(70.0%)	29	18	(62.1%)		
Blood glucose: HbA1c (%) – 26mo	Continuous	30		8.4 (SD 0.93)	29		8.07 (SD 0.77)		
Fasting plasma glucose (mmol/l) – 0mo	Continuous	30		8.82 (SD 1.74)	29		8.24 (SD 1.23)		
Body weight: Weight (kg) – 0mo	Continuous	30		70.4 (SD 11.7)	29		71.6 (SD 12.7)		
Height (cm)	Continuous	30		167.4 (SD 7.8)	29		165.2 (SD 8.5)		

		Gliclazide			Acarbose			Δ	p
		N	k	mean	N	k	mean		
Demographics: Age (years)	Continuous	30		55.89 (SD 10.2)	27		54.7 (SD 8.9)		
Sex (n male)	Dichotomous	30	21	(70.0%)	27	18	(66.7%)		
Blood glucose: HbA1c (%) – 26mo	Continuous	30		8.4 (SD 0.93)	27		8.06 (SD 0.82)		
Fasting plasma glucose (mmol/l) – 0mo	Continuous	30		8.82 (SD 1.74)	27		8.86 (SD 1.61)		
Body weight: Weight (kg) – 0mo	Continuous	30		70.4 (SD 11.7)	27		70.4 (SD 11.7)		
Height (cm)	Continuous	30		167.4 (SD 7.8)	27		167 (SD 8.8)		

	Metformin			Acarbose			Δ	p
	N	k	mean	N	k	mean		

Demographics: Age (years)	Continuous	29		54 (SD 10.3)	27		54.7 (SD 8.9)		
Sex (n male)	Dichotomous	29	18	(62.1%)	27	18	(66.7%)		
Blood glucose: HbA1c (%) – 26mo	Continuous	29		8.07 (SD 0.77)	27		8.06 (SD 0.82)		
Fasting plasma glucose (mmol/l) – 0mo	Continuous	29		8.24 (SD 1.23)	27		8.86 (SD 1.61)		
Body weight: Weight (kg) – 0mo	Continuous	29		71.6 (SD 12.7)	27		70.4 (SD 11.7)		
Height (cm)	Continuous	29		165.2 (SD 8.5)	27		167 (SD 8.8)		

Results

		Gliclazide			Metformin				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Blood glucose: HbA1c (%) – 6mo	Continuous	30		6.46 (SD 0.51)	29		6.37 (SD 0.48)		
Fasting plasma glucose (mmol/l) – 6mo	Continuous	30		6.59 (SD 1.09)	29		6.16 (SD 0.98)		
Body weight: Weight (kg) – 6mo	Continuous	30		71.2 (SD 11)	29		68.4 (SD 12.2)		

		Gliclazide			Acarbose				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Blood glucose: HbA1c (%) – 6mo	Continuous	30		6.46 (SD 0.51)	27		6.44 (SD 0.34)		
Fasting plasma glucose (mmol/l) – 6mo	Continuous	30		6.59 (SD 1.09)	27		6.36 (SD 0.64)		
Body weight: Weight (kg) – 6mo	Continuous	30		71.2 (SD 11)	27		70 (SD 12.1)		

		Metformin			Acarbose				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Blood glucose: HbA1c (%) – 6mo	Continuous	29		6.37 (SD 0.48)	27		6.44 (SD 0.34)		
Fasting plasma glucose (mmol/l) – 6mo	Continuous	29		6.16 (SD 0.98)	27		6.36 (SD 0.64)		
Body weight: Weight (kg) – 6mo	Continuous	29		68.4 (SD 12.2)	27		70 (SD 12.1)		

Table 110: Watanabe et al. (2005)

General	**Phase:**

	☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** Japan **Authors' conclusions:** The findings suggest that pioglitazone has anti-arteriosclerotic effects **Source of funding:** Unclear **Comments:** Unclear if double-blinded
Number and characteristics of patients	**Total number of patients:** 30 **Inclusion criteria:** patients with untreated type 2 diabetes, Hba1c between 6.5 to 8.0% **Exclusion criteria:** Patients with kidney disease
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** All treatment naive/ no OADs at screening **Details of washout period:** -
Lifestyle advice	-
Follow-up	**Total follow-up (wks):** 26 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 26 **Frequency of monitoring appointments:** -
Arms	**(1) Pioglitazone** N: 13 Treatment duration (wks): 26 Washout period (d): 0 Comments: Treatment naïve Treatment(s): Pioglitazone (Oral) Set dose (mg/d):17.3 Minimum dose (mg/d): 15 Details of dosing regimen: Pioglitazone started at 15 mg/day. The same dose was administered throughout the treatment period. **(2) Glibenclamide** N: 14 Treatment duration (wks): 26 Washout period (d): 0 Comments: Treatment naïve Treatment(s): Sulfonylurea (Oral) Mean dose (mg/d): 1.56 Minimum dose (mg/d): 1.25 Maximum dose (mg/d): 2.5 Details of dosing regimen: Glibenclamide 1.25-2.5 mg/day
Outcomes	
Baseline characteristics	

		Pioglitazone			Glibenclamide				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	15		62.9 (SD 10.3)	15		65.1 (SD 8.1)		
Sex (n male) a	Dichotomous	15	11	(73.3%)	15	12	(80.0%)		
Blood glucose: HbA1c (%) – 0wk	Continuous	15		6.9 (SD 0.2)	15		7.2 (SD 0.5)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	15		7.3704 (SD 1.37)	15		8.19735 (SD 1.73)		
Body weight: BMI (kg/m2) – 0wk	Continuous	15		24.4 (SD 4.4)	15		24.7 (SD 3.7)		
Blood pressure: Systolic blood pressure (mmHg) – 0wk	Continuous	15		129.5 (SD 11.9)	15		119.2 (SD 30.1)		

	Diastolic blood pressure (mmHg) – 0wk	Continuous	15		82.3 (SD 9)	15		85 (SD 7.8)		
	Lipids: Total cholesterol (mmol/l) – 0wk	Continuous	15		4.998738 (SD 1.06)	15		4.998738 (SD 0.796)		
	HDL cholesterol (mmol/l) – 0wk	Continuous	15		1.450746 (SD 0.458)	15		1.696416 (SD 1.19)		
	Triglycerides (mmol/l) – 0wk	Continuous	15		1.617857 (SD 0.893)	15		1.401089 (SD 0.624)		
	LDL cholesterol (mmol/l) – 0wk	Continuous	15		2.62479 (SD 0.727)	15		2.834256 (SD 0.44)		

[a] approximated to nearest integer (percentages only presented in text)

Results

		Pioglitazone			Glibenclamide				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 26wk	Percentage change from baseline	15		-11.1 (SD 4.3)	15		-11.5 (SD 5.6)		
HbA1c (%) – 26wk	Continuous	15		6.1 (SD 0.33)	15		6.3 (SD 0.4)		
Fasting plasma glucose (mmol/l) – 26wk	Percentage change from baseline	15		-0.64935 (SD 0.466)	15		-0.5439 (SD 0.644)		
Fasting plasma glucose (mmol/l) – 26wk	Continuous	15		6.4824 (SD 1.22)	15		7.2705 (SD 1.1)		
Body weight: BMI (kg/m2) – 26wk	Percentage change from baseline	15		0.3 (SD 2)	15		-3 (SD 12.4)		
BMI (kg/m2) – 26wk	Continuous	15		24.5 (SD 4.6)	15		24.1 (SD 5.3)		
BMI (kg/m2) – 26wk	Mean change	15		0.1	15		-0.6		
Adverse events: Edema peripheral – 26wk	Dichotomous	15	2		15	a			
Dropouts: Total dropouts – 26wk	Dichotomous	15	2	(13.3%)	15	1	(6.7%)		
Dropout due to AEs – 26wk	Dichotomous	15	2	(13.3%)	15	1	(6.7%)		
Blood pressure: Systolic blood pressure (mmHg) – 26wk	Continuous	15		125.8 (SD 17.7)	15		119.2 (SD 30.1)		
Systolic blood pressure (mmHg) – 26wk	Percentage change from baseline	15		-3 (SD 9.8)	15		-7.4 (SD 24.3)		
Diastolic blood pressure (mmHg) – 26wk	Continuous	15		73.8 (SD 24.8)	15		84.1 (SD 7.5)		
Diastolic blood pressure (mmHg) – 26wk	Percentage change from baseline	15		-11.6 (SD 26.8)	15		-0.9 (SD 6.2)		
Lipids: Total cholesterol (mmol/l) – 26wk	Percentage change from baseline	15		0.049134 (SD 0.23)	15		-0.028446 (SD 0.321)		
Total cholesterol (mmol/l) – 26wk	Continuous	15		5.0427 (SD 0.915)	15		4.910814 (SD 0.82)		
HDL cholesterol (mmol/l) – 26wk	Percentage change from baseline	15		0.19395 (SD 0.222)	15		-0.10344 (SD 0.427)		
HDL cholesterol (mmol/l) – 26wk	Continuous	15		1.546428 (SD 0.445)	15		1.613664 (SD 1.2)		
Triglycerides (mmol/l) – 26wk	Percentage change from baseline	15		-0.233703 (SD 0.312)	15		0.162576 (SD 0.504)		
Triglycerides (mmol/l) – 26wk	Continuous	15		1.160612 (SD 0.445)	15		1.547859 (SD 0.899)		
LDL cholesterol (mmol/l) – 26wk	Percentage change from baseline	15		0.23274 (SD 0.442)	15		0.11637 (SD 0.398)		
LDL cholesterol (mmol/l) – 26wk	Continuous	15		2.836842 (SD 0.853)	15		2.919594 (SD 0.724)		

[a] NR

Table 111: Yamanouchi et al. (2005)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** Japan **Authors' conclusions:** Pioglitazone, glimepiride and metformin are equally effective in reducing blood glucose in patients with newly diagnosed type 2 diabetes. However, their specific characteristics, such as rapid action on blood glucose levels of glimepiride and the favourable action on FBG and FFA of pioglitazone should be considered when choosing an appropraite agent **Source of funding:** Unclear **Comments:** unclear blinding
Number and characteristics of patients	**Total number of patients:** 114 **Inclusion criteria:** patients with short duration of type 2 diabetes controlled with diet alone for at elast 3 months, hba1c >=7%, FBG >=7.78 mmol/l, BMI between 22-35 kg/m2 **Exclusion criteria:** patients with unstable or rapidly progressive diabetic retinopathy, nephropathy, neuropathy, liver dysfuntion, impaired kidney function, anaemia, myocardial infarction, angina, congestive heart failure, cerebrovascualr event
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** All treatment naive/ no OADs at screening **Details of washout period:** -
Lifestyle advice	-
Follow-up	**Total follow-up (wks):** 52 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 52 **Frequency of monitoring appointments:** Patients were examined every month for 12 months
Arms	**(1) Metformin** N: 39 Treatment duration (wks): 52 Washout period (d): 0 Comments: all drug naïve Treatment(s): Metformin (Oral) – fixed-dose Set dose (mg/d):750 Details of dosing regimen: 750 mg/day **(2) Pioglitazone** N: 38 Treatment duration (wks): 52 Washout period (d): 0 Comments: all drug naïve Treatment(s): Pioglitazone (Oral) Minimum dose (mg/d): 30 Maximum dose (mg/d): 45 Details of dosing regimen: 30-45 mg/day **(3) Glimepiride** N: 37 Treatment duration (wks): 52 Washout period (d): 0 Comments: all drug naïve Treatment(s): Sulfonylurea (Oral) Minimum dose (mg/d): 1 Maximum dose (mg/d): 2 Details of dosing regimen: 1-2 mg/day (unclear targets for BG control)
Outcomes	

Baseline characteristics

		Metformin			Pioglitazone			Δ	p
		N	k	mean	N	k	mean		
Demographics: Age (years)	Continuous	39		54.7 (SD 9.8)	38		55.2 (SD 9.2)		
Sex (n male) a	Dichotomous	39	20	(51.3%)	38	18	(47.4%)		
Duration of diabetes (yrs)	Continuous	39		3 (SD 2.5)	38		3.2 (SD 2.1)		
Blood glucose: HbA1c (%) – 0wk	Continuous	39		9.9 (SD 0.7)	38		10.2 (SD 0.8)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	39		11.82 (SD 1.69)	38		11.97 (SD 1.9)		
Body weight: BMI (kg/m2) – 0wk	Continuous	39		26.2 (SD 3.8)	38		25.8 (SD 4.2)		
Blood pressure: Systolic blood pressure (mmHg) – 0wk	Continuous	39		143.3 (SD 18.8)	38		142.8 (SD 17.1)		
Diastolic blood pressure (mmHg) – 0wk	Continuous	39		86.3 (SD 10.1)	38		85.3 (SD 9.8)		
Lipids: Total cholesterol (mmol/l) – 0wk	Continuous	39		5.7 (SD 0.36)	38		5.77 (SD 0.57)		
HDL cholesterol (mmol/l) – 0wk	Continuous	39		1.33 (SD 0.09)	38		1.38 (SD 0.12)		
Triglycerides (mmol/l) – 0wk	Continuous	39		2.31 (SD 1.14)	38		2.47 (SD 1.26)		

[a] approximated to nearest integer (percentages only presented in text)

		Metformin			Glimepiride			Δ	p
		N	k	mean	N	k	mean		
Demographics: Age (years)	Continuous	39		54.7 (SD 9.8)	37		55.6 (SD 9.3)		
Sex (n male) a	Dichotomous	39	20	(51.3%)	37	19	(51.4%)		
Duration of diabetes (yrs)	Continuous	39		3 (SD 2.5)	37		3.3 (SD 2.6)		
Blood glucose: HbA1c (%) – 0wk	Continuous	39		9.9 (SD 0.7)	37		9.8 (SD 0.7)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	39		11.82 (SD 1.69)	37		12.05 (SD 1.64)		
Body weight: BMI (kg/m2) – 0wk	Continuous	39		26.2 (SD 3.8)	37		25.6 (SD 3.5)		
Blood pressure: Systolic blood pressure (mmHg) – 0wk	Continuous	39		143.3 (SD 18.8)	37		141.3 (SD 21.3)		
Diastolic blood pressure (mmHg) – 0wk	Continuous	39		86.3 (SD 10.1)	37		84.9 (SD 7.7)		
Lipids: Total cholesterol (mmol/l) – 0wk	Continuous	39		5.7 (SD 0.36)	37		5.89 (SD 0.49)		
HDL cholesterol (mmol/l) – 0wk	Continuous	39		1.33 (SD 0.09)	37		1.35 (SD 0.11)		
Triglycerides (mmol/l) – 0wk	Continuous	39		2.31 (SD 1.14)	37		2.63 (SD 1.37)		

[a] approximated to nearest integer (percentages only presented in text)

		Pioglitazone			Glimepiride			Δ	p
		N	k	mean	N	k	mean		
Demographics: Age (years)	Continuous	38		55.2 (SD 9.2)	37		55.6 (SD 9.3)		
Sex (n male) a	Dichotomous	38	18	(47.4%)	37	19	(51.4%)		

Duration of diabetes (yrs)	Continuous	38		3.2 (SD 2.1)	37		3.3 (SD 2.6)		
Blood glucose: HbA1c (%) – 0wk	Continuous	38		10.2 (SD 0.8)	37		9.8 (SD 0.7)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	38		11.97 (SD 1.9)	37		12.05 (SD 1.64)		
Body weight: BMI (kg/m2) – 0wk	Continuous	38		25.8 (SD 4.2)	37		25.6 (SD 3.5)		
Blood pressure: Systolic blood pressure (mmHg) – 0wk	Continuous	38		142.8 (SD 17.1)	37		141.3 (SD 21.3)		
Diastolic blood pressure (mmHg) – 0wk	Continuous	38		85.3 (SD 9.8)	37		84.9 (SD 7.7)		
Lipids: Total cholesterol (mmol/l) – 0wk	Continuous	38		5.77 (SD 0.57)	37		5.89 (SD 0.49)		
HDL cholesterol (mmol/l) – 0wk	Continuous	38		1.38 (SD 0.12)	37		1.35 (SD 0.11)		
Triglycerides (mmol/l) – 0wk	Continuous	38		2.47 (SD 1.26)	37		2.63 (SD 1.37)		

[a] approximated to nearest integer (percentages only presented in text)

Results

		Metformin			Pioglitazone				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 12wka	Continuous	39		8.1 (SD 0.9)	38		8.8 (SD 0.88)		
HbA1c (%) – 26wka	Continuous	39		8 (SD 0.6)	38		8 (SD 0.7)		
HbA1c (%) – 52wk	Continuous	39		7.8 (SD 1)	38		7.9 (SD 1)		
Fasting plasma glucose (mmol/l) – 52wk	Continuous	39		9.03 (SD 2.01)	38		7.93 (SD 2.25)		
Body weight: BMI (kg/m2) – 52wk	Continuous	39		25.5 (SD 4.2)	38		26.7 (SD 3.9)		
BMI (kg/m2) – 52wk	Mean change	39		-0.7	38		0.9		
Adverse events: Edema peripheral – 52wk	Dichotomous	39	b		38	4			
liver enzymes: abnormal ALT – 52wk	Dichotomous	39	0	(0.0%)	38	0	(0.0%)		
Liver enzymes: AST (U/l) – 52wk	Dichotomous	39	0	(0.0%)	38	0	(0.0%)		
Dropouts: Total dropouts – 52wk	Dichotomous	39	2	(5.1%)	38	3	(7.9%)		
Dropout due to AEs – 52wk	Dichotomous	39	0	(0.0%)	38	2	(5.3%)		
Blood pressure: Systolic blood pressure (mmHg) – 52wk	Continuous	39		138 (SD 14.8)	38		137.5 (SD 19.5)		
Diastolic blood pressure (mmHg) – 52wk	Continuous	39		82.7 (SD 8.7)	38		80.5 (SD 7.8)		
Lipids: Total cholesterol (mmol/l) – 52wk	Continuous	39		5.52 (SD 0.54)	38		5.54 (SD 0.76)		
HDL cholesterol (mmol/l) – 52wk	Continuous	39		1.32 (SD 0.12)	38		1.49 (SD 0.09)		
Triglycerides (mmol/l) – 52wk	Continuous	39		2.22 (SD 1.06)	38		2.08 (SD 1.08)		

[a] extracted from graph; some unclear error bars
[b] NR

		Metformin			Glimepiride				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 12wka	Continuous	39		8.1 (SD 0.9)	37		7.7 (SD 0.65)		

HbA1c (%) – 26wka	Continuous	39		8 (SD 0.6)	37		7.8 (SD 0.73)		
HbA1c (%) – 52wk	Continuous	39		7.8 (SD 1)	37		7.7 (SD 0.9)		
Fasting plasma glucose (mmol/l) – 52wk	Continuous	39		9.03 (SD 2.01)	37		8.79 (SD 1.78)		
Body weight:									
BMI (kg/m2) – 52wk	Continuous	39		25.5 (SD 4.2)	37		25.4 (SD 4)		
BMI (kg/m2) – 52wk	Mean change	39		-0.7	37		-0.2		
Adverse events:									
Edema peripheral – 52wkb	Dichotomous	39			37				
liver enzymes: abnormal ALT – 52wk	Dichotomous	39	0	(0.0%)	37	0	(0.0%)		
Liver enzymes: AST (U/l) – 52wk	Dichotomous	39	0	(0.0%)	37	0	(0.0%)		
Dropouts:									
Total dropouts – 52wk	Dichotomous	39	2	(5.1%)	37	3	(8.1%)		
Dropout due to AEs – 52wk	Dichotomous	39	0	(0.0%)	37	0	(0.0%)		
Blood pressure:									
Systolic blood pressure (mmHg) – 52wk	Continuous	39		138 (SD 14.8)	37		137.2 (SD 16.3)		
Diastolic blood pressure (mmHg) – 52wk	Continuous	39		82.7 (SD 8.7)	37		80.1 (SD 8.3)		
Lipids:									
Total cholesterol (mmol/l) – 52wk	Continuous	39		5.52 (SD 0.54)	37		5.7 (SD 0.72)		
HDL cholesterol (mmol/l) – 52wk	Continuous	39		1.32 (SD 0.12)	37		1.34 (SD 0.11)		
Triglycerides (mmol/l) – 52wk	Continuous	39		2.22 (SD 1.06)	37		2.58 (SD 1.26)		

[a] extracted from graph; some unclear error bars
[b] NR

		Pioglitazone			Glimepiride				
		N	k	mean	N	k	mean	Δ	p
Blood glucose:									
HbA1c (%) – 12wka	Continuous	38		8.8 (SD 0.88)	37		7.7 (SD 0.65)		
HbA1c (%) – 26wka	Continuous	38		8 (SD 0.7)	37		7.8 (SD 0.73)		
HbA1c (%) – 52wk	Continuous	38		7.9 (SD 1)	37		7.7 (SD 0.9)		
Fasting plasma glucose (mmol/l) – 52wk	Continuous	38		7.93 (SD 2.25)	37		8.79 (SD 1.78)		
Body weight:									
BMI (kg/m2) – 52wk	Continuous	38		26.7 (SD 3.9)	37		25.4 (SD 4)		
BMI (kg/m2) – 52wk	Mean change	38		0.9	37		-0.2		
Adverse events:									
Edema peripheral – 52wk	Dichotomous	38	4		37	b			
liver enzymes: abnormal ALT – 52wk	Dichotomous	38	0	(0.0%)	37	0	(0.0%)		
Liver enzymes: AST (U/l) – 52wk	Dichotomous	38	0	(0.0%)	37	0	(0.0%)		
Dropouts:									
Total dropouts – 52wk	Dichotomous	38	3	(7.9%)	37	3	(8.1%)		
Dropout due to AEs – 52wk	Dichotomous	38	2	(5.3%)	37	0	(0.0%)		
Blood pressure:									
Systolic blood pressure (mmHg) – 52wk	Continuous	38		137.5 (SD 19.5)	37		137.2 (SD 16.3)		
Diastolic blood pressure (mmHg) – 52wk	Continuous	38		80.5 (SD 7.8)	37		80.1 (SD 8.3)		
Lipids:									
Total cholesterol (mmol/l) – 52wk	Continuous	38		5.54 (SD 0.76)	37		5.7 (SD 0.72)		
HDL cholesterol (mmol/l) – 52wk	Continuous	38		1.49 (SD 0.09)	37		1.34 (SD 0.11)		

	Triglycerides (mmol/l) – 52wk	Continuous	38		2.08 (SD 1.08)	37		2.58 (SD 1.26)		

[a] extracted from graph; some unclear error bars
[b] NR

Table 112: Yang et al. (2014)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** - **Authors' conclusions:** - **Source of funding:** - **Comments:** -
Number and characteristics of patients	**Total number of patients:** 788 **Inclusion criteria:** Adults (30-70 years) newly diagnosed with T2DM in previous 12 months, either previously never had any OAD or had received OAD for 1 month at least 3 months prior to study enrollment, HbA1c between 7 and 10%, FBG <=11.1mmol/L and BMI between 19 and 30 kg/m2 **Exclusion criteria:** - Pre-randomisation phase: 4 week screening and run in phase to provide education on lifestyle modification
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** some on oral hypoglycaemic drugs and/or insulin **Details of washout period:** 4 week screening and run in phase to provide education on lifestyle modification Patients were either OAD naïve or did not have any OADs 3 months prior to enrollment Proportion of participants who were truly drug naïve not provided
Lifestyle advice	Details not reported. Patients recorded in questionnaires dietary intake the day prior to study visits.
Follow-up	**Total follow-up (wks):** 48 **Length of titration period (wks):** 4 **Length of maintenance period (wks):** 48 **Frequency of monitoring appointments:** Every 2 weeks or every 4 weeks after Week 4. Assessments at baseline, 24 and 48 weeks Only data at 24 weeks reported
Arms	**(1) Acarbose** N: 393 Treatment duration (wks): 48 Washout period (d): 28 Comments: Rescue medication permitted after 24 weeks, 5 patients received insulin rescue medication Treatment(s): Acarbose (Oral) – flexible-dose (dose-adjusted) Maximum dose (mg/d): 100 Frequency of dosing: three times a day **(2) Metformin** N: 395 Treatment duration (wks): 48 Washout period (d): 28 Comments: Rescue medication permitted after 24 weeks, 3 patients received insulin rescue medication Treatment(s): Metformin (Oral) – flexible-dose (dose-adjusted) Maximum dose (mg/d): 1500 Frequency of dosing: once a day
Outcomes	**General** Only data reported at 24 weeks were extracted as participants received rescue medication after this time

point with no adjustment to subsequent analyses

Baseline characteristics

		Acarbose		
		N	k	mean
ITT				
Demographics:				
Age (years)	Continuous	361		50.6 (SD 9.2)
Sex (n male)	Dichotomous	361	219	(60.7%)
Duration of diabetes (yrs)	Continuous	361		0.22 (SD 0.22)
Blood glucose:				
HbA1c (%) – 24wk	Continuous	361		7.49 (SD 1.26)
HbA1c (%) – 24wk	Continuous	361		7.49 (SD 1.26)
Fasting plasma glucose (mmol/l) – 24wk	Continuous	361		8.27 (SD 1.5)
Fasting plasma glucose (mmol/l) – 24wk	Continuous	361		8.27 (SD 1.5)
Body weight:				
BMI (kg/m2)	Continuous	361		25.5 (SD 2.7)
Weight (kg) – 0wk	Continuous	361		71.9712 (SD 7.62048) a
Weight (kg) – 0wk	Continuous	361		71.9712 (SD 7.62048) a
Weight (kg) – 24wk	Continuous	361		70.1 (SD 10.5)
Weight (kg) – 24wk	Continuous	361		70.1 (SD 10.5)

[a] estimated from BMI assuming mean height of 1.68m

		Metformin		
		N	k	mean
ITT				
Demographics:				
Age (years)	Continuous	350		50.2 (SD 9.3)
Sex (n male)	Dichotomous	350	211	(60.3%)
Duration of diabetes (yrs)	Continuous	350		0.26 (SD 0.25)
Blood glucose:				
HbA1c (%) – 24wk	Continuous	350		7.59 (SD 1.22)
HbA1c (%) – 24wk	Continuous	350		7.59 (SD 1.22)
Fasting plasma glucose (mmol/l) – 24wk	Continuous	350		8.44 (SD 1.42)
Fasting plasma glucose (mmol/l) – 24wk	Continuous	350		8.44 (SD 1.42)
Body weight:				
BMI (kg/m2)	Continuous	350		25.7 (SD 2.6)
Weight (kg) – 0wk	Continuous	350		72.53568 (SD 7.33824) a
Weight (kg) – 0wk	Continuous	350		72.53568 (SD 7.33824) a
Weight (kg) – 24wk	Continuous	350		70.7 (SD 10.6)
Weight (kg) – 24wk	Continuous	350		70.7 (SD 10.6)

[a] estimated from BMI assuming mean height of 1.68m

Results

		Acarbose		
		N	k	mean
Blood glucose:				
HbA1c (%) – 24wk	Mean change	360		-1.17 (SD 0.677643379035049) a
HbA1c (%) – 24wk	Mean change	360		-1.17 (SD 0.677643379035049) a
Fasting plasma glucose (mmol/l) – 24wk	Mean change	360		-1.35 (SD 1.25848056106509) a
Fasting plasma glucose (mmol/l) – 24wk	Mean change	360		-1.35 (SD 1.25848056106509) a
Body weight:				
Weight (kg) – 24wk	Mean change	360		-2.55 (SD 3.19460450116523) a
Weight (kg) – 24wk	Mean change	360		-2.55 (SD 3.19460450116523) a

Dropouts:				
Total dropouts – 24wk	Dichotomous	393	42	(10.7%)
Dropout due to AEs – 24wk	Dichotomous	393	9	(2.3%)

[a] Least square means reported; SD calculated from reported 95% CI

		Metformin		
		N	k	mean
Blood glucose:				
HbA1c (%) – 24wk	Mean change	350		-1.19 (SD 0.763617579973441) a
HbA1c (%) – 24wk	Mean change	350		-1.19 (SD 0.763617579973441) a
Fasting plasma glucose (mmol/l) – 24wk	Mean change	350		-1.74 (SD 1.33633076495352) a
Fasting plasma glucose (mmol/l) – 24wk	Mean change	350		-1.74 (SD 1.33633076495352) a
Body weight:				
Weight (kg) – 24wk	Mean change	350		-1.88 (SD 3.24537471488712) a
Weight (kg) – 24wk	Mean change	350		-1.88 (SD 3.24537471488712) a
Dropouts:				
Total dropouts – 24wk	Dichotomous	395	48	(12.2%)
Dropout due to AEs – 24wk	Dichotomous	395	11	(2.8%)

[a] Least square means reported; SD calculated from reported 95% CI

Table 113: Yoon et al. (2011)

General	**Phase:** ☑ monotherapy ☐ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** Korea **Authors' conclusions:** The efficacy of glimepiride, metformin, and rosiglitazone as antidiabetic monotherapies in drug-naïve Korean type 2 diabetic patients was similar in the three groups, with no statistical difference. This study is the first randomized controlled trial to evaluate the efficacy of commonly-used oral hypoglycemic agents in Korean type 2 diabetic patients **Source of funding:** supported by grants from the Korean Diabetes Association **Comments:** multicenter, randomized, double-blind trial
Number and characteristics of patients	**Total number of patients:** 349 **Inclusion criteria:** Eligible study participants were between the ages of 30 and 65 years, with HbA1c levels ranging from 6.5% to 9.5%. None of the subjects had ever taken an oral hypoglycemic agent. **Exclusion criteria:** Glucocorticoid users, pregnant women, patients who had clinically significant liver disease (AST, ALT>2.5 x upper normal limit), significant renal disease (serum creatinine>1.5 mg/dL in men,>1.4 mg/dL in women), a history of lactic acidosis, a history of unstable angina or severe angina pectoris, a history of or treatment for congestive heart failure, or contraindications to metformin or sulfonylurea treatment were excluded Pre-randomisation phase: There was a 4 week lifestyle intervention before study drugs were prescribed
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** All treatment naive/ no OADs at screening **Details of washout period:** 4 week lifestyle intervention prior to study drug administration
Lifestyle advice	During the lifestyle intervention period, we provided individualized education to each study subject, according to current, recommended guidelines for medical nutritional treatment. We also recommended that each subject perform at least 150 minutes per week of moderate-intensity aerobic physical activity, provided exercise was not contraindicated. Trained dietitians or diabetic nurse specialists provided the education and made these recommendations.

Follow-up

Total follow-up (wks): 52
Length of titration period (wks): 0
Length of maintenance period (wks): 48
Frequency of monitoring appointments: Participants were examined every 8 weeks for 48 weeks from the start of the randomization period

Arms

(1) Glimepiride
N: 118
Treatment duration (wks): 48
Washout period (d): 28
Treatment(s): Sulfonylurea (Oral) – flexible-dose (dose-adjusted)
Mean dose (mg/d): 4.5
Participants achieving full dose (n): 35
Frequency of dosing: variable
Compliance: To evaluate the study participants' medication compliance indirectly, we checked the number of remaining doses at each visit. The ratio of the remaining number of doses at the present visit to the number of doses prescribed at the previous visit was calculated. Subjects with a ratio greater than 30% were excluded in the outcome analysis, since their compliance rate was presumed to be less than 70%.
Details of dosing regimen: According to the results of HbA1c (<6.5% or =6.5%) and drug tolerability check that was performed at each visit, we performed scheduled up-titration of the study drugs. For glimepiride level 1 was 2 mg od, level 2 was 2 mg bid, level 3 was 4 mg od and 2 mg od and level 4 was 4 mg bid.

(2) Metformin
N: 114
Treatment duration (wks): 48
Washout period (d): 28
Treatment(s): Metformin (Oral) – flexible-dose (dose-adjusted)
Mean dose (mg/d): 1234.2
Participants achieving full dose (n): 32
Frequency of dosing: variable
Compliance: as glimepiride
Details of dosing regimen: According to the results of HbA1c (<6.5% or =6.5%) and drug tolerability check that was performed at each visit, we performed scheduled up-titration of the study drugs. For metformin, level 1 was 500 mg od, level 2 was 500 mg bid, level 3 was 1000 mg od and 500 mg od and level 4 was 1000 mg bid.

Outcomes

General
We used an intention-to-treat analysis method in analysing our data. The last observation carried forward (LOCF) method was used to fill in missing values at a later point in the study.
Data from 2/3 arms have been extracted in this evidence table as rosiglitazone is not licensed for use in the UK. All outcomes were extracted.
36/118 (30.5%) patients in the glimepiride and 43/114 (37.7%) in metformin group discontinued the study.
Hypoglycaemic events
All hypoglycaemic events (no patients) (Hypoglycemia was defined as the presence of typical adrenergic or neuroglycopenic symptoms and signs, regardless of the data for self-monitoring of blood glucose.)

Baseline characteristics

		Glimepiride			Metformin				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Demographics:									
Age (years)	Continuous	118		50.8 (SD 8.9)	114		51.8 (SD 8.5)		
Sex (n male)	Dichotomous	118	66	(55.9%)	114	66	(57.9%)		
Blood glucose:									
Fasting plasma glucose (mmol/l) – 0wk	Continuous	118		8.0475 (SD 1.78)	114		8.3805 (SD 1.8)		
Body weight:									
BMI (kg/m2)	Continuous	118		25.5 (SD 3.1)	114		25.7 (SD 3.2)		
Weight (kg) – 0wk	Continuous	118		67.9 (SD 10.9)	114		68.9 (SD 11.1)		
Waist circumference (cms)	Continuous	118		87 (SD 7.8)	114		88.7 (SD 7.2)		
Hip circumference (cm)	Continuous	118		96.2 (SD 5.6)	114		97.5 (SD 6.1)		
Waist/hip ratio	Continuous	118		0.91 (SD 0.05)	114		0.91 (SD 0.05)		

Blood pressure: Systolic blood pressure (mmHg)	Continuous	118		126.3 (SD 12.8)	114		128.2 (SD 12.4)		
Diastolic blood pressure (mmHg)	Continuous	118		78.4 (SD 8.7)	114		79.8 (SD 8.6)		
Lipids: Total cholesterol (mmol/l)	Continuous	118		4.918572 (SD 1.07)	114		4.830648 (SD 0.887)		
HDL cholesterol (mmol/l)	Continuous	118		med: 1.1637 (SD 0.31)	114		med: 1.11198 (SD 0.336)		
Triglycerides (mmol/l)	Continuous	118		med: 1.43383 (SD 1.29)	114		med: 1.62576 (SD 1.12)		
LDL cholesterol (mmol/l)	Continuous	118		2.867874 (SD 1.09)	114		2.74116 (SD 0.871)		
TC/HDL ratio	Continuous	118		med: 4.03 (SD 1.61)	114		med: 4.18 (SD 1.52)		
TG/HDL ratio	Continuous	118		med: 2.85 (SD 2.79)	114		med: 3.18 (SD 2.89)		
Other medication: Anti-hypertensive	Dichotomous	118	34	(28.8%)	114	33	(28.9%)		
Lipid-lowering medication	Dichotomous	118	35	(29.7%)	114	33	(28.9%)		
ITT Blood glucose: HbA1c (%) – 0wka	Continuous	118		7.8 (SD 0.736)	114		7.9 (SD 0.842)		

[a] SD estimated from graph

Results

		Glimepiride			Metformin				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Dropouts: Total dropouts – 48wk	Dichotomous	118	36	(30.5%)	114	43	(37.7%)		
Dropout due to AEs – 48wk	Dichotomous	118	10	(8.5%)	114	9	(7.9%)		
ITT Blood glucose: HbA1c (%) – 16wka	Continuous	118		6.75 (SD 0.652)	114		7.1 (SD 0.534)		
HbA1c (%) – 24wka	Continuous	118		6.73 (SD 0.435)	114		6.95 (SD 0.427)		
HbA1c (%) – 48wk	Mean change	118		-0.89 (SD 0.76)	114		-0.92 (SD 0.96)		
HbA1c (%) – 48wkb	Continuous	118		6.9 (SD 0.734)	114		7 (SD 0.736)		0.62c
HbA1c < 7% or <=7% – 48wk	Dichotomous	118	77	(65.3%)	114	67	(58.8%)		0.51c
Hba1c <6.5% – 48wk	Dichotomous	118	43	(36.4%)	114	28	(24.6%)		0.14c
Fasting plasma glucose (mmol/l) – 16wka	Continuous	118		7.1595 (SD 1.21)	114		7.52025 (SD 1.19)		
Fasting plasma glucose (mmol/l) – 24wka	Continuous	118		7.0485 (SD 1.21)	114		7.548 (SD 1.19)		
Fasting plasma glucose (mmol/l) – 48wka	Continuous	118		7.104 (SD 1.21)	114		7.2705 (SD 1.19)		0.52c
Body weight: Weight (kg) – 16wka	Continuous	118		68.3 (SD 9.78)	114		68.3 (SD 9.61)		
Weight (kg) – 24wka	Continuous	118		69 (SD 8.69)	114		68 (SD 9.61)		
Weight (kg) – 48wk	Mean change	118		1.4	114		-1.1		
Weight (kg) – 48wkd	Continuous	118		69.5 (SD 10.9)	114		68 (SD 10.7)		NR
Hypoglycaemic events: All hypoglycaemic events (no patients) – 48wk	Dichotomous	118	23	(19.5%)	114	4	(3.5%)		0.00

Adverse events:										
Any adverse event(s) – 48wk	Dichotomous	118	53	(44.9%)	114	32	(28.1%)		NR
Chest pain – 48wk	Dichotomous	118	3	(2.5%)	114	7	(6.1%)		NS
Edema peripheral – 48wk	Dichotomous	118	8	(6.8%)	114	1	(0.9%)		0.04
GI: diarrhoea – 48wk	Dichotomous	118	4	(3.4%)	114	10	(8.8%)		0.03
GI: discomfort – 48wk	Dichotomous	118	10	(8.5%)	114	10	(8.8%)		NS
liver function/liver enzymes – 48wk	Dichotomous	118	5	(4.2%)	114	0	(0.0%)		NS

[a] estimated from graph
[b] SD estimated from graph
[c] P-value across all 3 groups (data for rosiglitazone not shown in this evidence table)
[d] estimated from graph; assumed SE

For comparisons of data among the three treatment groups, a repeated measured ANOVA test was used. For nonparametric statistical analysis, the Kruskal- Wallis test was used. Wilcoxon's signed rank test was used for comparison of pre- and post-treatment values. For analysis of differences in the frequency of adverse events, the chi-square test and Fisher's exact test were used

E.1.2 First intensification

Table 1: Arechavaleta et al. (2010)

General	**Phase:** ☐ monotherapy ☑ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin + oral **Parallel / crossover:** Parallel **Country:** Multinational (unclear which Countries participated) **Authors' conclusions:** In patients with type 2 diabetes and inadequate glycaemic control on metformin monotherapy, the addition of sitagliptin or glimepiride led to similar improvement in glycaemic control after 30 weeks. Sitagliptin was generally well tolerated. Compared to treatment with glimepiride, treatment with sitagliptin was associated with a lower risk of hypoglycaemia and with weight loss versus weight gain **Source of funding:** Funded by Merck Sharp & Dohme, and authors of paper are Merck employees **Comments:** This was a multinational, double-blind, randomized, parallel group, non-inferiority study. Patients were randomsied using a concealed computer-generated allocation schedule
Number and characteristics of patients	**Total number of patients:** 1034 **Inclusion criteria:** Patients =18 years of age, with type 2 diabetes and with inadequate glycaemic control (defined as HbA1c = 6.5 and =9.0%) while on a stable dose of metformin (=1500 mg/day) as well as diet and exercise for at least 12 weeks prior to the screening visit, were eligible **Exclusion criteria:** history of type 1 diabetes, used any AHA besides metformin within 12 weeks of the screening visit, had renal function impairment prohibiting the use of metformin or had a fasting fingerstick glucose of <6.1 or >13.3 mmol/l at randomisation Pre-randomisation phase: a 2-week, placebo run-in period
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** all on oral hypoglycaemic drugs and/or insulin **Details of washout period:** All taking metformin monotherapy for 12 weeks before screening
Lifestyle advice	Patients received counselling on exercise and a diet consistent with American Diabetes Association recommendations throughout the study
Follow-up	**Total follow-up (wks):** 30 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 30 **Frequency of monitoring appointments:** -
Arms	**(1) Metformin + sitagliptin** N: 516 Treatment duration (wks): 30 Washout period (d): - Comments: All patients were already on a stable dose of metformin (at least 1500mg/day) Treatment(s): (a) Metformin (Oral) – fixed-dose Minimum dose (mg/d): 1500 (b) Sitagliptin (Oral) – fixed-dose Set dose (mg/d):100 Details of dosing regimen: Patients in the sitagliptin group were treated with sitagliptin 100 mg daily and matching glimepiride placebo **(2) Metformin + glimepiride** N: 519 Treatment duration (wks): - Washout period (d): - Treatment(s): (a) Metformin (Oral) Minimum dose (mg/d): 1500 (b) Sulfonylurea (Oral) – flexible-dose (dose-adjusted) Mean dose (mg/d): 2.1 Minimum dose (mg/d): 1 Maximum dose (mg/d): 6 Details of dosing regimen: patients in the glimepiride group received a matching sitagliptin placebo tablet and started glimepiride 1 mg/day. The glimepiride dose could be up-titrated during the first 18 weeks of the treatment period to a maximum dose of 6 mg/day, based on patient's self-administered blood glucose monitoring, as considered appropriate by the investigator following their usual practice. In the event of up-titration, glimepiride or matching placebo was increased to 2 mg and then further increased in 1- or 2-mg increments. At any time during the study, glimepiride could be down-titrated to prevent

	recurrent hypoglycaemic events
Outcomes	**General** Patients were to be discontinued from the study if they experienced repeated episodes of unexplained hypoglycaemia as defined by fasting plasma glucose (FPG) orfingerstick glucose <2.78 mmol/l with or without the symptoms of hypoglycaemia or <3.89 mmol/l with symptoms of hypoglycaemia. In addition, patients were to be discontinued from the study if they failed to meet prespecified, progressively stricter glycaemic control criteria. From randomization through week 12, patients were discontinued if FPG was consistently >13.33 mmol/l on at least 4 mg daily glimepiride/glimepiride placebo for at least 2 weeks; after week 12, patients were discontinued if their FPG was consistently >11.10 mmol/l on at least 4 mg daily glimepiride/glimepiride placebo for at least 2 weeks. The primary analysis was conducted in the per-protocol (PP) population, defined as those patients with a baseline measurement, a measurement at week 30, and with no major protocol violations (drug compliance <85%, use of prohibited medications, change of metformin dose or incorrect administration of double-blind study medication) identified prior to unblinding the data. To assess the robustness for the results in the PP population, analyses of HbA1c and FPG were also performed in the full analysis set (FAS), defined as all randomized patients who took at least one dose of study medication and had both a baseline measurement and at least one postbaseline measurement of the respective efficacy outcome **Hypoglycaemic events** Major/severe hypoglycaemic event (hypoglycaemia requiring the medical or non-medical assistance of others, or accompanied by the symptoms of neuroglycaemia.) symptomatic (confirmed) (1) symptomatic hypoglycaemia accompanied by a fingerstick blood glucose measurement =3.9 mmol/l and 2) symptomatic hypoglycaemia accompanied by a fingerstick blood glucose measurement =2.8 mmol/l) Symptomatic hypoglycaemia (symptomatic hypoglycaemia, whether or not blood glucose values were documented)

Baseline characteristics

		Metformin + sitagliptin			Metformin + glimepiride				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years) – 0wk	Continuous	516		56.3 (SD 9.7)	519		56.2 (SD 10.1)		
Sex (n male)	Dichotomous	516	284	(55.0%)	519	279	(53.8%)		
Duration of diabetes (yrs)	Continuous	516		6.8 (SD 4.6)	519		6.7 (SD 4.8)		
Blood glucose: HbA1c (%) – 0wk	Continuous	516		7.5 (SD 0.7)	519		7.5 (SD 0.8)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	516		8 (SD 1.8)	519		8.1 (SD 1.9)		
Body weight: BMI (kg/m2)	Continuous	516		29.7 (SD 4.5)	519		30.2 (SD 4.4)		
Weight (kg) – 0wk	Continuous	516		80.6 (SD 15.2)	519		82 (SD 16.7)		
ITT Blood glucose: HbA1c (%) – 0wk	Continuous	509		7.5 (SD 0.7)	509		7.51 (SD 0.76)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	509		8 (SD 1.9)	509		8.2 (SD 2)		
PP Blood glucose: HbA1c (%) – 0wk	Continuous	443		7.48 (SD 0.68)	436		7.49 (SD 0.74)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	446		7.9 (SD 1.8)	444		8 (SD 1.9)		

Results

	Metformin + sitagliptin	Metformin + glimepiride	Δ	p

		N	k	mean	N	k	mean		
Hypoglycaemic events: All hypoglycaemic events (no patients) – 30wk	Dichotomous	516	36	(7.0%)	518	114	(22.0%)		
Dropouts: Total dropouts – 30wk	Dichotomous	516	48	(9.3%)	519	51	(9.8%)		
ITT Blood glucose: HbA1c (%) – 30wk	Mean change	509		-0.46 (SD 0.921)	509		-0.52 (SD 0.921)	MD=0.070	a
HbA1c (%) – 30wk	Continuous	509		7.09 (SD 0.902) b	509		7.02 (SD 0.92)		
Fasting plasma glucose (mmol/l) – 30wk	Mean change	509		-0.8 (SD 2.3)	509		-0.9 (SD 2.3)	MD=0.100	c
Fasting plasma glucose (mmol/l) – 30wk	Continuous	509		7.3 (SD 1.9)	509		7.3 (SD 2)		
Hypoglycaemic events: All hypoglycaemic events (no events) – 30wk	Mean difference over whole trial period	516			518			MD=-15.000	d
All hypoglycaemic events (no events) – 30wk	Time-to-event	516			518				<0.001e
All hypoglycaemic events (no events) – 30wk	Time-to-event	516			518				<0.001f
All hypoglycaemic events (no events) – 30wk	Time-to-event	516			518				0.02g
All hypoglycaemic events (no events) – 30wkh	Count	103441	73		103441	460			
All hypoglycaemic events (no events) – 30wk	Time-to-event	516			518				<0.001i
Adverse events: Any adverse event(s) – 30wk	Dichotomous	516	244	(47.3%)	518	291	(56.2%)		
Any adverse event(s) – 30wk	Mean difference over whole trial period	516			518			MD=-8.900	j
Serious AE drug related – 30wk	Mean difference over whole trial period	516			518			MD=0.200	k
Serious AE drug related – 30wk	Dichotomous	516	1	(0.2%)	518	0	(0.0%)		
Death – 30wk	Mean difference over whole trial period	516			518			MD=-0.200	l
Death – 30wk	Dichotomous	516	0	(0.0%)	518	1	(0.2%)		
Dropouts: Dropout due to AEs – 30wk	Mean difference over whole trial period	516			518			MD=1.600	m

Dropout due to AEs – 30wkn	Dichotomous	516	18	(3.5%)	518	4	(0.8%)		
PP									
Blood glucose:									
HbA1c (%) – 12wko	Continuous	446		7.05 (SD 0.422)	444		6.95 (SD 1.05)		
HbA1c (%) – 30wk	Continuous	443		7.04 (SD 0.83)	436		6.98 (SD 0.89)		
HbA1c (%) – 30wk	Mean change	443			436			MD=0.070	p
Fasting plasma glucose (mmol/l) – 30wk	Continuous	446		7.2 (SD 1.7)	444		7.1 (SD 1.8)		
Fasting plasma glucose (mmol/l) – 30wk	Mean change	446			463			MD=0.200	q
Body weight:									
Weight (kg) – 12wko	Mean change	446		-0.5 (SD 2.11)	444		0.525 (SD 1.05)		
Weight (kg) – 30wk	Continuous	443			463			MD=-2.000	<0.001
Weight (kg) – 30wk	Mean change	446		-0.52 (SD 3.17)	444		1.15 (SD 4.21)		
Lipids:									
Total cholesterol (any) – 30wk	Percentage change from baseline	443			463			MD=-0.800	r
HDL cholesterol (any) – 30wk	Percentage change from baseline	443			463			MD=3.500	s
LDL cholesterol (any) – 30wk	Percentage change from baseline	443			463			MD=2.300	t

[a] CI= -0.02 to 0.16 (mean difference in change from baseline)
[b] SD calculated from reported SE
[c] CI= -0.1 to 0.3 (mean difference in change from baseline)
[d] % CI= -19.3 to -10.9
[e] 95% CI= 0.014 - 0.217 fingerstick blood glucose 2.8mmol
[f] 95% CI= 0.03 to 0.156) accompanied by fingerstick blood glucose measurement 3.9mmol
[g] 95% CI= 0.028 - 0.733 requiring medical or non- medical assistance, or accompanied by neurological symptoms
[h] (Used in the analysis); Person days estimated from reported person years
[i] 95% CI= 0.048 - 0.183) all events whether or not blood glucose values were documented
[j] % CI= -14.9 to -2.8
[k] % CI= -0.5 to 1.1
[l] % CI= -1.1 to 0.6
[m] % CI= 0.3 to 3.2
[n] Dropouts due to adverse events, serious adverse events and reactions (including hypoglycaemia)
[o] graph
[p] CI= -0.03 to 0.16 (mean difference in change from baseline)
[q] CI= -0.1 to 0.4 (mean difference in change from baseline)
[r] % CI= -2.3 to 1.3 (mean difference in change from baseline)
[s] % CI= 0.6 to 6.5 (mean difference in change from baseline)
[t] % CI= -1.9 to 6.5 (mean difference in change from baseline)

analysis of covariance (ANCOVA) with treatment, baseline HbA1c, and country as covariates was carried out.

Table 2: Bergenstal et al. (2010)

General	**Phase:** ☐ monotherapy ☑ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin + oral **Parallel / crossover:** Parallel

	Country: USA, India, Mexico **Authors' conclusions:** The goal of many clinicians who manage diabetes is to achieve optimum glucose control alongside weight loss and a minimum number of hypoglycaemic episodes. Addition of exenatide once weekly to metformin achieved this goal more often than did addition of maximum daily doses of either sitagliptin or pioglitazone **Source of funding:** Amylin Pharmaceuticals and Eli Lilly. **Comments:** Data from extension is available but has not been extracted. Extension involved all patients stopping sitaglipting or pioglitazone at 26 weeks and switched to 2mg exenatide once weekly (open label) in addition to metformin. No washout of previous drugs is stated.
Number and characteristics of patients	**Total number of patients:** 491 **Inclusion criteria:** aged 18 and older with type two diabetes treated with a stable dose of metformin for at least 2 months before screening. HbA1c 7.1 to 11.0%, BMI 25 to 45kg/m2. **Exclusion criteria:** Women who were pregnant
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** all on oral hypoglycaemic drugs and/or insulin **Details of washout period:** All on metformin
Lifestyle advice	Not stated
Follow-up	**Total follow-up (wks):** 26 **Length of titration period (wks):** - **Length of maintenance period (wks):** - **Frequency of monitoring appointments:** 4, 6, 10, 14, 18, 22, 26 weeks
Arms	**(1) Metformin + exenatide + placebo** N: 160 Treatment duration (wks): 26 Washout period (d): - Treatment(s): (a) Metformin (Oral) – flexible-dose (dose-adjusted) Mean dose (mg/d): 1504 (b) Exenatide (once weekly) (Subcutaneous) – fixed-dose Set dose (mg/d):2 Frequency of dosing: once weekly Details of dosing regimen: 2mg once per week **(2) Metformin + Sitagliptin + placebo** N: 166 Treatment duration (wks): 26 Washout period (d): - Treatment(s): (a) Metformin (Oral) – flexible-dose (dose-adjusted) Mean dose (mg/d): 1583 (b) Sitagliptin (Oral) Set dose (mg/d):100 Frequency of dosing: once a day Details of dosing regimen: 100mg once daily **(3) Metformin + pioglitazone + placebo** N: 165 Treatment duration (wks): 26 Washout period (d): - Treatment(s): (a) Metformin (Oral) – flexible-dose (dose-adjusted) Mean dose (mg/d): 1480 (b) Pioglitazone (Oral) – fixed-dose Set dose (mg/d):45 Frequency of dosing: once a day Details of dosing regimen: 45mg once per day
Outcomes	
Baseline characteristics	

		Metformin + exenatide + placebo			Metformin + Sitagliptin + placebo				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Demographics:									
Age (years)	Continuous	160		52 (SD 10)	166		52 (SD 11)		
Sex (n male)	Dichotomous	160	89	(55.6%)	166	86	(51.8%)		

Duration of diabetes (yrs)	Continuous	160		6 (SD 5)	166		5 (SD 4)		
Ethnicity-White	Dichotomous	160	53	(33.1%)	166	50	(30.1%)		
Ethnicity-Black	Dichotomous	160	19	(11.9%)	166	20	(12.0%)		
Ethnicity-Asian	Dichotomous	160	37	(23.1%)	166	42	(25.3%)		
Ethnicity-Hispanic	Dichotomous	160	50	(31.3%)	166	49	(29.5%)		
Ethincity-American Indian or Alaska native	Dichotomous	160	0	(0.0%)	166	3	(1.8%)		
Ethnicity-Other	Dichotomous	160	1	(0.6%)	166	2	(1.2%)		
Blood glucose: HbA1c (%) – 0wk	Continuous	160		8.6 (SD 1.2)	166		8.5 (SD 1.2)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	160		9.2 (SD 2.9)	166		9.1 (SD 2.5)		
Body weight: BMI (kg/m2) – 0wk	Continuous	160		32 (SD 5)	166		32 (SD 5)		
Weight (kg) – 0wk	Continuous	160		89 (SD 20)	166		87 (SD 20)		
Lipids: Total cholesterol (mmol/l) – 0wk	Mean change	160		4.5 (SD 1)	166		4.6 (SD 1.1)		
HDL cholesterol (mmol/l) – 0wk	Mean change	160		1.1 (SD 0.2)	166		1.1 (SD 0.3)		
Triglycerides (mmol/l) – 0wk	Mean change	160		1.9 (SD 1.1)	166		1.9 (SD 1.3)		
LDL cholesterol (mmol/l) – 0wk	Mean change	160		2.7 (SD 0.8)	166		2.7 (SD 0.9)		
Hba1c <=9.0% or <9% Blood glucose: HbA1c (%) – 0wk	Continuous	102		7.8 (SD 1.01)	106		7.7 (SD 1.03)		
baseline Hba1c >=9% Blood glucose: HbA1c (%) – 0wk	Continuous	58		9.9 (SD 0.762)	60		9.8 (SD 0.775)		

		Metformin + exenatide + placebo			**Metformin + pioglitazone + placebo**				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Demographics: Age (years)	Continuous	160		52 (SD 10)	165		53 (SD 10)		
Sex (n male)	Dichotomous	160	89	(55.6%)	165	79	(47.9%)		
Duration of diabetes (yrs)	Continuous	160		6 (SD 5)	165		6 (SD 5)		
Ethnicity-White	Dichotomous	160	53	(33.1%)	165	65	(39.4%)		
Ethnicity-Black	Dichotomous	160	19	(11.9%)	165	13	(7.9%)		
Ethnicity-Asian	Dichotomous	160	37	(23.1%)	165	40	(24.2%)		
Ethnicity-Hispanic	Dichotomous	160	50	(31.3%)	165	44	(26.7%)		
Ethincity-American Indian or Alaska native	Dichotomous	160	0	(0.0%)	165	0	(0.0%)		
Ethnicity-Other	Dichotomous	160	1	(0.6%)	165	3	(1.8%)		
Blood glucose: HbA1c (%) – 0wk	Continuous	160		8.6 (SD 1.2)	165		8.5 (SD 1.1)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	160		9.2 (SD 2.9)	165		9.1 (SD 2.4)		
Body weight: BMI (kg/m2) – 0wk	Continuous	160		32 (SD 5)	165		32 (SD 6)		
Weight (kg) – 0wk	Continuous	160		89 (SD 20)	165		88 (SD 20)		
Lipids: Total cholesterol (mmol/l) – 0wk	Mean change	160		4.5 (SD 1)	165		4.9 (SD 1.1)		
HDL cholesterol (mmol/l) – 0wk	Mean change	160		1.1 (SD 0.2)	165		1.1 (SD 0.3)		

Triglycerides (mmol/l) – 0wk	Mean change	160		1.9 (SD 1.1)	165		2.2 (SD 1.3)		
LDL cholesterol (mmol/l) – 0wk	Mean change	160		2.7 (SD 0.8)	165		2.9 (SD 1)		
Hba1c <=9.0% or <9%									
Blood glucose:									
HbA1c (%) – 0wk	Continuous	102		7.8 (SD 1.01)	109		7.8 (SD 1.04)		
baseline Hba1c >=9%									
Blood glucose:									
HbA1c (%) – 0wk	Continuous	58		9.9 (SD 0.762)	56		9.7 (SD 0.748)		

		Metformin + Sitagliptin + placebo			**Metformin + pioglitazone + placebo**				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Demographics:									
Age (years)	Continuous	166		52 (SD 11)	165		53 (SD 10)		
Sex (n male)	Dichotomous	166	86	(51.8%)	165	79	(47.9%)		
Duration of diabetes (yrs)	Continuous	166		5 (SD 4)	165		6 (SD 5)		
Ethnicity-White	Dichotomous	166	50	(30.1%)	165	65	(39.4%)		
Ethnicity-Black	Dichotomous	166	20	(12.0%)	165	13	(7.9%)		
Ethnicity-Asian	Dichotomous	166	42	(25.3%)	165	40	(24.2%)		
Ethnicity-Hispanic	Dichotomous	166	49	(29.5%)	165	44	(26.7%)		
Ethincity-American Indian or Alaska native	Dichotomous	166	3	(1.8%)	165	0	(0.0%)		
Ethnicity-Other	Dichotomous	166	2	(1.2%)	165	3	(1.8%)		
Blood glucose:									
HbA1c (%) – 0wk	Continuous	166		8.5 (SD 1.2)	165		8.5 (SD 1.1)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	166		9.1 (SD 2.5)	165		9.1 (SD 2.4)		
Body weight:									
BMI (kg/m2) – 0wk	Continuous	166		32 (SD 5)	165		32 (SD 6)		
Weight (kg) – 0wk	Continuous	166		87 (SD 20)	165		88 (SD 20)		
Lipids:									
Total cholesterol (mmol/l) – 0wk	Mean change	166		4.6 (SD 1.1)	165		4.9 (SD 1.1)		
HDL cholesterol (mmol/l) – 0wk	Mean change	166		1.1 (SD 0.3)	165		1.1 (SD 0.3)		
Triglycerides (mmol/l) – 0wk	Mean change	166		1.9 (SD 1.3)	165		2.2 (SD 1.3)		
LDL cholesterol (mmol/l) – 0wk	Mean change	166		2.7 (SD 0.9)	165		2.9 (SD 1)		
Hba1c <=9.0% or <9%									
Blood glucose:									
HbA1c (%) – 0wk	Continuous	106		7.7 (SD 1.03)	109		7.8 (SD 1.04)		
baseline Hba1c >=9%									
Blood glucose:									
HbA1c (%) – 0wk	Continuous	60		9.8 (SD 0.775)	56		9.7 (SD 0.748)		

Results

	Metformin + exenatide + placebo			**Metformin + Sitagliptin + placebo**				
	N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**

Blood glucose:									
Fasting plasma glucose (mmol/l) – 14wka	Mean change	160		-2 (SD 2.53)	166		-0.7 (SD 2.58)		
Fasting plasma glucose (mmol/l) – 26wk	Mean change	160		-1.8 (SD 2.58)	166		-0.9 (SD 2.63)		
Body weight:									
Weight (kg) – 14wka	Mean change	160		-1.9 (SD 2.53)	166		-0.7 (SD 2.58)		
Weight (kg) – 26wk	Mean change	160		-2.3 (SD 3.87)	166		-0.8 (SD 3.94)		
Hypoglycaemic events:									
Minor (confirmed) hypoglycaemia – 26wkb	Count	26117	2		28210	9			
Minor (confirmed) hypoglycaemia – 26wk	Dichotomous	160	2	(1.3%)	166	5	(3.0%)		
Adverse events:									
GI: nausea – 26wkc	Count	26117	62		28210	22			
GI: nausea – 26wkd	Dichotomous	160	38	(23.8%)	166	16	(9.6%)		
Any serious adverse event(s) – 26wk	Dichotomous	160	4	(2.5%)	166	5	(3.0%)		
Edema peripheral – 26wk	Dichotomous	160	2	(1.3%)	166	5	(3.0%)		
Fatigue – 26wk	Dichotomous	160	9	(5.6%)	166	0	(0.0%)		
GI: diarrhoea – 26wk	Dichotomous	160	29	(18.1%)	166	16	(9.6%)		
GI: vomiting – 26wk	Dichotomous	160	18	(11.3%)	166	4	(2.4%)		
GI: constipation – 26wk	Dichotomous	160	9	(5.6%)	166	3	(1.8%)		
Headache – 26wk	Dichotomous	160	15	(9.4%)	166	15	(9.0%)		
Infection (upper airway or other common) – 26wk	Dichotomous	160	6	(3.8%)	166	15	(9.0%)		
pruritus – 26wk	Dichotomous	160	8	(5.0%)	166	8	(4.8%)		
Sinusitis or sinus abnormality – 26wk	Dichotomous	160	5	(3.1%)	166	2	(1.2%)		
UTI – 26wk	Dichotomous	160	10	(6.3%)	166	9	(5.4%)		
Dropouts:									
Total dropouts – 26wk	Dichotomous	160	33	(20.6%)	166	22	(13.3%)		
Dropout due to AEs – 26wk	Dichotomous	160	11	(6.9%)	166	5	(3.0%)		
Blood pressure:									
Systolic blood pressure (mmHg) – 14wka	Mean change	160		-4.2 (SD 12.6)	166		-1.8 (SD 12.9)		
Systolic blood pressure (mmHg) – 26wka	Mean change	160		-4 (SD 12.6)	166		0 (SD 12.9)		
Lipids:									
Total cholesterol (mmol/l) – 26wka	Mean change	160		-0.1 (SD 1.01)	166		0.8 (SD 1.03)		
HDL cholesterol (mmol/l) – 26wka	Mean change	160		0.4 (SD 0.253)	166		0.4 (SD 0.258)		
Triglycerides (mmol/l) – 26wka	Percentage change from baseline	160		-4 (SD 37.9)	166		-4 (SD 38.7)		
LDL cholesterol (mmol/l) – 26wka	Mean change	160		-0.2 (SD 1.01)	166		0.4 (SD 0.644)		
Hba1c <=9.0% or <9%									
Blood glucose:									
HbA1c (%) – 26wk	Mean change	102		-1.1 (SD 1.29)	106		-0.5 (SD 1.97)		
baseline Hba1c >=9%									
Blood glucose:									
HbA1c (%) – 26wk	Mean change	58		-2 (SD 1.55)	60		-1.3 (SD 1.58)		

[a] graph
[b] (Used in the analysis); Patient days estimated assuming dropout halfway through the study
[c] Patient days estimated assuming dropout halfway through the study
[d] (Used in the analysis)

		Metformin + exenatide + placebo			Metformin + pioglitazone + placebo			Δ	p
		N	k	mean	N	k	mean		
Blood glucose: Fasting plasma glucose (mmol/l) – 14wka	Mean change	160		-2 (SD 2.53)	165		-1 (SD 1.28)		
Fasting plasma glucose (mmol/l) – 26wk	Mean change	160		-1.8 (SD 2.58)	165		-1.5 (SD 2.62)		
Body weight: Weight (kg) – 14wka	Mean change	160		-1.9 (SD 2.53)	165		1.5 (SD 2.57)		
Weight (kg) – 26wk	Mean change	160		-2.3 (SD 3.87)	165		2.8 (SD 3.93)		
Hypoglycaemic events: Minor (confirmed) hypoglycaemia – 26wkb	Count	26117	2		26936	1			
Minor (confirmed) hypoglycaemia – 26wk	Dichotomous	160	2	(1.3%)	165	1	(0.6%)		
Adverse events: GI: nausea – 26wkc	Count	26117	62		26936	9			
GI: nausea – 26wk	Dichotomous	160	38d	(23.8%)	165	8	(4.8%)		
Any serious adverse event(s) – 26wk	Dichotomous	160	4	(2.5%)	165	10	(6.1%)		
Edema peripheral – 26wk	Dichotomous	160	2	(1.3%)	165	13	(7.9%)		
Fatigue – 26wk	Dichotomous	160	9	(5.6%)	165	5	(3.0%)		
GI: diarrhoea – 26wk	Dichotomous	160	29	(18.1%)	165	12d	(7.3%)		
GI: vomiting – 26wk	Dichotomous	160	18	(11.3%)	165	5	(3.0%)		
GI: constipation – 26wk	Dichotomous	160	9	(5.6%)	165	2	(1.2%)		
Headache – 26wk	Dichotomous	160	15	(9.4%)	165	7	(4.2%)		
Infection (upper airway or other common) – 26wk	Dichotomous	160	6	(3.8%)	165	17	(10.3%)		
pruritus – 26wk	Dichotomous	160	8	(5.0%)	165	2	(1.2%)		
Sinusitis or sinus abnormality – 26wk	Dichotomous	160	5	(3.1%)	165	11	(6.7%)		
UTI – 26wk	Dichotomous	160	10	(6.3%)	165	6	(3.6%)		
Dropouts: Total dropouts – 26wk	Dichotomous	160	33	(20.6%)	165	34	(20.6%)		
Dropout due to AEs – 26wk	Dichotomous	160	11	(6.9%)	165	6	(3.6%)		
Blood pressure: Systolic blood pressure (mmHg) – 14wka	Mean change	160		-4.2 (SD 12.6)	165		-2.2 (SD 12.8)		
Systolic blood pressure (mmHg) – 26wka	Mean change	160		-4 (SD 12.6)	165		-2 (SD 12.8)		
Lipids: Total cholesterol (mmol/l) – 26wka	Mean change	160		-0.1 (SD 1.01)	165		0.16 (SD 1.03)		
HDL cholesterol (mmol/l) – 26wka	Mean change	160		0.4 (SD 0.253)	165		0.16 (SD 0.257)		
Triglycerides (mmol/l) – 26wka	Percentage change from baseline	160		-4 (SD 37.9)	165		-15 (SD 38.5)		
LDL cholesterol (mmol/l) – 26wka	Mean change	160		-0.2 (SD 1.01)	165		0.4 (SD 0.642)		
Hba1c <=9.0% or <9% Blood glucose: HbA1c (%) – 26wk	Mean change	102		-1.1 (SD 1.29)	109		-0.9 (SD 1.31)		
baseline Hba1c >=9% Blood glucose: HbA1c (%) – 26wk	Mean change	58		-2 (SD 1.55)	56		-1.5 (SD 1.53)		

[a] graph

[b] (Used in the analysis); Patient days estimated assuming dropout halfway through the study
[c] Patient days estimated assuming dropout halfway through the study
[d] (Used in the analysis)

		Metformin + Sitagliptin + placebo			Metformin + pioglitazone + placebo			Δ	p
		N	k	mean	N	k	mean		
Blood glucose: Fasting plasma glucose (mmol/l) – 14wka	Mean change	166		-0.7 (SD 2.58)	165		-1 (SD 1.28)		
Fasting plasma glucose (mmol/l) – 26wk	Mean change	166		-0.9 (SD 2.63)	165		-1.5 (SD 2.62)		
Body weight: Weight (kg) – 14wka	Mean change	166		-0.7 (SD 2.58)	165		1.5 (SD 2.57)		
Weight (kg) – 26wk	Mean change	166		-0.8 (SD 3.94)	165		2.8 (SD 3.93)		
Hypoglycaemic events: Minor (confirmed) hypoglycaemia – 26wkb	Count	28210	9		26936	1			
Minor (confirmed) hypoglycaemia – 26wk	Dichotomous	166	5	(3.0%)	165	1	(0.6%)		
Adverse events: GI: nausea – 26wkc	Count	28210	22		26936	9			
GI: nausea – 26wk	Dichotomous	166	16d	(9.6%)	165	8	(4.8%)		
Any serious adverse event(s) – 26wk	Dichotomous	166	5	(3.0%)	165	10	(6.1%)		
Edema peripheral – 26wk	Dichotomous	166	5	(3.0%)	165	13	(7.9%)		
Fatigue – 26wk	Dichotomous	166	0	(0.0%)	165	5	(3.0%)		
GI: diarrhoea – 26wk	Dichotomous	166	16	(9.6%)	165	12d	(7.3%)		
GI: vomiting – 26wk	Dichotomous	166	4	(2.4%)	165	5	(3.0%)		
GI: constipation – 26wk	Dichotomous	166	3	(1.8%)	165	2	(1.2%)		
Headache – 26wk	Dichotomous	166	15	(9.0%)	165	7	(4.2%)		
Infection (upper airway or other common) – 26wk	Dichotomous	166	15	(9.0%)	165	17	(10.3%)		
pruritus – 26wk	Dichotomous	166	8	(4.8%)	165	2	(1.2%)		
Sinusitis or sinus abnormality – 26wk	Dichotomous	166	2	(1.2%)	165	11	(6.7%)		
UTI – 26wk	Dichotomous	166	9	(5.4%)	165	6	(3.6%)		
Dropouts: Total dropouts – 26wk	Dichotomous	166	22	(13.3%)	165	34	(20.6%)		
Dropout due to AEs – 26wk	Dichotomous	166	5	(3.0%)	165	6	(3.6%)		
Blood pressure: Systolic blood pressure (mmHg) – 14wka	Mean change	166		-1.8 (SD 12.9)	165		-2.2 (SD 12.8)		
Systolic blood pressure (mmHg) – 26wka	Mean change	166		0 (SD 12.9)	165		-2 (SD 12.8)		
Lipids: Total cholesterol (mmol/l) – 26wka	Mean change	166		0.8 (SD 1.03)	165		0.16 (SD 1.03)		
HDL cholesterol (mmol/l) – 26wka	Mean change	166		0.4 (SD 0.258)	165		0.16 (SD 0.257)		
Triglycerides (mmol/l) – 26wka	Percentage change from baseline	166		-4 (SD 38.7)	165		-15 (SD 38.5)		
LDL cholesterol (mmol/l) – 26wka	Mean change	166		0.4 (SD 0.644)	165		0.4 (SD 0.642)		
Hba1c <=9.0% or <9%									
Blood glucose: HbA1c (%) – 26wk	Mean change	106		-0.5 (SD 1.97)	109		-0.9 (SD 1.31)		

	baseline Hba1c >=9%									
	Blood glucose: HbA1c (%) – 26wk	Mean change	60		-1.3 (SD 1.58)	56		-1.5 (SD 1.53)		

[a] graph
[b] (Used in the analysis); Patient days estimated assuming dropout halfway through the study
[c] Patient days estimated assuming dropout halfway through the study
[d] (Used in the analysis)

Table 3: Bolli et al. (2008)

General	**Phase:** ☐ monotherapy ☑ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin + oral **Parallel / crossover:** Parallel **Country:** Germany, UK, USA, Spain, Italy, Switzerland, Austria, South Africa and Australia **Authors' conclusions:** When added to metformin, vildagliptin demonstrates favourable safety and tolerability over 1 year. Vildagliptin provided additional Hba1c lowering to that achieved with metformin alone and comparable to that achieved with pioglitazone, with only pioglitazone causing weight gain **Source of funding:** Novartis **Comments:** Double-blind randomised controlled trial.
Number and characteristics of patients	**Total number of patients:** 576 **Inclusion criteria:** patients with type 2 diabetes with a Hba1c 7.5-11% while receiving a stable dose of metformin >=1500 mg/day. Patients were aged 18-77 years, BMI of 22-45 kg/m2 and with a FBG <15 mmol/l **Exclusion criteria:** history of type 1 diabetes or secondary forms of diabetes, acute metabolic diabetic complications, cardiovascular disease within the previous 6 months, liver disease and laboratory abnormalities
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** all on oral hypoglycaemic drugs and/or insulin **Details of washout period:** All patients were taking metformin monotherapy at baseline and this was continued
Lifestyle advice	-
Follow-up	**Total follow-up (wks):** 52 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 52 **Frequency of monitoring appointments:** Efficacy and tolerability were assessed at 4,12,16,24,32,40,52
Arms	**(1) Vildagliptin + Metformin** N: 295 Treatment duration (wks): 52 Washout period (d): 0 Comments: All patients were taking metformin monotherapy at baseline and this was continued Treatment(s): (a) Vildagliptin (Oral) – fixed-dose Set dose (mg/d):100 Frequency of dosing: twice a day Details of dosing regimen: 50 mg vildagliptin given twice daily (b) Metformin (Oral) Mean dose (mg/d): 2032 Details of dosing regimen: At baseline the mean metformin dose was 2020mg with no significant difference in dose **(2) Pioglitazone + metformin** N: 281 Treatment duration (wks): 52 Washout period (d): 0 Comments: All patients were taking metformin monotherapy at baseline and this was continued Treatment(s): (a) Pioglitazone (Oral) – fixed-dose Set dose (mg/d):30 Frequency of dosing: once a day (b) Metformin (Oral) Mean dose (mg/d): 2008

	Details of dosing regimen: At baseline the mean metformin dose was 2020mg with no significant difference in dose
Outcomes	**General** The primary efficacy variable was change in Hba1c in the PP population using LOCF for patients who discontinued early. The ITT population was used in the extension trial and is defined as all randomised patients that received at least one dose of study drug and had at least one post baseline assessment. However, the denominators for the ITT analysis were unclear but have been assumed to be the randomised population in this evidence table. 33/295 (11.2%) patients in the vildagliptin + metformin 37/281 (13.2%) in the pioglitazone + metformin group discontinued the study at 24 weeks Outcomes from the extension trial (Bolli 2009) are also reported in this evidence table. Outcomes from subgroup analyses were extracted only when denominators were clearly reported. All outcomes except lipid levels were extracted (units of measurement were unclear). **Hypoglycaemic events** Major/severe hypoglycaemic event (severe hypoglycaemia was defined as any episode requiring the assistance of another party) symptomatic (confirmed) (confirmed hypoglycaemia was defined as symptoms suggestive of low blood glucose confirmed by SMBG <3.1 mmol/l)

Baseline characteristics

		Vildagliptin + Metformin			Pioglitazone + metformin				
		N	k	mean	N	k	mean	Δ	p
Demographics:									
Age (years)	Continuous	295		56.3 (SD 9.3)	281		57 (SD 9.7)		
Sex (n male)	Dichotomous	295	182	(61.7%)	281	180	(64.1%)		
Duration of diabetes (yrs)	Continuous	295		6.4 (SD 4.9)	281		6.4 (SD 5.2)		
Blood glucose:									
HbA1c (%) – 0wk	Continuous	295		8.4 (SD 1)	281		8.4 (SD 0.9)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	295		10.9 (SD 2.6)	281		11 (SD 2.7)		
Body weight:									
BMI (kg/m2)	Continuous	295		32.2 (SD 5.6)	281		32.1 (SD 5.1) a		
Weight (kg) – 0wk	Continuous	295		91.8 (SD 18.5)	281		91.2 (SD 16.9) a		
ITT									
Blood glucose:									
HbA1c (%) – 4wkb	Continuous	295		8.425 (SD 0.859)	280		8.425 (SD 0.837)		

[a] No separate data reported for ITT population
[b] Data estimated from graphs; SD calculated from estimated SE

Results

		Vildagliptin + Metformin			Pioglitazone + metformin				
		N	k	mean	N	k	mean	Δ	p
Blood glucose:									
HbA1c reduction >=1% – 24wka	Dichotomous	295	141	(47.8%)	281	142	(50.5%)		
Hba1c reduction >=0.7% – 24wk	Dichotomous	295	182	(61.7%)	281	179 a	(63.7%)		
HbA1c < 7% or <=7% – 24wka	Dichotomous	295	80	(27.1%)	281	101	(35.9%)		
HbA1c <= 6.5% – 24wka	Dichotomous	295	58	(19.7%)	281	50	(17.8%)		
Hypoglycaemic events:									
Major/severe hypoglycaemic event – 24wk	Dichotomous	295	b		281	0			
Major/severe hypoglycaemic event – 52wk	Dichotomous	295	0	(0.0%)	281	0c	(0.0%)		
symptomatic (confirmed) – 24wkd	Count	46788	3		44100	0			

	symptomatic (confirmed) – 52wkc	Dichotomous	295	1	(0.3%)	281	1	(0.4%)		
	Dropouts: Total dropouts – 24wke	Dichotomous	295	33	(11.2%)	281	37	(13.2%)		
	Dropout due to AEs – 24wkf	Dichotomous	295	8	(2.7%)	281	9	(3.2%)		
	Drop out due to unsatisfactory effect – 24wk	Dichotomous	295	8	(2.7%)	281	8	(2.8%)		
	Drop out due to unsatisfactory effect – 52wkb	Dichotomous	295			281				
	ITT Blood glucose: HbA1c (%) – 16wkg	Continuous	295		7.52 (SD 0.859)	280		7.52 (SD 0.837)		
	HbA1c (%) – 24wkg	Continuous	295		7.52 (SD 1.03)	280		7.42 (SD 0.837)		
	HbA1c (%) – 52wk	Mean change	295		-0.6 (SD 0.964)	280		-0.6 (SD 1.45)		
	Fasting plasma glucose (mmol/l) – 52wk	Mean change	295		-1 (SD 2.63)	280		-1.6 (SD 2.99)		
	Body weight: Weight (kg) – 52wkh	Mean change	295		0.2 (SD 3.44)	280		2.6 (SD 5.02)		
	PP Blood glucose: HbA1c (%) – 24wk	Mean change	264		-0.88 (SD 0.859) i	246		-0.98 (SD 1.01)	MD=0.100 (CI: -0.050, 0.250)	
	HbA1c (%) – 24wk	Mean change	295		-0.88 (SD 0.859) i	281		-0.98 (SD 1.01)	MD=0.100 (CI: -0.050, 0.250)	
	HbA1c < 7% or <=7% – 24wk	Dichotomous	295			281				0.03
	Fasting plasma glucose (mmol/l) – 24wk	Mean change	264		-1.4 (SD 1.72)	246		-2.1 (SD 1.68)	MD=0.700 (CI: 0.300, 1.100)	
	Fasting plasma glucose (mmol/l) – 24wk	Mean change	295		-1.4 (SD 1.72)	281		-2.1 (SD 1.68)	MD=0.700 (CI: 0.300, 1.100)	
	Body weight: Weight (kg) – 16wk	Continuous	264		91.3 (SD 16.2)	246		93 (SD 15.7)		
	Weight (kg) – 24wk	Mean change	295		0.3 (SD 3.44)	281		1.9 (SD 3.35)	MD=-1.600 (CI: -2.188, -1.012)	<0.001
	Weight (kg) – 24wk	Mean change	264		0.3 (SD 3.44)	246		1.9 (SD 3.35)	MD=-1.600 (CI: -2.188, -1.012)	<0.001
	Safety population Adverse events: GI: nausea – 24wkb	Dichotomous	295			280				
	GI: nausea – 52wkj	Dichotomous	295	10	(3.4%)	280	5	(1.8%)		
	Any adverse event(s) – 24wk	Dichotomous	295	177	(60.0%)	280	158	(56.4%)		
	Any serious adverse event(s) – 24wk	Dichotomous	295	6	(2.0%)	280	13	(4.6%)		

Any serious adverse event(s) – 52wk	Dichotomous	295	12	(4.1%)	280	25	(8.9%)		
Back pain – 24wk	Dichotomous	295	10	(3.4%)	280	3	(1.1%)		
Back pain – 52wk	Dichotomous	295	15	(5.1%)	280	15	(5.4%)		
Cough – 24wk	Dichotomous	295	4	(1.4%)	280	10	(3.6%)		
Death – 24wk	Dichotomous	295	0	(0.0%)	280	0	(0.0%)		
Dizziness – 24wk	Dichotomous	295	14	(4.7%)	280	7	(2.5%)		
Dizziness – 52wk	Dichotomous	295	15	(5.1%)	280	11	(3.9%)		
Dyspepsia – 24wkb	Dichotomous	295			280				
Dyspepsia – 52wk	Dichotomous	295	8	(2.7%)	280	3	(1.1%)		
Edema peripheral – 24wk	Dichotomous	295	26	(8.8%)	280	17	(6.1%)		
Edema peripheral – 52wk	Dichotomous	295	32	(10.8%)	280	31	(11.1%)		
Gastrointestinal disorders (any) – 24wkb	Dichotomous	295			280				
Gastrointestinal disorders (any) – 52wk	Dichotomous	295	59	(20.0%)	280	41a	(14.6%)		
GI: diarrhoea – 24wk	Dichotomous	295	10	(3.4%)	280	8	(2.9%)		
GI: diarrhoea – 52wk	Dichotomous	295	14	(4.7%)	280	14	(5.0%)		
GI: vomiting – 24wkb	Dichotomous	295			280				
GI: vomiting – 52wk	Dichotomous	295	10	(3.4%)	280	4	(1.4%)		
GI: constipation – 24wk	Dichotomous	295	9	(3.1%)	280	3	(1.1%)		
GI: constipation – 52wk	Dichotomous	295	10	(3.4%)	280	4	(1.4%)		
Headache – 24wk	Dichotomous	295	16	(5.4%)	280	14	(5.0%)		
Headache – 52wk	Dichotomous	295	19	(6.4%)	280	17	(6.1%)		
Nasopharyngitis – 24wk	Dichotomous	295	12	(4.1%)	280	13	(4.6%)		
Nasopharyngitis – 52wk	Dichotomous	295	16	(5.4%)	280	20	(7.1%)		
Skin reaction – 24wkb	Dichotomous	295			280				
Skin reaction – 52wk	Dichotomous	295	5	(1.7%)	280	3a	(1.1%)		
cardiovascular/cerebrovascular – 24wk	Dichotomous	295	2	(0.7%)	280	4	(1.4%)		
cardiovascular/cerebrovascular – 52wk	Dichotomous	295	2	(0.7%)	280	6	(2.1%)		
BMI >=30kg/m2 Blood glucose: HbA1c (%) – 52wk	Mean change	176		-0.4 (SD 1.33)	172		-0.8 (SD 1.31)		
Body weight: Weight (kg) – 24wk	Continuous	158		0.2 (SD 3.98)	151		2.1 (SD 3.69)		

	Weight (kg) – 24wk	Mean change	295			281			MD=-1.800 (CI: -2.584, -1.016)	<0.001
	Weight (kg) – 52wkg	Mean change	176		0.29 (SD 2.65)	172		3.25 (SD 5.25)		
	Baseline Hba1c >8% Blood glucose: HbA1c (%) – 52wk	Mean change	171		-0.7 (SD 1.31)	162		-0.8 (SD 1.27)		
	Hba1c>9.0% Blood glucose: HbA1c (%) – 24wk	Mean change	73		-1.5 (SD 1.71)	69		-1.5 (SD 1.66)		
	HbA1c (%) – 52wk	Mean change	73		-1.1 (SD 1.71)	69		-0.9 (SD 1.66)		
	BMI>=35 Blood glucose: HbA1c (%) – 52wk	Mean change	82		-0.4 (SD 0.906)	76		-0.7 (SD 0.872)		
	Body weight: Weight (kg) – 24wk	Continuous	73		0.1 (SD 4.27)	70		2.6 (SD 4.18)		
	Weight (kg) – 24wk	Mean change	295			281			MD=-2.500 (CI: -3.872, -1.128)	<0.001
	Weight (kg) – 52wkg	Mean change	82		-0.1 (SD 4.44)	76		3.9 (SD 4.79)		

[a] approximated to nearest integer (percentages only presented in text)
[b] NR
[c] No of patients
[d] (Used in the analysis); Patient days estimated assuming dropout halfway through the study
[e] Dropouts at 52 weeks not reported
[f] Data not reported at 52 weeks
[g] estimated from graph
[h] Data estimated from graph, SD calculated from estimated SE
[i] assumed SE was 0.05 not 0.5 as reported
[j] Estimated from reported percentages

	Adjusted mean changes from baseline to endpoint were analysed using an ANCOVA with treatment and pooled centre as the classification variables and baseline as covariate. P-values for adverse events were not reported.

Table 4: Brady et al. (2014)

General	**Phase:** ☐ monotherapy ☑ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin + oral **Parallel / crossover:** Parallel **Country:** - **Authors' conclusions:** - **Source of funding:** - **Comments:** -
Number and characteristics of patients	**Total number of patients:** 99 **Inclusion criteria:** Adults (>/= 18 years) with T2DM intending to fast during Ramadan for at least 10 days; on stable dose of metformin (monotherapy or first intensification with a sulfonylurea or pioglitazone) **Exclusion criteria:** -
Previous glucose-lowering	**Any participants previously taking glucose-lowering therapy?** all on oral hypoglycaemic drugs and/or insulin **Details of washout period:** 14 days run-in period (dose titration)

therapy	All pre-study medication except for metformin were stopped or switched at baseline depending on randomisation to a sulfonylurea or liraglutide
Lifestyle advice	-
Follow-up	**Total follow-up (wks):** 12 **Length of titration period (wks):** 2 **Length of maintenance period (wks):** - **Frequency of monitoring appointments:** -
Arms	**(1) Metformin + Sulphonylurea** N: 52 Treatment duration (wks): 15 Washout period (d): 14 Comments: Individuals on a pre-study regime of metformin + pioglitazone were, if randomised to stay on pre-study therapy, had pioglitazone switched to a sulphonylurea. Those randomised to liraglutide who were previously taking a sulphonylurea had this discontinued at baseline. Treatment(s): (a) Metformin (Oral) Details of dosing regimen: No details provided (b) Sulfonylurea (Oral) Details of dosing regimen: Patients on sulfonylurea at baseline continued the drug post-randomisation with advice to use the dose once daily in the evening. Patients on twice daily dose were advised to administer half the previous morning dose in the morning and half in the evening. Patients starting a sulfonylurea or switching from pioglitazone were administered gliclizide or glimepiride with evening doses, titrated up over 2 to 4 weeks The sulfonylureas used were: gliclizide (n=44), glimepiride (n=4) and glibenclamide (n=1). The mean starting and maximum doses were different for patients on mono- or dual therapy (metformin plus sulfonylurea) at baseline. **(2) Metformin + Liraglutide** N: 47 Treatment duration (wks): 15 Washout period (d): 14 Comments: Individuals on a pre-study regime of metformin + pioglitazone were, if randomised to stay on pre-study therapy, had pioglitazone switched to a sulphonylurea. Those randomised to liraglutide who were previously taking a sulphonylurea had this discontinued at baseline. Treatment(s): (a) Metformin Details of dosing regimen: No details provided (b) Liraglutide (Subcutaneous) – forced titration Set dose (mg/d):0.6 Frequency of dosing: once a day Details of dosing regimen: Administered on starting evening dose of 0.6mg/day and titrated to 1.2mg/day for the rest of the study
Outcomes	**Dropouts** Dropout due to AEs (Baseline data were collected 2 weeks prior to Ramadan followed by a 2 week run in period for dose titration)
Baseline characteristics	
Results	

		Metformin + Sulphonylurea			Metformin + Liraglutide				
		N	k	mean	N	k	mean	Δ	p
Hypoglycaemic events: All hypoglycaemic events (no events) – 14wk	Count	4410	127	a	3871	32	b		
Major/severe hypoglycaemic event – 14wk	Dichotomous	52	0	(0.0%)	47	0	(0.0%)		
Adverse events: GI: nausea – 14wk	Dichotomous	52	0	(0.0%)	47	0	(0.0%)		
Dropouts: Total dropouts – 14wk	Dichotomous	52	14	(26.9%)	47	15	(31.9%)		
Dropout due to AEs – 14wk	Dichotomous	52	1	(1.9%)	47	1	(2.1%)		

[a] (Used in the analysis); estimated from unadjusted incidence rates per year and assuming dropouts at half-

	way through study. When 2 outliers are removed, number of events decreases to 63 [b] (Used in the analysis); estimated from incidence rates per year and assuming dropouts at half-way through study

Table 5: Chawla et al. (2013)

General	**Phase:** ☐ monotherapy ☑ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin + oral **Parallel / crossover:** Parallel **Country:** India **Authors' conclusions:** Sitagliptin was well tolerated without any incidence of hypoglycaemia. It was concluded that sitagliptin as an add on to metformin is as effective and well tolerated as pioglitazone. **Source of funding:** None stated **Comments:** -
Number and characteristics of patients	**Total number of patients:** 52 **Inclusion criteria:** Patients of either sex aged 18 years and older with type two diabetes, on metformin monotherapy of at least 1500mg per day for at least 1 month, with HbA1c 7.5 to 11% and fasting plasma glucose of at least greater than or equal to 140mg/dl **Exclusion criteria:** Patients with type one diabetes, fasting plasma glucose greater than 270mg/dl, HbA1c greater than 11%, severe cardiovascular diseases, alanine transaminase/aspartate transaminase more than three times normal, or direct bilirubin more than 1.3 times normal, or kidney diseases (serum creatinine more than 1.5 mg/dl).
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** all on oral hypoglycaemic drugs and/or insulin **Details of washout period:** All patients were already on metformin and this was continued for all patients
Lifestyle advice	not stated
Follow-up	**Total follow-up (wks):** 16 **Length of titration period (wks):** - **Length of maintenance period (wks):** - **Frequency of monitoring appointments:** 4 weeks, 12 weeks, 16 weeks
Arms	**(1) Metformin + sitagliptin** N: 25 Treatment duration (wks): 16 Washout period (d): - Treatment(s): (a) Metformin – fixed-dose Minimum dose (mg/d): 1500 (b) Sitagliptin – fixed-dose Set dose (mg/d):100 **(2) Metformin + pioglitazone** N: 25 Treatment duration (wks): - Washout period (d): - Treatment(s): (a) Metformin – fixed-dose Minimum dose (mg/d): 1500 (b) Pioglitazone – fixed-dose Set dose (mg/d):30
Outcomes	
Baseline characteristics	

		Metformin + sitagliptin			Metformin + pioglitazone				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Demographics: Age (years)	Continuous	25		49.48 (SD 9.71)	25		52.2 (SD 9.51)		

Sex (n male)	Dichotomous	25	15	(60.0%)	25	14	(56.0%)		
Duration of diabetes (yrs)	Continuous	25		4.107 (SD 3.72)	25		4.458 (SD 3.63)		
Blood glucose: HbA1c (%) – 0wk	Continuous	25		8.076 (SD 0.722)	25		8.228 (SD 0.822)		
Fasting plasma glucose (mmol/l)	Continuous	25		9.4415706 (SD 1.44)	25		9.8190114 (SD 1.74)		
Fasting plasma glucose (mmol/l)	Continuous	25		8.35476312 (SD 1.45)	25		8.13273912 (SD 1.28)		
Fasting plasma glucose (mmol/l)	Continuous	25		8.35476312 (SD 1.45)	25		9.8190114 (SD 1.74)		
Fasting plasma glucose (mmol/l)	Continuous	25		9.4415706 (SD 1.44)	25		8.13273912 (SD 1.28)		
Body weight: BMI (kg/m2)	Continuous	25		29.035 (SD 4.97)	25		28.707 (SD 3.73)		
Weight (kg) a	Mean change	25		-0.58	25		0.9		
Weight (kg)	Continuous	25		72.1 (SD 13.8)	25		72.68 (SD 10.8)		
Lipids: Total cholesterol (mmol/l)	Continuous	25		4.996152 (SD 1.12)	25		5.2785432 (SD 1.1)		
HDL cholesterol (mmol/l)	Continuous	25		1.1295648 (SD 0.141)	25		1.1409432 (SD 0.157)		
HDL cholesterol (mmol/l)	Continuous	25		1.1295648 (SD 0.141)	25		5.0664912 (SD 1.45)		
HDL cholesterol (mmol/l)	Continuous	25		4.6330776 (SD 2.03)	25		1.1409432 (SD 0.157)		
HDL cholesterol (mmol/l)	Continuous	25		4.6330776 (SD 2.03)	25		5.0664912 (SD 1.45)		
Triglycerides (mmol/l)	Mean change	25		-0.1129 (SD 0.112)	25		-0.200962 (SD 0.103)		
Triglycerides (mmol/l)	Continuous	25		0.4800508 (SD 0.0623)	25		0.4633416 (SD 0.0642)		
LDL cholesterol (mmol/l)	Continuous	25		2.9739 (SD 1.11)	25		3.20664 (SD 1.03)		

[a] SD not reported

Results

		Metformin + sitagliptin			Metformin + pioglitazone				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Blood glucose: HbA1c (%) – 16wk	Mean change	25		-0.656 (SD 0.21)	25		-0.748 (SD 0.35)		
HbA1c < 7% or <=7%	Dichotomous	25	6	(24.0%)	25	7	(28.0%)		
Fasting plasma glucose (mmol/l)	Continuous	25		9.4415706 (SD 1.44)	25		9.8190114 (SD 1.74)		
Fasting plasma glucose (mmol/l)	Continuous	25		9.4415706 (SD 1.44)	25		8.13273912 (SD 1.28)		
Fasting plasma glucose (mmol/l)	Continuous	25		8.35476312 (SD 1.45)	25		9.8190114 (SD 1.74)		
Fasting plasma glucose (mmol/l)	Continuous	25		8.35476312 (SD 1.45)	25		8.13273912 (SD 1.28)		
Body weight: Weight (kg) a	Mean change	25		-0.58	25		0.9		
Weight (kg)	Continuous	25		72.1 (SD 13.8)	25		72.68 (SD 10.8)		
Adverse events: GI: nausea – 16wk	Dichotomous	25	1	(4.0%)	25	0	(0.0%)		
Lipids: HDL cholesterol (mmol/l)	Continuous	25		4.6330776 (SD 2.03)	25		5.0664912 (SD 1.45)		
HDL cholesterol (mmol/l)	Continuous	25		4.6330776 (SD 2.03)	25		1.1409432 (SD 0.157)		
HDL cholesterol (mmol/l)	Continuous	25		1.1295648 (SD 0.141)	25		5.0664912 (SD 1.45)		

	HDL cholesterol (mmol/l)	Continuous	25		1.1295648 (SD 0.141)	25		1.1409432 (SD 0.157)		
	Triglycerides (mmol/l)	Continuous	25		0.4800508 (SD 0.0623)	25		0.4633416 (SD 0.0642)		
	Triglycerides (mmol/l)	Mean change	25		-0.1129 (SD 0.112)	25		-0.200962 (SD 0.103)		

[a] SD not reported

	Adverse events are reported, but are unclear and so have not been extracted.

Table 6: Derosa et al. (2007)

General	**Phase:** ☐ monotherapy ☑ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin + oral **Parallel / crossover:** Parallel **Country:** Italy **Authors' conclusions:** Nateglinide appears to improve glycemic control as well as the levels of some prothrombotic parameters compared to glibenclamide when administered in combination with metformin. **Source of funding:** Unclear funding **Comments:** multicenter, double-blind, randomized, controlled, parallel-group trial. Patients were randomized using envelopes containing randomization codes prepared by a statistician. A copy of the randomization code was provided only to the person responsible for performing the statistical analysis. The code was only broken after database lock, but could have been broken for individual patients in cases of emergency, such as hospitalization or suspicion of a serious adverse event. Nateglinide, glibenclamide and metformin were supplied as identical, opaque, white capsules in coded bottles to ensure the double-blind status of the study.
Number and characteristics of patients	**Total number of patients:** 248 **Inclusion criteria:** Caucasian patients aged >=18 of either sex were eligible for inclusion in the study if they had: 1) type 2 diabetes mellitus according to the American Diabetes Association (ADA) criteria (duration, >=6 months), 2) poor glycemic control (Hba1cl, >7.0%), 3) hypertension according to the World Health Organization criteria (systolic/diastolic blood pressure, >=130/>=85 mm Hg) and 4) they were overweight (body mass index [BMI], 25.0-28.0 kg/m2) **Exclusion criteria:** Patients were excluded if they had a history of ketoacidosis or had unstable or rapidly progressive diabetic retinopathy, nephropathy, or neuropathy; impaired hepatic function (defined as plasma aminotransferase and/or gamma-glutamyltransferase level higher than the upper limit of normal [ULN] for age and sex), impaired renal function (defined as serum creatinine level higher than the ULN for age and sex), or severe anemia. Patients with serious cardiovascular disease (CVD) (eg, New York Heart Association class I-IV congestive heart failure or a history of myocardial infarction or stroke) or cerebrovascular conditions within 6 months before study enrollment also were excluded. Women who were pregnant or breastfeeding or of childbearing potential and not taking adequate contraceptive precautions were also excluded
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** All treatment naive/ no OADs at screening **Details of washout period:** Assumed all patients were drug naïve (wording was unclear in full paper but referred to naïve patients)
Lifestyle advice	At baseline, patients began a controlled-energy dietbased on ADA recommendations. Each center's standard diet advice was given by a dietitian and/or specialist physician. Every two weeks dietitians and/or specialists provided instruction on dietary intake-recording procedures as part of a behavior-modification program and then from month one they used the patients' food diaries for counseling. During the study, behavior-modification sessions on weight-loss strategies were given to individual patients at baseline, one at 6 months, and four with all patients at 3, 6, 9, and 12 months. Individuals were also encouraged to increase their physical activity by walking briskly or riding a stationary bicycle for 20 to 30 min, 3 to 5 times per week. The recommended changes in physical activity throughout the study were not assessed.
Follow-up	**Total follow-up (wks):** 52 **Length of titration period (wks):** 26 **Length of maintenance period (wks):** 26 **Frequency of monitoring appointments:** values were assessed at screening, 3, 6, 9, and 12 months
Arms	**(1) Nateglinide + metformin**

N: 119

Treatment duration (wks): 52
Washout period (d): 0
Comments: All assumed to be drug naïve before the study

Treatment(s): (a) nateglinide (Oral) – forced titration

Mean dose (mg/d): 300
Minimum dose (mg/d): 180
Maximum dose (mg/d): 360
Compliance: Medication compliance was assessed by the investigators by counting the number of pills returned at the time of specified clinic visits
Details of dosing regimen: patients were titrated to nateglinide (starting dose 180 mg/day). Metformin (starting dose 1,500 mg/day) was added in each arm independently of the glycemic control after 1 month of run-in

(b) Metformin (Oral) – forced titration

Mean dose (mg/d): 2500
Minimum dose (mg/d): 1500
Maximum dose (mg/d): 3000

(2) Glibenclamide + metformin

N: 114

Treatment duration (wks): 52
Washout period (d): 0
Comments: All assumed to be drug naïve before the study

Treatment(s): (a) Sulfonylurea (Oral) – forced titration

Set dose (mg/d):15
Mean dose (mg/d): 12.5
Minimum dose (mg/d): 7.5
Maximum dose (mg/d): 15
Compliance: Medication compliance was assessed by the investigators by counting the number of pills returned at the time of specified clinic visits
Details of dosing regimen: patients were titrated to glibenclamide (starting dose 7.5 mg/day). Metformin (starting dose 1,500 mg/day) was added in each arm independently of the glycemic control after 1 month of run-in

(b) Metformin (Oral) – forced titration

Mean dose (mg/d): 2500
Minimum dose (mg/d): 1500
Maximum dose (mg/d): 3000

Outcomes

General

An intention-to-treat (ITT) analysis was conducted in patients who had received >=1 dose of study medication and had a subsequent efficacy observation. Patients were included in the tolerability analysis if they had received >=1 dose of trial medication after randomization and had undergone a subsequent tolerability observation.

Outcomes not extracted in this evidence table include measures of insulin resistance, fibrogen and other biochemical measures.

10/124 (8%) patients in the glibenclamide group and 5/124 (4%) in the nateglinide group discontinued the study.

Baseline characteristics

		Nateglinide + metformin			Glibenclamide + metformin				
		N	k	mean	N	k	mean	Δ	p
Demographics:									
Age (years)	Continuous	119		55 (SD 5)	114		56 (SD 4)		
Sex (n male)	Dichotomous	119	58	(48.7%)	114	58	(50.9%)		
Duration of diabetes (yrs)	Continuous	119		5 (SD 2)	114		4 (SD 2)		
Blood glucose:									
HbA1c (%) – 0wk	Continuous	119		8.1 (SD 1)	114		8.2 (SD 1.1)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	119		9.657 (SD 1.17)	114		9.8235 (SD 1.33)		
Body weight:									
BMI (kg/m2) – 0wk	Continuous	119		26.4 (SD 1.4)	114		26.5 (SD 1.5)		
Blood pressure:									
Systolic blood pressure (mmHg) – 0wk	Continuous	119		136.8 (SD 4.4)	114		137.4 (SD 4.6)		

	Diastolic blood pressure (mmHg) – 0wk	Continuous	119		87.3 (SD 3.8)	114		88.1 (SD 3.5)		
	Lipids: Total cholesterol (mmol/l) – 0wk	Continuous	119		5.06856 (SD 0.465)	114		4.99098 (SD 0.44)		
	HDL cholesterol (mmol/l) – 0wk	Continuous	119		1.08612 (SD 0.129)	114		1.08612 (SD 0.129)		
	Triglycerides (mmol/l) – 0wk	Continuous	119		1.76124 (SD 0.452)	114		1.81769 (SD 0.474)		
	LDL cholesterol (mmol/l) – 0wk	Continuous	119		3.12906 (SD 0.336)	114		3.07734 (SD 0.31)		

Results

		Nateglinide + metformin			Glibenclamide + metformin				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 52wk	Continuous	119		6.4 (SD 0.4)	114		7.3 (SD 0.6)		<0.05
Fasting plasma glucose (mmol/l) – 52wk	Continuous	119		7.659828 (SD 0.944)	114		7.548816 (SD 0.833)		NS
Body weight: BMI (kg/m2) – 12wk	Continuous	119		26.2 (SD 1.2)	114		26.5 (SD 1.5)		
BMI (kg/m2) – 26wk	Continuous	119		26.6 (SD 1.3)	114		26.7 (SD 1.6)		
BMI (kg/m2) – 52wk	Continuous	119			114				NS
Dropouts: Total dropouts – 52wk[a]	Dichotomous	124	5	(4.0%)	124	10	(8.1%)		
Blood pressure: Systolic blood pressure (mmHg) – 38wk	Continuous	119		136.1 (SD 3.9)	114		135.7 (SD 4)		
Systolic blood pressure (mmHg) – 52wk	Continuous	119		134.5 (SD 3.6)	114		135.4 (SD 3.8)		NS
Diastolic blood pressure (mmHg) – 26wk	Continuous	119		86.1 (SD 3.5)	114		88.3 (SD 3.6)		
Diastolic blood pressure (mmHg) – 52wk	Continuous	119			114				NS
Lipids: Total cholesterol (mmol/l) – 52wk	Continuous	119			114				NS
HDL cholesterol (mmol/l) – 52wk	Continuous	119			114				NS
Triglycerides (mmol/l) – 12wk	Continuous	119		1.6935 (SD 0.418)	114		1.77253 (SD 0.452)		
Triglycerides (mmol/l) – 52wk	Continuous	119			114				NS
LDL cholesterol (mmol/l) – 52wk	Continuous	119			114				NS

[a] Dropouts due to adverse events not explicitly provided

The null hypothesis was tested using analysis of variance and analysis of covariance (ANCOVA) models. The statistical significance of the independent
effects of treatments on the other variables was determined using ANCOVA.

Table 7: Derosa et al. (2009)

General

Phase:
☑ monotherapy
☑ dual therapy
☐ triple therapy
☐ insulin monotherapy
☐ insulin + oral

	Parallel / crossover: Parallel **Country:** Italy **Authors' conclusions:** Pioglitazone-metformin based therapeutic control is associated with the most quantitatively relvant improvement in insulin resistance related parameters, whereas the sulfonylurea-metformin inclu8ding protocol has less relevant effects **Source of funding:** not reported (the authors report no affiliation with or financial involvement in any organisation or entity with a direct financial interest in the subject matter or materials discussed in the manuscript) **Comments:** Multicenter, double-blind, randomised, controlled trial. Randomisation was done using a drawing of envelopes containing randmoisation codes prepared by a statistician. A copy of the code was provided only to the responsible person performing statistical analysis. The code was only broken after database lock, but could be broken in cases of emergency. The treatments were supplied as matching opaque white capsules in coded bottles to ensure the double-blind status of the study.
Number and characteristics of patients	**Total number of patients:** 271 **Inclusion criteria:** White patients, at least 18 years of age of either sex with type 2 diabetes according to the European Society of Cardiology abd the European Association for the Study of Diabetes guidelines criteria who were naïve and with poor glycaemic control (Hba1c >6.5%) and were overweight (BMI>=25 and <30 kg/m2) were enrolled **Exclusion criteria:** history of ketoacidosis, unstable or rapidly progressing diabetic retinopathy, nephropathy or neuropathy, impaired hepatic function, impaired renal function, severe anaemia, patients with serious cardiovascular disease or cerebrovascular conditions within 6 months before study enrollment were also excluded Pre-randomisation phase: patients underwent a euglycemic hyperinsulinemic clamp and followed by a 3 month period in which patients were randomised and titrated
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** All treatment naive/ no OADs at screening **Details of washout period:** States that patients were naïve but no details provided
Lifestyle advice	at baseline, patients began a controlled-energy diet (approx 600 kcal daily deficit) based on ADA recommendations. Each centre's standard diet advice was given by a dietitican and/or specialist physician. Dieticians and/or specialists each month for the first 3 months provided instruction on dietary intake, recording procedures as part of a behaviour modification program, and then from month 3 used the patients food diaries for counseling. During the study, behaviour-modification sessions on weight-loss strategies were given to individual patients at baseline and then every 3 months until the end of the trial. Individuals were also encouraged to increase their physical activity by walking briskly or riding a stationary bike for 20 to 30 minutes, 3-5 times per week.
Follow-up	**Total follow-up (wks):** 65 **Length of titration period (wks):** 13 **Length of maintenance period (wks):** 52 **Frequency of monitoring appointments:** Anthropometric and metabolic measurements were assessed at baseline, after 3 months and after 12 months
Arms	**(1) Pioglitazone (15 mg)** N: 69 Treatment duration (wks): 65 Washout period (d): 0 Treatment(s): Pioglitazone (Oral) – forced titration Set dose (mg/d):45 Minimum dose (mg/d): 15 Maximum dose (mg/d): 45 Frequency of dosing: once a day Compliance: medication compliance was assessed by counting the number of pills returned at the time of specified clinic visits Details of dosing regimen: Patients were assigned to receive pioglitazone 15 mg once a day, after lunch. After enrollment, every month for 3 months, the treatment was titrated to 30 mg then 45 mg (forced titration independent of glycaemic control) and patients were then followed for 12 months **(2) Metformin (1000 mg)** N: 67 Treatment duration (wks): 65 Washout period (d): 0 Treatment(s): Metformin (Oral) – forced titration Set dose (mg/d):3000 Minimum dose (mg/d): 1000 Maximum dose (mg/d): 3000 Frequency of dosing: twice a day Compliance: medication compliance was assessed by counting the number of pills returned at the time of specified clinic visits

Details of dosing regimen: Patients were assigned to receive metformin 1000 mg/day, as 500 mg twice a day after lunch and dinner. After enrollment, every month for 3 months, the treatment was titrated to 2000 mg then 3000 mg (forced titration independent of glycaemic control) and patients were then followed for 12 months

(3) Pioglitazone + metformin (15/850 mg)

N: 69

Treatment duration (wks): 65
Washout period (d): 0

Treatment(s): (a) Pioglitazone (Oral) – forced titration
Set dose (mg/d):45
Minimum dose (mg/d): 15
Maximum dose (mg/d): 45
Frequency of dosing: once a day
Compliance: medication compliance was assessed by counting the number of pills returned at the time of specified clinic visits
Details of dosing regimen: Patients were assigned to receive pioglitazone 15 mg once a day, after lunch. After enrollment, every month for 3 months, the treatment was titrated to 30 mg then 45 mg (forced titration independent of glycaemic control) and patients were then followed for 12 months

(b) Metformin (Oral) – forced titration
Set dose (mg/d):2550
Minimum dose (mg/d): 850
Maximum dose (mg/d): 2550
Frequency of dosing: once a day
Details of dosing regimen: Patients were assigned to receive metformin 850 mg once a day, after lunch. After enrollment, every month for 3 months, the treatment was titrated to 1700 mg then 2550 mg (forced titration independent of glycaemic control) and patients were then followed for 12 months

(4) Glimepiride + metformin (2/850mg)

N: 66

Treatment duration (wks): 65
Washout period (d): 0

Treatment(s): (a) Sulfonylurea (Oral) – forced titration
Set dose (mg/d):6
Minimum dose (mg/d): 2
Maximum dose (mg/d): 6
Frequency of dosing: once a day
Compliance: medication compliance was assessed by counting the number of pills returned at the time of specified clinic visits
Details of dosing regimen: Patients were assigned to receive glimepiride 2 mg once a day, after lunch. After enrollment, every month for 3 months, the treatment was titrated to 4 mg then 6 mg (forced titration independent of glycaemic control) and patients were then followed for 12 months

(b) Metformin (Oral) – forced titration
Set dose (mg/d):850
Frequency of dosing: once a day
Details of dosing regimen: Patients were assigned to receive metformin 850 mg once a day, after lunch and patients were then followed for 12 months

Outcomes

General

An ITT analysis was conducted in patients who had received at least one dose of the study medication and had a subsequent efficacy observation. Patients were included in the safety analysis if they had received 1 dose of trial medication after randomisation and had a subsequent safety observation.

Outcomes not extracted in this evidence table include fasting and postprandial insulin, glucose infusion rate and total glucose requirement.

240 patients completed the study

Total dropouts per group not clearly stated and therefore not extracted.

Baseline characteristics

		Pioglitazone (15 mg)			Metformin (1000 mg)			Δ	p
		N	k	mean	N	k	mean		
Demographics: Age (years)	Continuous	69		54 (SD 6)	67		55 (SD 5)		
Sex (n male)	Dichotomous	69	32	(46.4%)	67	34	(50.7%)		
Blood glucose: HbA1c (%) – 0mo	Continuous	69		9.2 (SD 1.3)	67		9.1 (SD 1.2)		

Fasting plasma glucose (mmol/l) – 0mo	Continuous	69		9.102 (SD 1.55)	67		8.9355 (SD 1.5)		
Postprandial plasma glucose (mmol/l) – 0mo	Continuous	69		10.9335 (SD 2.28)	67		10.656 (SD 2.11)		
Body weight: BMI (kg/m2) – 0mo	Continuous	69		27.5 (SD 1.7)	67		27.2 (SD 1.5)		
Weight (kg)	Continuous	69		76.7 (SD 5.3)	67		77.7 (SD 5.9)		
Height (cm)	Continuous	69		167 (SD 3)	67		169 (SD 5)		

		Pioglitazone (15 mg)			Pioglitazone + metformin (15/850 mg)			Δ	p
		N	k	mean	N	k	mean		
Demographics: Age (years)	Continuous	69		54 (SD 6)	69		57 (SD 7)		
Sex (n male)	Dichotomous	69	32	(46.4%)	69	34	(49.3%)		
Blood glucose: HbA1c (%) – 0mo	Continuous	69		9.2 (SD 1.3)	69		9.3 (SD 1.4)		
Fasting plasma glucose (mmol/l) – 0mo	Continuous	69		9.102 (SD 1.55)	69		9.2685 (SD 1.61)		
Postprandial plasma glucose (mmol/l) – 0mo	Continuous	69		10.9335 (SD 2.28)	69		10.989 (SD 2.33)		
Body weight: BMI (kg/m2) – 0mo	Continuous	69		27.5 (SD 1.7)	69		27.4 (SD 1.6)		
Weight (kg)	Continuous	69		76.7 (SD 5.3)	69		76.4 (SD 5.1)		
Height (cm)	Continuous	69		167 (SD 3)	69		167 (SD 4)		

		Pioglitazone (15 mg)			Glimepiride + metformin (2/850mg)			Δ	p
		N	k	mean	N	k	mean		
Demographics: Age (years)	Continuous	69		54 (SD 6)	66		57.7 (SD 7)		
Sex (n male)	Dichotomous	69	32	(46.4%)	66	32	(48.5%)		
Blood glucose: HbA1c (%) – 0mo	Continuous	69		9.2 (SD 1.3)	66		9 (SD 1.1)		
Fasting plasma glucose (mmol/l) – 0mo	Continuous	69		9.102 (SD 1.55)	66		9.324 (SD 1.66)		
Postprandial plasma glucose (mmol/l) – 0mo	Continuous	69		10.9335 (SD 2.28)	66		11.0445 (SD 2.44)		
Body weight: BMI (kg/m2) – 0mo	Continuous	69		27.5 (SD 1.7)	66		27.1 (SD 1.4)		
Weight (kg)	Continuous	69		76.7 (SD 5.3)	66		77.4 (SD 5.8)		
Height (cm)	Continuous	69		167 (SD 3)	66		169 (SD 5)		

		Metformin (1000 mg)			Pioglitazone + metformin (15/850 mg)			Δ	p
		N	k	mean	N	k	mean		
Demographics: Age (years)	Continuous	67		55 (SD 5)	69		57 (SD 7)		

Sex (n male)	Dichotomous	67	34	(50.7%)	69	34	(49.3%)	
Blood glucose: HbA1c (%) – 0mo	Continuous	67		9.1 (SD 1.2)	69		9.3 (SD 1.4)	
Fasting plasma glucose (mmol/l) – 0mo	Continuous	67		8.9355 (SD 1.5)	69		9.2685 (SD 1.61)	
Postprandial plasma glucose (mmol/l) – 0mo	Continuous	67		10.656 (SD 2.11)	69		10.989 (SD 2.33)	
Body weight: BMI (kg/m2) – 0mo	Continuous	67		27.2 (SD 1.5)	69		27.4 (SD 1.6)	
Weight (kg)	Continuous	67		77.7 (SD 5.9)	69		76.4 (SD 5.1)	
Height (cm)	Continuous	67		169 (SD 5)	69		167 (SD 4)	

		Metformin (1000 mg)			Glimepiride + metformin (2/850mg)				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	67		55 (SD 5)	66		57.7 (SD 7)		
Sex (n male)	Dichotomous	67	34	(50.7%)	66	32	(48.5%)		
Blood glucose: HbA1c (%) – 0mo	Continuous	67		9.1 (SD 1.2)	66		9 (SD 1.1)		
Fasting plasma glucose (mmol/l) – 0mo	Continuous	67		8.9355 (SD 1.5)	66		9.324 (SD 1.66)		
Postprandial plasma glucose (mmol/l) – 0mo	Continuous	67		10.656 (SD 2.11)	66		11.0445 (SD 2.44)		
Body weight: BMI (kg/m2) – 0mo	Continuous	67		27.2 (SD 1.5)	66		27.1 (SD 1.4)		
Weight (kg)	Continuous	67		77.7 (SD 5.9)	66		77.4 (SD 5.8)		
Height (cm)	Continuous	67		169 (SD 5)	66		169 (SD 5)		

		Pioglitazone + metformin (15/850 mg)			Glimepiride + metformin (2/850mg)				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	69		57 (SD 7)	66		57.7 (SD 7)		
Sex (n male)	Dichotomous	69	34	(49.3%)	66	32	(48.5%)		
Blood glucose: HbA1c (%) – 0mo	Continuous	69		9.3 (SD 1.4)	66		9 (SD 1.1)		
Fasting plasma glucose (mmol/l) – 0mo	Continuous	69		9.2685 (SD 1.61)	66		9.324 (SD 1.66)		
Postprandial plasma glucose (mmol/l) – 0mo	Continuous	69		10.989 (SD 2.33)	66		11.0445 (SD 2.44)		
Body weight: BMI (kg/m2) – 0mo	Continuous	69		27.4 (SD 1.6)	66		27.1 (SD 1.4)		
Weight (kg)	Continuous	69		76.4 (SD 5.1)	66		77.4 (SD 5.8)		
Height (cm)	Continuous	69		167 (SD 4)	66		169 (SD 5)		

Results

	Pioglitazone (15 mg)	Metformin (1000 mg)	Δ	p

		N	k	mean	N	k	mean		
Blood glucose: HbA1c (%) – 3mo	Continuous	69		8.8 (SD 1.1)	67		8.6 (SD 0.9)		
HbA1c (%) – 15moa	Continuous	69		8.2 (SD 0.7)	67		7.9 (SD 0.5)		NS
Fasting plasma glucose (mmol/l) – 3mo	Continuous	69		8.658 (SD 1.28)	67		8.4915 (SD 1.22)		
Fasting plasma glucose (mmol/l) – 15moa	Continuous	69		8.3805 (SD 1.17)	67		8.214 (SD 1.05)		NS
Postprandial plasma glucose (mmol/l) – 15moa	Continuous	69		10.1565 (SD 1.83)	67		9.4905 (SD 1.66)		<0.05
Body weight: BMI (kg/m2) – 3mo	Continuous	69		27.7 (SD 1.8)	67		27 (SD 1.4)		
BMI (kg/m2) – 15moa	Continuous	69		28.1 (SD 2)	67		26.7 (SD 1.2)		<0.05
Weight (kg) b	Continuous	69		77.25 (SD 5.02)	67		77.11 (SD 4)		
Weight (kg) c	Continuous	69		78.37 (SD 5.58)	67		76.25787 (SD 3.43)		
Dropouts: Dropout due to AEs – 15moa	Dichotomous	69	3	(4.3%)	67	5	(7.5%)		

[a] [do not use - outside time range]
[b] estimated using BMI and mean baseline height data
[c] [do not use - outside time range] estimated using BMI and mean baseline height data

		Pioglitazone (15 mg)			Pioglitazone + metformin (15/850 mg)			Δ	p
		N	k	mean	N	k	mean		
Blood glucose: HbA1c (%) – 3mo	Continuous	69		8.8 (SD 1.1)	69		8.1 (SD 0.6)		
HbA1c (%) – 15moa	Continuous	69		8.2 (SD 0.7)	69		7.2 (SD 0.3)		
Fasting plasma glucose (mmol/l) – 3mo	Continuous	69		8.658 (SD 1.28)	69		8.325 (SD 1.11)		
Fasting plasma glucose (mmol/l) – 15moa	Continuous	69		8.3805 (SD 1.17)	69		7.7145 (SD 0.555)		
Postprandial plasma glucose (mmol/l) – 15moa	Continuous	69		10.1565 (SD 1.83)	69		8.991 (SD 1.55)		
Body weight: BMI (kg/m2) – 3mo	Continuous	69		27.7 (SD 1.8)	69		27.2 (SD 1.5)		
BMI (kg/m2) – 15moa	Continuous	69		28.1 (SD 2)	69		26.9 (SD 1.3)		
Weight (kg) b	Continuous	69		77.25 (SD 5.02)	69		75.85808 (SD 4.18)		
Weight (kg) c	Continuous	69		78.37 (SD 5.58)	69		75.02 (SD 3.63)		
Dropouts: Dropout due to AEs – 15moa	Dichotomous	69	3	(4.3%)	69	2	(2.9%)		

[a] [do not use - outside time range]
[b] estimated using BMI and mean baseline height data
[c] [do not use - outside time range] estimated using BMI and mean baseline height data

		Pioglitazone (15 mg)			Glimepiride + metformin (2/850mg)			Δ	p
		N	k	mean	N	k	mean		
Blood glucose: HbA1c (%) – 3mo	Continuous	69		8.8 (SD 1.1)	66		8.5 (SD 0.8)		
HbA1c (%) – 15moa	Continuous	69		8.2 (SD 0.7)	66		7.8 (SD 0.4)		
Fasting plasma glucose (mmol/l) – 3mo	Continuous	69		8.658 (SD 1.28)	66		8.436 (SD 1.17)		
Fasting plasma glucose (mmol/l) – 15moa	Continuous	69		8.3805 (SD 1.17)	66		8.0475 (SD 0.888)		

Postprandial plasma glucose (mmol/l) – 15moa	Continuous	69		10.1565 (SD 1.83)	66		9.3795 (SD 1.66)		
Body weight:									
BMI (kg/m2) – 3mo	Continuous	69		27.7 (SD 1.8)	66		27.8 (SD 1.9)		
BMI (kg/m2) – 15moa	Continuous	69		28.1 (SD 2)	66		28.4 (SD 2.2)		
Weight (kg) b	Continuous	69		77.25 (SD 5.02)	66		79.39958 (SD 5.43)		
Weight (kg) c	Continuous	69		78.37 (SD 5.58)	66		81.11 (SD 6.28)		
Dropouts:									
Dropout due to AEs – 15moa	Dichotomous	69	3	(4.3%)	66	3	(4.5%)		

[a] [do not use - outside time range]
[b] estimated using BMI and mean baseline height data
[c] [do not use - outside time range] estimated using BMI and mean baseline height data

		Metformin (1000 mg)			Pioglitazone + metformin (15/850 mg)				
		N	k	mean	N	k	mean	Δ	p
Blood glucose:									
HbA1c (%) – 3mo	Continuous	67		8.6 (SD 0.9)	69		8.1 (SD 0.6)		
HbA1c (%) – 15moa	Continuous	67		7.9 (SD 0.5)	69		7.2 (SD 0.3)		
Fasting plasma glucose (mmol/l) – 3mo	Continuous	67		8.4915 (SD 1.22)	69		8.325 (SD 1.11)		
Fasting plasma glucose (mmol/l) – 15moa	Continuous	67		8.214 (SD 1.05)	69		7.7145 (SD 0.555)		
Postprandial plasma glucose (mmol/l) – 15moa	Continuous	67		9.4905 (SD 1.66)	69		8.991 (SD 1.55)		
Body weight:									
BMI (kg/m2) – 3mo	Continuous	67		27 (SD 1.4)	69		27.2 (SD 1.5)		
BMI (kg/m2) – 15moa	Continuous	67		26.7 (SD 1.2)	69		26.9 (SD 1.3)		
Weight (kg) b	Continuous	67		77.11 (SD 4)	69		75.85808 (SD 4.18)		
Weight (kg) c	Continuous	67		76.25787 (SD 3.43)	69		75.02 (SD 3.63)		
Dropouts:									
Dropout due to AEs – 15moa	Dichotomous	67	5	(7.5%)	69	2	(2.9%)		

[a] [do not use - outside time range]
[b] estimated using BMI and mean baseline height data
[c] [do not use - outside time range] estimated using BMI and mean baseline height data

		Metformin (1000 mg)			Glimepiride + metformin (2/850mg)				
		N	k	mean	N	k	mean	Δ	p
Blood glucose:									
HbA1c (%) – 3mo	Continuous	67		8.6 (SD 0.9)	66		8.5 (SD 0.8)		
HbA1c (%) – 15moa	Continuous	67		7.9 (SD 0.5)	66		7.8 (SD 0.4)		
Fasting plasma glucose (mmol/l) – 3mo	Continuous	67		8.4915 (SD 1.22)	66		8.436 (SD 1.17)		
Fasting plasma glucose (mmol/l) – 15moa	Continuous	67		8.214 (SD 1.05)	66		8.0475 (SD 0.888)		
Postprandial plasma glucose (mmol/l) – 15moa	Continuous	67		9.4905 (SD 1.66)	66		9.3795 (SD 1.66)		
Body weight:									
BMI (kg/m2) – 3mo	Continuous	67		27 (SD 1.4)	66		27.8 (SD 1.9)		
BMI (kg/m2) – 15moa	Continuous	67		26.7 (SD 1.2)	66		28.4 (SD 2.2)		
Weight (kg) b	Continuous	67		77.11 (SD 4)	66		79.39958 (SD 5.43)		

Weight (kg) c	Continuous	67		76.25787 (SD 3.43)	66		81.11 (SD 6.28)			
Dropouts:										
Dropout due to AEs – 15moa	Dichotomous	67	5	(7.5%)	66	3	(4.5%)			

[a] [do not use - outside time range]
[b] estimated using BMI and mean baseline height data
[c] [do not use - outside time range] estimated using BMI and mean baseline height data

		Pioglitazone + metformin (15/850 mg)			Glimepiride + metformin (2/850mg)			Δ	p
		N	k	mean	N	k	mean		
Blood glucose:									
HbA1c (%) – 3mo	Continuous	69		8.1 (SD 0.6)	66		8.5 (SD 0.8)		
HbA1c (%) – 15moa	Continuous	69		7.2 (SD 0.3)	66		7.8 (SD 0.4)		NS
Fasting plasma glucose (mmol/l) – 3mo	Continuous	69		8.325 (SD 1.11)	66		8.436 (SD 1.17)		
Fasting plasma glucose (mmol/l) – 15moa	Continuous	69		7.7145 (SD 0.555)	66		8.0475 (SD 0.888)		NS
Postprandial plasma glucose (mmol/l) – 15moa	Continuous	69		8.991 (SD 1.55)	66		9.3795 (SD 1.66)		NS
Body weight:									
BMI (kg/m2) – 3mo	Continuous	69		27.2 (SD 1.5)	66		27.8 (SD 1.9)		
BMI (kg/m2) – 15moa	Continuous	69		26.9 (SD 1.3)	66		28.4 (SD 2.2)		<0.05
Weight (kg) b	Continuous	69		75.85808 (SD 4.18)	66		79.39958 (SD 5.43)		
Weight (kg) c	Continuous	69		75.02 (SD 3.63)	66		81.11 (SD 6.28)		
Dropouts:									
Dropout due to AEs – 15moa	Dichotomous	69	2	(2.9%)	66	3	(4.5%)		

[a] [do not use - outside time range]
[b] estimated using BMI and mean baseline height data
[c] [do not use - outside time range] estimated using BMI and mean baseline height data

Repeated measures ANOVA and ANCOVA models were used to assess the null hypothesis. The statistical significance of the independent effects of treatment on the other parameters was determined by ANCOVA. A one sample t test was used to compare values obtained before and after treatment administration. Two sample t-tests were used for between group comparisons. The Bonferroni correction for multiple comparisons was also carried out.

Table 8: Derosa et al. (2010)

General	**Phase:** ☐ monotherapy ☑ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin + oral **Parallel / crossover:** Parallel **Country:** Italy **Authors' conclusions:** The addition of both sitagliptin or metformin to pioglitazone gave an improvement of Hba1c, FBG and PPG but metformin also led to a decrease of bodyweight and to a faster and better improvement of insulin resistance and inflammatory state parameters, even if sitagliptin produced a better beta-cell function **Source of funding:** Funding from the University of Pavia **Comments:** Multicenter, double blind, randomised trial. Patients were randomized using envelopes containing randomization codes prepared by a statistician. A copy of the randomization code was provided only to the person responsible for performing the statistical analysis. The code was only broken after database lock, but could have been broken for individual patients in cases of emergency. were supplied as identical, opaque, white capsules in coded bottles to ensure the double-blind status of the study.
Number and characteristics of patients	**Total number of patients:** 151 **Inclusion criteria:** patients with uncontrolled type 2 diabetes (Hba1c >7.5%) in therapy with pioglitazone. All patients were not well controlled with diet, physical activity and pioglitazone at the dose 30 mg/day

	Exclusion criteria: history of ketoacidosis, unstable or rapidly progressing diabetic retinopathy, nephropathy or neuropathy, impaired hepatic function, impaired renal function, severe anaemia, serious cardiovascular disease or cerebrovascular conditions within 6 months of enrollment.
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** all on oral hypoglycaemic drugs and/or insulin **Details of washout period:** all taking pioglitazone monotherapy at baseline
Lifestyle advice	Each center's standard diet advice was given by a dietitian and/or specialist physician. Every two weeks dietitians and/or specialists provided instruction on dietary intake-recording procedures as part of a behavior-modification program and then from month one they used the patients' food diaries for counseling. During the study, behavior-modification sessions on weight-loss strategies were given to individual patients at baseline, one at 6 months, and four with all patients at 3, 6, 9, and 12 months. Individuals were also encouraged to increase their physical activity by walking briskly or riding a stationary bicycle for 20 to 30 min, 3 to 5 times per week.
Follow-up	**Total follow-up (wks):** 52 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 52 **Frequency of monitoring appointments:** Outcomes reported at 3,6,9 and 12 months
Arms	**(1) Pioglitazone + sitagliptin** N: 75 Treatment duration (wks): 52 Washout period (d): 0 Comments: all taking pioglitazone monotherapy at baseline Treatment(s): (a) Pioglitazone (Oral) – fixed-dose Set dose (mg/d):30 Frequency of dosing: once a day (b) Sitagliptin (Oral) – fixed-dose Set dose (mg/d):100 Frequency of dosing: once a day **(2) Pioglitazone + metformin** N: 76 Treatment duration (wks): 52 Washout period (d): 0 Comments: all taking pioglitazone monotherapy at baseline Treatment(s): (a) Pioglitazone (Oral) – fixed-dose Set dose (mg/d):30 Frequency of dosing: twice a day Details of dosing regimen: 15 mg pioglitazone given bid (b) Metformin (Oral) – fixed-dose Set dose (mg/d):1700 Frequency of dosing: twice a day Details of dosing regimen: 850 mg metformin given bid
Outcomes	**General** An intention-to-treat (ITT) analysis was conducted in patients who had received >=1 dose of study medication and had a subsequent efficacy observation. Patients were included in the tolerability analysis if they had received >=1 dose of trial medication after randomization and had undergone a subsequent tolerability observation. Outcomes not extracted in this evidence table include measures of insulin resistance, fibrogen and other biochemical measures. 6/75 in the sitagliptin group and 8/76 in the metformin group discontinued the study
Baseline characteristics	

		Pioglitazone + sitagliptin			Pioglitazone + metformin				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Demographics:									
Age (years)	Continuous	75		57 (SD 5)	76		58 (SD 6)		
Sex (n male)	Dichotomous	75	37	(49.3%)	76	39	(51.3%)		
Duration of diabetes (yrs)	Continuous	75		5 (SD 2)	76		6 (SD 3)		
Blood glucose:									
HbA1c (%) – 0wk	Continuous	75		8.5 (SD 0.9)	76		8.4 (SD 0.8)		

Fasting plasma glucose (mmol/l) – 0wk	Continuous	75		7.937358 (SD 1.05)	76		7.881852 (SD 0.999)		
Body weight:									
BMI (kg/m2) – 0wk	Continuous	75		27.9 (SD 1.5)	76		27.7 (SD 1.3)		
Weight (kg) – 0wk	Continuous	75		78.7 (SD 6.2)	76		77.3 (SD 5.4)		

Results

		Pioglitazone + sitagliptin			Pioglitazone + metformin				
		N	k	mean	N	k	mean	Δ	p
Blood glucose:									
HbA1c (%) – 12wk	Continuous	75		8.2 (SD 0.7)	76		8 (SD 0.6)		
HbA1c (%) – 26wk	Continuous	75		7.7 (SD 0.5)	76		7.8 (SD 0.5)		
HbA1c (%) – 38wk	Continuous	75		7.4 (SD 0.4)	76		7.3 (SD 0.4)		
HbA1c (%) – 52wk	Continuous	75		7.1 (SD 0.3)	76		7 (SD 0.2)		NS
HbA1c (%) – 52wk	Continuous	69		7.1 (SD 0.3)	68		7 (SD 0.2)		NS
Fasting plasma glucose (mmol/l) – 12wk	Continuous	75		7.715334 (SD 0.944)	76		7.604322 (SD 0.888)		
Fasting plasma glucose (mmol/l) – 26wk	Continuous	75		7.382298 (SD 0.833)	76		7.271286 (SD 0.777)		
Fasting plasma glucose (mmol/l) – 38wk	Continuous	75		7.104768 (SD 0.722)	76		6.93825 (SD 0.666)		
Fasting plasma glucose (mmol/l) – 52wk	Continuous	75		6.827238 (SD 0.611)	76		6.66072 (SD 0.555)		NS
Body weight:									
BMI (kg/m2) – 12wk	Continuous	75		27.7 (SD 1.3)	76		27.5 (SD 1.2)		
BMI (kg/m2) – 26wk	Continuous	75		27.5 (SD 1.2)	76		27.2 (SD 0.9)		
BMI (kg/m2) – 38wk	Continuous	75		27.4 (SD 1.1)	76		26.9 (SD 0.8)		
BMI (kg/m2) – 52wk	Continuous	75		27.3 (SD 1)	76		26.7 (SD 0.7)		<0.05
BMI (kg/m2) – 52wk	Continuous	69		27.3 (SD 1)	68		26.7 (SD 0.7)		<0.05
Weight (kg) – 12wk	Continuous	75		78.2 (SD 6)	76		76.7 (SD 5)		
Weight (kg) – 26wk	Continuous	75		77.6 (SD 5.7)	76		75.9 (SD 4.7)		
Weight (kg) – 38wk	Continuous	75		77.3 (SD 5.4)	76		75 (SD 4.3)		
Weight (kg) – 52wk	Continuous	69		77.1 (SD 5.2)	68		74.5 (SD 4.1)		<0.05
Weight (kg) – 52wk	Continuous	75		77.1 (SD 5.2)	76		74.5 (SD 4.1)		<0.05
Dropouts:									
Total dropouts – 52wk	Dichotomous	75	6	(8.0%)	76	8	(10.5%)		
Dropout due to AEs – 52wk	Dichotomous	75	4a	(5.3%)	76	7	(9.2%)		

[a] Adverse events included hypoglycaemia (n=2)

The statistical significance of the independent effects of treatments on the other variables was determined using ANCOVA. A one-sample t test was used to compare values obtained before and after treatment administration; two- sample t tests were used for between-group comparisons. The Bonferroni correction for multiple comparisons also was carried out.

Table 9: Derosa et al. (2011)

General

Phase:

☐ monotherapy
☑ dual therapy
☐ triple therapy
☐ insulin monotherapy
☐ insulin + oral

Parallel / crossover: Parallel

Country: Italy

Authors' conclusions: Both treatments gave a similar improvement of glycemic control, without any differences between the two groups. Only exenatide gave a decrease of BMI, insulin resistance parameters such as fasting plasma insulin, HOMA-IR, and adiponectin and a decrease of inflammatory parameters such

	as tumor necrosis factor-alpha, and high sensitivity-C reactive protein. Furthermore, the values obtained with exenatide were significantly better than the values recorded with glimepiride. We can conclude that exenatide was better than glimepiride in improving insulin resistance and inflammatory state. Furthermore, adiponectin increase, and tumor necrosis factor-alpha reduction seem to be related to weight loss obtained with exenatide. **Source of funding:** Authors stated there was no affiliation or financial involvement with any organisation or entity with a direct financial interest in the subject matter. **Comments:** -
Number and characteristics of patients	**Total number of patients:** 111 **Inclusion criteria:** Caucasian type two diabetes patients aged 18 years and older of either sex with poor glycaemic control (expressed as HbA1c >8%) and over weight (BMI >= 25 and <30kg/m2). They were taking metformin at various doses and were intolerant to metformin at the highest doses (1500 to 3000mg/day) **Exclusion criteria:** History of ketoacidosis or unatable/rapidly progressive diabetic retinopathy, nephropathy, neuropathy; impaired hepatic function, renal function function or severe anaemia; Serious CVD or cerebrovascular conditions within 6 months before study enrolment; women who were pregnant, breast feeding, or of child bearning potential and not taking adequate contraceptive precautions. Pre-randomisation phase: None
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** all on oral hypoglycaemic drugs and/or insulin **Details of washout period:** None, all continued on baseline metformin.
Lifestyle advice	Patients began a controlled energy diet (600kcal daily deficit) based on AHA recommendations that included 50% of calories from carbohydrate, 30% from fat, 20% from proteins, max cholesterol 300mg/day, 35g/day fibre. Standard diet advice was given by a dietician and/or specialist doctor. Dietician and/or specialist doctor periodically provided instruction on dietary intake recording procedures as part of a behaviour modification programme, and then later used the patients food diaries for counselling. Individuals were also encouraged to increase their physical activity by walking briskly for 20 to 30 mins, 3 to 5 times per week, or by cycling.
Follow-up	**Total follow-up (wks):** 52 **Length of titration period (wks):** - **Length of maintenance period (wks):** 52 **Frequency of monitoring appointments:** baseline, 3, 6, 9 and 12 months
Arms	**(1) Metformin + Exenatide** N: 57 Treatment duration (wks): 52 Washout period (d): - Treatment(s): (a) Metformin Details of dosing regimen: Patients were on various doses (1000 to 2000 mg/day) and were intolerant to 2500 to 3000mg/day doses. (b) Exenatide (Subcutaneous) – fixed-dose Set dose (mg/d):20 Frequency of dosing: twice a day Details of dosing regimen: initially 5 micrograms were given twice a day and titrated after 1 month to 10 micrograms twice a day **(2) Metformin + Glimepiride** N: 54 Treatment duration (wks): 52 Washout period (d): - Treatment(s): (a) Metformin Details of dosing regimen: Patients were on various doses (1000 to 2000 mg/day) and were intolerant to 2500 to 3000mg/day doses. (b) Sulfonylurea (Oral) – fixed-dose Set dose (mg/d):6 Frequency of dosing: three times a day Details of dosing regimen: Initially, 1mg was given three times a day, then after 1 month it was titrated up to 2mg three times a day
Outcomes	**General** every patient who had received at least one dose of the study medication underwent a tolerability observation to exclude the presence of acute adverse reactions. Intention to treat analysus was conducted in patients who had received one or more doses of study medication, did not show any acute adverse reactions, and had a subsequent efficacy observation.

Baseline characteristics

		Metformin + Exenatide			Metformin + Glimepiride			Δ	p
		N	k	mean	N	k	mean		
Demographics: Age (years)	Continuous	57		56 (SD 7)	54		55 (SD 6)		
Sex (n male)	Dichotomous	57	28	(49.1%)	54	26	(48.1%)		
Blood glucose: HbA1c (%) – 0wk	Continuous	57		8.7 (SD 0.7)	54		8.8 (SD 0.8)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	57		8.103876 (SD 0.944)	54		6.327684 (SD 0.888)		
Body weight: BMI (kg/m2) – 0wk	Continuous	57		28.4 (SD 1.3)	54		28.5 (SD 1.4)		
Weight (kg) – 0wk	Continuous	57		80.2 (SD 7.5)	54		81.4 (SD 8.1)		

Results

		Metformin + Exenatide			Metformin + Glimepiride			Δ	p
		N	k	mean	N	k	mean		
Blood glucose: HbA1c (%) – 12wk	Continuous	55		8.1 (SD 0.6)	52		8.4 (SD 0.7)		
HbA1c (%) – 24wk	Continuous	54		7.9 (SD 0.5)	50		8.1 (SD 0.6)		
HbA1c (%) – 39wk	Continuous	52		7.7 (SD 0.4)	50		7.6 (SD 0.4)		
HbA1c (%) – 52wk	Continuous	52		7.5 (SD 0.3)	49		7.4 (SD 0.2)		
Fasting plasma glucose (mmol/l) – 12wk	Continuous	55		7.715334 (SD 0.722)	52		7.604322 (SD 0.666)		
Fasting plasma glucose (mmol/l) – 24wk	Continuous	54		7.271286 (SD 0.611)	50		7.160274 (SD 0.555)		
Fasting plasma glucose (mmol/l) – 39wk	Continuous	52		6.93825 (SD 0.5)	50		6.827238 (SD 0.444)		
Fasting plasma glucose (mmol/l) – 52wk	Continuous	52		6.605214 (SD 0.444)	49		6.438696 (SD 0.389)		
Body weight: BMI (kg/m2) – 12wk	Continuous	55		28 (SD 1.2)	52		28.6 (SD 1.5)		
BMI (kg/m2) – 24wk	Continuous	54		27.5 (SD 1.1)	50		28.5 (SD 1.4)		
BMI (kg/m2) – 39wk	Continuous	52		26.9 (SD 1)	50		28.8 (SD 1.6)		
BMI (kg/m2) – 52wk	Continuous	52		26.6 (SD 0.9)	49		28.2 (SD 1.3)		
Weight (kg) – 12wk	Continuous	55		79 (SD 7.3)	52		81.7 (SD 8.3)		
Weight (kg) – 24wk	Continuous	54		77.6 (SD 7)	50		81.4 (SD 8.2)		
Weight (kg) – 39wk	Continuous	52		75.9 (SD 6.7)	50		82.3 (SD 8.7)		
Weight (kg) – 52wk	Continuous	52		75.1 (SD 6.5)	49		80.5 (SD 7.7)		
Dropouts: Total dropouts – 52wk	Dichotomous	57	5	(8.8%)	54	5	(9.3%)		
Dropout due to AEs – 52wk	Dichotomous	57	4	(7.0%)	54	4	(7.4%)		

Table 10: Derosa et al. (2011)

General

Phase:
☐ monotherapy
☑ dual therapy
☐ triple therapy

	☐ insulin monotherapy ☐ insulin + oral **Parallel / crossover:** Parallel **Country:** Italy **Authors' conclusions:** Pioglitazone was better than glibenclamide in mitigating the variations of lipid components and inflammation parameters in TTD patients. **Source of funding:** Not stated **Comments:** -
Number and characteristics of patients	**Total number of patients:** 201 **Inclusion criteria:** caucasian type 2 diabetic patients aged =>18 years according to the ESC and EASD guidelines criteria, and with uncontrolled tyoe 2 diabetes (HbA1c >7%) in therapy with diet, physical activiey and metformin (mean dose= 1700 mg/day) **Exclusion criteria:** History of ketoacididosis or unstable/rapidly progressive diabetic retinopathy, nephropathy or neuropathy; imapired hepatic function, impaired renal function, or severe anaemia; patients with severe cardiovascular disease, cardiac failure, history of cardiac failure, MI, stroke, or cerebrovascular conditions within 6 months of study enrollment; post-menopause women with a history of osteoporosis (for the increased risk of distal upper limb or distal lower limb fractures reported with pioglitazone); women pregnant or breastfeeding, or of childbearing potential and not taking adequate contraceptive precautions were also excluded. Pre-randomisation phase: not stated
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** all on oral hypoglycaemic drugs and/or insulin **Details of washout period:** All continued baseline therapy during trial (assumed metformin monotherapy)
Lifestyle advice	Participants began a controlled energy diet (600kcal day deficit) based on AHA recommendations that included 50% of calories from carbohydrates, 30% from fat, and 20% from proteins, with a maximum cholesterol content of 300mg/day and 35g/day fibre. Standard diet advice was given by a dietician and/or specialist doctor. Dietician and/or specialist doctor periodically provided instruction on dietary intake recording procedures as part of a behaviour modification programme and then later used participants food diaries for counselling. Individuals were also encouraged to increase their physical activity by walking briskly for 20 to 30 mins 3-5 times per week, or by cycle.
Follow-up	**Total follow-up (wks):** 52 **Length of titration period (wks):** - **Length of maintenance period (wks):** - **Frequency of monitoring appointments:** 3, 6, 9, 12 months
Arms	**(1) Metformin + Pioglitzone** N: 99 Treatment duration (wks): 52 Washout period (d): - Treatment(s): (a) Metformin (Oral) – flexible-dose (dose-adjusted) Mean dose (mg/d): 1700 (b) Pioglitazone (Oral) – forced titration Set dose (mg/d):45 Details of dosing regimen: Forced titration every three months for 12 months. Given before the meal. During the first three months pioglitazone was given before lunch, during the second three months before lunch and dinner, and for the remainder of the trial was given before breakfast lunch and dinner. **(2) Metformin + Glibenclamide** N: 95 Treatment duration (wks): 52 Washout period (d): - Treatment(s): (a) Metformin (Oral) – flexible-dose (dose-adjusted) Mean dose (mg/d): 1700 (b) Sulfonylurea (Oral) – forced titration Set dose (mg/d):15 Details of dosing regimen: Forced titration every three months for 12 months. Given before the meal. During the first three months glibenclamide was given before lunch, during the second three months before lunch and dinner, and for the remainder of the trial was given before breakfast lunch and dinner.
Outcomes	**General** ITT analysis was conducted in all patients who had received => 1 dose of trial medicationand had subsequnet efficacy observation. Tolerability analysis was conducted in all patients who received =>1 dose of trial medication and had

undergone a subsequent tolerability observation.

Baseline characteristics

		Metformin + Pioglitzone			Metformin + Glibenclamide				
		N	k	mean	N	k	mean	Δ	p
Demographics: Sex (n male)	Dichotomous	102	51	(50.0%)	99	51	(51.5%)		
Blood glucose: HbA1c (%) – 0mo	Continuous	102		7.4 (SD 1.1)	99		7.5 (SD 1.2)		
Fasting plasma glucose (mmol/l) – 0mo	Continuous	102		7.937358 (SD 0.888)	99		7.826346 (SD 0.833)		
Body weight: BMI (kg/m2) – 3mo	Continuous	100		27.6 (SD 2.2)	98		28.5 (SD 3.4)		
BMI (kg/m2) – 3mo	Continuous	100		27.6 (SD 2.2)	99		28.2 (SD 3.1)		
BMI (kg/m2) – 3mo	Continuous	102		27.8 (SD 2.4)	98		28.5 (SD 3.4)		
BMI (kg/m2) – 3mo	Continuous	102		27.8 (SD 2.4)	99		28.2 (SD 3.1)		
Weight (kg) – 3mo	Continuous	102		79.6 (SD 8.9)	99		78.9 (SD 8.3)		
Weight (kg) – 3mo	Continuous	100		79.1 (SD 8.6)	98		79.5 (SD 8.7)		
Weight (kg) – 3mo	Continuous	100		79.1 (SD 8.6)	99		78.9 (SD 8.3)		
Weight (kg) – 3mo	Continuous	102		79.6 (SD 8.9)	98		79.5 (SD 8.7)		
Lipids: Total cholesterol (mmol/l) – 3mo	Continuous	100		4.93926 (SD 0.491)	99		4.93926 (SD 0.491)		
Total cholesterol (mmol/l) – 3mo	Continuous	102		5.01684 (SD 0.569)	98		4.9134 (SD 0.465)		
Total cholesterol (mmol/l) – 3mo	Continuous	102		5.01684 (SD 0.569)	99		4.93926 (SD 0.491)		
Total cholesterol (mmol/l) – 3mo	Continuous	100		4.93926 (SD 0.491)	98		4.9134 (SD 0.465)		
HDL cholesterol (mmol/l) – 3mo	Continuous	100		1.24128 (SD 0.233)	98		1.13784 (SD 0.155)		
HDL cholesterol (mmol/l) – 3mo	Continuous	100		1.24128 (SD 0.233)	99		1.13784 (SD 0.155)		
HDL cholesterol (mmol/l) – 3mo	Continuous	102		1.18956 (SD 0.207)	98		1.13784 (SD 0.155)		
HDL cholesterol (mmol/l) – 3mo	Continuous	102		1.18956 (SD 0.207)	99		1.13784 (SD 0.155)		
LDL cholesterol (mmol/l) – 3mo	Continuous	102		2.99976 (SD 0.207)	99		2.9739 (SD 0.207)		
LDL cholesterol (mmol/l) – 3mo	Continuous	100		2.94804 (SD 0.181)	98		2.94804 (SD 0.181)		
LDL cholesterol (mmol/l) – 3mo	Continuous	100		2.94804 (SD 0.181)	99		2.9739 (SD 0.207)		
LDL cholesterol (mmol/l) – 3mo	Continuous	102		2.99976 (SD 0.207)	98		2.94804 (SD 0.181)		

Results

		Metformin + Pioglitzone			Metformin + Glibenclamide				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 3mo	Continuous	100		7.2 (SD 1)	98		7.1 (SD 0.9)		
HbA1c (%) – 6mo	Continuous	100		7 (SD 0.8)	95		7 (SD 0.8)		
HbA1c (%) – 9mo	Continuous	99		6.8 (SD 0.6)	95		6.9 (SD 0.7)		
HbA1c (%) – 12mo	Continuous	99		6.4 (SD 0.3)	95		6.7 (SD 0.5)		
Fasting plasma glucose (mmol/l) – 3mo	Continuous	100		7.49331 (SD 0.611)	98		7.326792 (SD 0.722)		

Fasting plasma glucose (mmol/l) – 6mo	Continuous	100		6.827238 (SD 0.555)	95		6.93825 (SD 0.666)		
Fasting plasma glucose (mmol/l) – 9mo	Continuous	99		6.38319 (SD 0.389)	95		6.549708 (SD 0.555)		
Fasting plasma glucose (mmol/l) – 12mo	Continuous	99		5.384082 (SD 0.333)	95		5.883636 (SD 0.5)		
Body weight:									
BMI (kg/m2) – 3mo	Continuous	102		27.8 (SD 2.4)	99		28.2 (SD 3.1)		
BMI (kg/m2) – 3mo	Continuous	100		27.6 (SD 2.2)	99		28.2 (SD 3.1)		
BMI (kg/m2) – 3mo	Continuous	102		27.8 (SD 2.4)	98		28.5 (SD 3.4)		
BMI (kg/m2) – 3mo	Continuous	100		27.6 (SD 2.2)	98		28.5 (SD 3.4)		
BMI (kg/m2) – 6mo	Continuous	100		27.9 (SD 2.6)	95		28.6 (SD 3.6)		
BMI (kg/m2) – 9mo	Continuous	99		28 (SD 2.8)	95		28.9 (SD 3.9)		
BMI (kg/m2) – 12mo	Continuous	99		28.1 (SD 2.9)	95		28.7 (SD 3.7)		
Weight (kg) – 3mo	Continuous	102		79.6 (SD 8.9)	99		78.9 (SD 8.3)		
Weight (kg) – 3mo	Continuous	102		79.6 (SD 8.9)	98		79.5 (SD 8.7)		
Weight (kg) – 3mo	Continuous	100		79.1 (SD 8.6)	99		78.9 (SD 8.3)		
Weight (kg) – 3mo	Continuous	100		79.1 (SD 8.6)	98		79.5 (SD 8.7)		
Weight (kg) – 6mo	Continuous	100		79.8 (SD 9.1)	95		79.9 (SD 9.2)		
Weight (kg) – 9mo	Continuous	99		80.1 (SD 9.3)	95		80.6 (SD 9.7)		
Weight (kg) – 12mo	Continuous	99		80.4 (SD 9.5)	95		80.1 (SD 9.3)		
Dropouts:									
Total dropouts – 12mo	Dichotomous	102	3	(2.9%)	99	4	(4.0%)		
Dropout due to AEs – 12mo	Dichotomous	102	2	(2.0%)	99	3	(3.0%)		
Dropout due to hypoglycaemia – 12mo	Dichotomous	102	0	(0.0%)	99	3	(3.0%)		
drop out due to diarrhoea – 12mo	Dichotomous	102	1	(1.0%)	99	0	(0.0%)		
drop out due to nausea – 12mo	Dichotomous	102	1	(1.0%)	99	0	(0.0%)		
Lipids:									
Total cholesterol (mmol/l) – 3mo	Continuous	100		4.93926 (SD 0.491)	99		4.93926 (SD 0.491)		
Total cholesterol (mmol/l) – 3mo	Continuous	102		5.01684 (SD 0.569)	98		4.9134 (SD 0.465)		
Total cholesterol (mmol/l) – 3mo	Continuous	102		5.01684 (SD 0.569)	99		4.93926 (SD 0.491)		
Total cholesterol (mmol/l) – 3mo	Continuous	100		4.93926 (SD 0.491)	98		4.9134 (SD 0.465)		
Total cholesterol (mmol/l) – 6mo	Continuous	100		4.86168 (SD 0.414)	95		4.99098 (SD 0.543)		
Total cholesterol (mmol/l) – 9mo	Continuous	99		4.75824 (SD 0.336)	95		5.01684 (SD 0.569)		
Total cholesterol (mmol/l) – 12mo	Continuous	99		4.68066 (SD 0.259)	95		4.88754 (SD 0.44)		
HDL cholesterol (mmol/l) – 3mo	Continuous	102		1.18956 (SD 0.207)	98		1.13784 (SD 0.155)		
HDL cholesterol (mmol/l) – 3mo	Continuous	102		1.18956 (SD 0.207)	99		1.13784 (SD 0.155)		
HDL cholesterol (mmol/l) – 3mo	Continuous	100		1.24128 (SD 0.233)	99		1.13784 (SD 0.155)		
HDL cholesterol (mmol/l) – 3mo	Continuous	100		1.24128 (SD 0.233)	98		1.13784 (SD 0.155)		
HDL cholesterol (mmol/l) – 6mo	Continuous	100		1.24128 (SD 0.233)	95		1.11198 (SD 0.129)		
HDL cholesterol (mmol/l) – 9mo	Continuous	99		1.26714 (SD 0.259)	95		1.13784 (SD 0.155)		
HDL cholesterol (mmol/l) – 12mo	Continuous	99		1.293 (SD 0.31)	95		1.11198 (SD 0.129)		
LDL cholesterol (mmol/l) – 3mo	Continuous	100		2.94804 (SD 0.181)	98		2.94804 (SD 0.181)		

LDL cholesterol (mmol/l) – 3mo	Continuous	100		2.94804 (SD 0.181)	99		2.9739 (SD 0.207)	
LDL cholesterol (mmol/l) – 3mo	Continuous	102		2.99976 (SD 0.207)	98		2.94804 (SD 0.181)	
LDL cholesterol (mmol/l) – 3mo	Continuous	102		2.99976 (SD 0.207)	99		2.9739 (SD 0.207)	
LDL cholesterol (mmol/l) – 6mo	Continuous	100		2.89632 (SD 0.155)	95		2.9739 (SD 0.207)	
LDL cholesterol (mmol/l) – 9mo	Continuous	99		2.8446 (SD 0.129)	95		2.99976 (SD 0.207)	
LDL cholesterol (mmol/l) – 12mo	Continuous	99		2.7153 (SD 0.103)	95		2.92218 (SD 0.181)	

Table 11: Ferrannini et al. (2009)

General	**Phase:** ☐ monotherapy ☑ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin + oral **Parallel / crossover:** Parallel **Country:** Argentina, Belgium, Canada, Denmark, Egypt, Colombia, Germany, Greece, Guatemala, Hong Kong, Israel, Italy, Lithuania, The Netherlands, Peru, South Africa, Spain, Turkey, UK, USA **Authors' conclusions:** When metformin alone fails to maintain sufficient glycaemic control, the addition of vildagliptin provides comparable efficacy to that of glimepiride after 52 weeks and displays a favourable AE profile, with no weight gain and a significant reduction in hypoglycaemia compared with glimepiride **Source of funding:** Novartis Pharmaceuticals **Comments:** multicentre, randomized, double-blind, active-controlled study.
Number and characteristics of patients	**Total number of patients:** 2789 **Inclusion criteria:** Male and female patients (non-fertile or using a medically approved birth control method) with T2DM and HbA1c of 6.5–8.5%, who had received metformin for >=3 months and were on a stable dose of >=1500 mg daily for a minimum of >=4 weeks prior to visit 1, were aged 18–73 years and had a body mass index (BMI) of 22–45 kg/m2 were eligible to participate **Exclusion criteria:** Patients with a history of type 1 diabetes or secondary forms of diabetes were excluded, as were those who had experienced acute metabolic diabetic complications in the past 6 months, acute infections that might affect blood glucose control in the 4 weeks prior to visit 1, serious cardiac conditions or clinically significant liver or renal disease
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** all on oral hypoglycaemic drugs and/or insulin **Details of washout period:** All taking metformin monotherapy at study start and this continued
Lifestyle advice	-
Follow-up	**Total follow-up (wks):** 104 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 104 **Frequency of monitoring appointments:** Further visits were scheduled at weeks 4, 8, 12, 16, 20, 24, 32, 40, 46, 52 and 104
Arms	**(1) Metformin + vildagliptin** N: 1396 Treatment duration (wks): 52 Washout period (d): 0 Comments: All on metformin monotherapy at study start Treatment(s): (a) Metformin (Oral) Mean dose (mg/d): 1904 Details of dosing regimen: Dose remained unchanged

(b) Vildagliptin (Oral) – fixed-dose

Set dose (mg/d):100
Frequency of dosing: twice a day
Details of dosing regimen: vildagliptin (50 mg twice daily)

(2) Metformin + glimepiride

N: 1393

Treatment duration (wks): 52
Washout period (d): 0
Comments: All on metformin monotherapy at study start

Treatment(s): (a) Metformin (Oral)

Mean dose (mg/d): 1893
Details of dosing regimen: Dose remained unchanged

(b) Sulfonylurea (Oral) – flexible-dose (dose-adjusted)

Minimum dose (mg/d): 2
Maximum dose (mg/d): 6
Details of dosing regimen: glimepiride (starting dose 2 mg/day). Glimepiride/matched control could be up-titrated (to a maximum of 6 mg/day) at weeks 4, 8 or any later visit if FPG exceeded 6.2 mmol/l or down-titrated in cases of recurrent hypoglycaemia. After week 24, rescue medication (pioglitazone) could

be prescribed if patients reached the highest tolerated glimepiride dose/matched control and whose HbA1c was >8.0%

Outcomes

General

The primary analysis was based on the per protocol (PP) population with last available post-randomization assessment before rescue medication initiation, up to and including week 52 using the last observation carried forward).

There were 2789 randomized patients included in this interim analysis.

The safety (SAF) population comprised patients who received at least one dose of study drug and had at least one post-baseline safety assessment, up to and including the week 52 visit. The PP population included patients in any of the following categories: (i) completed at least 48 weeks of treatmentwithout taking rescue medication and without major protocol violation; (ii) began rescue medication owing to lack of efficacy after 24 weeks of treatment (as per protocol) without major protocol violation; and (iii) discontinued the study owing to lack of efficacy (as per protocol) without major protocol violation. The intent-to- treat (ITT) population was made up of patients included in the RAN population who received at least one dose of studydrug andhadat least one post-baseline assessment of

the primary efficacy variable HbA1c

Adverse event outcomes including hypoglycaemia were not extracted in this evidence table as this included patients who were taking rescue therapy.

222/1396 (16%) in the vildagliptin group and 275/1393 (19.7%) in the glimepiride group discontinued the study

5.1% in the vildagliptin arm and 3.7% in the gilmepiride arm were using rescue therapy

Hypoglycaemic events

Minor (confirmed) hypoglycaemia (Hypoglycaemic events (symptoms suggestive of hypoglycaemia and confirmed by self monitoring plasma glucose <3.1 mmol/l) and severe hypoglycaemia (any episode requiring the assistance of another party).)

Major/severe hypoglycaemic event (severe hypoglycaemia was defined as any episode requiring the assistance of another party)

symptomatic (confirmed) (Hypoglycaemic events (defined as symptoms suggestive of hypoglycaemia and confirmed by self-monitored plasma glucose <3.1 mmol/l))

confirmed hypoglycaemia (Hypoglycaemic events (symptoms suggestive of hypoglycaemia and confirmed by self monitoring plasma glucose <3.1 mmol/l) and severe hypoglycaemia (any episode requiring the assistance of another party).)

moderate hypoglycaemia (Hypoglycaemic events (symptoms suggestive of hypoglycaemia and confirmed by self monitoring plasma glucose <3.1 mmol/l) and severe hypoglycaemia (any episode requiring the assistance of another party).)

Baseline characteristics

		Metformin + vildagliptin			Metformin + glimepiride				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Demographics: Age (years)	Continuous	1396		57.5 (SD 9.06)	1393		57.46 (SD 9.28)		
Sex (n male)	Dichotomous	1396	737	(52.8%)	1393	753	(54.1%)		
Duration of diabetes (yrs)	Continuous	1396		5.71 (SD 5.18)	1393		5.75 (SD 5.03)		

Blood glucose: HbA1c (%) – 0wk	Continuous	1396		7.31 (SD 0.64)	1393		7.3 (SD 0.65)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	1396		9.16 (SD 2.29)	1393		9.16 (SD 2.23)		
Body weight: BMI (kg/m2)	Continuous	1396		31.8 (SD 5.27)	1393		31.69 (SD 5.25)		
Weight (kg) – 0wka	Continuous	1396		89.75232 (SD 14.9)	1393		89.441856 (SD 14.8)		
PP Blood glucose: HbA1c (%) – 12wkb	Continuous	1118		7.33 (SD 0.956)	1072		7.367 (SD 1.24)		
2-year follow-up (reported in Matthews et al. 2010) Demographics: Age (years)	Continuous	1562		57.5 (SD 9.07)	1556		57.5 (SD 9.19)		
Sex (n male)	Dichotomous	1562	829	(53.1%)	1556	838	(53.9%)		
Duration of diabetes (yrs)	Continuous	1562		5.7 (SD 5.2)	1556		5.7 (SD 5)		
Ethnicity-White	Dichotomous	1562	1364	(87.3%)	1556	1343	(86.3%)		
Ethnicity-Black	Dichotomous	1562	18	(1.2%)	1556	19	(1.2%)		
Ethnicity-Asian	Dichotomous	1562	44	(2.8%)	1556	46	(3.0%)		
Ethnicity-Hispanic	Dichotomous	1562	129	(8.3%)	1556	133	(8.5%)		
Ethnicity-Other	Dichotomous	1562	7	(0.4%)	1556	15	(1.0%)		
Blood glucose: HbA1c (%) – 0wk	Continuous	1562		7.3 (SD 0.7)	1556		7.3 (SD 0.7)		
Body weight: BMI (kg/m2)	Continuous	1562		31.9 (SD 5.3)	1556		31.7 (SD 5.3)		
Weight (kg) – 0wk	Continuous	1562		89.5 (SD 18.1)	1556		88.9 (SD 17.8)		
2-year follow-up (reported in Matthews et al. 2010) - PP Body weight: Weight (kg) – 104wkc	Mean change	850		-0.3 (SD 2.92)	881		1.2 (SD 2.97)		
Weight (kg) – 104wkd	Continuous	850		89.4 (SD 14.6)	881		88.8 (SD 14.8)		

[a] estimated from BMI assuming mean height of 1.68m
[b] Estimated from graphs, SD calculated from estimated SE
[c] SD calculated from SE
[d] SD estimated from SE

Results

		Metformin + vildagliptin			Metformin + glimepiride				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Blood glucose: HbA1c (%) – 52wk	Mean change	1396			1393				a
HbA1c < 7% or <=7% – 52wk	Dichotomous	1396			1393				0.006b
Fasting plasma glucose (mmol/l) – 52wk	Continuous	1396			1393				NS
Body weight: Weight (kg) – 52wk	Mean change	1396			1393			MD=-1.790 (CI: -2.104, -1.476)	<0.001
Dropouts: Total dropouts – 52wk	Dichotomous	1396	222	(15.9%)	1393	275	(19.7%)		
Dropout due to AEs – 52wk	Dichotomous	1396	67	(4.8%)	1393	107	(7.7%)		
Drop out due to unsatisfactory effect – 52wk	Dichotomous	1396	17	(1.2%)	1393	15	(1.1%)		

	PP									
	Blood glucose:									
	HbA1c (%) – 16wkc	Continuous	1118		6.8 (SD 0.669)	1072		6.6 (SD 0.655)		
	HbA1c (%) – 24wkc	Continuous	1118		6.78 (SD 0.669)	1072		6.63 (SD 0.655)		
	HbA1c (%) – 52wkd	Mean change	1118		-0.44 (SD 0.669)	1072		-0.53 (SD 0.655)		
	HbA1c < 7% or <=7% – 52wk	Dichotomous	1118	605e	(54.1%)	1072	595	(55.5%)		
	HbA1c < 7% or <=7% – 52wk	Dichotomous	1118	569b	(50.9%)	1072	595	(55.5%)		
	HbA1c < 7% or <=7% – 52wk	Dichotomous	1118	569b	(50.9%)	1072	475f	(44.3%)		
	HbA1c < 7% or <=7% – 52wk	Dichotomous	1118	605e	(54.1%)	1072	475f	(44.3%)		
	Fasting plasma glucose (mmol/l) – 52wk	Mean change	1118		-1.01 (SD 2.01)	1072		-1.14 (SD 1.96)		
	Body weight:									
	Weight (kg) – 52wkd	Mean change	1118		-0.23 (SD 3.68)	1072		1.56 (SD 3.93)		
	2-year follow-up (reported in Matthews et al. 2010)									
	Dropouts:									
	Total dropouts – 104wkg	Dichotomous	1562	569	(36.4%)	1556	604	(38.8%)		
	2-year follow-up (reported in Matthews et al. 2010) - ITT									
	Dropouts:									
	Dropout due to AEs – 104wkh	Dichotomous	1562	123	(7.9%)	1556	160	(10.3%)		
	2-year follow-up (reported in Matthews et al. 2010) - PP									
	Blood glucose:									
	HbA1c (%) – 0wk	Mean change	850			881			MD=0.300	i
	HbA1c (%) – 104wkj	Mean change	850		-0.1 (SD 0)	881		-0.1 (SD 0)		
	HbA1c < 7% or <=7% – 0wk	Mean change	850			881				k
	HbA1c < 7% or <=7% – 104wk	Dichotomous	850	314	(36.9%)	881	337	(38.3%)		
	Hba1c <6.5% – 0wk	Mean change	850			881				0.004l
	Hba1c <6.5% – 104wk	Dichotomous	850	201	(23.6%)	881	226	(25.7%)		
	Fasting plasma glucose (mmol/l) – 0wk	Mean change	850			881				0.006l
	Fasting plasma glucose (mmol/l) – 104wkm	Mean change	850		-0.5 (SD 2.92)	881		-0.7 (SD 2.97)		
	Body weight:									
	Weight (kg) – 0wk	Mean change	850			881			MD=1.500 (CI: 1.108, 1.892)	<0.001
	Weight (kg) – 104wkn	Continuous	850		89.4 (SD 14.6)	881		88.8 (SD 14.8)		
	Weight (kg) – 104wkd	Mean change	850		-0.3 (SD 2.92)	881		1.2 (SD 2.97)		

	Lipids:									
	Total cholesterol (mmol/l) – 0wk	Mean change	850			881				<0.001
	HDL cholesterol (mmol/l) – 0wk	Mean change	850			881				<0.001
	Triglycerides (mmol/l) – 0wk	Mean change	850			881				0.039
	2-year follow-up (reported in Matthews et al. 2010) - Baseline Hba1c >=7%									
	Blood glucose:									
	Composite end point (HbA1c <7, no hypo, no weight gain) – 104wk	Dichotomous	1036	309	(29.8%)	980	190	(19.4%)		

[a] only 97.5% CI reported
[b] without hypoglycaemia
[c] estimated from graph
[d] SD calculated from SE
[e] approximated to nearest integer (percentages only presented in text)
[f] without hypoglycaemia; approximated to nearest integer (percentages only presented in text)
[g] Data estimated from percentages
[h] Data estimated from percentages. Inconsistency in information provided in text for overall population compared to safety population. Data extracted here is for overall population
[i] 97.5% CI= 0.0 to 0.2
[j] SE reported as 0. Adjusted mean for baseline HbAic
[k] effect estimate not reported, not significant
[l] effect estimate not reported
[m] SE= 0.1
[n] SD estimated from SE

	Primary and secondary endpoint changes from baseline were assessed using an analysis of covariance model (ANCOVA; classification variables: treatment and pooled centre; covariate: baseline value).

Table 12: Filozof & (2010)

General	**Phase:** ☐ monotherapy ☑ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin + oral **Parallel / crossover:** Parallel **Country:** Not reported (assumed Europe) **Authors' conclusions:** In patients with type 2 diabetes inadequately controlled with metformin, addition of vildagliptin provided similar Hba1c lowering efficacy compared with gliclazide after 52 weeks of treatment. Although both treatments were well tolerated, vildagliptin treated patients had fewer hypoglycaemia events and did not gain weight. **Source of funding:** Novartis **Comments:** Double-blind trial (using double-dummy approach)
Number and characteristics of patients	**Total number of patients:** 1007 **Inclusion criteria:** Male and female patients aged 18-78 years with type 2 diabetes and Hba1c 7.5 to 11%, who had received metformin for at least 3 months and were on a stable dose of >=1500 mg daily for >=4 weeks prior to visit 1 **Exclusion criteria:** type 1 diabetes, secondary forms of diabetes and patients experiencing acute metabolic diabetic complicationswithin the past 6 months, serious cardiac conditions, clinically significant renal or liver disease
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** all on oral hypoglycaemic drugs and/or insulin **Details of washout period:** All patients were taking metformin monotherapy and this continued during the treatment period
Lifestyle advice	-
Follow-up	**Total follow-up (wks):** 52

	Length of titration period (wks): 0 **Length of maintenance period (wks):** 52 **Frequency of monitoring appointments:** Patients were followed up at 4,8,12,16,20,24,32,40 and 52 weeks
Arms	**(1) Metformin + vildagliptin** N: 513 Treatment duration (wks): 52 Washout period (d): 0 Comments: All on metformin monotherapy which was continued Treatment(s): (a) Metformin (Oral) Details of dosing regimen: Stable dose of >=1500 mg/day (b) Vildagliptin (Oral) – fixed-dose Set dose (mg/d):100 Frequency of dosing: twice a day Details of dosing regimen: 50 mg bid **(2) Metformin + gliclazide** N: 494 Treatment duration (wks): 52 Washout period (d): 0 Comments: All on metformin monotherapy which was continued Treatment(s): (a) Metformin (Oral) Details of dosing regimen: Stable dose of >=1500 mg/day (b) Sulfonylurea (Oral) – flexible-dose (dose-adjusted) Minimum dose (mg/d): 80 Maximum dose (mg/d): 320 Details of dosing regimen: Gliclazide had to be uptitrated from a starting dose of 80 mg/day to a max 320 mg/day if FPG>7 mmol/l or fasting blood glucose was >6.36.3 based on the fasting finger stick measurement performed at the study centre. Patients were uptitrated to the next dose level at week 4 (160 mg), week 8 (240 mg) and week 12 (320 mg)
Outcomes	**General** ITT population consisted of randomised patients who had received at least one dose of the study drug and had a baseline and at least one post-baseline assessment. The PP population included patients in the ITT population with more than 24 weeks of treatment, with no major protocol violations and who underwent the final valid assessment of Hba1c within 7 days after the last dose of study drug and either (i) completed more than 48 weeks of treatment or (ii) had <48 weeks of treatment but discontinued due to unsatisfactory response. The safety population included patients who received at least one dose of the study drug and at least one postbaseline safety assessment. LOCF method was used. 106/513 (20.7%) patients in the vildalgiptin arm and 82/494 (16.6%) in the gliclazide group discontinued the study Outcomes not extracted in this evidence table include beta cell function and other insulin resistance parameters **Hypoglycaemic events** symptomatic (confirmed) (Hypoglycaemic events were defined as sypmtoms suggestive of hypoglycaemia and confirmed with a BG <3.1 mmol/l)
Baseline characteristics	

		Metformin + vildagliptin			Metformin + gliclazide				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Demographics: Age (years)	Continuous	513		59.2 (SD 9.9)	494		59.7 (SD 10.2)		
Sex (n male)	Dichotomous	513	268	(52.2%)	494	256	(51.8%)		
Duration of diabetes (yrs)	Continuous	512		6.4 (SD 5.1)	494		6.8 (SD 5.3)		
Blood glucose: HbA1c (%) – 0wk	Continuous	513		8.5 (SD 1)	494		8.5 (SD 1)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	513		10.8 (SD 2.8)	494		10.6 (SD 2.8)		
Body weight: BMI (kg/m2)	Continuous	513		31.2 (SD 5)	494		30.8 (SD 5)		
Weight (kg) – 0wk	Continuous	511		85.7 (SD 16.6)	494		84.2 (SD 17.9)		

	PP Blood glucose: HbA1c (%) – 4wka	Continuous	386		8.425 (SD 0.98)	393		8.45 (SD 0.99)			
	[a] Estimated from graph; SD estimated from assumed reported SE										

Results

		Metformin + vildagliptin			Metformin + gliclazide				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Blood glucose: HbA1c (%) – 52wk	Continuous	513			494			MD=0.210 (CI: -0.160, 0.580)	
HbA1c < 7% or <=7% – 52wk	Dichotomous	513			494				NS
Hba1c <6.5% – 52wk	Dichotomous	513			494				0.041
Fasting plasma glucose (mmol/l) – 52wk	Continuous	513			494				0.257
Body weight: Weight (kg) – 52wk	Continuous	513			494				<0.001
Hypoglycaemic events: symptomatic (confirmed) – 52wk	Dichotomous	513			494				
Dropouts: Total dropouts – 52wk	Dichotomous	513	106	(20.7%)	494	82	(16.6%)		
Dropout due to AEs – 52wk	Dichotomous	513	33	(6.4%)	494	22	(4.5%)		
Drop out due to unsatisfactory effect – 52wk	Dichotomous	513	22	(4.3%)	494	13	(2.6%)		
Men Blood glucose: HbA1c (%) – 52wk	Mean change	197		-0.8 (SD 1.12)	200		-0.94 (SD 1.27)		
Women Blood glucose: HbA1c (%) – 52wk	Mean change	189		-0.82 (SD 1.24)	193		-0.8 (SD 1.25)		
PP Blood glucose: HbA1c (%) – 16wka	Continuous	386		7.45 (SD 0.786)	393		7.3 (SD 0.793)		
HbA1c (%) – 24wka	Continuous	386		7.42 (SD 0.786)	393		7.26 (SD 0.595)		
HbA1c (%) – 32wka	Continuous	386		7.57 (SD 0.786)	393		7.55 (SD 0.793)		
HbA1c (%) – 52wkb	Mean change	386		-0.81 (SD 1.18)	393		-0.85 (SD 1.19)		
HbA1c < 7% or <=7% – 52wkc	Dichotomous	386	114	(29.5%)	393	125	(31.8%)		
Hba1c <6.5% – 52wk	Dichotomous	386	59c	(15.3%)	393	83	(21.1%)		
Fasting plasma glucose (mmol/l) – 52wk	Mean change	386		-1.31 (SD 2.75)	393		-1.52 (SD 2.78)		
Body weight: Weight (kg) – 52wkd	Mean change	386		0.08	393		1.36		

Safety population Hypoglycaemic events: symptomatic (confirmed) – 52wke	Count	167440	6		164892	11			
Adverse events: Any adverse event(s) – 52wkf	Dichotomous	510	315	(61.8%)	493	302	(61.3%)		
Asthenia – 52wk	Dichotomous	510	11	(2.2%)	493	24	(4.9%)		
Bronchitis – 52wk	Dichotomous	510	10	(2.0%)	493	20	(4.1%)		
Death – 52wk	Dichotomous	510	1	(0.2%)	493	1	(0.2%)		
Fatigue – 52wk	Dichotomous	510	10	(2.0%)	493	20	(4.1%)		
GI: diarrhoea – 52wk	Dichotomous	510	26	(5.1%)	493	27	(5.5%)		
Headache – 52wk	Dichotomous	510	16	(3.1%)	493	28	(5.7%)		
Nasopharyngitis – 52wk	Dichotomous	510	32	(6.3%)	493	28	(5.7%)		
Pain (extremity) – 52wk	Dichotomous	510	14	(2.7%)	493	22	(4.5%)		
Tremor – 52wk	Dichotomous	510	9	(1.8%)	493	24	(4.9%)		
BMI >=30kg/m2 Blood glucose: HbA1c (%) – 52wk	Mean change	200		-0.77 (SD 1.13)	200		-0.86 (SD 1.13)		
BMI <30.0 kg/m2 Blood glucose: HbA1c (%) – 52wk	Mean change	186		-0.85 (SD 1.09)	193		-0.88 (SD 1.39)		
Baseline Hba1c <=8% Blood glucose: HbA1c (%) – 52wk	Mean change	157		-0.47 (SD 0.752)	148		-0.54 (SD 0.973)		
Baseline Hba1c >=8 Blood glucose: HbA1c (%) – 52wk	Mean change	229		-1.05 (SD 1.21)	245		-1.07 (SD 1.41)		
Hba1c <=9.0% or <9% Blood glucose: HbA1c (%) – 52wk	Mean change	295		-0.64 (SD 1.03)	293		-0.62 (SD 1.2)		
Hba1c>9.0% Blood glucose: HbA1c (%) – 52wk	Mean change	91		-1.38 (SD 1.34)	100		-1.59 (SD 1.1)		
Age >=65 years Blood glucose: HbA1c (%) – 52wkg	Mean change	143		-0.98 (SD 1.08)	159		-0.91 (SD 1.39)		
Age <65 years Blood glucose: HbA1c (%) – 52wk	Mean change	243		-0.71 (SD 1.09)	234		-0.84 (SD 1.22)		
BMI>=35 Blood glucose: HbA1c (%) – 52wk	Mean change	81		-0.85 (SD 1.17)	67		-0.65 (SD 1.23)		

[a] estimated from graph
[b] SD estimated from SE
[c] approximated to nearest integer (percentages only presented in text)
[d] SD not reported
[e] Patient days calculated from overall randomised population as information on dropout rates for safety population not provided. Assumed dropout occurred halfway through the study
[f] assumed no of events; approximated to nearest integer (percentages only presented in text)
[g] SD calculated from reported SE

ANCOVA was used to assess the primary and secondary efficacy variablesbased on the PP population. Treatment and pooled centre were used as variables and baseline value as a covariate. No p-values were reported for adverse events.

Table 13: Forst et al. (2010)

General	**Phase:** ☐ monotherapy ☑ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin + oral **Parallel / crossover:** Parallel **Country:** 45 centres in Uk (19), Germany (17), France (5), Slovakia (5), Ukraine (5), Sweden (4) **Authors' conclusions:** The addition of linagliptin to ongoing metformin treatment in patients with Type 2 diabetes was well tolerated and resulted in significant and clinically relevant improvements in glycaemic control, with 5 mg linagliptin being the most effective dose **Source of funding:** Authors are employees of Boehringer Ingelheim, the sponsors of the study **Comments:** Linagliptin 10mg was used in one arm of the trial. This has not been extracted or analysed since this dose is not licensed. The placebo arm of the trial has also not been extracted since patients in this group were on metformin alone + placebo. Thus, 2 out of the 5 randomised arms are used. Patients were withdrawn from the study if they had FPG >13.3mmol/l (measured on 2 separate days) at any visit; if they showed clinical signs of severe hypoglycaemia or a blood glucose level <2/5mmol/l; if their dose of metformin changed; if they received concommitant drugs that interfered with study medication.
Number and characteristics of patients	**Total number of patients:** 333 **Inclusion criteria:** Males and females with type two diabetes for at least 3 months, aged 21 to 75 years with a BMI of 25 to 40kg/m2. All patients had inadequate glycaemic control despite having been treated previously with metformin and one other oral hypoglycaemic aget (other than roziglitazone or pioglitazone). Antidiabetic therapy had to be unchanged for 10 weeks prior to screening. For patients on metformin combination therapy inadequate glycaemic control was defined as HbA1c 7 to 9% For patients on metformin monotherapy inadequate glycaemic control was defined as 7.5 to 10% **Exclusion criteria:** Plasma glucose concentrations of >13.3mmol/l measured on two separate days; treated with roziglitazone or pioglitazone within 6 months, or with insulin within 3 months; clinically relevant cardiovascular disease, myocardial infarction, stoke, TIA, within 6 months before enrolment; one or more specified clinical laboratory abnormalities. Pre-randomisation phase: Patients already receiving metformin monotherapy entered a 2 week open label run in phase Patients already taking metformin combination therapy entered a 6 week period where the other OHA was no longer administrated, with an open label run in phase for the last two weeks of this period. On completion of the run in phase, patients with HbA1c 7.5 to 10% were randomised to one of the 5 treatment options
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** all on oral hypoglycaemic drugs and/or insulin **Details of washout period:** Participants on metformin monotherapy continued with baseline therapy Participants on metformion combination therapy entered a 6 week washout period where metformin was maintained but other OHAs were discontinued for the duration of the trial.
Lifestyle advice	Not stated
Follow-up	**Total follow-up (wks):** 14 **Length of titration period (wks):** - **Length of maintenance period (wks):** 12 **Frequency of monitoring appointments:** 2,4,8,12,14 weeks
Arms	**(1) Metformin + linagliptin 1mg** N: 65 Treatment duration (wks): 12 Washout period (d): 6 Comments: Patients on metformin monotherapy entered 2 week open label run in Patients on metformin combination therapy entered 6 week washout, and open label metformin monotherapy for last two weeks of this period. Treatment(s): (a) Metformin Mean dose (mg/d): 1500 Details of dosing regimen: Unclear, patients continued the dose of metformin that they received at enrolment throughout the entire study. (b) Linagliptin (Oral) – fixed-dose Set dose (mg/d):1 Frequency of dosing: once a day Details of dosing regimen: Linagliptin 1mg daily in the morning with 150ml water, within 30 mins of finishing breakfast

(2) Metformin + linagliptin 5mg

N: 66

Treatment duration (wks): 12
Washout period (d): 6
Comments: Patients on metformin monotherapy entered 2 week open label run in

Patients on metformin combination therapy entered 6 week washout, and open label metformin monotherapy for last two weeks of this period.

Treatment(s): (a) Metformin

Mean dose (mg/d): 1500
Details of dosing regimen: Unclear, patients continued the dose of metformin that they received at enrolment throughout the entire study.

(b) Linagliptin (Oral) – fixed-dose

Set dose (mg/d):5
Frequency of dosing: once a day
Details of dosing regimen: Linagliptin 5mg daily in the morning with 150ml water, within 30 mins of finishing breakfast

(3) Metformin + Glimepiride

N: 65

Treatment duration (wks): 12
Washout period (d): 6
Comments: Patients on metformin monotherapy entered 2 week open label run in

Patients on metformin combination therapy entered 6 week washout, and open label metformin monotherapy for last two weeks of this period.

Treatment(s): (a) Metformin

Mean dose (mg/d): 1500
Details of dosing regimen: Unclear, patients continued the dose of metformin that they received at enrolment throughout the entire study.

(b) Sulfonylurea (Oral) – flexible-dose (dose-adjusted)

Minimum dose (mg/d): 1
Details of dosing regimen: Glimepiride waas taken immediately before or during breakfast.
Patients took 1mg for 4 weeks. After this dosing was at the investigators discretion.

Outcomes

General

Primary analysis was done on the ITT set- All randomised patients with at least baseline data and one adequate measurement of HbA1c following at least one day of randomised treatment.

PP set was created for sensitivity analysis

Treated set was used for safety analysis- all patients who were dispensed study medication and had taken at least one dose of investigational treatment.

Baseline characteristics

		Metformin + linagliptin 1mg			Metformin + linagliptin 5mg				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Demographics: Age (years)	Continuous	65		59.2 (SD 8.4)	66		59.6 (SD 9.8)		
Sex (n male)	Dichotomous	65	36	(55.4%)	66	37	(56.1%)		
Duration of diabetes (yrs)	Continuous	65		6.9 (SD 5.9)	66		7.3 (SD 7.5)		
Ethnicity-White	Dichotomous	65	64	(98.5%)	66	66	(100.0%)		
Ethnicity-Black	Dichotomous	65	0	(0.0%)	66	0	(0.0%)		
Ethnicity-Asian	Dichotomous	65	1	(1.5%)	66	0	(0.0%)		
Blood glucose: HbA1c (%) – 0wk	Continuous	65		8.2 (SD 0.7)	66		8.5 (SD 0.8)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	65		10.1 (SD 2.3)	66		10.5 (SD 2.4)		
Body weight: BMI (kg/m2)	Continuous	65		32.3 (SD 4.3)	66		90.7 (SD 14.2)		
Weight (kg) – 0wk	Continuous	65		92.5 (SD 16.9)	66		90.7 (SD 14.2)		

		Metformin + linagliptin 1mg			Metformin + Glimepiride				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	65		59.2 (SD 8.4)	65		59.4 (SD 9.9)		
Sex (n male)	Dichotomous	65	36	(55.4%)	65	41	(63.1%)		
Duration of diabetes (yrs)	Continuous	65		6.9 (SD 5.9)	65		6.7 (SD 5.9)		
Ethnicity-White	Dichotomous	65	64	(98.5%)	65	64	(98.5%)		
Ethnicity-Black	Dichotomous	65	0	(0.0%)	65	0	(0.0%)		
Ethnicity-Asian	Dichotomous	65	1	(1.5%)	65	1	(1.5%)		
Blood glucose: HbA1c (%) – 0wk	Continuous	65		8.2 (SD 0.7)	65		8.2 (SD 0.7)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	65		10.1 (SD 2.3)	65		10 (SD 2.2)		
Body weight: BMI (kg/m2)	Continuous	65		32.3 (SD 4.3)	65		31.5 (SD 4.2)		
Weight (kg) – 0wk	Continuous	65		92.5 (SD 16.9)	65		90.5 (SD 15)		

		Metformin + linagliptin 5mg			Metformin + Glimepiride				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	66		59.6 (SD 9.8)	65		59.4 (SD 9.9)		
Sex (n male)	Dichotomous	66	37	(56.1%)	65	41	(63.1%)		
Duration of diabetes (yrs)	Continuous	66		7.3 (SD 7.5)	65		6.7 (SD 5.9)		
Ethnicity-White	Dichotomous	66	66	(100.0%)	65	64	(98.5%)		
Ethnicity-Black	Dichotomous	66	0	(0.0%)	65	0	(0.0%)		
Ethnicity-Asian	Dichotomous	66	0	(0.0%)	65	1	(1.5%)		
Blood glucose: HbA1c (%) – 0wk	Continuous	66		8.5 (SD 0.8)	65		8.2 (SD 0.7)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	66		10.5 (SD 2.4)	65		10 (SD 2.2)		
Body weight: BMI (kg/m2)	Continuous	66		90.7 (SD 14.2)	65		31.5 (SD 4.2)		
Weight (kg) – 0wk	Continuous	66		90.7 (SD 14.2)	65		90.5 (SD 15)		

Results

		Metformin + linagliptin 1mg			Metformin + linagliptin 5mg				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 12wk	Mean change	64		-0.14 (SD 0.92)	62		-0.75 (SD 1.08) a		
HbA1c (%) – 12wk	Mean change	64		-0.14 (SD 0.92)	62		-0.5 (SD 0.81)		
HbA1c (%) – 12wka	Mean change	64		-0.39 (SD 1.1)	62		-0.75 (SD 1.08)		
HbA1c (%) – 12wk	Mean change	64		-0.39 (SD 1.1) a	62		-0.5 (SD 0.81)		
HbA1c reduction >=1% – 12wk	Dichotomous	64	18	(28.1%)	62	9	(14.5%)		
Fasting plasma glucose (mmol/l) – 12wk	Mean change	62		-0.36 (SD 1.18)	64		-1.22 (SD 1.2)		

Fasting plasma glucose (mmol/l) – 12wk	Continuous	64		-0.17 (SD 1.6) b	62		-1.93 (SD 1.57)	
end point HbA1c <=7% – 12wk	Dichotomous	64	10	(15.6%)	62	9	(14.5%)	
Body weight: Weight (kg) – 12wkc	Mean change	64		0.57	62		-0.15	
Hypoglycaemic events: All hypoglycaemic events (no patients) – 12wk	Dichotomous	65	0	(0.0%)	66	0	(0.0%)	
Adverse events: GI: nausea – 12wk	Dichotomous	65	0	(0.0%)	66	4	(6.1%)	
Any adverse event(s) – 12wk	Dichotomous	65	25	(38.5%)	66	32	(48.5%)	
Any serious adverse event(s) – 12wk	Dichotomous	65	3	(4.6%)	66	1	(1.5%)	
Cough – 12wk	Dichotomous	65	1	(1.5%)	66	2	(3.0%)	
Dyspepsia – 12wk	Dichotomous	65	0	(0.0%)	66	1	(1.5%)	
Fatigue – 12wk	Dichotomous	65	1	(1.5%)	66	1	(1.5%)	
GI: diarrhoea – 12wk	Dichotomous	65	1	(1.5%)	66	2	(3.0%)	
GI: constipation – 12wk	Dichotomous	65	0	(0.0%)	66	1	(1.5%)	
Infection (upper airway or other common) – 12wk	Dichotomous	65	1	(1.5%)	66	0	(0.0%)	
Nasopharyngitis – 12wk	Dichotomous	65	4	(6.2%)	66	5	(7.6%)	
Pain (muscoskeletal) – 12wk	Dichotomous	65	0	(0.0%)	66	2	(3.0%)	
UTI – 12wk	Dichotomous	65	0	(0.0%)	66	0	(0.0%)	
Dropouts: Total dropouts – 12wk	Dichotomous	65	13	(20.0%)	66	10	(15.2%)	
Dropout due to AEs – 12wk	Dichotomous	65	5	(7.7%)	66	3	(4.5%)	
Men Blood glucose: HbA1c (%) – 12wk	Mean change	36		-0.26 (SD 0.95)	33		-0.42 (SD 0.77)	
Women Blood glucose: HbA1c (%) – 12wk	Mean change	28		0.01 (SD 0.87)	29		-0.58 (SD 0.86)	
BMI <30.0 kg/m2 Blood glucose: HbA1c (%) – 12wk	Mean change	23		-0.26 (SD 0.78)	22		-0.64 (SD 0.63)	
Baseline Hba1c <8% Blood glucose: HbA1c (%) – 12wk	Mean change	27		0.15 (SD 1.04)	21		-0.12 (SD 0.8)	
baseline Hba1c >=8 to <9% Blood glucose: HbA1c (%) – 12wk	Mean change	26		-0.48 (SD 0.61)	26		-0.58 (SD 0.73)	
Hba1c>9.0% Blood glucose: HbA1c (%) – 12wk	Mean change	11		-0.05 (SD 1.02)	15		-0.87 (SD 0.8)	
Age >=65 years Blood glucose: HbA1c (%) – 12wk	Mean change	24		-0.18 (SD 0.86)	20		-0.51 (SD 0.95)	
Age <65 years Blood glucose: HbA1c (%) – 12wk	Mean change	40		-0.12 (SD 0.96)	42		-0.49 (SD 0.75)	
BMI>=35 Blood glucose: HbA1c (%) – 12wk	Mean change	19		0.04 (SD 1.14)	17		-0.58 (SD 0.75)	
BMI 30-35 Blood glucose: HbA1c (%) – 12wk	Mean change	22		-0.18 (SD 0.85)	23		-0.3 (SD 0.98)	

[a] mean placebo corrected change in HbA1c
[b] Mean placebo corrected change from baseline
[c] no dispersion reported

		Metformin + linagliptin 1mg			Metformin + Glimepiride			Δ	p
		N	k	mean	N	k	mean		
Hypoglycaemic events: All hypoglycaemic events (no patients) – 12wk	Dichotomous	65	0	(0.0%)	65	3	(4.6%)		
Adverse events: GI: nausea – 12wk	Dichotomous	65	0	(0.0%)	65	0	(0.0%)		
Any adverse event(s) – 12wk	Dichotomous	65	25	(38.5%)	65	29	(44.6%)		
Any serious adverse event(s) – 12wk	Dichotomous	65	3	(4.6%)	65	1	(1.5%)		
Cough – 12wk	Dichotomous	65	1	(1.5%)	65	0	(0.0%)		
Dyspepsia – 12wk	Dichotomous	65	0	(0.0%)	65	2	(3.1%)		
Fatigue – 12wk	Dichotomous	65	1	(1.5%)	65	0	(0.0%)		
GI: diarrhoea – 12wk	Dichotomous	65	1	(1.5%)	65	3	(4.6%)		
GI: constipation – 12wk	Dichotomous	65	0	(0.0%)	65	1	(1.5%)		
Infection (upper airway or other common) – 12wk	Dichotomous	65	1	(1.5%)	65	1	(1.5%)		
Nasopharyngitis – 12wk	Dichotomous	65	4	(6.2%)	65	4	(6.2%)		
Pain (muscoskeletal) – 12wk	Dichotomous	65	0	(0.0%)	65	0	(0.0%)		
UTI – 12wk	Dichotomous	65	0	(0.0%)	65	0	(0.0%)		
Dropouts: Total dropouts – 12wk	Dichotomous	65	13	(20.0%)	65	4	(6.2%)		
Dropout due to AEs – 12wk	Dichotomous	65	5	(7.7%)	65	3	(4.6%)		

		Metformin + linagliptin 5mg			Metformin + Glimepiride			Δ	p
		N	k	mean	N	k	mean		
Hypoglycaemic events: All hypoglycaemic events (no patients) – 12wk	Dichotomous	66	0	(0.0%)	65	3	(4.6%)		
Adverse events: GI: nausea – 12wk	Dichotomous	66	4	(6.1%)	65	0	(0.0%)		
Any adverse event(s) – 12wk	Dichotomous	66	32	(48.5%)	65	29	(44.6%)		
Any serious adverse event(s) – 12wk	Dichotomous	66	1	(1.5%)	65	1	(1.5%)		
Cough – 12wk	Dichotomous	66	2	(3.0%)	65	0	(0.0%)		
Dyspepsia – 12wk	Dichotomous	66	1	(1.5%)	65	2	(3.1%)		
Fatigue – 12wk	Dichotomous	66	1	(1.5%)	65	0	(0.0%)		
GI: diarrhoea – 12wk	Dichotomous	66	2	(3.0%)	65	3	(4.6%)		
GI: constipation – 12wk	Dichotomous	66	1	(1.5%)	65	1	(1.5%)		
Infection (upper airway or other common) – 12wk	Dichotomous	66	0	(0.0%)	65	1	(1.5%)		
Nasopharyngitis – 12wk	Dichotomous	66	5	(7.6%)	65	4	(6.2%)		
Pain (muscoskeletal) – 12wk	Dichotomous	66	2	(3.0%)	65	0	(0.0%)		
UTI – 12wk	Dichotomous	66	0	(0.0%)	65	0	(0.0%)		
Dropouts: Total dropouts – 12wk	Dichotomous	66	10	(15.2%)	65	4	(6.2%)		
Dropout due to AEs – 12wk	Dichotomous	66	3	(4.5%)	65	3	(4.6%)		

No blood glucose measures available for the glimepiride arm.

Table 14: Gallwitz et al. (2012)

General	**Phase:** ☐ monotherapy ☑ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin + oral **Parallel / crossover:** Parallel **Country:** 14 countries (Austria, Czech Republic, Finland, France, Germany, Hungary, Ireland, Israel, Italy, Mexico, Poland, Spain, Switzerland, and the UK) **Authors' conclusions:** These findings provide evidence for the benefi ts of exenatide versus glimepiride for control of glycaemic deterioration in patients with type-2 diabetes inadequately controlled by metformin alone **Source of funding:** Eli Lilly and Amylin Pharmaceuticals **Comments:** open-label, randomised controlled European Exenatide (EUREXA) trial. We used a computer-generated randomisation sequence to randomly assign patients.
Number and characteristics of patients	**Total number of patients:** 1029 **Inclusion criteria:** Eligible participants had type 2 diabetes; were overweight to obese (body-mass index [BMI] =25 kg/m² to <40 kg/m²); aged 18–85 years; had been on stable, maximum tolerated doses of metformin; and had developed suboptimum glycaemic control, defined by a glycated haemoglobin (HbA1c) concentration of 6·5% and more or 9·0% and less **Exclusion criteria:** contraindications for metformin or glimepiride, according to the product-specific label; active or untreated malignancy or remission for less than 5 years; evidence of renal or liver disease or dysfunction; haemoglobinopathy or clinically signifi cant chronic anaemia; active proliferative retinopathy or macular oedema; or severe gastrointestinal disease. Excluded drugs were those aff ecting gastrointestinal motility, chronic systemic gluco corticoids, prescription drugs to promote weight loss in the past 3 months, and treatment for more than 2 weeks in the past 3 months with insulin, thiazolidinediones, a-glucosidase inhibitors, sulphonylureas, or meglitinides
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** all on oral hypoglycaemic drugs and/or insulin **Details of washout period:** Al patients were treated with metformin alone at baseline (this was continued during the study period)
Lifestyle advice	-
Follow-up	**Total follow-up (wks):** 156 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 156 **Frequency of monitoring appointments:** Maximum of 3 year follow-up
Arms	**(1) Metformin + exenatide** N: 515 Treatment duration (wks): 156 Washout period (d): 0 Comments: all continued pre-study metformin Treatment(s): (a) Metformin (Oral) Mean dose (mg/d): 1956 (b) Exenatide (Subcutaneous) Set dose (mg/d):20 Mean dose (mg/d): 17.35 Frequency of dosing: twice a day Details of dosing regimen: Exenatide was injected subcutaneously within 60 min before breakfast and evening meals, starting at 5 µg twice daily for 4 weeks, followed by 10 µg twice daily for the remaining study period. If patients had daily episodes of nausea for more than 1 week, the 10 µg dose was reduced to 5 µg twice daily and could be increased again after nausea subsided. **(2) Metformin + glimepiride** N: 514 Treatment duration (wks): 156 Washout period (d): 0 Comments: all continued pre-study metformin Treatment(s): (a) Metformin (Oral) Mean dose (mg/d): 1989 (b) Sulfonylurea (Oral) Mean dose (mg/d): 2.01 Minimum dose (mg/d): 1 Details of dosing regimen: The recommended starting dose for patients in the glimepiride group was 1 mg per day, given once daily immediately before breakfast. Attending

	physicians established the glimepiride dose as per their usual practice, and investigators were instructed to adjust the dose every 4 weeks, according to tolerability, up to the maximum tolerated dose in accordance with the country specific summary of product characteristics
Outcomes	**General** The primary outcome was time to inadequate glycaemic control, defined as an HbA1c concentration of more than 9% after the first 3 months of treatment, or more than 7% at two consecutive visits 3 months apart after the first 6 months. We defined treatment failure in line with recommendations of diabetes associations and the known timecourse of changes in HbA1c concentration, and allowed quick identifi cation of patients with poor glycaemic control who needed alternative treatment. Because the primary outcome was a time-to-event measure, we regarded a study period of 2–3 years as appropriate. Patients who had treatment failure were discontinued, but could enrol in an extension study to examine further treatment options Analyses were by intention to treat with the caveat that only randomly assigned patients receiving at least one dose of study treatment, and with baseline and at least one post-baseline HbA1c measurement were included. We analysed the as-treated population according to treatment actually received and included only patients with at least 6 months' follow-up for HbA1c. Ssafety analyses were based on all patients who received study drug 174/515 (33.8%) patients in the exenatide group and 128/514 (25%) in glimepiride group discontinued the study Outcomes not extracted in this evidence table include measures of insulin resistance, outcomes from an OGTT test

Baseline characteristics

		Metformin + exenatide			Metformin + glimepiride				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	515		56 (SD 10)	514		56 (SD 9.1)		
Sex (n male)	Dichotomous	515	272	(52.8%)	514	252	(49.0%)		
Duration of diabetes (yrs)	Continuous	515		5.8 (SD 4.8)	514		5.5 (SD 4.3)		
Blood glucose: HbA1c (%) – 0wk	Continuous	515		7.5 (SD 0.7)	514		7.4 (SD 0.7)		
Fasting plasma glucose (mmol/l)	Continuous	515		8.9 (SD 2.3)	514		8.6 (SD 1.9)		
Body weight: BMI (kg/m2)	Continuous	515		32.6 (SD 4.2)	514		32.3 (SD 3.9)		
Weight (kg) – 0wk	Continuous	515		92.8 (SD 16.7)	514		91.1 (SD 14.8)		
Blood pressure: Systolic blood pressure (mmHg) – 0wk	Continuous	515		132.8 (SD 15.7)	514		133.4 (SD 15.1)		
Diastolic blood pressure (mmHg) – 0wk	Continuous	515		80.4 (SD 9.4)	514		79.8 (SD 9.9)		

Results

		Metformin + exenatide			Metformin + glimepiride				
		N	k	mean	N	k	mean	Δ	p
Adverse events: Study drug exposure – 0wk		515			514				NR
Study drug exposure – 156wka	Continuous	515		101.9 (SD 73.8)	514		113.1 (SD 70.9)		
Dropouts: Total dropouts – 156wk	Dichotomous	515	174	(33.8%)	514	128	(24.9%)		

	Dropout due to AEs – 0wk	Dichotomous	515			514				0.001
	Dropout due to AEs – 156wk	Dichotomous	515	49	(9.5%)	514	17	(3.3%)		
	Drop out due to unsatisfactory effect – 156wk	Dichotomous	515	8	(1.6%)	514	11	(2.1%)		
	Blood pressure: Diastolic blood pressure (mmHg) – 0wk	Continuous	515			514				NR
	ITT Blood glucose: HbA1c (%) – 12wkb	Continuous	490		6.8 (SD 0.904)	487		6.75 (SD 0.676)		
	HbA1c (%) – 26wkb	Continuous	490		6.75 (SD 0.678)	487		6.78 (SD 0.901)		
	HbA1c (%) – 52wkc	Continuous	331		6.84 (SD 0.791)	371		6.93 (SD 1.33)		
	HbA1c (%) – 104wkc	Continuous	230		6.93 (SD 0.774)	264		7.12 (SD 0.788)		
	HbA1c (%) – 156wkc	Continuous	182		7.08 (SD 0.757)	197		7.23 (SD 0.752)		
	HbA1c (%) – 156wkc	Continuous	515		7.08 (SD 0.757)	514		7.23 (SD 0.752)		
	HbA1c (%) – 182wkc	Continuous	138		7.14 (SD 1.36)	124		7.37 (SD 1.01)		
	HbA1c < 7% or <=7% – 156wk	Dichotomous	515	218	(44.5%)	514	150	(30.8%)		<0.0001
	HbA1c < 7% or <=7% – 156wk	Dichotomous	490	218	(44.5%)	487	150	(30.8%)		<0.0001
	HbA1c <= 6.5% – 156wk	Dichotomous	490	140	(28.6%)	487	87	(17.9%)		0.0001
	HbA1c <= 6.5% – 156wk	Dichotomous	515	140	(28.6%)	514	87	(17.9%)		0.0001
	Body weight: Weight (kg) – 156wk	Continuous	515			514				<0.0001
	Weight (kg) – 156wk	Mean change	490		-3.32 (SD 5.45)	487		1.15 (SD 4.18)		
	Blood pressure: Systolic blood pressure (mmHg) – 156wkd	Mean change	490		-1.9	487		1.1		
	Systolic blood pressure (mmHg) – 156wk	Continuous	515			514			MD=-5.200 (CI: -7.600, -2.800)	<0.0001

Safety population Hypoglycaemic events: All hypoglycaemic events (no events) – 156wk{(Used in the analysis); Patient days estimated from overall randomised population for which dropout rates are provided; assumed dropouts occurred halfway through the study. Events calculated from reported episo	Count	467376	1946		491400	7162			
All hypoglycaemic events (no events) – 156wk	Dichotomous	515			514			RaR=0.290 (CI: 198.957, 0.000)	<0.0001
All hypoglycaemic events (no patients) – 156wke	Dichotomous	511	186	(36.4%)	508	338	(66.5%)		<0.0001
All hypoglycaemic events (no patients) – 156wke	Dichotomous	515	186	(36.4%)	514	338	(66.5%)		<0.0001
Major/severe hypoglycaemic event – 156wk	Dichotomous	515	1	(0.2%)	514	0	(0.0%)		NS
Major/severe hypoglycaemic event – 156wk	Dichotomous	511	1	(0.2%)	508	0	(0.0%)		NS
symptomatic (confirmed) – 156wkf	Dichotomous	515	102	(20.0%)	514	240	(47.2%)		<0.0001 f
symptomatic (confirmed) – 156wkf	Dichotomous	511	102	(20.0%)	508	240	(47.2%)		<0.0001 f
symptomatic (confirmed) – 156wkg	Dichotomous	515	34	(6.7%)	514	63	(12.4%)		<0.0001 f
symptomatic (confirmed) – 156wkg	Dichotomous	511	34	(6.7%)	508	63	(12.4%)		<0.0001 f
symptomatic (confirmed) – 156wk	Dichotomous	515	34g	(6.7%)	514	240f	(47.2%)		<0.0001 f
symptomatic (confirmed) – 156wk	Dichotomous	515	102f	(20.0%)	514	63g	(12.4%)		<0.0001 f
symptomatic (confirmed) – 156wk	Dichotomous	511	34g	(6.7%)	508	240f	(47.2%)		<0.0001 f
symptomatic (confirmed) – 156wk	Dichotomous	511	102f	(20.0%)	508	63g	(12.4%)		<0.0001 f
Nocturnal hypoglycaemia – 156wk	Dichotomous	511	53	(10.4%)	508	82	(16.1%)		0.007
Nocturnal hypoglycaemia – 156wk	Dichotomous	515	53	(10.4%)	514	82	(16.1%)		0.007
Non-nocturnal (day) – 156wk	Dichotomous	515	178	(34.8%)	514	333	(65.6%)		<0.0001
Non-nocturnal (day) – 156wk	Dichotomous	511	178	(34.8%)	508	333	(65.6%)		<0.0001
Adverse events: GI: nausea – 156wk	Dichotomous	511	147	(28.8%)	508	11	(2.2%)		
Any serious adverse event(s) – 156wk	Dichotomous	511	73	(14.3%)	508	68	(13.4%)		
Arthralgia – 156wk	Dichotomous	511	21	(4.1%)	508	42	(8.3%)		

Back pain – 156wk	Dichotomous	511	52	(10.2%)	508	54	(10.6%)		
Bronchitis – 156wk	Dichotomous	511	34	(6.7%)	508	31	(6.1%)		
Death – 156wk	Dichotomous	511	5	(1.0%)	508	5	(1.0%)		
Dyspepsia – 156wk	Dichotomous	511	26	(5.1%)	508	21	(4.1%)		
GI: diarrhoea – 156wk	Dichotomous	511	62	(12.1%)	508	33	(6.5%)		
GI: vomiting – 156wk	Dichotomous	511	44	(8.6%)	508	12	(2.4%)		
Headache – 156wk	Dichotomous	511	56	(11.0%)	508	48	(9.4%)		
Nasopharyngitis – 156wk	Dichotomous	511	96	(18.8%)	508	93	(18.3%)		
pharyngitis – 156wk	Dichotomous	511	26	(5.1%)	508	21	(4.1%)		
Temperature/influenza – 156wk	Dichotomous	511	55	(10.8%)	508	35	(6.9%)		

[a] mean weeks treatment time
[b] estimated from graph
[c] estimated from graph; SD calculated from 95% CI
[d] No SD reported
[e] at least one episode
[f] BG<3.9 mmol/l
[g] BG<2.8 mmol/l

We used a mixed model repeated measures analysis for continuous variables, with terms for visit, treatment, and interaction, and included the baseline value as a covariate. We included only visits with more than 25% of originally enrolled patients and made no imputations for missing data. Least-squares means with 95% CI were derived from the model for 1, 2, and 3 years (visits eight, 12, and 16). Analyses of covariance (ANCOVA), including terms for treatment, baseline HbA1c stratum, and baseline values were done for changes from baseline to treatment failure or other endpoint. For secondary outcomes not identified at each study visit, we used last observation carried forward to account for missing values. Percentages of patients with adverse events after treatment, and those who had hypoglycaemia, were compared between treatment groups with Pearson's ?² test. P-values for adverse events were not reported.

Table 15: Gallwitz et al. (2012)

General	**Phase:** ☐ monotherapy ☑ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin + oral **Parallel / crossover:** Parallel **Country:** 16 countries (Bulgaria, Denmark, France, Germany, Hong Kong, Hungary, India, Ireland, Italy, Netherlands, Norway, Poland, South Africa, Sweden, the UK, and the USA) **Authors' conclusions:** The results of this long-term randomised active-controlled trial advance the clinical evidence and comparative eff ectiveness bases for treatment options available to patients with type 2 diabetes mellitus. The findings could improve decision making for clinical treatment when metformin alone is insufficient. **Source of funding:** Boehringer Ingelheim **Comments:** randomised, double-blind, parallel-group with double-dummy approach. Assignment used a central interactive voice or web response system with randomisation codes generated by the study sponsor. Study investigators and participants were masked to treatment assignment for the duration of the trial.
Number and characteristics of patients	**Total number of patients:** 1552 **Inclusion criteria:** Eligible study participants were aged 18–80 years, had type 2 diabetes, were receiving metformin at a stable dose of 1500 mg/day or more (or a maximum tolerated dose less than 1500 mg/day) alone or with one other oral antidiabetic drug, and had HbA1c 6·5–10·0% (on metformin alone) or 6·0–9·0% (on metformin and one additional oral antidiabetic drug) and a body-mass index (BMI) of 40 kg/m² or less irrespective of ethnicity

	Exclusion criteria: diagnoses of myocardial infarction, stroke, or transient ischaemic attack in the 6 months before screening, impaired hepatic function at screening, and treatment with rosiglitazone, pioglitazone, a glucagon-like peptide 1 (GLP-1) analogue or agonist, insulin, or an antiobesity drug in the 3 months before screening. Pre-randomisation phase: Participants receiving metformin monotherapy entered a 2-week open-label placebo run-in period. Those receiving metformin and one additional oral antidiabetic drug entered a 6-week washout period followed by the 2-week open-label placebo run-in. By the start of the placebo run-in, the HbA1c inclusion criterion was 6·5–10·0% for all participants
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** all on oral hypoglycaemic drugs and/or insulin **Details of washout period:** All taking metformin (either as monotherapy or in combination with other OADs) at baseline. Patients who were taking metformin in combination were washed off other OADs before the treatment period started.
Lifestyle advice	-
Follow-up	**Total follow-up (wks):** 113 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 104 **Frequency of monitoring appointments:** -
Arms	**(1) Metformin + linagliptin** N: 776 Treatment duration (wks): 104 Washout period (d): 0 Comments: only patients on combination therapy at baseline were washed off OADs (except for metformin) Treatment(s): (a) Metformin (Oral) Details of dosing regimen: Metformin dose was unchanged throughout the study. 92% in Linagliptin group were receiving >=1500 mg of metformin at baseline (b) Linagliptin (Oral) – fixed-dose Set dose (mg/d):5 Frequency of dosing: once a day Details of dosing regimen: 5 mg once daily **(2) Metformin + glimepiride** N: 775 Treatment duration (wks): 104 Washout period (d): 0 Comments: only patients on combination therapy at baseline were washed off OADs (except for metformin) Treatment(s): (a) Metformin (Oral) Details of dosing regimen: Metformin dose was unchanged throughout the study. 94% in glimepiride group were receiving >=1500 mg of metformin at baseline (b) Sulfonylurea (Oral) – flexible-dose (dose-adjusted) Mean dose (mg/d): 2.45 Details of dosing regimen: (initially 1 mg once daily) added to ongoing metformin. After the starting dose of 1 mg once daily, glimepiride was uptitrated stepwise in 1 mg increments up to a maximum of 4 mg once daily, at 4-week intervals during the fi rst 12 weeks of treatment. Glimepiride was uptitrated by investigators if the patients' self-monitored fasting plasma glucose (FPG) values were greater than 6·1 mmol/L. At any time, glimepiride could be downtitrated to prevent recurrent hypoglycaemic events.
Outcomes	**General** Rescue treatment (pioglitazone) could be started during the trial if a participant had a confirmed FPG higher than 13·3 mmol/L at any visit or HbA1c higher than 8·5% from week 28 to week 104. If participants did not meet these prespecified glycaemic control criteria despite rescue treatment, they discontinued participation in the trial. Patients included in the completers cohort were those who met glycaemic targets (i.e. were not given rescue medication) Outcome data was extracted in this evidence table from the completers cohort only. Post-hoc analyses from Gallwitz (2013) are also reported in this table as analyses were reported from the completers cohort. 189/776 (24.4%) patients in the linagliptin group and 171/775 (22.1%) in the glimepiride group discontinued the study **Blood glucose** HbA1c < 7% or <=7% (This was a composite endpoint of the proportion of patients achieving a Hba1c <7% after 2 years of treatment without body weight gain (defined as >1 kg increase from baseline) and without investigator defined hypos (BG <3.9 mmol/l or needing assistance from another person to administer resuscitative action intended to increase plasma glucose levels)

Baseline characteristics

		Metformin + linagliptin			Metformin + glimepiride			Δ	p
		N	k	mean	N	k	mean		
Previous blood glucose lowering drugs: Metformina	Dichotomous	776	706	(91.0%)	775	711	(91.7%)		
Metforminb	Dichotomous	776	58	(7.5%)	775	44	(5.7%)		
Metformin	Dichotomous	776	706a	(91.0%)	775	44b	(5.7%)		
Metformin	Dichotomous	776	58b	(7.5%)	775	711a	(91.7%)		
Study completers/observed cases									
Demographics: Age (years)	Continuous	233		60.4 (SD 8.4)	271		60.7 (SD 9.2)		
Sex (n male)	Dichotomous	233	120	(51.5%)	271	178	(65.7%)		
Blood glucose: HbA1c (%) – 0wk	Continuous	233		7.2 (SD 0.6)	271		7.3 (SD 0.6)		
Fasting plasma glucose (mmol/l)	Continuous	233		7.99 (SD 1.46)	271		8.47 (SD 1.86)		
Body weight: BMI (kg/m2)	Continuous	233		29.8 (SD 4.6)	271		30.8 (SD 4.6)		
Weight (kg) – 0wk	Continuous	233		83.8 (SD 16.9)	271		88 (SD 16.6)		
Previous blood glucose lowering drugs: Combination therapy	Dichotomous	233	44	(18.9%)	271	49c	(18.1%)		
any monotherapy (1 previous OAD)	Dichotomous	233	189	(81.1%)	271	222	(81.9%)		

[a] dose >=1500 mg
[b] dose <1500 mg
[c] approximated to nearest integer (percentages only presented in text)

Results

		Metformin + linagliptin			Metformin + glimepiride			Δ	p
		N	k	mean	N	k	mean		
Dropouts: Total dropouts – 104wk	Dichotomous	776	189	(24.4%)	775	171	(22.1%)		
Dropout due to AEs – 104wk	Dichotomous	776	61	(7.9%)	775	90	(11.6%)		
Study completers/observed cases									
Blood glucose: HbA1c (%) – 16wka	Continuous	233		6.62 (SD 0.305)	271		6.5 (SD 0.165)		
HbA1c (%) – 28wka	Continuous	233		6.62 (SD 0.305)	271		6.48 (SD 0.165)		
HbA1c (%) – 52wkb	Continuous	233		6.53 (SD 0.534)	271		6.53 (SD 0.494)		
HbA1c (%) – 104wkc	Mean change	233		-0.56 (SD 0.458)	271		-0.63 (SD 0.494)	MD=0.080 (CI: 0.002, 0.158)	0.0468
HbA1c < 7% or <=7% – 104wkd	Dichotomous	233	126	(54.1%)	271	62	(22.9%)	OR=3.860 (CI: 9.620, 1.549)	<0.0001
Body weight: Weight (kg) – 12wka	Mean change	233		-1 (SD 1.53)	271		0.4 (SD 1.65)		
Weight (kg) – 28wka	Mean change	233		-1.2 (SD 3.05)	271		1.05 (SD 3.29)		

	Weight (kg) – 52wkb	Mean change	233		-1.65 (SD 3.82)	271		0.95 (SD 3.29)		
	Weight (kg) – 104wkb	Mean change	233		-2.06 (SD 3.21)	271		0.98 (SD 3.79)	MD=-3.040 (CI: -3.830, -2.250)	<0.0001
	Hypoglycaemic events:									
	All hypoglycaemic events (no patients) – 104wk	Dichotomous	233	14	(6.0%)	271	114e	(42.1%)		NR
	Major/severe hypoglycaemic event – 104wk	Dichotomous	233	0	(0.0%)	271	1	(0.4%)		NR

[a] estimated from graph
[b] estimated from graph, SD estimated from SE
[c] adjusted for baseline hba1c, treatment and number of previous oral antidiabetic drugs. SD estimated from SE
[d] without hypo or weight gain
[e] approximated to nearest integer (percentages only presented in text)

	Hba1c and body weight were evaluated in the completers cohort with available data (OC) using ANCOVA models that adjusted for treatment, baseline Hba1c and previous OADs

Table 16: Gerich et al. (2005)

General	**Phase:** ☐ monotherapy ☑ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin + oral **Parallel / crossover:** Parallel **Country:** - **Authors' conclusions:** - **Source of funding:** - **Comments:** -
Number and characteristics of patients	**Total number of patients:** 428 **Inclusion criteria:** Drug naïve adults (18-77 years) with T2DM **Exclusion criteria:** - Pre-randomisation phase: 2 week screening period
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** All treatment naive/ no OADs at screening **Details of washout period:** -
Lifestyle advice	Not reported
Follow-up	**Total follow-up (wks):** 104 **Length of titration period (wks):** 16 **Length of maintenance period (wks):** 88 **Frequency of monitoring appointments:** After 2 week screening period, patients randomised for 4 weeks of fixed dose followed by a 12 week titration period and 88 week monitoring period. Baseline, weeks 20, 28, 40, 52, 64, 76, 88, 96 and 104
Arms	**(1) Metformin + nateglinide** N: 219 Treatment duration (wks): 104 Washout period (d): 0 Treatment(s): (a) Metformin (Oral) (b) nateglinide (Oral) **(2) Metformin + glyburide** N: 209 Treatment duration (wks): 104

Washout period (d): 0
Treatment(s): (a) Metformin (Oral)
(b) Sulfonylurea (Oral)

Outcomes

Baseline characteristics

		Metformin + nateglinide		
		N	k	mean
ITT				
Demographics:				
Age (years)	Continuous	208		52.6 (SD 11.6)
Sex (n male)	Dichotomous	208	106	(51.0%)
Duration of diabetes (yrs)	Continuous	208		1.5 (SD 2.9)
Blood glucose:				
HbA1c (%) – 52wk	Continuous	208		8.4 (SD 1.2)
HbA1c (%) – 52wk	Continuous	208		8.4 (SD 1.2)
Fasting plasma glucose (mmol/l) – 52wk	Continuous	208		10 (SD 2.5)
Fasting plasma glucose (mmol/l) – 52wk	Continuous	208		10 (SD 2.5)
Body weight:				
BMI (kg/m2)	Continuous	208		33.3 (SD 6)
Weight (kg) – 0wk	Continuous	208		93.98592 (SD 16.9344) a
aged >=65 (reported in Schwarz et al. 2008)				
Demographics:				
Age (years)	Continuous	33		70.1 (SD 2.9)
Sex (n male)	Dichotomous	33	17	(51.5%)
Sex (n male)	Dichotomous	33	17	(51.5%)
Duration of diabetes (yrs)	Continuous	33		1.7 (SD 3.7)
Ethnicity-White	Dichotomous	33	26	(78.8%)
Ethnicity-Black	Dichotomous	33	3	(9.1%)
Ethnicity-Other	Dichotomous	33	4	(12.1%)
Blood glucose:				
HbA1c (%) – 0wk	Continuous	33		7.8 (SD 0.9)
HbA1c (%) – 0wk	Continuous	33		7.8 (SD 0.9)
Fasting plasma glucose (mmol/l) – 0wk	Continuous	33		8.714442 (SD 1.776192)
Fasting plasma glucose (mmol/l) – 0wk	Continuous	33		8.714442 (SD 1.776192)
Body weight:				
BMI (kg/m2)	Continuous	33		30.4 (SD 4.9)
Weight (kg) – 0wk	Continuous	33		85.80096 (SD 13.82976) a

[a] estimated from BMI assuming mean height of 1.68m

		Metformin + glyburide		
		N	k	mean
ITT				
Demographics:				
Age (years)	Continuous	198		53.5 (SD 11.6)
Sex (n male)	Dichotomous	198	95	(48.0%)
Duration of diabetes (yrs)	Continuous	198		2 (SD 4.3)
Blood glucose:				
HbA1c (%) – 52wk	Continuous	198		8.3 (SD 1.1)
HbA1c (%) – 52wk	Continuous	198		8.3 (SD 1.1)
Fasting plasma glucose (mmol/l) – 52wk	Continuous	198		9.9 (SD 2.3)
Fasting plasma glucose (mmol/l) – 52wk	Continuous	198		9.9 (SD 2.3)
Body weight:				
BMI (kg/m2)	Continuous	198		33.5 (SD 5.6)

Weight (kg) – 0wk	Continuous	198		94.5504 (SD 15.80544) a
aged >=65 (reported in Schwarz et al. 2008)				
Demographics:				
Age (years)	Continuous	33		70.4 (SD 3.8)
Sex (n male)	Dichotomous	33	15	(45.5%)
Sex (n male)	Dichotomous	33	18	(54.5%)
Duration of diabetes (yrs)	Continuous	33		2.5 (SD 5.4)
Ethnicity-White	Dichotomous	33	28	(84.8%)
Ethnicity-Black	Dichotomous	33	4	(12.1%)
Ethnicity-Other	Dichotomous	33	4	(12.1%)
Blood glucose:				
HbA1c (%) – 0wk	Continuous	33		7.7 (SD 0.8) b
HbA1c (%) – 0wk	Continuous	33		7.7 (SD 0.8) b
Fasting plasma glucose (mmol/l) – 0wk	Continuous	33		8.825454 (SD 1.998216)
Fasting plasma glucose (mmol/l) – 0wk	Continuous	33		8.825454 (SD 1.998216)
Body weight:				
BMI (kg/m2)	Continuous	33		33.5 (SD 6.1)
Weight (kg) – 0wk	Continuous	33		94.5504 (SD 17.21664) a

[a] estimated from BMI assuming mean height of 1.68m
[b] reported as SD 8 in paper but assumed typo

Results

		Metformin + nateglinide		
		N	**k**	**mean**
Dropouts:				
Total dropouts – 104wk	Dichotomous	219	78	(35.6%)
Dropout due to AEs – 104wk	Dichotomous	219	27	(12.3%)
ITT				
Blood glucose:				
HbA1c (%) – 16wk	Continuous	208		6.65 (SD 1.44) a
HbA1c (%) – 16wk	Continuous	208		6.65 (SD 1.44) a
HbA1c (%) – 28wk	Continuous	208		6.5 (SD 1.44) a
HbA1c (%) – 28wk	Continuous	208		6.5 (SD 1.44) a
HbA1c (%) – 52wk	Continuous	208		6.65 (SD 1.44) a
HbA1c (%) – 52wk	Continuous	208		6.65 (SD 1.44) a
HbA1c (%) – 104wk	Mean change	208		-1.2 (SD 1.44) b
HbA1c (%) – 104wk	Mean change	208		-1.2 (SD 1.44) b
Fasting plasma glucose (mmol/l) – 52wk	Mean change	208		-2.2 (SD 2.88) b
Fasting plasma glucose (mmol/l) – 52wk	Mean change	208		-2.2 (SD 2.88) b
Fasting plasma glucose (mmol/l) – 104wk	Mean change	208		-1.6 (SD 2.88) b
Fasting plasma glucose (mmol/l) – 104wk	Mean change	208		-1.6 (SD 2.88) b
Body weight:				
Weight (kg) – 104wk	Mean change	208		-0.4 (SD 5.7688) b
Hypoglycaemic events:				
symptomatic (confirmed) – 104wk	Dichotomous	208	17c	(8.2%)
aged >=65 (reported in Schwarz et al. 2008)				
Blood glucose:				
HbA1c (%) – 16wk	Continuous	35		6.25 (SD 0.295803989154981)
HbA1c (%) – 16wk	Continuous	35		6.25 (SD 0.295803989154981)
HbA1c (%) – 28wk	Continuous	35		6.2 (SD 0.51)
HbA1c (%) – 28wk	Continuous	35		6.2 (SD 0.51)

HbA1c (%) – 52wk	Mean change	33		-1.4 (SD 1.1489) d
HbA1c (%) – 52wk	Continuous	33		6.3 (SD 0.57) d
HbA1c (%) – 52wk	Mean change	33		-1.4 (SD 1.1489) d
HbA1c (%) – 52wk	Continuous	33		6.3 (SD 0.57) d
HbA1c (%) – 104wk	Mean change	33		-1.2 (SD 0.57) e
HbA1c (%) – 104wk	Mean change	33		-1.2 (SD 0.57) e
HbA1c (%) – 104wk	Continuous	33		6.3 (SD 0.57) d
HbA1c (%) – 104wk	Continuous	33		6.3 (SD 0.57) d
HbA1c < 7% or <=7% – 104wk	Dichotomous	20	14	(70.0%)
HbA1c <= 6.5% – 104wk	Dichotomous	20	12	(60.0%)
Fasting plasma glucose (mmol/l) – 16wk	Continuous	35		6.216672 (SD 6.56755848881455E-02)
Fasting plasma glucose (mmol/l) – 16wk	Continuous	35		6.216672 (SD 6.56755848881455E-02)
Fasting plasma glucose (mmol/l) – 52wk	Continuous	33		6.771732 (SD 1.5942884712937)
Fasting plasma glucose (mmol/l) – 52wk	Continuous	33		6.771732 (SD 1.5942884712937)
Fasting plasma glucose (mmol/l) – 104wk	Mean change	33		-1.443156 (SD 1.91314616555244)
Fasting plasma glucose (mmol/l) – 104wk	Mean change	33		-1.443156 (SD 1.91314616555244)
Hypoglycaemic events:				
All hypoglycaemic events (no patients) – 104wk	Dichotomous	35	1f	(2.9%)
Adverse events:				
GI: nausea – 104wk	Dichotomous	35	5	(14.3%)
Bronchitis – 104wk	Dichotomous	35	3	(8.6%)
Dyspepsia – 104wk	Dichotomous	35	1	(2.9%)
Edema peripheral – 104wk	Dichotomous	35	5	(14.3%)
Fatigue – 104wk	Dichotomous	35	8	(22.9%)
GI: diarrhoea – 104wk	Dichotomous	35	8	(22.9%)
GI: constipation – 104wk	Dichotomous	35	4	(11.4%)
Infection (upper airway or other common) – 104wk	Dichotomous	35	1	(2.9%)
Nasopharyngitis – 104wk	Dichotomous	35	3	(8.6%)
Dropouts:				
Total dropouts – 104wk	Dichotomous	35	14	(40.0%)
Dropout due to AEs – 104wk	Dichotomous	35	10	(28.6%)

[a] SD estimated from reported SE in graph
[b] SD estimated from reported SE
[c] Estimated from reported percentages
[d] SD estimated from assumed SE
[e] assumed SE reported in text and converted
[f] mild

		Metformin + glyburide		
		N	**k**	**mean**
Dropouts:				
Total dropouts – 104wk	Dichotomous	209	87	(41.6%)
Dropout due to AEs – 104wk	Dichotomous	209	28	(13.4%)
ITT				
Blood glucose:				
HbA1c (%) – 16wk	Continuous	198		6.4 (SD 1.407) a
HbA1c (%) – 16wk	Continuous	198		6.4 (SD 1.407) a
HbA1c (%) – 28wk	Continuous	198		6.3 (SD 1.407) a

HbA1c (%) – 28wk	Continuous	198		6.3 (SD 1.407) a
HbA1c (%) – 52wk	Continuous	198		6.5 (SD 1.407) a
HbA1c (%) – 52wk	Continuous	198		6.5 (SD 1.407) a
HbA1c (%) – 104wk	Mean change	198		-1.5 (SD 1.41) b
HbA1c (%) – 104wk	Mean change	198		-1.5 (SD 1.41) b
Fasting plasma glucose (mmol/l) – 52wk	Mean change	198		-2.8 (SD 2.81) b
Fasting plasma glucose (mmol/l) – 52wk	Mean change	198		-2.8 (SD 2.81) b
Fasting plasma glucose (mmol/l) – 104wk	Mean change	198		-2.4 (SD 2.81) b
Fasting plasma glucose (mmol/l) – 104wk	Mean change	198		-2.4 (SD 2.81) b
Body weight: Weight (kg) – 104wk	Mean change	198		0.8 (SD 7.0356) b
Hypoglycaemic events: symptomatic (confirmed) – 104wk	Dichotomous	198	35c	(17.7%)
aged >=65 (reported in Schwarz et al. 2008) Blood glucose: HbA1c (%) – 16wk	Continuous	40		6.35 (SD 0.316227766016838)
HbA1c (%) – 16wk	Continuous	40		6.35 (SD 0.316227766016838)
HbA1c (%) – 28wk	Continuous	40		6.15 (SD 0.3)
HbA1c (%) – 28wk	Continuous	40		6.15 (SD 0.3)
HbA1c (%) – 52wk	Continuous	33		6.3 (SD 0.57) d
HbA1c (%) – 52wk	Continuous	33		6.3 (SD 0.57) d
HbA1c (%) – 52wk	Mean change	33		-1.4 (SD 0.5744) d
HbA1c (%) – 52wk	Mean change	33		-1.4 (SD 0.5744) d
HbA1c (%) – 104wk	Continuous	33		6.525 (SD 0.8616) e
HbA1c (%) – 104wk	Continuous	33		6.525 (SD 0.8616) e
HbA1c (%) – 104wk	Mean change	33		-1.2 (SD 1.15) f
HbA1c (%) – 104wk	Mean change	33		-1.2 (SD 1.15) f
HbA1c < 7% or <=7% – 104wk	Dichotomous	20	13	(65.0%)
HbA1c <= 6.5% – 104wk	Dichotomous	20	8	(40.0%)
Fasting plasma glucose (mmol/l) – 16wk	Continuous	40		6.494202 (SD 3.51050767610612E-02)
Fasting plasma glucose (mmol/l) – 16wk	Continuous	40		6.494202 (SD 3.51050767610612E-02)
Fasting plasma glucose (mmol/l) – 52wk	Continuous	33		6.605214 (SD 0.956573082776219)
Fasting plasma glucose (mmol/l) – 52wk	Continuous	33		6.605214 (SD 0.956573082776219)
Fasting plasma glucose (mmol/l) – 104wk	Mean change	33		-1.998216 (SD 1.91314616555244)
Fasting plasma glucose (mmol/l) – 104wk	Mean change	33		-1.998216 (SD 1.91314616555244)
Hypoglycaemic events: All hypoglycaemic events (no patients) – 104wk	Dichotomous	40	8g	(20.0%)
Adverse events: GI: nausea – 104wk	Dichotomous	40	5	(12.5%)
Bronchitis – 104wk	Dichotomous	40	4	(10.0%)
Dyspepsia – 104wk	Dichotomous	40	5	(12.5%)
Edema peripheral – 104wk	Dichotomous	40	5	(12.5%)

	Fatigue – 104wk	Dichotomous	40	3	(7.5%)
	GI: diarrhoea – 104wk	Dichotomous	40	8	(20.0%)
	GI: constipation – 104wk	Dichotomous	40	5	(12.5%)
	Infection (upper airway or other common) – 104wk	Dichotomous	40	5	(12.5%)
	Nasopharyngitis – 104wk	Dichotomous	40	7	(17.5%)
	Dropouts:				
	Total dropouts – 104wk	Dichotomous	40	19	(47.5%)
	Dropout due to AEs – 104wk	Dichotomous	40	11	(27.5%)

[a] SD estimated from reported SE in graph
[b] SD estimated from reported SE
[c] Estimated from reported percentages
[d] SD estimated from assumed SE
[e] SD estimated from SE in graph
[f] assumed SE reported in text and converted
[g] four mild, 3 moderate, 1 severe (requiring assistance from another party)

Table 17: Goke et al. (2010)

General	**Phase:** ☐ monotherapy ☑ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin + oral **Parallel / crossover:** Parallel **Country:** International (unclear which countries) **Authors' conclusions:** lower risk of hypoglycaemia and reduced body weight were observed with saxagliptin vs. glipizide. No other clinically significant differences were observed between groups in safety profile. No significant between-group differences were observed for reductions in glycaemic parameters. After week 24, a smaller weekly rise in HbA1c was observed with saxagliptin vs. glipizide as add-on therapy to metformin. **Source of funding:** Funded, designed and supervised by Bristol-Myers Squibb and AstraZenec **Comments:** 52 week (with 52 week extension), international, multicentre, double-blind trial. Randomised using an interactive we-response system using a balanced block randomisation schedule. Blinding was ensuring using a double dummy approach
Number and characteristics of patients	**Total number of patients:** - **Inclusion criteria:** aged >=18 years with HbA1c > 6.5–10% and had been taking a stable dose of metformin monotherapy >=1500 mg/day for at least 8 weeks before enrolment. **Exclusion criteria:** type 1 diabetes, history of ketoacidosis, insulin therapy within one year of enrolment, treatment with thiazolidinedione within the 12 weeks prior to enrolment, previous DPP-4 treatment, congestive heart failure, significant CV history within the past 6 monthsactive liver disease and/or significant abnormal liver function or any clinically significant laboratory abnormality at screening The following prespecified, progressively more stringent glycaemic control criteria were applied: FPG> 270 mg/dl (15.0 mmol/l) at week 3; FPG > 240 mg/dl (13.3 mmol/l) at week 12; > 220 mg/dl (12.2 mmol/l) at week 18; or > 200 mg/dl (11.1 mmol/l) at week 24; HbA1c > 8% at weeks 30 or 39; > 7.5% at weeks 52, 65, or 78; or > 7% at week 91. Pre-randomisation phase: There was a 2 week, single blind, placebo controlled run in period
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** all on oral hypoglycaemic drugs and/or insulin **Details of washout period:** All patients were taking metformin monotherapy at study entry
Lifestyle advice	the lead in period included advice on diet and exercise
Follow-up	**Total follow-up (wks):** 52 **Length of titration period (wks):** - **Length of maintenance period (wks):** - **Frequency of monitoring appointments:** -
Arms	**(1) Metformin + saxagliptin**

N: 428
Treatment duration (wks): 52
Washout period (d): -
Comments: All patients were on a stable dose of metformin to begin with and had a 2 week single blind placebo controlled lead in period that included advice on diet and exercise
Treatment(s): (a) Metformin (Oral) – fixed-dose
Minimum dose (mg/d): 1500
Details of dosing regimen: All patients received open label metformin at 1500, 2000, 2500 or 3000 mg daily based on individual metformin dose at enrolment for the duration of the study, the dose remained stable throughout the study
(b) Saxagliptin (Oral) – fixed-dose
Set dose (mg/d):5

(2) Metformin + glipizide

N: 430
Treatment duration (wks): 52
Washout period (d): -
Comments: All patients were on a stable dose of metformin to begin with and had a 2 week single blind placebo controlled lead in period that included advice on diet and exercise
Treatment(s): (a) Metformin (Oral)
Minimum dose (mg/d): 1500
Details of dosing regimen: All patients received open label metformin at 1500, 2000, 2500 or 3000 mg daily based on individual metformin dose at enrolment for the duration of the study, the dose remained stable throughout the study
(b) Sulfonylurea (Oral) – forced titration
Minimum dose (mg/d): 5
Maximum dose (mg/d): 20
Details of dosing regimen: glipizide titrated from 5 to 20 mg/day. Glipizide titration was carried out in 3-week intervals from 5 mg/day to 10 mg/day, from 10 mg/day to 15 mg/day and from 15 mg/day to 20 mg/day. Titration was to optimal effect (FPG <= 110 mg/dl) ormaximum tolerable dose, as decided by the investigator. Furthermore, glipizide could be downtitrated once at a subsequent visit if hypoglycaemic events occurred.

Outcomes

General

Safety and tolerability were analysed using descriptive statistics in all patients who took >=1 dose of study drug. Efficacy variables were analysed in the full analysis set, defined as all randomised patients who received >=1 dose of randomised study drug and had >=1 non-missing baseline and >=1 postbaseline efficacy data assessment. The primary efficacy analysis was conducted on a PP analysis set which included patients who completed the 52 week traetment period, and had both a baseline and week 52 Hba1c measurement and no significant protocol deviations.

Hypoglycaemic events

symptomatic (confirmed) (Confirmed hypoglycaemia was defined as a finger-stick glucose value <=50 mg/dl with associated symptoms)

Baseline characteristics

		Metformin + saxagliptin			Metformin + glipizide			Δ	p
		N	k	mean	N	k	mean		
Demographics: Age (years) – 0wk	Continuous	428		57.5 (SD 10.3)	430		57.6 (SD 10.4)		
Sex (n male)	Dichotomous	428	212	(49.5%)	430	232	(54.0%)		
Duration of diabetes (yrs)	Continuous	428		5.5 (SD 4.5)	430		5.4 (SD 4.7)		
Blood glucose: HbA1c (%) – 0wk	Continuous	428		7.7 (SD 0.9)	430		7.7 (SD 0.9)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	428		9.047478 (SD 2.29)	430		8.936466 (SD 2.18)		
Body weight: BMI (kg/m2)	Continuous	428		31.5 (SD 5.7)	430		31.3 (SD 6.17)		
Weight (kg) – 0wk	Continuous	428		88.7 (SD 18.6)	430		88.6 (SD 19.6)		

Results

	Metformin + saxagliptin	Metformin + glipizide	Δ	p

		N	k	mean	N	k	mean		
Blood glucose: HbA1c (%) – 52wk	Mean change	293		-0.74 (SD 0.565)	293		-0.8 (SD 0.856)	MD=0.060 (CI: -0.044, 0.164)	
HbA1c (%) – 52wk	Mean change	428		-0.74 (SD 0.565)	430		-0.8 (SD 0.856)	MD=0.060 (CI: -0.044, 0.164)	
HbA1c (%) – 104wk	Mean change	423		-0.41 (SD 0.826) a	423		-0.35 (SD 0.826)		
HbA1c (%) – 104wk	Continuous	426			426			MD=-0.050 (CI: -0.168, 0.068)	b
HbA1c < 7% or <=7% – 0wk	Dichotomous	428			430			MD=-5.200	c
HbA1c <= 6.5% – 0wk	Dichotomous	428			430			MD=1.700 (CI: -4.800, 8.200)	
HbA1c <= 6.5% – 52wk	Dichotomous	428	152	(35.5%)	430	145	(33.7%)		
Fasting plasma glucose (mmol/l) – 52wk	Mean change	428		-0.499554 (SD 1.84)	430		-0.888096 (SD 1.84)	MD=0.333 (CI: 0.094, 0.572)	
Fasting plasma glucose (mmol/l) – 104wk	Continuous	426			426			MD=-0.150 (CI: -0.454, 0.155)	d
Fasting plasma glucose (mmol/l) – 104wke	Mean change	420		-0.693825 (SD 2.18)	420		-0.5439588 (SD 2.29)		
Body weight: Weight (kg) – 52wkf	Mean change	428		-1.1	430		1.1	MD=-2.200 (CI: -2.700, -1.700)	<0.001
Weight (kg) – 104wk	Mean change	424		-1.5 (SD 4.12) e	426		1.3 (SD 4.13)		
Weight (kg) – 104wk	Continuous	426			426			MD=-2.800 (CI: -3.388, -2.212)	g
Hypoglycaemic events: All hypoglycaemic events (no events) – 52wkh	Count	134680	19		136682	750			
All hypoglycaemic events (no events) – 104wki	Count	215852	24		210028	896			
symptomatic (confirmed) – 52wk	Dichotomous	428	2j	(0.5%)	430	66k	(15.3%)		
symptomatic (confirmed) – 52wk	Dichotomous	428	0k	(0.0%)	430	283l	(65.8%)		
symptomatic (confirmed) – 52wk	Dichotomous	428	0m	(0.0%)	430	146j	(34.0%)		

symptomatic (confirmed) – 52wk	Dichotomous	428	0m	(0.0%)	430	151n	(35.1%)		
symptomatic (confirmed) – 52wk	Dichotomous	428	0m	(0.0%)	430	283l	(65.8%)		
symptomatic (confirmed) – 52wk	Dichotomous	428	0m	(0.0%)	430	66k	(15.3%)		
symptomatic (confirmed) – 52wk	Dichotomous	428	0k	(0.0%)	430	146j	(34.0%)		
symptomatic (confirmed) – 52wk	Dichotomous	428	0k	(0.0%)	430	151n	(35.1%)		
symptomatic (confirmed) – 52wk	Dichotomous	428	5l	(1.2%)	430	146j	(34.0%)		
symptomatic (confirmed) – 52wkl	Dichotomous	428	5	(1.2%)	430	283	(65.8%)		
symptomatic (confirmed) – 52wkj	Dichotomous	428	2	(0.5%)	430	146	(34.0%)		
symptomatic (confirmed) – 52wkn	Dichotomous	428	3	(0.7%)	430	151	(35.1%)		
symptomatic (confirmed) – 52wkk	Dichotomous	428	0	(0.0%)	430	66	(15.3%)		
symptomatic (confirmed) – 52wkm	Dichotomous	428	0	(0.0%)	430	38	(8.8%)		
symptomatic (confirmed) – 52wk	Dichotomous	428	5l	(1.2%)	430	66k	(15.3%)		
symptomatic (confirmed) – 52wk	Dichotomous	428	2j	(0.5%)	430	283l	(65.8%)		
symptomatic (confirmed) – 52wk	Dichotomous	428	5l	(1.2%)	430	151n	(35.1%)		
symptomatic (confirmed) – 52wk	Dichotomous	428	0k	(0.0%)	430	38m	(8.8%)		
symptomatic (confirmed) – 52wk	Dichotomous	428	3n	(0.7%)	430	66k	(15.3%)		
symptomatic (confirmed) – 52wk	Dichotomous	428	3n	(0.7%)	430	38m	(8.8%)		
symptomatic (confirmed) – 52wk	Dichotomous	428	3n	(0.7%)	430	283l	(65.8%)		
symptomatic (confirmed) – 52wk	Dichotomous	428	3n	(0.7%)	430	146j	(34.0%)		
symptomatic (confirmed) – 52wk	Dichotomous	428	2j	(0.5%)	430	38m	(8.8%)		
symptomatic (confirmed) – 52wk	Dichotomous	428	2j	(0.5%)	430	151n	(35.1%)		
symptomatic (confirmed) – 52wk	Dichotomous	428	5l	(1.2%)	430	38m	(8.8%)		

symptomatic (confirmed) – 104wko	Dichotomous	428	15	(3.5%)	430	165	(38.4%)		
symptomatic (confirmed) – 104wk	Dichotomous	428	24p	(5.6%)	430	165o	(38.4%)		
symptomatic (confirmed) – 104wkp	Dichotomous	428	24	(5.6%)	430	896	(208.4%)		
symptomatic (confirmed) – 104wk	Dichotomous	428	15o	(3.5%)	430	896p	(208.4%)		
symptomatic (unconfirmed) hypoglycaemia – 52wkq	Dichotomous	428	9	(2.1%)	430	104	(24.2%)		
Adverse events:									
Any adverse event(s) – 52wk	Dichotomous	428	260	(60.7%)	430	293	(68.1%)		
Any adverse event(s) – 104wk	Dichotomous	428	287	(67.1%)	430	312	(72.6%)		
Any serious adverse event(s) – 52wk	Dichotomous	428	39	(9.1%)	430	32	(7.4%)		
Any serious adverse event(s) – 104wk	Dichotomous	428	54	(12.6%)	430	55	(12.8%)		
Death – 52wk	Dichotomous	428	2	(0.5%)	430	2	(0.5%)		
Death – 104wk	Dichotomous	428	4	(0.9%)	430	2	(0.5%)		
GI: diarrhoea – 52wk	Dichotomous	428	22	(5.1%)	430	16	(3.7%)		
GI: diarrhoea – 104wk	Dichotomous	428	25	(5.8%)	430	17	(4.0%)		
Hypertension – 104wk	Dichotomous	428	19	(4.4%)	430	30	(7.0%)		
Infection (upper airway or other common) – 104wk	Dichotomous	428	25	(5.8%)	430	16	(3.7%)		
Nasopharyngitis – 52wk	Dichotomous	428	41	(9.6%)	430	37	(8.6%)		
Nasopharyngitis – 104wk	Dichotomous	428	46	(10.7%)	430	41	(9.5%)		
Dropouts:									
Total dropouts – 52wk	Dichotomous	428	116	(27.1%)	430	109	(25.3%)		
Total dropouts – 104wk	Dichotomous	428	263	(61.4%)	430	283	(65.8%)		
Dropout due to AEs – 52wkr	Dichotomous	428	26	(6.1%)	430	27	(6.3%)		
Dropout due to AEs – 104wkr	Dichotomous	428	32	(7.5%)	430	36	(8.4%)		
Baseline Hba1c >=7%									
Blood glucose:									
HbA1c (%) – 52wk	Mean change	324		-0.65 (SD 0.882)	320		-0.77 (SD 0.894)	MD=0.120 (CI: -0.017, 0.257)	
HbA1c (%) – 52wk	Mean change	428		-0.65 (SD 0.882)	430		-0.77 (SD 0.894)	MD=0.120 (CI: -0.017, 0.257)	
HbA1c < 7% or <=7% – 52wk	Dichotomous	324	138	(42.6%)	320	153	(47.8%)		

	HbA1c < 7% or <=7% – 104wk	Dichotomous	324	75	(23.1%)	320	73	(22.8%)		

[a] adjusted mean
[b] 95% CI= -0.17 to 0.06
[c] CI= -12.9 to 2.5
[d] 95% CI= -8.1 to 2.8
[e] adjusted
[f] SE estimated from graph
[g] 95% CI= -3.3 to -2.2
[h] (Used in the analysis); reviewer estimated patient days
[i] (Used in the analysis)
[j] >=3.5 to <3.9 mmol/l, reviewer estimated patient days
[k] <=2.8 mmol/l, no events
[l] >2.8 to <3.5, no events; reviewer estimated patient days
[m] <=2.8 mmol/, no patients
[n] <=3.9 mmol/l, no events; reviewer estimated patient days
[o] patients over entire trial- finger stick glucose <50mg/dl with symptoms
[p] events over entire trial- finger stick glucose <50mg/dl with symptoms
[q] no fingerstick obtained; reveiwer estimated patient days
[r] Data included dropouts due to SAEs

Paper ID 700132 reports that 'the majority of these hypoglycaemic events (83.7% of total events in the glipizide group, and 79.2% of total events in the saxagliptin group) occurred during the 52 week study period. During the entire 104 week study period, no patients in the saxagliptin group had confirmed hypoglycaemia compared with 9.1% of patients in the glipizide group (95% CI for difference= -12.2% to -6.6%).

Efficacy analyses were conducted using ANCOVA. A mixed model for repeated measures was used to analyse changes in HbA1c, FPG and weight from baseline of the initial study to week 104, with terms for treatment group, baseline value, time and time by treatment group. Proportions reporting hypoglycaemic events were analysed using the Fisher exact test. P-values for adverse events were not reported.

Table 18: Hanefeld et al. (2004)

General	**Phase:** ☐ monotherapy ☑ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin + oral **Parallel / crossover:** Parallel **Country:** Europe (Hungary, Finland, U.K., Slovak Republic, Belgium, Estonia, Lithuania, Denmark, Italy, Greece, Sweden, and the Netherlands) and Canada **Authors' conclusions:** Clinically equivalent improvements in glycemic control were observed for both combinations. Compared with metformin plus SU, addition of pioglitazone to SU resulted in a reduction of the urinary albumin-to-creatinine ratio, a small but significant rise in LDL cholesterol, and significantly greater improvements in triglyceride levels and HDL cholesterol levels. Metformin plus SU was associated with a significant reduction in LDL cholesterol. SU plus pioglitazone is an effective and well-tolerated combination regimen that may provide additional beneficial effects for patients with type 2 diabetes **Source of funding:** Takeda and Eli Lilly **Comments:** multicenter, randomized, double-blind, parallel group study
Number and characteristics of patients	**Total number of patients:** 639 **Inclusion criteria:** Male and female patients aged 35-75 years with type 2 diabetes inadequately managed with SU therapy alone (at >=50% of the maximal recommended dose or at the maximal tolerated dose for >=3 months) and with stable or worsening glycemic control for >=3 months were eligible if their HbA1c was between 7.5 and 11.0% and their fasting C-peptide was >=1.5 ng/ml at screening **Exclusion criteria:** type 1 diabetes or ketoacidosis; a history of myocardial infarction, transient ischemic attacks, or stroke in the previous 6 months; symptomatic heart failure; malabsorption or pancreatitis; familial polyposis coli; malignant disease in the previous 10 years; a history of or states associated with lactic acidosis or hypoxemia; or substance abuse. Female patients had to be postmenopausal, sterilized, or using satisfactory contraception, and pregnant or breast-feeding women were excluded. Previous treatment with metformin, pioglitazone, or other TZDs was not permitted.
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** all on oral hypoglycaemic drugs and/or insulin **Details of washout period:** All patients were taking sulfonylurea monotherapy at study entry
Lifestyle advice	-

Follow-up	**Total follow-up (wks):** 104 **Length of titration period (wks):** 12 **Length of maintenance period (wks):** 92 **Frequency of monitoring appointments:** HbA1c, FPG, and insulin levels were measured at baseline and at weeks 4, 8, 12, 16, 24, 32, 42, and 52
Arms	**(1) Pioglitazone + sulfonylurea** N: 0 Treatment duration (wks): 104 Washout period (d): 0 Comments: No washout as patients were taking sulfonylurea at baseline and this was continued throughout the study Treatment(s): (a) Sulfonylurea (Oral) – forced titration Details of dosing regimen: Patients also received SU at their prestudy dose, and increases were not permitted. The SU dose could be down titrated only if the patient experienced symptomatic hypoglycemia with an increase to the original dose at the next visit, where possible. (b) Pioglitazone (Oral) – forced titration Set dose (mg/d):37 Maximum dose (mg/d): 45 Frequency of dosing: once a day Details of dosing regimen: Patients started with pioglitazone 15 mg o.d.and dose levels were increased at weeks 4, 8, and 12. Cessation of titration or down titration was permitted only on the basis of tolerability issues, including actual hypoglycemia or increased risk of hypoglycemia. Patients continued to the next dose level unless the investigator considered that the increase could put them at risk of hypoglycemia (increase postponed for one visit from week 4 to week 8 or the week 8 dose was maintained for the rest of the study), if the patient reported symptomatic hypoglycemia (one-step reduction followed by an increase at the following visit, if possible), or if the patient experienced adverse events that required dose reduction (one-step reduction at week 8 or 12 with no further down titration). The maximal tolerated doses of pioglitazone or metformin established at week 12 remained unchanged throughout the 104 study period **(2) Metformin + sulfonylurea** N: 0 Treatment duration (wks): 104 Washout period (d): 0 Comments: No washout as patients were taking sulfonylurea at baseline and this was continued throughout the study Treatment(s): (a) Sulfonylurea (Oral) – forced titration Details of dosing regimen: Patients also received SU at their prestudy dose, and increases were not permitted. The SU dose could be down titrated only if the patient experienced symptomatic hypoglycemia with an increase to the original dose at the next visit, where possible. (b) Metformin (Oral) – forced titration Set dose (mg/d):2081 Maximum dose (mg/d): 2550 Details of dosing regimen: Patients received either pioglitazone up to Patients received metformin 850 mg with pioglitazone placebo up to three times daily (maximal dose of 2,550 mg metformin). Patients started with metformin 850 mg o.d., and dose levels were increased at weeks 4, 8, and 12.
Outcomes	**General** An intent-to-treat (ITT) analysis with last observation carried forward was used to assess efficacy. The ITT population included all patients who had received at least one dose of study medication and had HbA1c recorded at baseline and at least once after baseline. All patients who had received at least one dose of study medication were included in the safety analysis 2 year data from Seufery (2008)/Charbonnel (2005) are also reported in this evidence table. Because down titration of study medication was not permitted after week 12, adverse events thought to be drug related after this point were managed by temporary interruption of study medication or permanent discontinuation
Baseline characteristics	

	Pioglitazone + sulfonylurea			Metformin + sulfonylurea				
	N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**

Demographics: Age (years)	Continuous	319		60 (SD 9)	320		60 (SD 8)		
Age (years)	Continuous	319		60 (SD 8.8)	320		60 (SD 8)		
Sex (n male)	Dichotomous	319	171	(53.6%)	320	175	(54.7%)		
Sex (n male)	Dichotomous	319	171	(53.6%)	320	176	(55.0%)		
Sex (n male)	Dichotomous	319	172a	(53.9%)	320	175	(54.7%)		
Sex (n male)	Dichotomous	319	172a	(53.9%)	320	176	(55.0%)		
Duration of diabetes (yrs)	Continuous	319		7 (SD 6)	320		7.1 (SD 5.6)		
Duration of diabetes (yrs)	Continuous	319		7 (SD 5.6)	320		7 (SD 6)		
Duration of diabetes (yrs)	Continuous	319		7 (SD 5.6)	320		7.1 (SD 5.6)		
Duration of diabetes (yrs)	Continuous	319		7 (SD 6)	320		7 (SD 6)		
Blood glucose: HbA1c (%) – 0wk	Continuous	319		8.8 (SD 1)	320		8.8 (SD 1)		
HbA1c (%) – 0wk	Continuous	319		8.82 (SD 0.98)	320		8.8 (SD 0.97)		
HbA1c (%) – 0wk	Continuous	319		8.82 (SD 0.98)	320		8.8 (SD 1)		
HbA1c (%) – 0wk	Continuous	319		8.8 (SD 1)	320		8.8 (SD 0.97)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	319		11.8 (SD 2.7)	320		12 (SD 2.9)		
Body weight: BMI (kg/m2) – 0wk	Continuous	319		30.2 (SD 4.4)	320		30 (SD 4.6)		
Weight (kg) – 0wk	Continuous	319		85.3 (SD 15.1)	320		84.9 (SD 14.5)		
Waist circumference (cms) – 0wk	Continuous	319		103 (SD 10.9)	320		103 (SD 11)		
Adverse events: Liver enzymes: AST (U/l) – 0wkb	Continuous	319		30 (SD 15.6)	320		30 (SD 15.6)		
Lipids: HDL cholesterol (mmol/l) – 0wk	Continuous	319		1.09 (SD 0.24)	320		1.11 (SD 0.27)		
Triglycerides (mmol/l) – 0wk	Continuous	319		2.47 (SD 1.69)	320		2.38 (SD 1.72)		
LDL cholesterol (mmol/l) – 0wk	Continuous	319		3.57 (SD 0.86)	320		3.58 (SD 0.92)		
TC/HDL ratio – 0wk	Continuous	319		5.45 (SD 1.47)	320		5.38 (SD 1.53)		
Renal function: albumin:creatinine ratio – 0wk	Continuous	319		0.07 (SD 0.25)	320		0.11 (SD 0.56)		

[a] approximated to nearest integer (percentages only presented in text)
[b] Alanine aminotransferase (units/l)

Results

		Pioglitazone + sulfonylurea			Metformin + sulfonylurea				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Blood glucose: HbA1c (%) – 16wka	Mean change	319		-1.25 (SD 0.893)	320		-1.6 (SD 0.894)		
HbA1c (%) – 24wka	Mean change	319		-1.39 (SD 0.893)	320		-1.7 (SD 0.894)		
HbA1c (%) – 52wk	Mean change	319		-1.2 (SD 1.02) b	320		-1.36 (SD 1.02) c		
HbA1c (%) – 52wkd	Continuous	319		7.61 (SD 1.07)	320		7.45 (SD 1.07)		
HbA1c (%) – 104wkb	Mean change	319		-1.03 (SD 1.25)	320		-1.16 (SD 1.79)		
HbA1c < 7% or <=7% – 52wk	Dichotomous	319	124e	(38.9%)	320	128	(40.0%)		
HbA1c < 7% or <=7% – 104wke	Dichotomous	319	96	(30.1%)	320	91	(28.4%)		

Fasting plasma glucose (mmol/l) – 16wka	Mean change	319		-3 (SD 1.79)	320		-3.1 (SD 1.79)		
Fasting plasma glucose (mmol/l) – 24wka	Mean change	319		-2.8 (SD 1.61)	320		-3 (SD 1.79)		
Fasting plasma glucose (mmol/l) – 52wka	Mean change	319		-2.2 (SD 1.43)	320		-2.35 (SD 2.68)		
Fasting plasma glucose (mmol/l) – 52wk	Continuous	319		9.7 (SD 0.15)	320		9.6 (SD 0.15)		
Fasting plasma glucose (mmol/l) – 104wka	Mean change	319		-2 (SD 1.79)	320		-1.9 (SD 2.68)		
Body weight:									
Weight (kg) – 52wkf	Mean change	319		2.8	320		-1		
Weight (kg) – 104wk	Mean change	319		3.2 (SD 4.7)	320		-1.7 (SD 4.5)		
Hypoglycaemic events:									
All hypoglycaemic events (no patients) – 52wk	Dichotomous	319	34e	(10.7%)	320	46	(14.4%)		
All hypoglycaemic events (no patients) – 104wkg	Dichotomous	319	36	(11.3%)	320	50	(15.6%)		
Major/severe hypoglycaemic event – 52wk	Dichotomous	319	0	(0.0%)	320	0	(0.0%)		
Adverse events:									
Any adverse event(s) – 52wk	Dichotomous	319	191	(59.9%)	320	198	(61.9%)		
Any adverse event(s) – 104wk	Dichotomous	319	217	(68.0%)	320	224	(70.0%)		
Any serious adverse event(s) – 52wk	Dichotomous	319	21	(6.6%)	320	31	(9.7%)		
Arthralgia – 104wk	Dichotomous	319	17	(5.3%)	320	13	(4.1%)		
Back pain – 104wk	Dichotomous	319	10	(3.1%)	320	16	(5.0%)		
cardiovascular AE – 52wke	Dichotomous	319	10	(3.1%)	320	13	(4.1%)		
cardiac: CHF – 104wk	Dichotomous	319	2	(0.6%)	320	3	(0.9%)		
Edema peripheral – 52wk	Dichotomous	320	22	(6.9%)	319	5e	(1.6%)		
Edema peripheral – 104wk	Dichotomous	319	34	(10.7%)	320	9	(2.8%)		
Edema peripheral – 104wk	Dichotomous	319	26	(8.2%)	320	9	(2.8%)		
Gastrointestinal disorders (any) – 52wk	Dichotomous	319	39	(12.2%)	320	75h	(23.4%)		
Gastrointestinal disorders (any) – 104wk	Dichotomous	319	20	(6.3%)	320	62	(19.4%)		
GI: diarrhoea – 52wk	Dichotomous	319	8	(2.5%)	320	40	(12.5%)		
GI: diarrhoea – 104wk	Dichotomous	319	11	(3.4%)	320	46	(14.4%)		
Hypertension – 104wk	Dichotomous	319	21	(6.6%)	320	30	(9.4%)		
Infection (upper airway or other common) – 104wk	Dichotomous	319	5	(1.6%)	320	7	(2.2%)		
Liver enzymes: AST (U/l) – 52wk	Continuous	319		26 (SD 14.2)	320		28 (SD 15.1)		
Temperature/influenza – 104wk	Dichotomous	319	9	(2.8%)	320	14	(4.4%)		
Dropouts:									
Total dropouts – 104wki	Dichotomous	319	88	(27.6%)	320	70	(21.9%)		
Dropout due to AEs – 52wk	Dichotomous	319	20	(6.3%)	320	19e	(5.9%)		
Dropout due to AEs – 104wk	Dichotomous	319	26	(8.2%)	320	32	(10.0%)		
Drop out due to unsatisfactory effect – 104wk	Dichotomous	319	25	(7.8%)	320	12	(3.8%)		
Lipids:									
HDL cholesterol (mmol/l) – 52wk	Continuous	319		1.25 (SD 0.01)	320		1.19 (SD 0.01)		
Triglycerides (mmol/l) – 52wk	Continuous	319		2.01 (SD 0.06)	320		2.15 (SD 0.06)		
LDL cholesterol (mmol/l) – 52wk	Continuous	319		3.66 (SD 0.04)	320		3.41 (SD 0.04)		
TC/HDL ratio – 52wk	Continuous	319		4.86 (SD 0.05)	320		4.87 (SD 0.05)		
Renal function:									
albumin:creatinine ratio – 52wk	Continuous	319		0.09 (SD 0.01)	320		0.09 (SD 0.01)		

	[a] estimated from graph [b] SD estimated from reported SE in graph [c] SE estimated from graph [d] SD estimated from reported SE [e] approximated to nearest integer (percentages only presented in text) [f] EXCLUDE unless details of dosing for S [g] (Used in the analysis) [h] approximated to nearest integer (percentages only presented in text); approximated to nearest integer (percentages only presented in text) [i] Dropouts at 52 weeks were unclear and therefore have not been extracted
	Statistical analysis of the primary efficacy variable (change in HbA1c from baseline to week 52) was performed using an ANCOVA model with the factor "treatment" and the baseline value as a continuous covariate.

Table 19: Hermansen et al. (2007)

General	**Phase:** ☐ monotherapy ☑ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin + oral **Parallel / crossover:** Parallel **Country:** Multinational- participating countries not stated **Authors' conclusions:** Sitagliptin 100mg once daily improved glycaemic control and beta cell function in patients with TTD who had inadequate glycaemic control with gimepiride or glimepiride plus metformin. The addition of sitagliptin was well tolerated, with a modest increase in hypoglycaemia and body weight consistent with glimepiride therapy and the observed degree of glycaemic improvement. **Source of funding:** Funded by Merck & co **Comments:** Only dual therapy arms were extracted, triple therapy arms are available. Patients were given pioglitazone as rescue therapy- once rescue therapy was given the patients were removed from efficacy analyses.
Number and characteristics of patients	**Total number of patients:** 441 **Inclusion criteria:** men and wommen aged 18 to 75 years with TTD. Patients were already taking glimepiride alone (at any dose) or in combination with Metformin (at any dose); were taking another OHA in mono, dual or triple therapy; or no OHAs over the prior 8 weeks. **Exclusion criteria:** History of type 1 diabetes; treated with insulin within 8 weeks of the screening visit; renal dysfunction ; hisotry of hypersensitivity, intolerance or a contraindication to the use of glimepiride, sulfonylurea agents, metformin or pioglitazone. Pre-randomisation phase: No OHAs at baseline with HbA1c >=9%: Discontinued previous therapy and switched to glimepiride alone or glimepiride + metformin (unclear what does were given) and entered a 4 week titration period, then a dose stabilization run in period of 10 weeks. If HbA1c was =>7.5% and <=10.5% after this run in period, patients then entered a 2 week single blind placebo run in period. OHA monotherapy at baseline with HbA1c >=7.5% Discontinued previous therapy and switched to glimepiride alone or glimepiride + metformin (unclear what does were given) and entered a 4 week titration period, then a dose stabilization run in period of 10 weeks. If HbA1c was =>7.5% and <=10.5% after this run in period, patients then entered a 2 week single blind placebo run in period. OHA dual or triple therapy at baseline with HbA1c >=6.5% and <=10.5%: Discontinued previous therapy and switched to glimepiride alone or glimepiride + metformin (unclear what does were given) and entered a 4 week titration period, then a dose stabilization run in period of 10 weeks. If HbA1c was =>7.5% and <=10.5% after this run in period, patients then entered a 2 week single blind placebo run in period. Already on glimepiride (alone or with metformin 1500mg to 300mg) with HbA1c >=7.5% and <=10.5%: Therapy was maintained and patients entered a 2 week single blind placebo run in. Patients were then randomised to receive additional sitagliptin or placebo in addition to glimepiride or glimepiride + metformin.
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** some on oral hypoglycaemic drugs and/or insulin **Details of washout period:** Abstract states that there was a screening and drug wash off period, a stablization period and a placebo run in peiod. Patients on anything other than glimepiride or metformin discontinued their previous drugs. Patients not on any OHAs started taking glimepiride alone or in combo with metformin.

Lifestyle advice	Abstract states that there was a diet/exercise runin but this is not described in further detail in the paper.
Follow-up	**Total follow-up (wks):** 24 **Length of titration period (wks):** 4 **Length of maintenance period (wks):** - **Frequency of monitoring appointments:** 24 weeks study + up to 16 weeks run in (4 weeks titration, 10 weeks stabilization, 2 weeks placebo run in) Unclear how often monitoring appointments took place. Text states 6, 12 ans 24 weeks.
Arms	**(1) Gimepiride + metformin + placebo** N: 113 Treatment duration (wks): 24 Washout period (d): - Treatment(s): (a) Sulfonylurea Minimum dose (mg/d): 4 Maximum dose (mg/d): 8 Details of dosing regimen: Not stated (b) Metformin (Oral) – flexible-dose (dose-adjusted) Minimum dose (mg/d): 1500 Maximum dose (mg/d): 3000 Details of dosing regimen: Not stated **(2) Glimepiride + sitagliptin** N: 106 Treatment duration (wks): 24 Washout period (d): - Treatment(s): (a) Sulfonylurea – flexible-dose (dose-adjusted) Minimum dose (mg/d): 4 Maximum dose (mg/d): 8 Details of dosing regimen: Not stated (b) Sitagliptin – fixed-dose Set dose (mg/d):100 Details of dosing regimen: Not stated
Outcomes	**General** During the study period, patients not meeting specific, progressively lower glycaemic goals were provided with open lable rescue medication (pioglitazone) until the completion of the study period. Patients remained in the study to provide additional safety data but were discontinued if they were on rescue therapy for at least 4 weeks and had an FPG consistently >200mg/dl. - Patients receiving rescue therapy were not included in the efficacy analyses and have been extracted. - Patients rceiving rescue therapy were included in the safety data so this has NOT been extracted. Data is also available for the Glimepiride + metformin + sitagliptin arm but this has not been extracted as this is triple therapy

Baseline characteristics

		Gimepiride + metformin + placebo			Glimepiride + sitagliptin				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	113		57.7 (SD 8.9)	106		54.4 (SD 10.3)		
Sex (n male)	Dichotomous	113	59	(52.2%)	106	56	(52.8%)		
Duration of diabetes (yrs)	Continuous	113		10.6 (SD 6.8)	106		7.2 (SD 5)		
Ethnicity-White	Dichotomous	113	81	(71.7%)	106	61	(57.5%)		
Ethnicity-Black	Dichotomous	113	9	(8.0%)	106	7	(6.6%)		
Ethnicity-Asian	Dichotomous	113	13	(11.5%)	106	6	(5.7%)		
Ethnicity-Hispanic	Dichotomous	113	7	(6.2%)	106	26	(24.5%)		
Ethnicity-Other	Dichotomous	113	3	(2.7%)	106	6	(5.7%)		
Blood glucose: HbA1c (%) – 0wk	Continuous	113		8.26 (SD 0.68)	106		8.42 (SD 0.79)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	113		9.9022704 (SD 2.36)	106		10.1353956 (SD 1.84)		
Body weight: BMI (kg/m2)	Continuous	113		30.7 (SD 6.2)	106		31 (SD 6.7)		

	Weight (kg)	Continuous	113		86.7 (SD 21.1)	106		85.8 (SD 22.5)		

Results

		Gimepiride + metformin + placebo			Glimepiride + sitagliptin				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 24wk	Mean change	105		0.3 (SD 0.868)	102		-0.3 (SD 0.946)		
Fasting plasma glucose (mmol/l) – 24wk	Mean change	105		0.7160274 (SD 2.38)	102		-0.04884528 (SD 2.6)		
Dropouts:									
Total dropouts – 24wk	Dichotomous	113	21	(18.6%)	106	23	(21.7%)		
Dropout due to AEs – 24wk	Dichotomous	113	2	(1.8%)	106	4	(3.8%)		

Adverse events data available but not extacted since data include participants treated with rescue therapy

Table 20: Jeon & (2011)

General

Phase:
☐ monotherapy
☑ dual therapy
☐ triple therapy
☐ insulin monotherapy
☐ insulin + oral

Parallel / crossover: Parallel

Country: Korea

Authors' conclusions: Vildagliptin-metformin treatment provided blood glucose control efficacy comparable to that of glimepiride-metformin treatment and resulted in better adverse event profiles with lower risks of hypoglycemia and weight gain

Source of funding: supported by research grant from Chungbuk National University

Comments: randomized, open-label, trial

Number and characteristics of patients

Total number of patients: 106

Inclusion criteria: Type 2 diabetic patients with HbA1c levels greater than 7.0% who were naïve or were receiving monotherapy with oral hypoglycemic agents such as glimepiride (2 to 4 mg) or metformin (500 to 1,000 mg) for less than six months prior to the visit were eligible to participate

Exclusion criteria: Patients with a history of diabetic ketoacidosis, clinically significant liver or renal disease, congestive heart failure requiring pharmacological treatment, coronary artery percutaneous intervention or unstable angina within the past six months, and those over 80 years of age were excluded. Patients with serum creatinine >133 µmol/L, alanine aminotransferase or aspartate aminotransferase >3 times the upper limit of normal and total bilirubin >34 µmol/L were also excluded

Pre-randomisation phase: All the patients who received previous medications had to undergo a wash-out period of at least two weeks

Previous glucose-lowering therapy

Any participants previously taking glucose-lowering therapy? some on oral hypoglycaemic drugs and/or insulin

Details of washout period: All the patients who received previous medications had to undergo a wash-out period of at least two weeks (some were naïve)

Lifestyle advice

-

Follow-up

Total follow-up (wks): 32

Length of titration period (wks): 0

Length of maintenance period (wks): 32

Frequency of monitoring appointments: Measurements were taken at week 0, 4, 12, 24, and 32

Arms

(1) Metformin + vildagliptin

N: 54
Treatment duration (wks): 32
Washout period (d): 14
Comments: wash off period of at least 2 weeks
Treatment(s): (a) Metformin (Oral) – fixed-dose
Set dose (mg/d):1000
Frequency of dosing: twice a day
Details of dosing regimen: 500 mg bid
(b) Vildagliptin (Oral) – fixed-dose
Set dose (mg/d):100
Frequency of dosing: twice a day
Details of dosing regimen: 50 mg bid

(2) Metformin + glimepiride

N: 52
Treatment duration (wks): 32
Washout period (d): 14
Comments: wash off period of at least 2 weeks
Treatment(s): (a) Metformin (Oral) – fixed-dose
Set dose (mg/d):1000
Frequency of dosing: twice a day
Details of dosing regimen: 500 mg bid
(b) Sulfonylurea (Oral) – fixed-dose
Set dose (mg/d):4
Frequency of dosing: twice a day
Details of dosing regimen: 2 mg bid

Outcomes

General

No details of ITT analysis reported (assumed PP analysis carried out). Patients who discontinued medication due to adverse events were not included in the final analysis

1/52 (1.9%) patients in the sulfonylurea group and 3/54 (5.6%) in the vildagliptin group discontinued the study

Hypoglycaemic events

Major/severe hypoglycaemic event (Severe hypoglycemia was defined in the patients with transient dysfunction of

the central nervous system who were unable to treat themselves)

confirmed hypoglycaemia (Hypoglycemia was defined as a finger stick glucose concentration of less than 3.9 mmol/L without loss of consciousness.)

Baseline characteristics

		Metformin + vildagliptin			Metformin + glimepiride			Δ	p
		N	k	mean	N	k	mean		
PP									
Demographics:									
Age (years)	Continuous	51		53.51 (SD 10.4)	51		55.38 (SD 11)		
Sex (n male)	Dichotomous	51	35	(68.6%)	51	31	(60.8%)		
Duration of diabetes (yrs)	Continuous	51		5.89 (SD 1.64)	51		5.92 (SD 1.74)		
Blood glucose:									
HbA1c (%) – 0wk	Continuous	51		8.01 (SD 1.2)	51		8.13 (SD 0.86)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	51		8.78 (SD 2.32)	51		9.34 (SD 2.14)		
Body weight:									
BMI (kg/m2)	Continuous	51		22.69 (SD 7.75)	51		23.07 (SD 4.24)		
Weight (kg) – 0wka	Continuous	51		64.040256 (SD 21.9)	51		65.112768 (SD 12)		

[a] estimated from BMI assuming mean height of 1.68m

Results

	Metformin + vildagliptin			Metformin + glimepiride			Δ	p
	N	k	mean	N	k	mean		

Blood glucose: HbA1c (%) – 32wk	Continuous	54			52				0.855
HbA1c < 7% or <=7% – 32wk	Dichotomous	54			52				NR
Fasting plasma glucose (mmol/l) – 32wk	Continuous	54			52				0.508
Body weight: Weight (kg) – 32wk	Continuous	54			52				<0.05
Hypoglycaemic events: Major/severe hypoglycaemic event – 32wk	Dichotomous	54			52				NR
confirmed hypoglycaemia – 32wk	Dichotomous	54			52				<0.05
Dropouts: Total dropouts – 32wk	Dichotomous	51	3	(5.9%)	51	1	(2.0%)		
PP Blood glucose: HbA1c (%) – 32wk[a]	Mean change	51		-0.94	51		-1		
HbA1c < 7% or <=7% – 32wk[b]	Dichotomous	51	26	(51.0%)	51	29	(56.9%)		
Fasting plasma glucose (mmol/l) – 32wk	Mean change	51		-1.54 (SD 2.41)	51		-2.16 (SD 2.51)		
Body weight: Weight (kg) – 32wk	Mean change	51		0.23 (SD 0.69)	51		2.35 (SD 1.21)		
Hypoglycaemic events: Major/severe hypoglycaemic event – 32wk[c]	Dichotomous	51	0	(0.0%)	51	0	(0.0%)		
confirmed hypoglycaemia – 32wk[d]	Dichotomous	51	1	(2.0%)	51	10	(19.6%)		
Adverse events: GI: nausea – 32wk	Dichotomous	51	1	(2.0%)	51	0	(0.0%)		
Any adverse event(s) – 32wk	Dichotomous	51	5	(9.8%)	51	10	(19.6%)		
Any serious adverse event(s) – 32wk	Dichotomous	51	0	(0.0%)	51	1	(2.0%)		
Gastrointestinal disorders (any) – 32wk	Dichotomous	51	4	(7.8%)	51	0	(0.0%)		
GI: diarrhoea – 32wk	Dichotomous	51	1	(2.0%)	51	0	(0.0%)		
GI: vomiting – 32wk	Dichotomous	51	2	(3.9%)	51	0	(0.0%)		
GI: abdominal pain – 32wk	Dichotomous	51	0	(0.0%)	51	0	(0.0%)		
Dropouts: Dropout due to AEs – 32wk	Dichotomous	51	3	(5.9%)	51	1	(2.0%)		

[a] SD estimated from graph
[b] approximated to nearest integer (percentages only presented in text)
[c] one patient in the trail required medical assistance due to loss of consciousness
[d] (Used in the analysis)

The means and frequencies of variables were evaluated using Student's t-test and the chi squared test, respectively. P-values were not reported for between group comparisons of adverse events

Table 21: Maffioli et al. (2013)

General

Phase:
☐ monotherapy
☑ dual therapy
☐ triple therapy
☐ insulin monotherapy
☐ insulin + oral

Parallel / crossover: Parallel

Country: Italy

Authors' conclusions: Pioglitazone was more effective than glibenclamide in improving inflammation and hepatic steatosis indices

Source of funding: Not reported

Comments: Randomised, double-blind, trial. Double-dummy approach was used to ensure the blind status of the study. Randomisation was carried out using drawing of envelopes containing randomisation codes

	prepared by a statistician. A copy of the code was provided only to the responsible individual carrying out statistical analysis
Number and characteristics of patients	**Total number of patients:** 170 **Inclusion criteria:** type 2 diabetes, at least 18 years old, naïve to treatment, and with poor glycaemic control (Hba1c >8%) and overweight or obese (BMI 25-34.9 kg/m2) with hepatic steatosis **Exclusion criteria:** history of ketoacidosis, rapidly progressive diabetic retinopathy, nephropathy, neuropathy, patients with impaired renal function or muscle toxicity, type 1 diabetes, patients with valvular heart disease, women who were pregnant or breastfeeding or who might become pregnant, patients with contraindications to pioglitazone Pre-randomisation phase: There was a 3 month run-in period with metformin 850 mg tid before randomisation to add on therapy
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** all on oral hypoglycaemic drugs and/or insulin **Details of washout period:** -
Lifestyle advice	patients were already following a controlled energy diet on the basis of the ADA recommendations. Patients were also encouraged to increase their physical activitiy by walking briskly for 20-30 minutes, 3-5 times per week or by cycling
Follow-up	**Total follow-up (wks):** 38 **Length of titration period (wks):** 12 **Length of maintenance period (wks):** 26 **Frequency of monitoring appointments:** Parameters were measured at baseline and after 6 months
Arms	**(1) Metformin + glibenclamide** N: 84 Treatment duration (wks): 26 Washout period (d): 0 Treatment(s): (a) Metformin (Oral) – forced titration Set dose (mg/d):2550 Details of dosing regimen: patients were given 850 mg tid before randomisation and this was continued (b) Sulfonylurea (Oral) – fixed-dose Set dose (mg/d):10 Frequency of dosing: twice a day Details of dosing regimen: glibenclamide 5 mg was given bid for 6 months **(2) Metformin + pioglitazone** N: 86 Treatment duration (wks): 26 Washout period (d): 0 Treatment(s): (a) Metformin (Oral) – fixed-dose Set dose (mg/d):2550 Frequency of dosing: three times a day Details of dosing regimen: patients were given 850 mg tid before randomisation and this was continued (b) Pioglitazone (Oral) – fixed-dose Set dose (mg/d):30 Frequency of dosing: twice a day Details of dosing regimen: 15 mg bid
Outcomes	**General** ITT analysis was carried out in patients who had received one or more doses of study medication, did not show any acute adverse reaction and had undergone a subsequent efficacy observation. Data were extracted for the first 6 month period only (before rosuvastatin was added onto both arms) 2/84 patients in the glibenclamide group and 3/86 in the pioglitazone group were not included in the analysis
Baseline characteristics	

		Metformin + glibenclamide			Metformin + pioglitazone				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Demographics:									
Age (years)	Continuous	84		61.4 (SD 5.6)	86		62.8 (SD 6.3)		
Sex (n male)	Dichotomous	84	42	(50.0%)	86	41	(47.7%)		

ITT										
Blood glucose: HbA1c (%) – 0wk	Continuous	84		8.198828 (SD 1.45)	86		8.400084 (SD 1.24)			
Fasting plasma glucose (mmol/l) – 0wk	Continuous	84		7.8 (SD 0.7)	86		7.9 (SD 0.9)			
Body weight: BMI (kg/m2) – 0wk	Continuous	84		30.2 (SD 2.9)	86		30 (SD 3)			
Weight (kg) – 0wk	Continuous	84		83.1 (SD 8.8)	86		83.5 (SD 9)			
Adverse events: liver enzymes: abnormal ALT – 0wk	Continuous	84		59 (SD 13)	86		57 (SD 12)			
Liver enzymes: AST (U/l) – 0wk	Continuous	84		53 (SD 10)	86		51 (SD 9)			
Lipids: Total cholesterol (mmol/l) – 0wk	Continuous	84		5.4 (SD 0.3)	86		5.4 (SD 0.6)			
HDL cholesterol (mmol/l) – 0wk	Continuous	84		1.2 (SD 0.2)	86		1.1 (SD 0.2)			
Triglycerides (mmol/l) – 0wk	Continuous	84		1.7 (SD 0.4)	86		1.7 (SD 0.4)			
LDL cholesterol (mmol/l) – 0wk	Continuous	84		3.8 (SD 0.4)	86		3.9 (SD 0.4)			

Results

		Metformin + glibenclamide			Metformin + pioglitazone				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Dropouts: Total dropouts – 26wk	Dichotomous	84	2	(2.4%)	86	3	(3.5%)		
Dropout due to AEs – 26wk	Dichotomous	84	2	(2.4%)	86	1	(1.2%)		
ITT									
Blood glucose: HbA1c (%) – 26wk	Continuous	82		7.402952 (SD 1.75)	83		7.796316 (SD 1.45)		<0.05
HbA1c (%) – 26wk	Continuous	82		7.402952 (SD 1.75)	83		7.796316 (SD 1.45)		NS
HbA1c (%) – 26wk	Continuous	84		7.402952 (SD 1.75)	86		7.796316 (SD 1.45)		<0.05
HbA1c (%) – 26wk	Continuous	84		7.402952 (SD 1.75)	86		7.796316 (SD 1.45)		NS
Fasting plasma glucose (mmol/l) – 26wk	Continuous	82		6.7 (SD 0.4)	83		7.5 (SD 0.7)		<0.05
Fasting plasma glucose (mmol/l) – 26wk	Continuous	84		6.7 (SD 0.4)	86		7.5 (SD 0.7)		<0.05
Body weight: BMI (kg/m2) – 26wk	Continuous	82		30.4 (SD 3.1)	83		30.3 (SD 3.2)		NS
BMI (kg/m2) – 26wk	Continuous	84		30.4 (SD 3.1)	86		30.3 (SD 3.2)		NS
Weight (kg) – 26wk	Continuous	84		83.6 (SD 8.9)	86		84.4 (SD 9.2)		NS
Weight (kg) – 26wk	Continuous	82		83.6 (SD 8.9)	83		84.4 (SD 9.2)		NS
Adverse events: liver enzymes: abnormal ALT – 26wk	Continuous	82		57 (SD 12)	83		54 (SD 11)		
liver enzymes: abnormal ALT – 26wk	Dichotomous	84			86				NS
Liver enzymes: AST (U/l) – 26wk	Continuous	84		50 (SD 9)	86		49 (SD 8)		NS
Liver enzymes: AST (U/l) – 26wk	Continuous	82		50 (SD 9)	83		49 (SD 8)		NS
Lipids: Total cholesterol (mmol/l) – 26wk	Mean change	84			86				NS
Total cholesterol (mmol/l) – 26wk	Continuous	82		5.2 (SD 0.5)	83		4.9 (SD 0.4)		

	HDL cholesterol (mmol/l) – 26wk	Continuous	82		1.2 (SD 0.2)	83		1.2 (SD 0.2)		
	HDL cholesterol (mmol/l) – 26wk	Mean change	84			86				NS
	Triglycerides (mmol/l) – 26wk	Continuous	82		1.6 (SD 0.3)	83		1.5 (SD 0.3)		
	Triglycerides (mmol/l) – 26wk	Mean change	84			86				NS
	LDL cholesterol (mmol/l) – 26wk	Continuous	82		3.7 (SD 0.3)	83		3.4 (SD 0.3)		
	LDL cholesterol (mmol/l) – 26wk	Mean change	84			86				<0.05
	Continuous variables were tested using two way ANCOVA									

Table 22: Matthews et al. (2005)

General	**Phase:** ☐ monotherapy ☑ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin + oral **Parallel / crossover:** Parallel **Country:** 9 European countries and Australia **Authors' conclusions:** Compared to established combinations of metformin plus gliclazide, this study indicates potential benefits of addition of pioglitazone to metformin in terms of improvements in microalbuminuria and specific abnormalities associated with diabetic dyslipidemia **Source of funding:** Takeda and Eli Lilly **Comments:** Double-blind, double-dummy trial. Patients were randomised using block randomisation via a central telephone system (QTONE)
Number and characteristics of patients	**Total number of patients:** 630 **Inclusion criteria:** Male and female patients with type 2 diabetes inadequately managed with metformin or sulphonylurea monotherapy (at =50% of the maximum recommended dose or at the maximum tolerated dose for =3 months) were eligible for entry into the study. Inclusion criteria were: (1) age 35–75 years (inclusive); (2) HbA1c 7.5–11.0% (inclusive); (3) fasting C-peptide levels =0.50 nmol/l (1.5 ng/ml); and (4) stable or worsening glycaemic control for =3 months prior to screening **Exclusion criteria:** type 1 diabetes, ketoacidosis, symptomatic heart failure, acute malabsorption or chronic pancreatitis, familial polyposis coli, malignant disease in the previous 10 years, substance abuse or myocardial infarction, transient ischaemic attacks or stroke in the previous 6 months, or were pregnant. Patients previously treated with insulin, gliclazide, pioglitazone or other sulphonylureas or TZDs were not eligible for entry
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** all on oral hypoglycaemic drugs and/or insulin **Details of washout period:** All patients were taking metformin monotherapy and this was continued throughout the study
Lifestyle advice	Dietary advice was given at baseline with the target of body weight normalisation. Patients were instructed to adhere to a disease and body weight oriented diet for the entire course of the study.If body weight increased by more than 5% during treatment or Hba1c increased to greater than 9% after completed dose titration, patients were given further intensive dietary advice
Follow-up	**Total follow-up (wks):** 104 **Length of titration period (wks):** 16 **Length of maintenance period (wks):** 88 **Frequency of monitoring appointments:** HbA1c, FPG, and insulin levels were measured at baseline and at weeks 4, 8, 12, 16, 24, 32, 42, and 52
Arms	**(1) Metformin + pioglitazone** N: 317 Treatment duration (wks): 104 Washout period (d): 0 Comments: No wash off as metformin monotherapy (at study entry) was continued Treatment(s): (a) Metformin (Oral)

Mean dose (mg/d): 1726
Details of dosing regimen: No change in metformin dose from the pre-study level was allowed at any stage of the study

(b) Pioglitazone (Oral) – forced titration

Set dose (mg/d):45
Mean dose (mg/d): 39
Participants achieving full dose (n): 222
Frequency of dosing: once a day
Details of dosing regimen: During a 16-week forced-titration phase, the pioglitazone dose was increased in a step-wise manner to 30 and 45 mg. Cessation of titration or down titration was only permitted on the basis of tolerability issues, including actual hypoglycaemia or increased risk of hypoglycaemia. Patients continued to the next dose level, unless the investigaor considered that the increase could put them at risk of hypoglycaemia, or the patient reported symptomatic hypoglycaemia. The dose achieved at week 16 was maintained for the remaining study.

At the end of week 16, 70% of patients had been titrated to the maximum dose of pioglitazone (45 mg od)

(2) Metformin + gliclazide

N: 313

Treatment duration (wks): 104
Washout period (d): 0
Comments: No wash off as metformin monotherapy (at study entry) was continued

Treatment(s): (a) Metformin (Oral)

Mean dose (mg/d): 1705
Details of dosing regimen: No change in metformin dose from the pre-study level was allowed at any stage of the study

(b) Sulfonylurea (Oral) – forced titration

Set dose (mg/d):320
Mean dose (mg/d): 212
Participants achieving full dose (n): 103
Frequency of dosing: twice a day
Details of dosing regimen: During a 16-week forced-titration phase, the sulfonylurea dose was increased in a step-wise manner to 160 mg, 240 mg (160 and 80 mg) and 320 mg (160 mg twice daily), according to tolerability.

At the end of week 16, 33% of patients had been titrated to the maximum dose of gliclazide (320 mg/day)

Outcomes

General

An intent-to-treat (ITT) analysis was used to assess efficacy. The ITT population included all patients who had received at least one dose of study medication and had HbA1c recorded at baseline and at least once after baseline. All patients who had received at least one dose of study medication were included in the safety analysis

2 year outcomes from Charbonnel (2005)/Seufert (2008) are also reported in this evidence table.

At year 2, 84/317 (26.5%) paients in the pioglitazone group and 75/313 (24%) in the gliclazide arm discontinued the study

Baseline characteristics

		Metformin + pioglitazone			Metformin + gliclazide			Δ	p
		N	k	mean	N	k	mean		
Demographics: Age (years)	Continuous	317		56 (SD 9.2)	313		57 (SD 9)		
Sex (n male)	Dichotomous	317	161	(50.8%)	313	154	(49.2%)		
Duration of diabetes (yrs)	Continuous	317		5.8 (SD 5.1)	313		5.5 (SD 5.1)		
Blood glucose: HbA1c (%) – 0wk	Continuous	317		8.71 (SD 1)	313		8.53 (SD 0.89)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	317		11.8 (SD 3.1)	313		11.3 (SD 2.6)		
Body weight: BMI (kg/m2)	Continuous	317		32.6 (SD 5)	313		32.6 (SD 5.8)		
Weight (kg) – 0wk	Continuous	317		91.8 (SD 16.2)	313		92.7 (SD 17.4)		
Waist circumference (cms)	Continuous	317		107 (SD 12)	313		106 (SD 12.8)		

Lipids: Total cholesterol (mmol/l)	Mean change	317		5.64 (SD 1.14)	313		5.58 (SD 1.15)		
HDL cholesterol (mmol/l)	Mean change	317		1.1 (SD 0.25)	313		1.09 (SD 0.23)		
Triglycerides (mmol/l)	Mean change	317		2.9 (SD 1.94)	313		2.78 (SD 1.89)		
LDL cholesterol (mmol/l)	Mean change	317		3.34 (SD 0.98)	313		3.28 (SD 0.93)		
Renal function: albumin:creatinine ratio	Continuous	317		0.06 (SD 0.14)	313		0.05 (SD 0.16)		

Results

		Metformin + pioglitazone			Metformin + gliclazide				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Blood glucose: HbA1c (%) – 16wka	Mean change	317		-0.98 (SD 0.712)	313		-1.45 (SD 0.531)		
HbA1c (%) – 24wka	Mean change	317		-1.15 (SD 0.89)	313		-1.39 (SD 0.885)		
HbA1c (%) – 52wkb	Mean change	317		-0.99 (SD 1.6)	313		-1.01 (SD 1.59)		
HbA1c (%) – 104wkc	Mean change	317		-0.89 (SD 1.07)	313		-0.77 (SD 0.761)		0.2
HbA1c < 7% or <=7% – 104wk	Dichotomous	317	97	(30.6%)	313	79d	(25.2%)		0.128
Fasting plasma glucose (mmol/l) – 16wka	Mean change	317		-2.3 (SD 2.14)	313		-2.4 (SD 2.12)		
Fasting plasma glucose (mmol/l) – 24wka	Mean change	317		-2.3 (SD 1.6)	313		-2.25 (SD 1.59)		
Fasting plasma glucose (mmol/l) – 52wka	Mean change	317		-2.1 (SD 2.31)	313		-1.6 (SD 2.12)		
Fasting plasma glucose (mmol/l) – 104wk	Continuous	317			313				NS
Fasting plasma glucose (mmol/l) – 104wka	Mean change	317		-1.8 (SD 2.14)	313		-1.1 (SD 2.12)		
Body weight: Weight (kg) – 104wk	Mean change	317		2.3 (SD 5.3)	313		1.1 (SD 4.6)		
Weight (kg) – 104wk	Continuous	317			313				NR
Hypoglycaemic events: All hypoglycaemic events (no patients) – 52wk	Dichotomous	317	4	(1.3%)	313	35	(11.2%)		
All hypoglycaemic events (no patients) – 104wk	Dichotomous	317	7	(2.2%)	313	36	(11.5%)		NR
Adverse events: Any adverse event(s) – 52wk	Dichotomous	317	176e	(55.5%)	313	628f	(200.6%)		
Any adverse event(s) – 52wk	Dichotomous	317	533f	(168.1%)	313	182e	(58.1%)		
Any adverse event(s) – 52wkf	Dichotomous	317	533	(168.1%)	313	628	(200.6%)		
Any adverse event(s) – 52wke	Dichotomous	317	176	(55.5%)	313	182	(58.1%)		
Any adverse event(s) – 104wk	Dichotomous	317	207	(65.3%)	313	214	(68.4%)		
Any serious adverse event(s) – 52wkf	Dichotomous	317	17	(5.4%)	313	27	(8.6%)		
Arthralgia – 104wk	Dichotomous	317	9	(2.8%)	313	19	(6.1%)		
Back pain – 104wk	Dichotomous	317	14	(4.4%)	313	23	(7.3%)		
cardiac: CHF – 104wk	Dichotomous	317	5	(1.6%)	313	2	(0.6%)		
Edema peripheral – 52wk	Dichotomous	317	20	(6.3%)	313	7	(2.2%)		

	Edema peripheral – 104wk	Dichotomous	317	21	(6.6%)	313	6	(1.9%)		
	Gastrointestinal disorders (any) – 104wk	Dichotomous	317	12	(3.8%)	313	16	(5.1%)		
	GI: diarrhoea – 104wk	Dichotomous	317	5	(1.6%)	313	13	(4.2%)		
	Hypertension – 104wk	Dichotomous	317	25	(7.9%)	313	38	(12.1%)		
	Infection (upper airway or other common) – 104wk	Dichotomous	317	16	(5.0%)	313	20	(6.4%)		
	Temperature/influenza – 104wk	Dichotomous	317	16	(5.0%)	313	10	(3.2%)		
	Study drug exposure – 104wkg	Continuous	317		11	313		11		
	Dropouts:									
	Total dropouts – 52wkh	Dichotomous	317	56	(17.7%)	313	42	(13.4%)		
	Total dropouts – 104wk	Dichotomous	317	84	(26.5%)	313	75	(24.0%)		
	Dropout due to AEs – 52wk	Dichotomous	317	13	(4.1%)	313	14	(4.5%)		
	Dropout due to AEs – 104wk	Dichotomous	317	22	(6.9%)	313	19	(6.1%)		
	Drop out due to unsatisfactory effect – 104wk	Dichotomous	317	12	(3.8%)	313	17	(5.4%)		

[a] estimated from graph
[b] estimated from graph; SD estimated from SE
[c] SD estimated from SE in graph
[d] approximated to nearest integer (percentages only presented in text)
[e] No patients
[f] No of events
[g] mean duration of treatment
[h] estimated from percentages provided

Statistical analysis of the primary efficacy variable (change in HbA1c from baseline to week 52) was performed using an ANCOVA model with the factor “treatment” and the baseline value as a continuous covariate. P-values for between group comparisons for adverse events were not reported.

Table 23: Nauck et al. (2007)

General	**Phase:** ☐ monotherapy ☑ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin + oral **Parallel / crossover:** Parallel **Country:** Australia, Austria, Belgium, South America, Czech Republic, Denmark, Finland, France, Germany, Hong Kong, Hungary, Italy, Malaysia, Netherlands, New Zealand, Norway, Poland, USA, South Africa, Spain, Taiwan etc. **Authors' conclusions:** In this study, the addition of sitagliptin compared with glipizide provided similar HbA1c-lowering efficacy over 52 weeks in patients on ongoing metformin therapy. Sitagliptin was generally well tolerated, with a lower risk of hypoglycaemia relative to glipizide and with weight loss compared with weight gain with glipizide **Source of funding:** funded by Merck & Co **Comments:** multinational, randomized, parallel group, non-inferiority study with an active-controlled, double-blind treatment period
Number and characteristics of patients	**Total number of patients:** 1172 **Inclusion criteria:** Men and women (age 18–78 years) with type 2 diabetes who were not currently on an OHA, were taking any OHA in monotherapy or were taking metformin in combination with another OHA were potentially eligible to participate in the study if they all met screening criteria **Exclusion criteria:** history of type 1 diabetes, insulin use within 8 weeks of screening, renal function impairment inconsistent with the use of metformin or a fasting plasma glucose (FPG) (or a fasting fingerstick glucose) at or just prior to randomization >15.0 mmol/l (270 mg/dl). Other treatments for hyperglycaemia were prohibited during the study. Patients were discontinued for lack of efficacy based on progressively stricter glycaemic criteria: from randomization through Week 6 for patients on two tablets (5-mg tablets) of glipizide/glipizide placebo for at least 2 weeks, FPG > 14.4 mmol/l (270 mg/dl); from Week6 through Week12 for patients on maximal dose (four 5-mg tablets) of glipizide/glipizide placebo for at least 2 weeks, FPG > 13.3 mmol/l (240 mg/dl); from Week 12 through Week 18 for patients on maximal dose of glipizide/glipizide placebo for at least 2 weeks, FPG >12.2 mmol/l (220 mg/dl); from Week 18 through Week 30, FPG>11.1 mmol/l (220 mg/dl) and from Week 30 toWeek 52, HbA1c > 8.0%.

	Pre-randomisation phase: Patients who were already on metformin >=1500 mg/day and had an HbA1c >=6.5 and <=10% directly entered a 2-week placebo run-in period and were eligible to be randomised. Patients not currently on an OHA, patients on an OHA other than metformin monotherapy at a dose >=1500 mg/day or patients on metformin in combination with another OHA entered a metformin monotherapy treatment titration and dose-stable period of at least 8 weeks. Patients with an HbA1c >=6.5 and <=10% after the metformin dose-stable period entered a 2-week single-blind placebo run-in period.
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** all on oral hypoglycaemic drugs and/or insulin **Details of washout period:** Patients were put onto a metformin monotherapy run-in period before randomisation. Ar screening they were naïve, on monotherapy or on combination therapy
Lifestyle advice	Patients received counselling on exercise and a diet consistent with American Diabetes Association recommendations throughout the study
Follow-up	**Total follow-up (wks):** 114 **Length of titration period (wks):** 8 **Length of maintenance period (wks):** 104 **Frequency of monitoring appointments:** -
Arms	**(1) Metformin + sitagliptin** N: 588 Treatment duration (wks): 104 Washout period (d): 0 Comments: All on a metformin monotherapy run-in period before randomisation to sitagliptin or sulfonylurea Treatment(s): (a) Metformin (Oral) Minimum dose (mg/d): 1500 Details of dosing regimen: Patients had a metformin monotherapy titration period before randomisation (b) Sitagliptin (Oral) – fixed-dose Set dose (mg/d):100 Frequency of dosing: once a day **(2) Metformin + glipizide** N: 584 Treatment duration (wks): - Washout period (d): 0 Comments: All on a metformin monotherapy run-in period before randomisation to sitagliptin or sulfonylurea Treatment(s): (a) Metformin (Oral) Minimum dose (mg/d): 1500 Details of dosing regimen: Patients had a metformin monotherapy titration period before randomisation (b) Sulfonylurea (Oral) – flexible-dose (dose-adjusted) Mean dose (mg/d): 9.2 Maximum dose (mg/d): 20 Participants achieving full dose (n): 93 Details of dosing regimen: After the starting dose of 5 mg/day, glipizide was uptitrated according to protocol-specified criteria to a potential maximum dose of 20 mg/day. In 3-week intervals during the first 18 weeks of treatment, glipizide was uptitrated if premeal fingerstick glucose values were >6.1 mmol/l (110 mg/dl). At the investigator's discretion, uptitration of glipizide was withheld if the investigator considered that uptitration would place the patient at risk for hypoglycaemia. At any time during the study, glipizide could be downtitrated to prevent recurrent hypoglycaemic events. At the end of 2 years, approximately 16% of the PP population received the max dose of 20 mg/day
Outcomes	**General** The primary efficacy analysis assessed whether the study treatments were non-inferior with regard to the HbA1c change from baseline at Week 52 using a per-protocol (PP) approach. The PP population consists of patients who completed all 52 weeks of treatment and did not have any reasons for exclusion from this population, including no baseline data, no treatment data at Week 52 or major protocol violations. Additional efficacy analyses were based on the all patients– treated (APT) population that consisted of all randomized patients who received at least one dose of study treatment and who had both a baseline and at least one post-baseline measurement; missing values in the APT analysis were handled by the last observation carried forward approach. After 52 weeks 202/588 (34%) patients in the sitagliptin group and 172/584 (29.5%) in the glipizide group discontinued the study. After 104 weeks 129/588 (21.3%) in the sitagliptin group and 137/584 (23.5%) in the glipizide group discontinued the study. Outcomes not extracted in this evidence table include several measures of insulin resistance

2 year data from the extension trial (Seck 2010) are also reported in this evidence table and pre-specified analyses relating to hypoglycaemia reported in Krobot (1012) are also reported here.

Hypoglycaemic events

Major/severe hypoglycaemic event (An event that required medical assistance)

confirmed hypoglycaemia (BG<3.9 mmol/l)

Baseline characteristics

		Metformin + sitagliptin			Metformin + glipizide				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	588		56.8 (SD 9.3)	584		56.6 (SD 9.8)		
Sex (n male)	Dichotomous	588	336	(57.1%)	584	358	(61.3%)		
Duration of diabetes (yrs)	Continuous	588		6.5 (SD 6.1)	584		6.2 (SD 5.4)		
Body weight: BMI (kg/m2)	Continuous	588		31.2 (SD 5)	584		31.3 (SD 5.2)		
Weight (kg) – 0wk	Continuous	588		89.5 (SD 17.4)	584		89.7 (SD 17.5)		
Previous blood glucose lowering drugs: Diet alone (i.e. drug naïve)	Dichotomous	588	25	(4.3%)	584	28	(4.8%)		
any monotherapy (1 previous OAD)	Dichotomous	588	386	(65.6%)	584	397	(68.0%)		
any dual therapy (2 previous OAD)	Dichotomous	588	177	(30.1%)	584	159	(27.2%)		
PP Demographics: Duration of diabetes (yrs)	Continuous	382		5.8 (SD 5.7)	411		5.7 (SD 4.9)		
Blood glucose: HbA1c (%) – 0wk	Continuous	382		7.3 (SD 0.6)	411		7.3 (SD 0.7)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	382		8.75 (SD 1.87)	411		8.84 (SD 2.14)		
Body weight: BMI (kg/m2)	Continuous	382		30.9 (SD 4.8)	411		31.3 (SD 5)		
Weight (kg) – 0wka	Continuous	382		87.21216 (SD 13.5)	411		88.34112 (SD 14.1)		
Weight (kg) – 12wk	Continuous	382		88.5 (SD 16.8)	411		90.3 (SD 16.5)		
PP (2 year) Blood glucose: HbA1c (%) – 6wk	Continuous	248		7.3 (SD 0.64)	256		7.31 (SD 0.74)		

[a] estimated from BMI assuming mean height of 1.68m

Results

		Metformin + sitagliptin			Metformin + glipizide				
		N	k	mean	N	k	mean	Δ	p
Body weight: Weight (kg) – 12wka	Mean change	588		-1.1 (SD 1.7)	584		0.9 (SD 1.69)		
Weight (kg) – 24wka	Mean change	588		-1.3 (SD 3.64)	584		1.2 (SD 3.62)		
Weight (kg) – 52wkb	Mean change	588		-1.5 (SD 6.8)	584		1.1 (SD 6.78)		
Weight (kg) – 104wk	Mean change	576		-1.6 (SD 8.57)	559		0.7 (SD 8.44)		
Waist circumference (cms) – 52wk	Mean change	588		-1.4 (SD 5.8)	584		0.7 (SD 6)		

Hypoglycaemic events:										
All hypoglycaemic events (no events) – 52wkc	Count	177268	50		181272	657			
All hypoglycaemic events (no events) – 104wkc	Count	306852	57		312676	805			
All hypoglycaemic events (no patients) – 52wk	Dichotomous	588	29	(4.9%)	584	187	(32.0%)		
All hypoglycaemic events (no patients) – 104wk	Dichotomous	588	31	(5.3%)	584	199	(34.1%)		
Major/severe hypoglycaemic event – 52wk	Dichotomous	588	2d	(0.3%)	584	7	(1.2%)		
Major/severe hypoglycaemic event – 52wk	Dichotomous	588	1	(0.2%)	584	7	(1.2%)		
Major/severe hypoglycaemic event – 52wk	Count	588			584			HR=0.080 (CI: 54.885, 0.000)	<0.001
Major/severe hypoglycaemic event – 52wk	Dichotomous	588	1	(0.2%)	584	22d	(3.8%)		
Major/severe hypoglycaemic event – 52wkd	Dichotomous	588	2	(0.3%)	584	22	(3.8%)		
Major/severe hypoglycaemic event – 104wk	Dichotomous	588	1	(0.2%)	584	9	(1.5%)		
symptomatic (confirmed) – 52wkd	Dichotomous	588	31	(5.3%)	584	448	(76.7%)		
symptomatic (confirmed) – 52wk	Count	588			584			HR=0.050 (CI: 399.655, 0.000)	<0.001
confirmed hypoglycaemia – 52wke	Dichotomous	43	31	(72.1%)	598	435	(72.7%)		
confirmed hypoglycaemia – 104wk	Dichotomous	49	35f	(71.4%)	726	242g	(33.3%)		
confirmed hypoglycaemia – 104wkf	Dichotomous	49	35	(71.4%)	726	554	(76.3%)		
confirmed hypoglycaemia – 104wkg	Dichotomous	49	14	(28.6%)	726	242	(33.3%)		
confirmed hypoglycaemia – 104wkh	Dichotomous	49	4	(8.2%)	726	61	(8.4%)		
confirmed hypoglycaemia – 104wk	Dichotomous	49	4h	(8.2%)	726	554f	(76.3%)		
confirmed hypoglycaemia – 104wk	Dichotomous	49	35f	(71.4%)	726	61h	(8.4%)		

confirmed hypoglycaemia – 104wk	Dichotomous	49	14g	(28.6%)	726	61h	(8.4%)		
confirmed hypoglycaemia – 104wk	Dichotomous	49	14g	(28.6%)	726	554f	(76.3%)		
confirmed hypoglycaemia – 104wk	Dichotomous	49	4h	(8.2%)	726	242g	(33.3%)		
Adverse events: GI: nausea – 52wk	Dichotomous	588	15	(2.6%)	584	16	(2.7%)		
Any adverse event(s) – 52wk	Dichotomous	588	419	(71.3%)	584	444	(76.0%)		
Any adverse event(s) – 104wk	Dichotomous	588	452	(76.9%)	584	480	(82.2%)		
Any serious adverse event(s) – 52wk	Dichotomous	588	43	(7.3%)	584	44	(7.5%)		
Any serious adverse event(s) – 104wk	Dichotomous	588	64	(10.9%)	584	73	(12.5%)		
Study drug-related adverse event – 52wk	Dichotomous	588	85	(14.5%)	584	177	(30.3%)		
Chest pain – 104wk	Dichotomous	588	11	(1.9%)	584	4	(0.7%)		
Cough – 104wk	Dichotomous	588	23	(3.9%)	584	32	(5.5%)		
Death – 52wk	Dichotomous	588	1	(0.2%)	584	2	(0.3%)		
Death – 104wk	Dichotomous	588	1	(0.2%)	584	8	(1.4%)		
Dizziness – 104wk	Dichotomous	588	26	(4.4%)	584	19	(3.3%)		
Dyspepsia – 104wk	Dichotomous	588	11	(1.9%)	584	20	(3.4%)		
Edema peripheral – 104wk	Dichotomous	588	13	(2.2%)	584	22	(3.8%)		
Fatigue – 104wk	Dichotomous	588	18	(3.1%)	584	11	(1.9%)		
GI: diarrhoea – 52wk	Dichotomous	588	34	(5.8%)	584	32	(5.5%)		
GI: vomiting – 52wk	Dichotomous	588	5	(0.9%)	584	9	(1.5%)		
GI: abdominal pain – 52wk	Dichotomous	588	16	(2.7%)	584	12	(2.1%)		
Hypoesthesia – 104wk	Dichotomous	588	1	(0.2%)	584	10	(1.7%)		
Infection (upper airway or other common) – 104wk	Dichotomous	588	73	(12.4%)	584	79	(13.5%)		
liver enzymes: abnormal ALT – 52wk	Mean change	588		-1.3 (SD 11.9)	584		0.9 (SD 8.2)		
Liver enzymes: AST (U/l) – 52wk	Mean change	588		-0.4 (SD 6.1)	584		0.7 (SD 6.3)		
Nasopharyngitis – 104wk	Dichotomous	588	71	(12.1%)	584	61	(10.4%)		
Osteoarthritis – 104wk	Dichotomous	588	18	(3.1%)	584	8	(1.4%)		
Pain (extremity) – 104wk	Dichotomous	588	21	(3.6%)	584	9	(1.5%)		

Sinusitis or sinus abnormality – 104wk	Dichotomous	588	26	(4.4%)	584	18	(3.1%)		
Skin reaction – 104wk	Dichotomous	588	9	(1.5%)	584	3	(0.5%)		
UTI – 104wk	Dichotomous	588	44	(7.5%)	584	25	(4.3%)		
Study drug exposure – 52wki	Continuous	588		297.1	584		287.5		
Dropouts:									
Total dropouts – 52wk	Dichotomous	588	200	(34.0%)	584	172	(29.5%)		
Total dropouts – 104wk	Dichotomous	588	333	(56.6%)	584	320	(54.8%)		
Dropout due to AEs – 52wkj	Dichotomous	588	24	(4.1%)	584	29	(5.0%)		
Dropout due to AEs – 104wk	Dichotomous	588	32	(5.4%)	584	38j	(6.5%)		
drop out due to SAE – 52wkj	Dichotomous	588	6	(1.0%)	584	7	(1.2%)		
drop out due to SAE – 104wkj	Dichotomous	588	11	(1.9%)	584	15	(2.6%)		
Men									
Hypoglycaemic events:									
Major/severe hypoglycaemic event – 52wkd	Dichotomous	336	1	(0.3%)	358	5	(1.4%)		
symptomatic (confirmed) – 52wk	Count	336			358			HR=0.060 (CI: 123.270, 0.000)	<0.001
symptomatic (confirmed) – 52wkd	Dichotomous	336	14	(4.2%)	358	206	(57.5%)		
Women									
Hypoglycaemic events:									
Major/severe hypoglycaemic event – 52wkd	Dichotomous	252	1	(0.4%)	226	17	(7.5%)		
symptomatic (confirmed) – 52wk	Count	252			226			HR=0.040 (CI: 319.724, 0.000)	<0.001
symptomatic (confirmed) – 52wkd	Dichotomous	252	17	(6.7%)	226	242	(107.1%)		
PP									
Blood glucose:									
HbA1c (%) – 12wka	Continuous	382		6.73 (SD 0.195)	411		6.62 (SD 0.203)		
HbA1c (%) – 30wka	Continuous	382		6.6 (SD 0.195)	411		6.55 (SD 0.203)		
HbA1c (%) – 52wkb	Mean change	588		-0.67 (SD 0.798)	584		-0.67 (SD 0.827)	MD=-0.001 (CI: -0.090, 0.088)	
HbA1c (%) – 52wkb	Mean change	382		-0.67 (SD 0.798)	411		-0.67 (SD 0.827)	MD=-0.001 (CI: -0.090, 0.088)	
HbA1c (%) – 52wk	Continuous	382		6.84 (SD 0.66)	411		6.86 (SD 0.69)		

HbA1c < 7% or <=7% – 52wk	Dichotomous	588	240	(62.8%)	584	242	(58.9%)	MD=3.900 (CI: -2.800, 10.600)	k
HbA1c < 7% or <=7% – 52wk	Dichotomous	382	240	(62.8%)	411	242	(58.9%)	MD=3.900 (CI: -2.800, 10.600)	k
Hba1c <6.5% – 52wkl	Dichotomous	588	111	(29.1%)	584	119	(29.0%)	MD=-0.100 (CI: -6.400, 6.200)	k
Hba1c <6.5% – 52wkl	Dichotomous	382	111	(29.1%)	411	119	(29.0%)	MD=-0.100 (CI: -6.400, 6.200)	k
Fasting plasma glucose (mmol/l) – 12wka	Continuous	382		7.55 (SD 0.977)	411		7.45 (SD 1.01)		
Fasting plasma glucose (mmol/l) – 30wka	Continuous	382		7.5 (SD 0.977)	411		7.5 (SD 1.01)		
Fasting plasma glucose (mmol/l) – 52wk	Mean change	382		-0.56 (SD 2.49)	407		-0.42 (SD 2.57)	MD=-0.140 (CI: -0.380, 0.100)	
Fasting plasma glucose (mmol/l) – 52wk	Continuous	382		8.04 (SD 1.84)	407		8.22 (SD 2.2)		
Fasting plasma glucose (mmol/l) – 52wk	Mean change	588		-0.56 (SD 2.49)	584		-0.42 (SD 2.57)	MD=-0.140 (CI: -0.380, 0.100)	
Randomised set/treated set									
Blood glucose:									
HbA1c < 7% or <=7% – 52wk	Dichotomous	588	300m	(52.1%)	584	285l	(51.0%)		
HbA1c < 7% or <=7% – 52wk	Dichotomous	576	300m	(52.1%)	559	285l	(51.0%)		
Hba1c <6.5% – 52wk	Dichotomous	576	138m	(24.0%)	559	140l	(25.0%)		
Hba1c <6.5% – 52wk	Dichotomous	588	138m	(24.0%)	584	140l	(25.0%)		
Body weight:									
Weight (kg) – 52wk	Continuous	588			584			MD=-2.500 (CI: -3.100, -1.900)	
Weight (kg) – 104wk	Continuous	588			584			MD=-2.300 (CI: -3.000, -1.600)	
Baseline Hba1c <7%									
Blood glucose:									
HbA1c (%) – 52wkn	Mean change	112		-0.26 (SD 0.212)	117		-0.14 (SD 0.541)		
baseline Hba1c >=7% to <8%									
Blood glucose:									
HbA1c (%) – 52wkn	Mean change	167		-0.53 (SD 0.388)	179		-0.59 (SD 0.535)		
baseline Hba1c >=8 to <9%									
Blood glucose:									
HbA1c (%) – 52wkn	Mean change	82		-1.13 (SD 0.634)	82		-1.11 (SD 0.724)		

	baseline Hba1c >=9%									
	Blood glucose:									
	HbA1c (%) – 52wko	Mean change	21		-1.68 (SD 0.733)	33		-1.76 (SD 0.747)		
	HbA1c (%) – 52wk	Mean change	21		-0.94p	33		-1.76 (SD 0.747) o		
	HbA1c (%) – 52wk	Mean change	21		-1.68 (SD 0.733) o	33		-1.31p		
	HbA1c (%) – 52wkp	Mean change	21		-0.94	33		-1.31		
	Age >=65 years									
	Hypoglycaemic events:									
	Major/severe hypoglycaemic event – 52wkd	Dichotomous	120	0	(0.0%)	123	3	(2.4%)		
	symptomatic (confirmed) – 52wk	Count	120			123			HR=0.020 (CI: 621.947, 0.000)	<0.001
	symptomatic (confirmed) – 52wkd	Dichotomous	120	4	(3.3%)	123	132	(107.3%)		
	Age <65 years									
	Hypoglycaemic events:									
	Major/severe hypoglycaemic event – 52wkd	Dichotomous	468	2	(0.4%)	461	19	(4.1%)		
	symptomatic (confirmed) – 52wkd	Dichotomous	468	27	(5.8%)	461	316	(68.5%)		
	symptomatic (confirmed) – 52wk	Count	468			461			HR=0.060 (CI: 216.638, 0.000)	<0.001
	PP (2 year)									
	Blood glucose:									
	HbA1c (%) – 104wkb	Mean change	588		-0.54 (SD 0.763)	584		-0.51 (SD 0.735)	MD=-0.030 (CI: -0.130, 0.070)	
	HbA1c (%) – 104wkb	Mean change	248		-0.54 (SD 0.763)	256		-0.51 (SD 0.735)	MD=-0.030 (CI: -0.130, 0.070)	
	HbA1c (%) – 104wk	Continuous	248		6.77 (SD 0.58)	256		6.8 (SD 0.59)		
	HbA1c < 7% or <=7% – 104wk	Dichotomous	248	157	(63.3%)	256	151	(59.0%)		
	Hba1c <6.5% – 104wk	Dichotomous	248			256				
	Fasting plasma glucose (mmol/l) – 104wk	Continuous	588			584			MD=-0.100 (CI: -0.400, 0.200)	
	Fasting plasma glucose (mmol/l) – 104wk	Mean change	248		-1.1 (SD 2.41)	256		-1 (SD 2.45)		
	APT (2 year)									
	Blood glucose:									
	HbA1c < 7% or <=7% – 104wk	Dichotomous	576	242	(42.0%)	559	218	(39.0%)		

[a] estimated from graph

	[b] SD estimated from 95% CI [c] (Used in the analysis); reviewer estimated patient days [d] numerator is total number of events [e] denominator is number of episodes with BG levels obtained [f] BG <3.9 mmol/l; denominator is number of episodes with BG levels obtained [g] BG <3.3 mmol/l; denominator is number of episodes with BG levels obtained [h] BG <2.8 mmol/l; denominator is number of episodes with BG levels obtained [i] days [j] Inconsistencies in reported data in trial flow diagram and safety table. Data derived from safety table [k] difference in proportion [l] approximated to nearest integer (percentages only presented in text) [m] approximated to nearest integer (percentages only presented in text); approximated to nearest integer (percentages only presented in text) [n] PP; SD estimated from graph [o] PP [p] No SDs reported
	ANCOVA was used to compare the treatment groups for efficacy endpoints, focusing on change from baseline at Week 52, with baseline values and prior OHA status as covariates. The proportion of patients achieving an HbA1c < 7 or <6.5% was compared between treatments using a logistic regression analysis. Subgroup analyses for the primary efficacy endpoint. P-values for adverse events were not reported. For hypoglycaemia Log-log regression was used to assess the absolute and relative risk og hypoglycaemic events on a given day in relation to patient factors. Covariates that varied within patient were the most recent Hba1c value and time (days since randomisation). Absolute risks were estimated using population averaged generalised estimating equations (GEE). All analyses were clustered on patient.

Table 24: Nauck et al. (2009)

General	**Phase:** ☐ monotherapy ☑ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin + oral **Parallel / crossover:** Parallel **Country:** 21 countries participated. **Authors' conclusions:** In subjects with type 2 diabetes, once-daily liraglutide induced similar glycemic control, reduced body weight, and lowered the occurrence of hypoglycemia compared with glimepiride, when both had background therapy of metformin. **Source of funding:** Novo Nordisk **Comments:** Double-blind
Number and characteristics of patients	**Total number of patients:** 1091 **Inclusion criteria:** People with type 2 diabetes, aged 18 to 80 years, HbA1c between 7 and 11% (monotherapy) or 7 and 10% (combination therapy), BMI <=40kg/m2 **Exclusion criteria:** Used insulin within 3 months (except short term treatment) Pre-randomisation phase: Randomisation occurred after a 3 week forced metformin titration period (dose inclreased up to 2000mg/day- 100mg morning, 1000mg evening). This was followed by a 3 week metformin maintenance period. People already on metformin at baseline could go through a modified titration period or adviance straight to the maintenance period.
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** all on oral hypoglycaemic drugs and/or insulin **Details of washout period:** Not provided- unclear if baseline drugs were stopped (except metformin) but have assumed they were. On monotherapy or combination therapy at screening
Lifestyle advice	Not stated
Follow-up	**Total follow-up (wks):** 26 **Length of titration period (wks):** 3 **Length of maintenance period (wks):** 23 **Frequency of monitoring appointments:** 8, 12, 18, 26
Arms	**(1) Metformin + Liraglutide 0.6 + placebo** N: 242 Treatment duration (wks): 26 Washout period (d): - Treatment(s): (a) Metformin (Oral) – fixed-dose

	Set dose (mg/d):2000 Frequency of dosing: twice a day Details of dosing regimen: 1000 mg given twice a day Metformin could be decreased to a minimum of 1500mg/day in the case of unacceptable hypoglycaemia or other adverse events, but had to be maintained between 1500 and 200mg/day during the maintenace period. (b) Liraglutide (Subcutaneous) – fixed-dose Set dose (mg/d):0.6 Frequency of dosing: once a day Details of dosing regimen: Injected once daily at any time of the day in the upper arm, abdomen or thigh. Subjects were encouraged to inject at the same time each day **(2) Metformin + liraglutide 1.2mg + placebo** N: 241 Treatment duration (wks): 26 Washout period (d): - Treatment(s): (a) Metformin (Oral) – fixed-dose Set dose (mg/d):2000 Frequency of dosing: twice a day Details of dosing regimen: 1000 mg given twice a day Metformin could be decreased to a minimum of 1500mg/day in the case of unacceptable hypoglycaemia or other adverse events, but had to be maintained between 1500 and 200mg/day during the maintenace period. (b) Liraglutide (Subcutaneous) – fixed-dose Set dose (mg/d):1.2 Frequency of dosing: once a day Details of dosing regimen: Participants were titrated up to 1.2 in increments of 0.6mg each week Injected once daily at any time of the day in the upper arm, abdomen or thigh. Subjects were encouraged to inject at the same time each day **(3) Metformin + liraglutide 1.8mg + placebo** N: 242 Treatment duration (wks): 26 Washout period (d): - Treatment(s): (a) Metformin (Oral) – fixed-dose Set dose (mg/d):2000 Frequency of dosing: twice a day Details of dosing regimen: 1000 mg given twice a day Metformin could be decreased to a minimum of 1500mg/day in the case of unacceptable hypoglycaemia or other adverse events, but had to be maintained between 1500 and 200mg/day during the maintenace period. (b) Liraglutide (Subcutaneous) – fixed-dose Set dose (mg/d):1.8 Frequency of dosing: once a day Details of dosing regimen: Participants were titrated up to 1.8 in increments of 0.6mg each week Injected once daily at any time of the day in the upper arm, abdomen or thigh. Subjects were encouraged to inject at the same time each day **(4) Metformin + glimepiride + placebo** N: 244 Treatment duration (wks): 26 Washout period (d): - Treatment(s): (a) Metformin (Oral) – fixed-dose Set dose (mg/d):2000 Frequency of dosing: twice a day Details of dosing regimen: 1000 mg given twice a day Metformin could be decreased to a minimum of 1500mg/day in the case of unacceptable hypoglycaemia or other adverse events, but had to be maintained between 1500 and 200mg/day during the maintenace period. (b) Sulfonylurea (Oral) – forced titration Set dose (mg/d):4 Frequency of dosing: once a day Details of dosing regimen: Titrated up to 4mg with 1, 2 3 and 4 mg doses at weeks 1, 2 and 3. Taken once daily in the morning.
Outcomes	**General** The analysis of efficacy end points were based on ITT- defined as subjects who were exposed to at least one dose of trial product and had one postbaseline measurement of the parameter.

Each end point was analysed using ANCOVA eith treatment, country and previous antidiabetic treatment as covariates.

Missing data were imputed as the last observation carried forward.

5 arms are available but only 4 are extracted, since one of the arms is monotherapy (Metformin + liraglutide placebo + glimepiride placebo).

Baseline characteristics

		Metformin + Liraglutide 0.6 + placebo			Metformin + liraglutide 1.2mg + placebo				
		N	k	mean	N	k	mean	Δ	p
Demographics:									
Age (years) – 0wk	Continuous	242		56 (SD 11)	241		57 (SD 9)		
Sex (n male) – 0wk	Dichotomous	242	150	(62.0%)	241	130	(53.9%)		
Duration of diabetes (yrs) – 0wk	Continuous	242		7 (SD 5)	241		7 (SD 5)		
Blood glucose:									
HbA1c (%) – 0wk	Continuous	242		8.4 (SD 0.9)	241		8.3 (SD 1)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	242		10.2 (SD 2.4)	241		9.9 (SD 2.3)		
Body weight:									
BMI (kg/m2) – 0wk	Continuous	242		30.5 (SD 4.8)	241		31.1 (SD 4.8)		
Weight (kg) – 0wka	Continuous	242		86.0832 (SD 13.5)	241		87.77664 (SD 13.5)		
Blood pressure:									
Systolic blood pressure (mmHg) – 0wk	Continuous	242		131 (SD 14)	241		132 (SD 14)		
Diastolic blood pressure (mmHg) – 0wk	Continuous	242		80 (SD 8)	241		80 (SD 10)		
Previous blood glucose lowering drugs:									
Metformin – 0wk	Dichotomous	242	70	(28.9%)	241	78	(32.4%)		
Sulfonylurea – 0wk	Dichotomous	242	9	(3.7%)	241	12	(5.0%)		
Combination therapy – 0wk	Dichotomous	242	161	(66.5%)	241	150	(62.2%)		
Repaglinide – 0wk	Dichotomous	242	2	(0.8%)	241	1	(0.4%)		
Baseline montherapy									
Blood glucose:									
HbA1c (%) – 12wkb	Continuous	81		8.3 (SD 0.9)	91		8.3 (SD 1.19)		
HbA1c (%) – 12wkb	Continuous	81		7.15 (SD 0.9)	91		7.055 (SD 0.873)		
HbA1c (%) – 12wkb	Continuous	81		7.15 (SD 0.9)	91		8.3 (SD 1.19)		
HbA1c (%) – 12wkb	Continuous	81		8.3 (SD 0.9)	91		7.055 (SD 0.873)		
Baseline combination therapy									
Blood glucose:									
HbA1c (%) – 12wkb	Continuous	161		7.95 (SD 1.16)	150		7.55 (SD 1.22)		
HbA1c (%) – 12wkb	Continuous	161		7.95 (SD 1.16)	150		8.3 (SD 1.22)		
HbA1c (%) – 12wkb	Continuous	161		8.45 (SD 1.27)	150		7.55 (SD 1.22)		
HbA1c (%) – 12wkb	Continuous	161		8.45 (SD 1.27)	150		8.3 (SD 1.22)		

[a] estimated from BMI assuming mean height of 1.68m

[b] Data estimated from graphs. SD estimated from reported 2xSEM

		Metformin + Liraglutide 0.6 + placebo			Metformin + liraglutide 1.8mg + placebo				
		N	k	mean	N	k	mean	Δ	p
Demographics:									
Age (years) – 0wk	Continuous	242		56 (SD 11)	242		57 (SD 9)		
Sex (n male) – 0wk	Dichotomous	242	150	(62.0%)	242	143	(59.1%)		

Duration of diabetes (yrs) – 0wk	Continuous	242		7 (SD 5)	242		8 (SD 5)		
Blood glucose:									
HbA1c (%) – 0wk	Continuous	242		8.4 (SD 0.9)	242		8.4 (SD 1)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	242		10.2 (SD 2.4)	242		10.1 (SD 2.3)		
Body weight:									
BMI (kg/m2) – 0wk	Continuous	242		30.5 (SD 4.8)	242		30.9 (SD 4.6)		
Weight (kg) – 0wka	Continuous	242		86.0832 (SD 13.5)	242		87.21216 (SD 13)		
Blood pressure:									
Systolic blood pressure (mmHg) – 0wk	Continuous	242		131 (SD 14)	242		131 (SD 14)		
Diastolic blood pressure (mmHg) – 0wk	Continuous	242		80 (SD 8)	242		79 (SD 8)		
Previous blood glucose lowering drugs:									
Metformin – 0wk	Dichotomous	242	70	(28.9%)	242	72	(29.8%)		
Sulfonylurea – 0wk	Dichotomous	242	9	(3.7%)	242	11	(4.5%)		
Combination therapy – 0wk	Dichotomous	242	161	(66.5%)	242	159	(65.7%)		
Repaglinide – 0wk	Dichotomous	242	2	(0.8%)	242	0	(0.0%)		
Baseline montherapy									
Blood glucose:									
HbA1c (%) – 12wkb	Continuous	81		8.3 (SD 0.9)	83		8.25 (SD 1.14)		
HbA1c (%) – 12wkb	Continuous	81		7.15 (SD 0.9)	83		6.905 (SD 1.14)		
HbA1c (%) – 12wkb	Continuous	81		7.15 (SD 0.9)	83		8.25 (SD 1.14)		
HbA1c (%) – 12wkb	Continuous	81		8.3 (SD 0.9)	83		6.905 (SD 1.14)		
Baseline combination therapy									
Blood glucose:									
HbA1c (%) – 12wkb	Continuous	161		7.95 (SD 1.16)	159		7.65 (SD 1.26)		
HbA1c (%) – 12wkb	Continuous	161		7.95 (SD 1.16)	159		8.405 (SD 1.26)		
HbA1c (%) – 12wkb	Continuous	161		8.45 (SD 1.27)	159		7.65 (SD 1.26)		
HbA1c (%) – 12wkb	Continuous	161		8.45 (SD 1.27)	159		8.405 (SD 1.26)		

[a] estimated from BMI assuming mean height of 1.68m
[b] Data estimated from graphs. SD estimated from reported 2xSEM

		Metformin + Liraglutide 0.6 + placebo			Metformin + glimepiride + placebo				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Demographics:									
Age (years) – 0wk	Continuous	242		56 (SD 11)	244		57 (SD 9)		
Sex (n male) – 0wk	Dichotomous	242	150	(62.0%)	244	139	(57.0%)		
Duration of diabetes (yrs) – 0wk	Continuous	242		7 (SD 5)	244		8 (SD 5)		
Blood glucose:									
HbA1c (%) – 0wk	Continuous	242		8.4 (SD 0.9)	244		8.4 (SD 1)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	242		10.2 (SD 2.4)	244		10 (SD 2.6)		
Body weight:									
BMI (kg/m2) – 0wk	Continuous	242		30.5 (SD 4.8)	244		31.2 (SD 4.6)		
Weight (kg) – 0wka	Continuous	242		86.0832 (SD 13.5)	244		88.05888 (SD 13)		
Blood pressure:									
Systolic blood pressure (mmHg) – 0wk	Continuous	242		131 (SD 14)	244		132 (SD 16)		

Diastolic blood pressure (mmHg) – 0wk	Continuous	242		80 (SD 8)	244		80 (SD 8)		
Previous blood glucose lowering drugs:									
Metformin – 0wk	Dichotomous	242	70	(28.9%)	244	82	(33.6%)		
Sulfonylurea – 0wk	Dichotomous	242	9	(3.7%)	244	7	(2.9%)		
Combination therapy – 0wk	Dichotomous	242	161	(66.5%)	244	155	(63.5%)		
Repaglinide – 0wk	Dichotomous	242	2	(0.8%)	244	0	(0.0%)		
Baseline montherapy									
Blood glucose:									
HbA1c (%) – 12wkb	Continuous	81		8.3 (SD 0.9)	89		8.15 (SD 0.943)		
HbA1c (%) – 12wkb	Continuous	81		7.15 (SD 0.9)	89		6.9 (SD 1.18)		
HbA1c (%) – 12wkb	Continuous	81		7.15 (SD 0.9)	89		8.15 (SD 0.943)		
HbA1c (%) – 12wkb	Continuous	81		8.3 (SD 0.9)	89		6.9 (SD 1.18)		
Baseline combination therapy									
Blood glucose:									
HbA1c (%) – 12wkb	Continuous	161		7.95 (SD 1.16)	155		7.7 (SD 1.25)		
HbA1c (%) – 12wkb	Continuous	161		7.95 (SD 1.16)	155		8.55 (SD 1.25)		
HbA1c (%) – 12wkb	Continuous	161		8.45 (SD 1.27)	155		7.7 (SD 1.25)		
HbA1c (%) – 12wkb	Continuous	161		8.45 (SD 1.27)	155		8.55 (SD 1.25)		

[a] estimated from BMI assuming mean height of 1.68m
[b] Data estimated from graphs. SD estimated from reported 2xSEM

		Metformin + liraglutide 1.2mg + placebo			Metformin + liraglutide 1.8mg + placebo				
		N	k	mean	N	k	mean	Δ	p
Demographics:									
Age (years) – 0wk	Continuous	241		57 (SD 9)	242		57 (SD 9)		
Sex (n male) – 0wk	Dichotomous	241	130	(53.9%)	242	143	(59.1%)		
Duration of diabetes (yrs) – 0wk	Continuous	241		7 (SD 5)	242		8 (SD 5)		
Blood glucose:									
HbA1c (%) – 0wk	Continuous	241		8.3 (SD 1)	242		8.4 (SD 1)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	241		9.9 (SD 2.3)	242		10.1 (SD 2.3)		
Body weight:									
BMI (kg/m2) – 0wk	Continuous	241		31.1 (SD 4.8)	242		30.9 (SD 4.6)		
Weight (kg) – 0wka	Continuous	241		87.77664 (SD 13.5)	242		87.21216 (SD 13)		
Blood pressure:									
Systolic blood pressure (mmHg) – 0wk	Continuous	241		132 (SD 14)	242		131 (SD 14)		
Diastolic blood pressure (mmHg) – 0wk	Continuous	241		80 (SD 10)	242		79 (SD 8)		
Previous blood glucose lowering drugs:									
Metformin – 0wk	Dichotomous	241	78	(32.4%)	242	72	(29.8%)		
Sulfonylurea – 0wk	Dichotomous	241	12	(5.0%)	242	11	(4.5%)		
Combination therapy – 0wk	Dichotomous	241	150	(62.2%)	242	159	(65.7%)		
Repaglinide – 0wk	Dichotomous	241	1	(0.4%)	242	0	(0.0%)		
Baseline montherapy									
Blood glucose:									
HbA1c (%) – 12wkb	Continuous	91		8.3 (SD 1.19)	83		8.25 (SD 1.14)		
HbA1c (%) – 12wkb	Continuous	91		7.055 (SD 0.873)	83		6.905 (SD 1.14)		
HbA1c (%) – 12wkb	Continuous	91		7.055 (SD 0.873)	83		8.25 (SD 1.14)		

HbA1c (%) – 12wkb	Continuous	91		8.3 (SD 1.19)	83		6.905 (SD 1.14)	
Baseline combination therapy								
Blood glucose:								
HbA1c (%) – 12wkb	Continuous	150		7.55 (SD 1.22)	159		7.65 (SD 1.26)	
HbA1c (%) – 12wkb	Continuous	150		7.55 (SD 1.22)	159		8.405 (SD 1.26)	
HbA1c (%) – 12wkb	Continuous	150		8.3 (SD 1.22)	159		7.65 (SD 1.26)	
HbA1c (%) – 12wkb	Continuous	150		8.3 (SD 1.22)	159		8.405 (SD 1.26)	

[a] estimated from BMI assuming mean height of 1.68m
[b] Data estimated from graphs. SD estimated from reported 2xSEM

		Metformin + liraglutide 1.2mg + placebo			Metformin + glimepiride + placebo				
		N	k	mean	N	k	mean	Δ	p
Demographics:									
Age (years) – 0wk	Continuous	241		57 (SD 9)	244		57 (SD 9)		
Sex (n male) – 0wk	Dichotomous	241	130	(53.9%)	244	139	(57.0%)		
Duration of diabetes (yrs) – 0wk	Continuous	241		7 (SD 5)	244		8 (SD 5)		
Blood glucose:									
HbA1c (%) – 0wk	Continuous	241		8.3 (SD 1)	244		8.4 (SD 1)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	241		9.9 (SD 2.3)	244		10 (SD 2.6)		
Body weight:									
BMI (kg/m2) – 0wk	Continuous	241		31.1 (SD 4.8)	244		31.2 (SD 4.6)		
Weight (kg) – 0wka	Continuous	241		87.77664 (SD 13.5)	244		88.05888 (SD 13)		
Blood pressure:									
Systolic blood pressure (mmHg) – 0wk	Continuous	241		132 (SD 14)	244		132 (SD 16)		
Diastolic blood pressure (mmHg) – 0wk	Continuous	241		80 (SD 10)	244		80 (SD 8)		
Previous blood glucose lowering drugs:									
Metformin – 0wk	Dichotomous	241	78	(32.4%)	244	82	(33.6%)		
Sulfonylurea – 0wk	Dichotomous	241	12	(5.0%)	244	7	(2.9%)		
Combination therapy – 0wk	Dichotomous	241	150	(62.2%)	244	155	(63.5%)		
Repaglinide – 0wk	Dichotomous	241	1	(0.4%)	244	0	(0.0%)		
Baseline montherapy									
Blood glucose:									
HbA1c (%) – 12wkb	Continuous	91		8.3 (SD 1.19)	89		8.15 (SD 0.943)		
HbA1c (%) – 12wkb	Continuous	91		7.055 (SD 0.873)	89		6.9 (SD 1.18)		
HbA1c (%) – 12wkb	Continuous	91		7.055 (SD 0.873)	89		8.15 (SD 0.943)		
HbA1c (%) – 12wkb	Continuous	91		8.3 (SD 1.19)	89		6.9 (SD 1.18)		
Baseline combination therapy									
Blood glucose:									
HbA1c (%) – 12wkb	Continuous	150		7.55 (SD 1.22)	155		7.7 (SD 1.25)		
HbA1c (%) – 12wkb	Continuous	150		7.55 (SD 1.22)	155		8.55 (SD 1.25)		
HbA1c (%) – 12wkb	Continuous	150		8.3 (SD 1.22)	155		7.7 (SD 1.25)		
HbA1c (%) – 12wkb	Continuous	150		8.3 (SD 1.22)	155		8.55 (SD 1.25)		

[a] estimated from BMI assuming mean height of 1.68m
[b] Data estimated from graphs. SD estimated from reported 2xSEM

		Metformin + liraglutide 1.8mg + placebo			Metformin + glimepiride + placebo				
		N	k	mean	N	k	mean	Δ	p
Demographics:									
Age (years) – 0wk	Continuous	242		57 (SD 9)	244		57 (SD 9)		
Sex (n male) – 0wk	Dichotomous	242	143	(59.1%)	244	139	(57.0%)		
Duration of diabetes (yrs) – 0wk	Continuous	242		8 (SD 5)	244		8 (SD 5)		
Blood glucose:									
HbA1c (%) – 0wk	Continuous	242		8.4 (SD 1)	244		8.4 (SD 1)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	242		10.1 (SD 2.3)	244		10 (SD 2.6)		
Body weight:									
BMI (kg/m2) – 0wk	Continuous	242		30.9 (SD 4.6)	244		31.2 (SD 4.6)		
Weight (kg) – 0wka	Continuous	242		87.21216 (SD 13)	244		88.05888 (SD 13)		
Blood pressure:									
Systolic blood pressure (mmHg) – 0wk	Continuous	242		131 (SD 14)	244		132 (SD 16)		
Diastolic blood pressure (mmHg) – 0wk	Continuous	242		79 (SD 8)	244		80 (SD 8)		
Previous blood glucose lowering drugs:									
Metformin – 0wk	Dichotomous	242	72	(29.8%)	244	82	(33.6%)		
Sulfonylurea – 0wk	Dichotomous	242	11	(4.5%)	244	7	(2.9%)		
Combination therapy – 0wk	Dichotomous	242	159	(65.7%)	244	155	(63.5%)		
Repaglinide – 0wk	Dichotomous	242	0	(0.0%)	244	0	(0.0%)		
Baseline montherapy									
Blood glucose:									
HbA1c (%) – 12wkb	Continuous	83		8.25 (SD 1.14)	89		8.15 (SD 0.943)		
HbA1c (%) – 12wkb	Continuous	83		6.905 (SD 1.14)	89		6.9 (SD 1.18)		
HbA1c (%) – 12wkb	Continuous	83		6.905 (SD 1.14)	89		8.15 (SD 0.943)		
HbA1c (%) – 12wkb	Continuous	83		8.25 (SD 1.14)	89		6.9 (SD 1.18)		
Baseline combination therapy									
Blood glucose:									
HbA1c (%) – 12wkb	Continuous	159		7.65 (SD 1.26)	155		7.7 (SD 1.25)		
HbA1c (%) – 12wkb	Continuous	159		7.65 (SD 1.26)	155		8.55 (SD 1.25)		
HbA1c (%) – 12wkb	Continuous	159		8.405 (SD 1.26)	155		7.7 (SD 1.25)		
HbA1c (%) – 12wkb	Continuous	159		8.405 (SD 1.26)	155		8.55 (SD 1.25)		

[a] estimated from BMI assuming mean height of 1.68m
[b] Data estimated from graphs. SD estimated from reported 2xSEM

Results

		Metformin + Liraglutide 0.6 + placebo			Metformin + liraglutide 1.2mg + placebo				
		N	k	mean	N	k	mean	Δ	p
Blood glucose:									
HbA1c (%) – 12wka	Continuous	242		7.6 (SD 1.26)	241		7.3 (SD 0.776)		
HbA1c (%) – 26wk	Mean change	242		-0.7 (SD 1.56)	241		-1 (SD 1.55)		
HbA1c (%) – 26wka	Continuous	242		7.75 (SD 1.26)	241		7.6 (SD 1.55)		

HbA1c (%) – 52wka	Continuous	242		7.85 (SD 1.56)	241		7.6 (SD 1.16)
HbA1c (%) – 104wkb	Mean change	242		-0.4 (SD 1.56)	241		-0.6 (SD 1.55)
HbA1c (%) – 104wka	Continuous	242		8.07 (SD 1.56)	241		7.8 (SD 1.55)
HbA1c < 7% or <=7% – 26wk	Dichotomous	242	68	(28.1%)	241	85	(35.3%)
HbA1c <= 6.5% – 26wk	Dichotomous	242	27	(11.2%)	241	48	(19.9%)
Fasting plasma glucose (mmol/l) – 12wk	Continuous	242		8.8 (SD 3.11) a	241		8 (SD 3.1) c
Fasting plasma glucose (mmol/l) – 26wk	Continuous	242		9.1 (SD 2.5)	241		8.5 (SD 2.6)
Fasting plasma glucose (mmol/l) – 52wk	Continuous	242		8.9 (SD 3.11) a	241		8.5 (SD 3.1) c
Fasting plasma glucose (mmol/l) – 104wk	Continuous	242		9.4 (SD 2.7)	241		8.9 (SD 2.8)
Composite end point (HbA1c <7, no hypo, no weight gain) – 104wk	Dichotomous	242	32	(13.2%)	241	56	(23.2%)
Body weight:							
Weight (kg) – 12wkc	Continuous	242		86.9 (SD 15.6)	241		87 (SD 15.5)
Weight (kg) – 26wk	Mean change	242		-1.8 (SD 3.11)	241		-2.6 (SD 3.1)
Weight (kg) – 26wkc	Continuous	242		86 (SD 15.6)	241		86.7 (SD 15.5)
Weight (kg) – 52wka	Continuous	242		85.75 (SD 15.6)	241		86 (SD 15.5)
Weight (kg) – 104wkc	Continuous	242		86 (SD 15.6)	241		86 (SD 15.5)
Weight (kg) – 104wkb	Mean change	242		-2.1 (SD 4.67)	241		-3 (SD 5.43)
Adverse events:							
GI: nausea – 104wk	Dichotomous	242	30	(12.4%)	241	42	(17.4%)
Bronchitis – 104wk	Dichotomous	242	10	(4.1%)	241	13	(5.4%)
Cough – 104wk	Dichotomous	242	8	(3.3%)	241	6	(2.5%)
Dyspepsia – 104wk	Dichotomous	242	12	(5.0%)	241	6	(2.5%)
GI: diarrhoea – 104wk	Dichotomous	242	31	(12.8%)	241	27	(11.2%)
GI: vomiting – 104wk	Dichotomous	242	19	(7.9%)	241	18	(7.5%)
GI: gastritis – 104wk	Dichotomous	242	11	(4.5%)	241	8	(3.3%)
Headache – 104wk	Dichotomous	242	26	(10.7%)	241	34	(14.1%)
Hypertension – 104wk	Dichotomous	242	11	(4.5%)	241	13	(5.4%)
Infection (upper airway or other common) – 104wk	Dichotomous	242	11	(4.5%)	241	15	(6.2%)
metabolism and nutritional disorders – 104wk	Dichotomous	242	28	(11.6%)	241	42	(17.4%)
Musculoskeletal and connective tissue disorders – 104wk	Dichotomous	242	53	(21.9%)	241	59	(24.5%)
Nasopharyngitis – 104wk	Dichotomous	242	43	(17.8%)	241	36	(14.9%)
Nervous system disorders – 104wk	Dichotomous	242	45	(18.6%)	241	59	(24.5%)
renal or urinary disorder – 104wk	Dichotomous	242	13	(5.4%)	241	9	(3.7%)
Dropouts:							
Total dropouts – 26wk	Dichotomous	242	34	(14.0%)	241	44	(18.3%)
Total dropouts – 104wk	Dichotomous	242	111	(45.9%)	241	104	(43.2%)
Dropout due to AEs – 26wk	Dichotomous	242	11	(4.5%)	241	23	(9.5%)
Drop out due to unsatisfactory effect – 26wk	Dichotomous	242	19	(7.9%)	241	8	(3.3%)
Blood pressure:							
Systolic blood pressure (mmHg) – 104wk	Mean change	242		0.2 (SD 14)	241		-2.5 (SD 14)
Diastolic blood pressure (mmHg) – 104wk	Mean change	242		0.4 (SD 9.33)	241		-0.8 (SD 9.31)

Baseline montherapy									
Blood glucose: HbA1c (%) – 12wkd	Continuous	81		7.15 (SD 0.9)	91		7.055 (SD 0.873)		
HbA1c (%) – 12wkd	Continuous	81		8.3 (SD 0.9)	91		8.3 (SD 1.19)		
HbA1c (%) – 12wkd	Continuous	81		8.3 (SD 0.9)	91		7.055 (SD 0.873)		
HbA1c (%) – 12wkd	Continuous	81		7.15 (SD 0.9)	91		8.3 (SD 1.19)		
HbA1c (%) – 26wkd	Continuous	81		7.35 (SD 1.12)	91		7.15 (SD 0.954)		
HbA1c < 7% or <=7% – 26wk	Dichotomous	81	35	(43.2%)	91	48	(52.7%)		
HbA1c <= 6.5% – 26wk	Dichotomous	81	17	(21.0%)	91	29	(31.9%)		
Baseline combination therapy									
Blood glucose: HbA1c (%) – 12wkd	Continuous	161		7.95 (SD 1.16)	150		7.55 (SD 1.22)		
HbA1c (%) – 12wkd	Continuous	161		8.45 (SD 1.27)	150		8.3 (SD 1.22)		
HbA1c (%) – 12wkd	Continuous	161		7.95 (SD 1.16)	150		8.3 (SD 1.22)		
HbA1c (%) – 12wkd	Continuous	161		8.45 (SD 1.27)	150		7.55 (SD 1.22)		
HbA1c (%) – 26wkd	Continuous	161		8.05 (SD 1.37)	150		7.65 (SD 1.33)		
HbA1c < 7% or <=7% – 26wk	Dichotomous	161	33	(20.5%)	150	37	(24.7%)		
HbA1c <= 6.5% – 26wk	Dichotomous	161	10	(6.2%)	150	19	(12.7%)		

[a] Data estimated from graphs. SD estimated from reported SE
[b] SD estimated from SE
[c] Graph
[d] Data estimated from graphs. SD estimated from reported 2xSEM

		Metformin + Liraglutide 0.6 + placebo			**Metformin + liraglutide 1.8mg + placebo**				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Blood glucose: HbA1c (%) – 12wka	Continuous	242		7.6 (SD 1.26)	242		7.35 (SD 1.26)		
HbA1c (%) – 26wk	Mean change	242		-0.7 (SD 1.56)	242		-1 (SD 1.56)		
HbA1c (%) – 26wka	Continuous	242		7.75 (SD 1.26)	242		7.6 (SD 1.56)		
HbA1c (%) – 52wka	Continuous	242		7.85 (SD 1.56)	242		7.65 (SD 1.17)		
HbA1c (%) – 104wkb	Mean change	242		-0.4 (SD 1.56)	242		-0.6 (SD 1.56)		
HbA1c (%) – 104wka	Continuous	242		8.07 (SD 1.56)	242		7.82 (SD 1.56)		
HbA1c < 7% or <=7% – 26wk	Dichotomous	242	68	(28.1%)	242	103	(42.6%)		
HbA1c <= 6.5% – 26wk	Dichotomous	242	27	(11.2%)	242	60	(24.8%)		
Fasting plasma glucose (mmol/l) – 12wk	Continuous	242		8.8 (SD 3.11) a	242		8.2 (SD 1.56) c		
Fasting plasma glucose (mmol/l) – 26wk	Continuous	242		9.1 (SD 2.5)	242		8.5 (SD 2.4)		
Fasting plasma glucose (mmol/l) – 52wk	Continuous	242		8.9 (SD 3.11) a	242		8.6 (SD 3.11) c		
Fasting plasma glucose (mmol/l) – 104wk	Continuous	242		9.4 (SD 2.7)	242		9 (SD 2.5)		
Composite end point (HbA1c <7, no hypo, no weight gain) – 104wk	Dichotomous	242	32	(13.2%)	242	62	(25.6%)		

Body weight:										
Weight (kg) – 12wkc	Continuous	242		86.9 (SD 15.6)	242		85.5 (SD 15.6)			
Weight (kg) – 26wk	Mean change	242		-1.8 (SD 3.11)	242		-2.8 (SD 3.11)			
Weight (kg) – 26wkc	Continuous	242		86 (SD 15.6)	242		85 (SD 15.6)			
Weight (kg) – 52wka	Continuous	242		85.75 (SD 15.6)	242		85 (SD 15.6)			
Weight (kg) – 104wkc	Continuous	242		86 (SD 15.6)	242		85.5 (SD 15.6)			
Weight (kg) – 104wkb	Mean change	242		-2.1 (SD 4.67)	242		-2.9 (SD 5.44)			
Adverse events:										
GI: nausea – 104wk	Dichotomous	242	30	(12.4%)	242	52	(21.5%)			
Bronchitis – 104wk	Dichotomous	242	10	(4.1%)	242	12	(5.0%)			
Cough – 104wk	Dichotomous	242	8	(3.3%)	242	2	(0.8%)			
Dyspepsia – 104wk	Dichotomous	242	12	(5.0%)	242	22	(9.1%)			
GI: diarrhoea – 104wk	Dichotomous	242	31	(12.8%)	242	40	(16.5%)			
GI: vomiting – 104wk	Dichotomous	242	19	(7.9%)	242	24	(9.9%)			
GI: gastritis – 104wk	Dichotomous	242	11	(4.5%)	242	13	(5.4%)			
Headache – 104wk	Dichotomous	242	26	(10.7%)	242	35	(14.5%)			
Hypertension – 104wk	Dichotomous	242	11	(4.5%)	242	11	(4.5%)			
Infection (upper airway or other common) – 104wk	Dichotomous	242	11	(4.5%)	242	15	(6.2%)			
metabolism and nutritional disorders – 104wk	Dichotomous	242	28	(11.6%)	242	34	(14.0%)			
Musculoskeletal and connective tissue disorders – 104wk	Dichotomous	242	53	(21.9%)	242	57	(23.6%)			
Nasopharyngitis – 104wk	Dichotomous	242	43	(17.8%)	242	36	(14.9%)			
Nervous system disorders – 104wk	Dichotomous	242	45	(18.6%)	242	61	(25.2%)			
renal or urinary disorder – 104wk	Dichotomous	242	13	(5.4%)	242	12	(5.0%)			
Dropouts:										
Total dropouts – 26wk	Dichotomous	242	34	(14.0%)	242	51	(21.1%)			
Total dropouts – 104wk	Dichotomous	242	111	(45.9%)	242	124	(51.2%)			
Dropout due to AEs – 26wk	Dichotomous	242	11	(4.5%)	242	29	(12.0%)			
Drop out due to unsatisfactory effect – 26wk	Dichotomous	242	19	(7.9%)	242	13	(5.4%)			
Blood pressure:										
Systolic blood pressure (mmHg) – 104wk	Mean change	242		0.2 (SD 14)	242		-2 (SD 14)			
Diastolic blood pressure (mmHg) – 104wk	Mean change	242		0.4 (SD 9.33)	242		-0.5 (SD 9.33)			
Baseline montherapy										
Blood glucose:										
HbA1c (%) – 12wkd	Continuous	81		7.15 (SD 0.9)	83		6.905 (SD 1.14)			
HbA1c (%) – 12wkd	Continuous	81		8.3 (SD 0.9)	83		8.25 (SD 1.14)			
HbA1c (%) – 12wkd	Continuous	81		8.3 (SD 0.9)	83		6.905 (SD 1.14)			
HbA1c (%) – 12wkd	Continuous	81		7.15 (SD 0.9)	83		8.25 (SD 1.14)			
HbA1c (%) – 26wkd	Continuous	81		7.35 (SD 1.12)	83		6.95 (SD 1.14)			
HbA1c < 7% or <=7% – 26wk	Dichotomous	81	35	(43.2%)	83	55	(66.3%)			
HbA1c <= 6.5% – 26wk	Dichotomous	81	17	(21.0%)	83	32	(38.6%)			
Baseline combination therapy										
Blood glucose:										
HbA1c (%) – 12wkd	Continuous	161		7.95 (SD 1.16)	159		7.65 (SD 1.26)			
HbA1c (%) – 12wkd	Continuous	161		8.45 (SD 1.27)	159		8.405 (SD 1.26)			

HbA1c (%) – 12wkd	Continuous	161		7.95 (SD 1.16)	159		8.405 (SD 1.26)		
HbA1c (%) – 12wkd	Continuous	161		8.45 (SD 1.27)	159		7.65 (SD 1.26)		
HbA1c (%) – 26wkd	Continuous	161		8.05 (SD 1.37)	159		7.75 (SD 1.26)		
HbA1c < 7% or <=7% – 26wk	Dichotomous	161	33	(20.5%)	159	48	(30.2%)		
HbA1c <= 6.5% – 26wk	Dichotomous	161	10	(6.2%)	159	28	(17.6%)		

[a] Data estimated from graphs. SD estimated from reported SE
[b] SD estimated from SE
[c] Graph
[d] Data estimated from graphs. SD estimated from reported 2xSEM

		Metformin + Liraglutide 0.6 + placebo			Metformin + glimepiride + placebo				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 12wka	Continuous	242		7.6 (SD 1.26)	244		7.4 (SD 1.56)		
HbA1c (%) – 26wk	Mean change	242		-0.7 (SD 1.56)	244		0.1 (SD 1.56)		
HbA1c (%) – 26wka	Continuous	242		7.75 (SD 1.26)	244		7.7 (SD 1.27)		
HbA1c (%) – 52wka	Continuous	242		7.85 (SD 1.56)	244		7.7 (SD 1.56)		
HbA1c (%) – 104wkb	Mean change	242		-0.4 (SD 1.56)	244		-0.5 (SD 1.56)		
HbA1c (%) – 104wka	Continuous	242		8.07 (SD 1.56)	244		7.9 (SD 1.56)		
HbA1c < 7% or <=7% – 26wk	Dichotomous	242	68	(28.1%)	244	89	(36.5%)		
HbA1c <= 6.5% – 26wk	Dichotomous	242	27	(11.2%)	244	54	(22.1%)		
Fasting plasma glucose (mmol/l) – 12wk	Continuous	242		8.8 (SD 3.11) a	244		8.5 (SD 3.12) c		
Fasting plasma glucose (mmol/l) – 26wk	Continuous	242		9.1 (SD 2.5)	244		8.9 (SD 2.5)		
Fasting plasma glucose (mmol/l) – 52wk	Continuous	242		8.9 (SD 3.11) a	244		8.9 (SD 3.12) c		
Fasting plasma glucose (mmol/l) – 104wk	Continuous	242		9.4 (SD 2.7)	244		9.5 (SD 2.8)		
Composite end point (HbA1c <7, no hypo, no weight gain) – 104wk	Dichotomous	242	32	(13.2%)	244	16	(6.6%)		
Body weight: Weight (kg) – 12wkc	Continuous	242		86.9 (SD 15.6)	244		89.5 (SD 15.6)		
Weight (kg) – 26wk	Mean change	242		-1.8 (SD 3.11)	244		1 (SD 3.12)		
Weight (kg) – 26wkc	Continuous	242		86 (SD 15.6)	244		90 (SD 15.6)		
Weight (kg) – 52wka	Continuous	242		85.75 (SD 15.6)	244		90 (SD 15.6)		
Weight (kg) – 104wkc	Continuous	242		86 (SD 15.6)	244		90 (SD 15.6)		
Weight (kg) – 104wkb	Mean change	242		-2.1 (SD 4.67)	244		0.7 (SD 4.68)		
Adverse events: GI: nausea – 104wk	Dichotomous	242	30	(12.4%)	244	10	(4.1%)		
Bronchitis – 104wk	Dichotomous	242	10	(4.1%)	244	15	(6.1%)		
Cough – 104wk	Dichotomous	242	8	(3.3%)	244	13	(5.3%)		
Dyspepsia – 104wk	Dichotomous	242	12	(5.0%)	244	7	(2.9%)		
GI: diarrhoea – 104wk	Dichotomous	242	31	(12.8%)	244	14	(5.7%)		
GI: vomiting – 104wk	Dichotomous	242	19	(7.9%)	244	1	(0.4%)		

GI: gastritis – 104wk	Dichotomous	242	11	(4.5%)	244	4	(1.6%)		
Headache – 104wk	Dichotomous	242	26	(10.7%)	244	32	(13.1%)		
Hypertension – 104wk	Dichotomous	242	11	(4.5%)	244	12	(4.9%)		
Infection (upper airway or other common) – 104wk	Dichotomous	242	11	(4.5%)	244	12	(4.9%)		
metabolism and nutritional disorders – 104wk	Dichotomous	242	28	(11.6%)	244	25	(10.2%)		
Musculoskeletal and connective tissue disorders – 104wk	Dichotomous	242	53	(21.9%)	244	68	(27.9%)		
Nasopharyngitis – 104wk	Dichotomous	242	43	(17.8%)	244	49	(20.1%)		
Nervous system disorders – 104wk	Dichotomous	242	45	(18.6%)	244	54	(22.1%)		
renal or urinary disorder – 104wk	Dichotomous	242	13	(5.4%)	244	14	(5.7%)		
Dropouts:									
Total dropouts – 26wk	Dichotomous	242	34	(14.0%)	244	34	(13.9%)		
Total dropouts – 104wk	Dichotomous	242	111	(45.9%)	244	131	(53.7%)		
Dropout due to AEs – 26wk	Dichotomous	242	11	(4.5%)	244	8	(3.3%)		
Drop out due to unsatisfactory effect – 26wk	Dichotomous	242	19	(7.9%)	244	9	(3.7%)		
Blood pressure:									
Systolic blood pressure (mmHg) – 104wk	Mean change	242		0.2 (SD 14)	244		0.3 (SD 14.1)		
Diastolic blood pressure (mmHg) – 104wk	Mean change	242		0.4 (SD 9.33)	244		-0 (SD 9.37)		
Baseline montherapy									
Blood glucose:									
HbA1c (%) – 12wkd	Continuous	81		7.15 (SD 0.9)	89		6.9 (SD 1.18)		
HbA1c (%) – 12wkd	Continuous	81		8.3 (SD 0.9)	89		8.15 (SD 0.943)		
HbA1c (%) – 12wkd	Continuous	81		8.3 (SD 0.9)	89		6.9 (SD 1.18)		
HbA1c (%) – 12wkd	Continuous	81		7.15 (SD 0.9)	89		8.15 (SD 0.943)		
HbA1c (%) – 26wkd	Continuous	81		7.35 (SD 1.12)	89		7.05 (SD 0.943)		
HbA1c < 7% or <=7% – 26wk	Dichotomous	81	35	(43.2%)	89	50	(56.2%)		
HbA1c <= 6.5% – 26wk	Dichotomous	81	17	(21.0%)	89	32	(36.0%)		
Baseline combination therapy									
Blood glucose:									
HbA1c (%) – 12wkd	Continuous	161		7.95 (SD 1.16)	155		7.7 (SD 1.25)		
HbA1c (%) – 12wkd	Continuous	161		8.45 (SD 1.27)	155		8.55 (SD 1.25)		
HbA1c (%) – 12wkd	Continuous	161		7.95 (SD 1.16)	155		8.55 (SD 1.25)		
HbA1c (%) – 12wkd	Continuous	161		8.45 (SD 1.27)	155		7.7 (SD 1.25)		
HbA1c (%) – 26wkd	Continuous	161		8.05 (SD 1.37)	155		7.8 (SD 1.25)		
HbA1c < 7% or <=7% – 26wk	Dichotomous	161	33	(20.5%)	155	39	(25.2%)		
HbA1c <= 6.5% – 26wk	Dichotomous	161	10	(6.2%)	155	22	(14.2%)		

[a] Data estimated from graphs. SD estimated from reported SE
[b] SD estimated from SE
[c] Graph
[d] Data estimated from graphs. SD estimated from reported 2xSEM

	Metformin + liraglutide 1.2mg + placebo			Metformin + liraglutide 1.8mg + placebo				
	N	k	mean	N	k	mean	Δ	p

Blood glucose: HbA1c (%) – 12wka	Continuous	241		7.3 (SD 0.776)	242		7.35 (SD 1.26)			
HbA1c (%) – 26wk	Mean change	241		-1 (SD 1.55)	242		-1 (SD 1.56)			
HbA1c (%) – 26wka	Continuous	241		7.6 (SD 1.55)	242		7.6 (SD 1.56)			
HbA1c (%) – 52wka	Continuous	241		7.6 (SD 1.16)	242		7.65 (SD 1.17)			
HbA1c (%) – 104wkb	Mean change	241		-0.6 (SD 1.55)	242		-0.6 (SD 1.56)			
HbA1c (%) – 104wka	Continuous	241		7.8 (SD 1.55)	242		7.82 (SD 1.56)			
HbA1c < 7% or <=7% – 26wk	Dichotomous	241	85	(35.3%)	242	103	(42.6%)			
HbA1c <= 6.5% – 26wk	Dichotomous	241	48	(19.9%)	242	60	(24.8%)			
Fasting plasma glucose (mmol/l) – 12wkc	Continuous	241		8 (SD 3.1)	242		8.2 (SD 1.56)			
Fasting plasma glucose (mmol/l) – 26wk	Continuous	241		8.5 (SD 2.6)	242		8.5 (SD 2.4)			
Fasting plasma glucose (mmol/l) – 52wkc	Continuous	241		8.5 (SD 3.1)	242		8.6 (SD 3.11)			
Fasting plasma glucose (mmol/l) – 104wk	Continuous	241		8.9 (SD 2.8)	242		9 (SD 2.5)			
Composite end point (HbA1c <7, no hypo, no weight gain) – 104wk	Dichotomous	241	56	(23.2%)	242	62	(25.6%)			
Body weight: Weight (kg) – 12wkc	Continuous	241		87 (SD 15.5)	242		85.5 (SD 15.6)			
Weight (kg) – 26wk	Mean change	241		-2.6 (SD 3.1)	242		-2.8 (SD 3.11)			
Weight (kg) – 26wkc	Continuous	241		86.7 (SD 15.5)	242		85 (SD 15.6)			
Weight (kg) – 52wka	Continuous	241		86 (SD 15.5)	242		85 (SD 15.6)			
Weight (kg) – 104wkc	Continuous	241		86 (SD 15.5)	242		85.5 (SD 15.6)			
Weight (kg) – 104wkb	Mean change	241		-3 (SD 5.43)	242		-2.9 (SD 5.44)			
Adverse events: GI: nausea – 104wk	Dichotomous	241	42	(17.4%)	242	52	(21.5%)			
Bronchitis – 104wk	Dichotomous	241	13	(5.4%)	242	12	(5.0%)			
Cough – 104wk	Dichotomous	241	6	(2.5%)	242	2	(0.8%)			
Dyspepsia – 104wk	Dichotomous	241	6	(2.5%)	242	22	(9.1%)			
GI: diarrhoea – 104wk	Dichotomous	241	27	(11.2%)	242	40	(16.5%)			
GI: vomiting – 104wk	Dichotomous	241	18	(7.5%)	242	24	(9.9%)			
GI: gastritis – 104wk	Dichotomous	241	8	(3.3%)	242	13	(5.4%)			
Headache – 104wk	Dichotomous	241	34	(14.1%)	242	35	(14.5%)			
Hypertension – 104wk	Dichotomous	241	13	(5.4%)	242	11	(4.5%)			
Infection (upper airway or other common) – 104wk	Dichotomous	241	15	(6.2%)	242	15	(6.2%)			
metabolism and nutritional disorders – 104wk	Dichotomous	241	42	(17.4%)	242	34	(14.0%)			
Musculoskeletal and connective tissue disorders – 104wk	Dichotomous	241	59	(24.5%)	242	57	(23.6%)			
Nasopharyngitis – 104wk	Dichotomous	241	36	(14.9%)	242	36	(14.9%)			
Nervous system disorders – 104wk	Dichotomous	241	59	(24.5%)	242	61	(25.2%)			
renal or urinary disorder – 104wk	Dichotomous	241	9	(3.7%)	242	12	(5.0%)			
Dropouts: Total dropouts – 26wk	Dichotomous	241	44	(18.3%)	242	51	(21.1%)			
Total dropouts – 104wk	Dichotomous	241	104	(43.2%)	242	124	(51.2%)			
Dropout due to AEs – 26wk	Dichotomous	241	23	(9.5%)	242	29	(12.0%)			

Drop out due to unsatisfactory effect – 26wk	Dichotomous	241	8	(3.3%)	242	13	(5.4%)		
Blood pressure:									
Systolic blood pressure (mmHg) – 104wk	Mean change	241		-2.5 (SD 14)	242		-2 (SD 14)		
Diastolic blood pressure (mmHg) – 104wk	Mean change	241		-0.8 (SD 9.31)	242		-0.5 (SD 9.33)		
Baseline montherapy									
Blood glucose:									
HbA1c (%) – 12wkd	Continuous	91		7.055 (SD 0.873)	83		6.905 (SD 1.14)		
HbA1c (%) – 12wkd	Continuous	91		8.3 (SD 1.19)	83		8.25 (SD 1.14)		
HbA1c (%) – 12wkd	Continuous	91		8.3 (SD 1.19)	83		6.905 (SD 1.14)		
HbA1c (%) – 12wkd	Continuous	91		7.055 (SD 0.873)	83		8.25 (SD 1.14)		
HbA1c (%) – 26wkd	Continuous	91		7.15 (SD 0.954)	83		6.95 (SD 1.14)		
HbA1c < 7% or <=7% – 26wk	Dichotomous	91	48	(52.7%)	83	55	(66.3%)		
HbA1c <= 6.5% – 26wk	Dichotomous	91	29	(31.9%)	83	32	(38.6%)		
Baseline combination therapy									
Blood glucose:									
HbA1c (%) – 12wkd	Continuous	150		7.55 (SD 1.22)	159		7.65 (SD 1.26)		
HbA1c (%) – 12wkd	Continuous	150		8.3 (SD 1.22)	159		8.405 (SD 1.26)		
HbA1c (%) – 12wkd	Continuous	150		7.55 (SD 1.22)	159		8.405 (SD 1.26)		
HbA1c (%) – 12wkd	Continuous	150		8.3 (SD 1.22)	159		7.65 (SD 1.26)		
HbA1c (%) – 26wkd	Continuous	150		7.65 (SD 1.33)	159		7.75 (SD 1.26)		
HbA1c < 7% or <=7% – 26wk	Dichotomous	150	37	(24.7%)	159	48	(30.2%)		
HbA1c <= 6.5% – 26wk	Dichotomous	150	19	(12.7%)	159	28	(17.6%)		

[a] Data estimated from graphs. SD estimated from reported SE
[b] SD estimated from SE
[c] Graph
[d] Data estimated from graphs. SD estimated from reported 2xSEM

		Metformin + liraglutide 1.2mg + placebo			**Metformin + glimepiride + placebo**				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Blood glucose:									
HbA1c (%) – 12wka	Continuous	241		7.3 (SD 0.776)	244		7.4 (SD 1.56)		
HbA1c (%) – 26wk	Mean change	241		-1 (SD 1.55)	244		0.1 (SD 1.56)		
HbA1c (%) – 26wka	Continuous	241		7.6 (SD 1.55)	244		7.7 (SD 1.27)		
HbA1c (%) – 52wka	Continuous	241		7.6 (SD 1.16)	244		7.7 (SD 1.56)		
HbA1c (%) – 104wkb	Mean change	241		-0.6 (SD 1.55)	244		-0.5 (SD 1.56)		
HbA1c (%) – 104wka	Continuous	241		7.8 (SD 1.55)	244		7.9 (SD 1.56)		
HbA1c < 7% or <=7% – 26wk	Dichotomous	241	85	(35.3%)	244	89	(36.5%)		
HbA1c <= 6.5% – 26wk	Dichotomous	241	48	(19.9%)	244	54	(22.1%)		
Fasting plasma glucose (mmol/l) – 12wkc	Continuous	241		8 (SD 3.1)	244		8.5 (SD 3.12)		
Fasting plasma glucose (mmol/l) – 26wk	Continuous	241		8.5 (SD 2.6)	244		8.9 (SD 2.5)		

Fasting plasma glucose (mmol/l) – 52wkc	Continuous	241		8.5 (SD 3.1)	244		8.9 (SD 3.12)		
Fasting plasma glucose (mmol/l) – 104wk	Continuous	241		8.9 (SD 2.8)	244		9.5 (SD 2.8)		
Composite end point (HbA1c <7, no hypo, no weight gain) – 104wk	Dichotomous	241	56	(23.2%)	244	16	(6.6%)		
Body weight:									
Weight (kg) – 12wkc	Continuous	241		87 (SD 15.5)	244		89.5 (SD 15.6)		
Weight (kg) – 26wk	Mean change	241		-2.6 (SD 3.1)	244		1 (SD 3.12)		
Weight (kg) – 26wkc	Continuous	241		86.7 (SD 15.5)	244		90 (SD 15.6)		
Weight (kg) – 52wka	Continuous	241		86 (SD 15.5)	244		90 (SD 15.6)		
Weight (kg) – 104wkc	Continuous	241		86 (SD 15.5)	244		90 (SD 15.6)		
Weight (kg) – 104wkb	Mean change	241		-3 (SD 5.43)	244		0.7 (SD 4.68)		
Adverse events:									
GI: nausea – 104wk	Dichotomous	241	42	(17.4%)	244	10	(4.1%)		
Bronchitis – 104wk	Dichotomous	241	13	(5.4%)	244	15	(6.1%)		
Cough – 104wk	Dichotomous	241	6	(2.5%)	244	13	(5.3%)		
Dyspepsia – 104wk	Dichotomous	241	6	(2.5%)	244	7	(2.9%)		
GI: diarrhoea – 104wk	Dichotomous	241	27	(11.2%)	244	14	(5.7%)		
GI: vomiting – 104wk	Dichotomous	241	18	(7.5%)	244	1	(0.4%)		
GI: gastritis – 104wk	Dichotomous	241	8	(3.3%)	244	4	(1.6%)		
Headache – 104wk	Dichotomous	241	34	(14.1%)	244	32	(13.1%)		
Hypertension – 104wk	Dichotomous	241	13	(5.4%)	244	12	(4.9%)		
Infection (upper airway or other common) – 104wk	Dichotomous	241	15	(6.2%)	244	12	(4.9%)		
metabolism and nutritional disorders – 104wk	Dichotomous	241	42	(17.4%)	244	25	(10.2%)		
Musculoskeletal and connective tissue disorders – 104wk	Dichotomous	241	59	(24.5%)	244	68	(27.9%)		
Nasopharyngitis – 104wk	Dichotomous	241	36	(14.9%)	244	49	(20.1%)		
Nervous system disorders – 104wk	Dichotomous	241	59	(24.5%)	244	54	(22.1%)		
renal or urinary disorder – 104wk	Dichotomous	241	9	(3.7%)	244	14	(5.7%)		
Dropouts:									
Total dropouts – 26wk	Dichotomous	241	44	(18.3%)	244	34	(13.9%)		
Total dropouts – 104wk	Dichotomous	241	104	(43.2%)	244	131	(53.7%)		
Dropout due to AEs – 26wk	Dichotomous	241	23	(9.5%)	244	8	(3.3%)		
Drop out due to unsatisfactory effect – 26wk	Dichotomous	241	8	(3.3%)	244	9	(3.7%)		
Blood pressure:									
Systolic blood pressure (mmHg) – 104wk	Mean change	241		-2.5 (SD 14)	244		0.3 (SD 14.1)		
Diastolic blood pressure (mmHg) – 104wk	Mean change	241		-0.8 (SD 9.31)	244		-0 (SD 9.37)		
Baseline montherapy									
Blood glucose:									
HbA1c (%) – 12wkd	Continuous	91		7.055 (SD 0.873)	89		6.9 (SD 1.18)		
HbA1c (%) – 12wkd	Continuous	91		8.3 (SD 1.19)	89		8.15 (SD 0.943)		
HbA1c (%) – 12wkd	Continuous	91		8.3 (SD 1.19)	89		6.9 (SD 1.18)		
HbA1c (%) – 12wkd	Continuous	91		7.055 (SD 0.873)	89		8.15 (SD 0.943)		
HbA1c (%) – 26wkd	Continuous	91		7.15 (SD 0.954)	89		7.05 (SD 0.943)		
HbA1c < 7% or <=7% – 26wk	Dichotomous	91	48	(52.7%)	89	50	(56.2%)		

HbA1c <= 6.5% – 26wk	Dichotomous	91	29	(31.9%)	89	32	(36.0%)		
Baseline combination therapy									
Blood glucose: HbA1c (%) – 12wkd	Continuous	150		7.55 (SD 1.22)	155		7.7 (SD 1.25)		
HbA1c (%) – 12wkd	Continuous	150		8.3 (SD 1.22)	155		8.55 (SD 1.25)		
HbA1c (%) – 12wkd	Continuous	150		7.55 (SD 1.22)	155		8.55 (SD 1.25)		
HbA1c (%) – 12wkd	Continuous	150		8.3 (SD 1.22)	155		7.7 (SD 1.25)		
HbA1c (%) – 26wkd	Continuous	150		7.65 (SD 1.33)	155		7.8 (SD 1.25)		
HbA1c < 7% or <=7% – 26wk	Dichotomous	150	37	(24.7%)	155	39	(25.2%)		
HbA1c <= 6.5% – 26wk	Dichotomous	150	19	(12.7%)	155	22	(14.2%)		

[a] Data estimated from graphs. SD estimated from reported SE
[b] SD estimated from SE
[c] Graph
[d] Data estimated from graphs. SD estimated from reported 2xSEM

		Metformin + liraglutide 1.8mg + placebo			Metformin + glimepiride + placebo				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 12wka	Continuous	242		7.35 (SD 1.26)	244		7.4 (SD 1.56)		
HbA1c (%) – 26wk	Mean change	242		-1 (SD 1.56)	244		0.1 (SD 1.56)		
HbA1c (%) – 26wka	Continuous	242		7.6 (SD 1.56)	244		7.7 (SD 1.27)		
HbA1c (%) – 52wka	Continuous	242		7.65 (SD 1.17)	244		7.7 (SD 1.56)		
HbA1c (%) – 104wkb	Mean change	242		-0.6 (SD 1.56)	244		-0.5 (SD 1.56)		
HbA1c (%) – 104wka	Continuous	242		7.82 (SD 1.56)	244		7.9 (SD 1.56)		
HbA1c < 7% or <=7% – 26wk	Dichotomous	242	103	(42.6%)	244	89	(36.5%)		
HbA1c <= 6.5% – 26wk	Dichotomous	242	60	(24.8%)	244	54	(22.1%)		
Fasting plasma glucose (mmol/l) – 12wkc	Continuous	242		8.2 (SD 1.56)	244		8.5 (SD 3.12)		
Fasting plasma glucose (mmol/l) – 26wk	Continuous	242		8.5 (SD 2.4)	244		8.9 (SD 2.5)		
Fasting plasma glucose (mmol/l) – 52wkc	Continuous	242		8.6 (SD 3.11)	244		8.9 (SD 3.12)		
Fasting plasma glucose (mmol/l) – 104wk	Continuous	242		9 (SD 2.5)	244		9.5 (SD 2.8)		
Composite end point (HbA1c <7, no hypo, no weight gain) – 104wk	Dichotomous	242	62	(25.6%)	244	16	(6.6%)		
Body weight: Weight (kg) – 12wkc	Continuous	242		85.5 (SD 15.6)	244		89.5 (SD 15.6)		
Weight (kg) – 26wk	Mean change	242		-2.8 (SD 3.11)	244		1 (SD 3.12)		
Weight (kg) – 26wkc	Continuous	242		85 (SD 15.6)	244		90 (SD 15.6)		
Weight (kg) – 52wka	Continuous	242		85 (SD 15.6)	244		90 (SD 15.6)		
Weight (kg) – 104wkc	Continuous	242		85.5 (SD 15.6)	244		90 (SD 15.6)		
Weight (kg) – 104wkb	Mean change	242		-2.9 (SD 5.44)	244		0.7 (SD 4.68)		
Adverse events: GI: nausea – 104wk	Dichotomous	242	52	(21.5%)	244	10	(4.1%)		

Bronchitis – 104wk	Dichotomous	242	12	(5.0%)	244	15	(6.1%)		
Cough – 104wk	Dichotomous	242	2	(0.8%)	244	13	(5.3%)		
Dyspepsia – 104wk	Dichotomous	242	22	(9.1%)	244	7	(2.9%)		
GI: diarrhoea – 104wk	Dichotomous	242	40	(16.5%)	244	14	(5.7%)		
GI: vomiting – 104wk	Dichotomous	242	24	(9.9%)	244	1	(0.4%)		
GI: gastritis – 104wk	Dichotomous	242	13	(5.4%)	244	4	(1.6%)		
Headache – 104wk	Dichotomous	242	35	(14.5%)	244	32	(13.1%)		
Hypertension – 104wk	Dichotomous	242	11	(4.5%)	244	12	(4.9%)		
Infection (upper airway or other common) – 104wk	Dichotomous	242	15	(6.2%)	244	12	(4.9%)		
metabolism and nutritional disorders – 104wk	Dichotomous	242	34	(14.0%)	244	25	(10.2%)		
Musculoskeletal and connective tissue disorders – 104wk	Dichotomous	242	57	(23.6%)	244	68	(27.9%)		
Nasopharyngitis – 104wk	Dichotomous	242	36	(14.9%)	244	49	(20.1%)		
Nervous system disorders – 104wk	Dichotomous	242	61	(25.2%)	244	54	(22.1%)		
renal or urinary disorder – 104wk	Dichotomous	242	12	(5.0%)	244	14	(5.7%)		
Dropouts:									
Total dropouts – 26wk	Dichotomous	242	51	(21.1%)	244	34	(13.9%)		
Total dropouts – 104wk	Dichotomous	242	124	(51.2%)	244	131	(53.7%)		
Dropout due to AEs – 26wk	Dichotomous	242	29	(12.0%)	244	8	(3.3%)		
Drop out due to unsatisfactory effect – 26wk	Dichotomous	242	13	(5.4%)	244	9	(3.7%)		
Blood pressure:									
Systolic blood pressure (mmHg) – 104wk	Mean change	242		-2 (SD 14)	244		0.3 (SD 14.1)		
Diastolic blood pressure (mmHg) – 104wk	Mean change	242		-0.5 (SD 9.33)	244		-0 (SD 9.37)		
Baseline montherapy									
Blood glucose:									
HbA1c (%) – 12wkd	Continuous	83		6.905 (SD 1.14)	89		6.9 (SD 1.18)		
HbA1c (%) – 12wkd	Continuous	83		8.25 (SD 1.14)	89		8.15 (SD 0.943)		
HbA1c (%) – 12wkd	Continuous	83		8.25 (SD 1.14)	89		6.9 (SD 1.18)		
HbA1c (%) – 12wkd	Continuous	83		6.905 (SD 1.14)	89		8.15 (SD 0.943)		
HbA1c (%) – 26wkd	Continuous	83		6.95 (SD 1.14)	89		7.05 (SD 0.943)		
HbA1c < 7% or <=7% – 26wk	Dichotomous	83	55	(66.3%)	89	50	(56.2%)		
HbA1c <= 6.5% – 26wk	Dichotomous	83	32	(38.6%)	89	32	(36.0%)		
Baseline combination therapy									
Blood glucose:									
HbA1c (%) – 12wkd	Continuous	159		7.65 (SD 1.26)	155		7.7 (SD 1.25)		
HbA1c (%) – 12wkd	Continuous	159		8.405 (SD 1.26)	155		8.55 (SD 1.25)		
HbA1c (%) – 12wkd	Continuous	159		7.65 (SD 1.26)	155		8.55 (SD 1.25)		
HbA1c (%) – 12wkd	Continuous	159		8.405 (SD 1.26)	155		7.7 (SD 1.25)		
HbA1c (%) – 26wkd	Continuous	159		7.75 (SD 1.26)	155		7.8 (SD 1.25)		
HbA1c < 7% or <=7% – 26wk	Dichotomous	159	48	(30.2%)	155	39	(25.2%)		
HbA1c <= 6.5% – 26wk	Dichotomous	159	28	(17.6%)	155	22	(14.2%)		

[a] Data estimated from graphs. SD estimated from reported SE
[b] SD estimated from SE
[c] Graph
[d] Data estimated from graphs. SD estimated from reported 2xSEM

Table 25: Papathanassiou et al. (2009)

General	**Phase:** ☐ monotherapy ☑ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin + oral **Parallel / crossover:** Parallel **Country:** Greece **Authors' conclusions:** In patients with type 2 diabetes already on metformin, addition of pioglitazone as compared with glimepiride, improved endothelial function despite similar glycaemic control. The improvement in endothelial function was mainly due to a reduction in insulin resistance. **Source of funding:** Funded in part by Michaelidion Cardiac Center, University of Ioannina Greece **Comments:** Open label, randomised trial
Number and characteristics of patients	**Total number of patients:** 28 **Inclusion criteria:** patients with type 2 diabetes not optimally controlled on metformin monotherapy, treated for the the last 6 months prior to the study, Hba1c >6.5% and normal liver and renal function **Exclusion criteria:** cardiovascular disease, chronic heart failure, liver or renal disease, anameia, thyroid dysfunction, and new onset of a ny new medications within the previous 8 weeks
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** all on oral hypoglycaemic drugs and/or insulin **Details of washout period:** All taking metformin monotherapy at study entry
Lifestyle advice	Patients were asked to maintain the same diet and level of physical activiity throughout the study
Follow-up	**Total follow-up (wks):** 26 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 26 **Frequency of monitoring appointments:** Clinical assessments were performed at 1,3 and 6 months
Arms	**(1) Metformin + pioglitazone** N: 14 Treatment duration (wks): 26 Washout period (d): 0 Comments: All patients continued pre-study metformin (no details of dosing) Treatment(s): (a) Metformin (Oral) Details of dosing regimen: Metformin was continued (no details of dosing) (b) Pioglitazone (Oral) – fixed-dose Set dose (mg/d):30 Frequency of dosing: once a day **(2) Metformin + glimepiride** N: 14 Treatment duration (wks): 26 Washout period (d): 0 Comments: All patients continued pre-study metformin (no details of dosing) Treatment(s): (a) Metformin (Oral) Details of dosing regimen: Metformin was continued (no details of dosing) (b) Sulfonylurea (Oral) – fixed-dose Set dose (mg/d):4 Frequency of dosing: once a day
Outcomes	**General** ITT analysis carried out Outcomes not extracted in this evidence table include measures of insulin resistance, heart rate, flow mediated dilation, nitrate mediated dilation No patients discontinued the study

Baseline characteristics		**Metformin + pioglitazone**	**Metformin + glimepiride**	**Δ**	**p**

		N	k	mean	N	k	mean		
Demographics: Age (years)	Continuous	14		62.8 (SD 7.2)	14		63.6 (SD 7.3)		
Sex (n male)	Dichotomous	14	3	(21.4%)	14	3	(21.4%)		
Duration of diabetes (yrs)	Continuous	14		5.3 (SD 3.6)	14		5.3 (SD 6.5)		
Blood glucose: HbA1c (%) – 0wk	Continuous	14		7.7 (SD 0.7)	14		7.4 (SD 0.8)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	14		8.7 (SD 2.5)	14		8.2 (SD 1.4)		
Body weight: BMI (kg/m2) – 0wk	Continuous	14		33.9 (SD 7)	14		31.9 (SD 5.5)		
Weight (kg) – 0wk	Continuous	14		85.9 (SD 18.7)	14		81.4 (SD 15.3)		
Waist circumference (cms) – 0wk	Continuous	14		111.2 (SD 13.3)	14		110.1 (SD 11.4)		
Blood pressure: Systolic blood pressure (mmHg) – 0wk	Continuous	14		149.5 (SD 14.3)	14		152.4 (SD 16.6)		
Diastolic blood pressure (mmHg) – 0wk	Continuous	14		82.5 (SD 6.9)	14		77.3 (SD 10.6)		
Lipids: Total cholesterol (mmol/l) – 0wk	Mean change	14		5.8 (SD 1)	14		5.4 (SD 1)		
HDL cholesterol (mmol/l) – 0wk	Mean change	14		1.3 (SD 0.3)	14		1.5 (SD 0.3)		
Triglycerides (mmol/l) – 0wk	Mean change	14		1.7 (SD 0.5)	14		2 (SD 1.4)		
LDL cholesterol (mmol/l) – 0wk	Mean change	14		3.7 (SD 0.9)	14		3 (SD 1)		

Results

		Metformin + pioglitazone			Metformin + glimepiride				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 26wk	Mean change	14		-0.6 (SD 0.85)	14		-0.56 (SD 0.57)		NS
HbA1c (%) – 26wk	Continuous	14		7.1 (SD 0.8)	14		6.9 (SD 0.5)		
Fasting plasma glucose (mmol/l) – 26wk	Mean change	14		-1.07 (SD 2.18)	14		-0.42 (SD 1.16)		NS
Body weight: BMI (kg/m2) – 26wk	Continuous	14		34.1 (SD 7.3)	14		32 (SD 5.1)		
BMI (kg/m2) – 26wk	Mean change	14		0.23 (SD 0.82)	14		0.15 (SD 1.5)		NS
Weight (kg) – 26wka	Mean change	14		0.649152 (SD 2.31)	14		0.42336 (SD 4.23)		
Weight (kg) – 26wk	Continuous	14		86.4 (SD 19.2)	14		82 (SD 15.4)		NS
Waist circumference (cms) – 26wk	Mean change	14		-1.86 (SD 1.88)	14		1.86 (SD 3.11)		0.002
Dropouts: Total dropouts – 26wk	Dichotomous	14	0	(0.0%)	14	0	(0.0%)		
Dropout due to AEs – 26wk	Dichotomous	14	0	(0.0%)	14	0	(0.0%)		
Blood pressure: Systolic blood pressure (mmHg) – 26wk	Mean change	14		-8.67 (SD 19)	14		-11.08 (SD 20)		NS
Diastolic blood pressure (mmHg) – 26wk	Mean change	14		-2.52 (SD 6.48)	14		0.22 (SD 11.3)		NS
Lipids: Total cholesterol (mmol/l) – 26wk	Mean change	14		0.06 (SD 0.85)	14		0.24 (SD 0.73)		NS
HDL cholesterol (mmol/l) – 26wk	Mean change	14		0.14 (SD 0.2)	14		-0.07 (SD 0.22)		0.036

Triglycerides (mmol/l) – 26wk	Mean change	14		0.01 (SD 0.33)	14		0.25 (SD 0.53)		NS
LDL cholesterol (mmol/l) – 26wk	Mean change	14		-0.09 (SD 0.79)	14		0.19 (SD 0.61)		NS

[a] estimated from BMI assuming mean height of 1.68m

Chi squared and unpaired t-tests were used to compare categorical and continuous variables between the two groups at baseline. To assess changes from baseline to follow up, the paired t-test was used. Analysis of data was based on ITT analysis of repeated measures ANOVA adjusting for confounding factors (baseline clinical and demographic characteristics with a statistical difference of p<0.2 between groups) was carried out.

Table 26: Pfutzner et al. (2011)

General

Phase:
☐ monotherapy
☑ dual therapy
☐ triple therapy
☐ insulin monotherapy
☐ insulin + oral

Parallel / crossover: Parallel

Country: Germany

Authors' conclusions: With comparable glycemic control, the fixed PM combination was more efficacious on HDL cholesterol improvement than the GM combination. Additional positive effects were observed for biomarkers of lipid metabolism, b-cell function, activity of the visceral adipose tissue, and chronic systemic inflammation

Source of funding: Unclear but some authors employees of Takeda

Comments: prospective, comparative, randomized, double-blind, parallel, two-arm multicenter trial.

Number and characteristics of patients

Total number of patients: 305

Inclusion criteria: The trial population consisted of male and female individuals with type 2 diabetes, 18–75 years old, pretreated with metformin as monotherapy in an individually maximal tolerated dosage with baseline values for hemoglobin A1c (HbA1c) of >=6.5% and dyslipidemia defined as HDL cholesterol <=1.03 mmol/L (40 mg/dL) and/or triglyceride >=1.7 mmL (150 mg/dL)

Exclusion criteria: type 1 diabetes mellitus, hypersensitivity to the study drugs or to drugs with similar chemical structures, history of severe or multiple allergies, a history of significant cardiovascular respiratory, gastrointestinal, hepatic, neurological, psychiatric, and/or hematological disease, and pretreatment with antidiabetes therapy other than metformin within the last 3 months.

Previous glucose-lowering therapy

Any participants previously taking glucose-lowering therapy? all on oral hypoglycaemic drugs and/or insulin

Details of washout period: All patients were taking metformin monotherapy at study start and this continued during the treatment period

Lifestyle advice

-

Follow-up

Total follow-up (wks): 24

Length of titration period (wks): 0

Length of maintenance period (wks): 24

Frequency of monitoring appointments: -

Arms

(1) Metformin + pioglitazone

N: 146

Treatment duration (wks): 24
Washout period (d): 0
Comments: All patients were on metformin monotherapy and this continued during the treatment period

Treatment(s): (a) Metformin (Oral) – fixed-dose
Set dose (mg/d):1700
Frequency of dosing: twice a day
(b) Pioglitazone (Oral) – fixed-dose
Set dose (mg/d):30
Frequency of dosing: twice a day

(2) Metformin + glimepiride

N: 142

Treatment duration (wks): 24
Washout period (d): 0

Comments: All patients were on metformin monotherapy and this continued during the treatment period

Treatment(s): (a) Metformin (Oral) – fixed-dose
Set dose (mg/d):1700
Frequency of dosing: twice a day
(b) Sulfonylurea (Oral) – fixed-dose
Set dose (mg/d):2
Frequency of dosing: once a day

Outcomes

General

All randomised patients who received at least one dose of study medication were included in the ''all patients treated'' analysis set. Thus, patients with HDL cholesterol values measured at baseline and at least once post-baseline were included into the full analysis set. All analyses of safety data were performed for the ''all patients treated'' analysis set; all

analyses of efficacy were performed for the full analysis set. Missing data were accounted for by means of the last observation- carried-forward approach.

61 patients (32 vs. 29) discontinued the study

Outcomes not extracted in this evidence table include measures of insulin resistance

Baseline characteristics

		Metformin + pioglitazone			Metformin + glimepiride				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	146		59 (SD 10)	142		59 (SD 10)		
Sex (n male)	Dichotomous	146	96	(65.8%)	142	91	(64.1%)		
Duration of diabetes (yrs)	Continuous	146		6.2 (SD 5.4)	142		5.9 (SD 4.8)		
Blood glucose: HbA1c (%) – 0wk	Continuous	146		7.3 (SD 0.9)	142		7.3 (SD 0.8)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	146		8.8 (SD 2.3)	142		8.6 (SD 2.3)		
Body weight: BMI (kg/m2)	Continuous	146		32.6 (SD 4.9)	142		32.5 (SD 5.3)		
Weight (kg) – 0wk	Continuous	146		96.2 (SD 17.5)	142		94.1 (SD 18)		
Blood pressure: Systolic blood pressure (mmHg) – 0wk	Continuous	146		138 (SD 15)	142		137 (SD 13)		
Diastolic blood pressure (mmHg) – 0wk	Continuous	146		82 (SD 9)	142		82 (SD 7)		
Lipids: Total cholesterol (mmol/l) – 0wk	Continuous	146		5.18 (SD 1.24)	142		5.05 (SD 1.22)		
HDL cholesterol (mmol/l) – 0wk	Continuous	146		1.19 (SD 0.27)	142		1.2 (SD 0.26)		
Triglycerides (mmol/l) – 0wk	Continuous	146		2.49 (SD 1.48)	142		2.36 (SD 1.45)		
LDL cholesterol (mmol/l) – 0wk	Continuous	146		2.8 (SD 0.9)	142		2.69 (SD 0.81)		

Results

		Metformin + pioglitazone			Metformin + glimepiride				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 24wk	Continuous	139		6.5 (SD 0.9)	136		6.3 (SD 0.8)		NS
HbA1c (%) – 24wk	Continuous	146		6.5 (SD 0.9)	142		6.3 (SD 0.8)		NS
HbA1c (%) – 24wk	Mean change	139		-0.8 (SD 0.9)	136		-1 (SD 0.9)		

Fasting plasma glucose (mmol/l) – 24wk	Mean change	146		-1.2 (SD 2.1)	142		-1.2 (SD 2.2)		
Fasting plasma glucose (mmol/l) – 24wk	Continuous	146		7.6 (SD 2.2)	142		7.4 (SD 1.9)		NS
Body weight: Weight (kg) – 24wk	Continuous	146		96.9 (SD 17.8)	142		94.8 (SD 18.2)		NS
Hypoglycaemic events: All hypoglycaemic events (no events) – 24wka	Count	23352	2		22764	5			
All hypoglycaemic events (no patients) – 24wk	Dichotomous	146	2	(1.4%)	142	5	(3.5%)		NR
Adverse events: Edema peripheral – 24wk	Dichotomous	146	8	(5.5%)	142	4	(2.8%)		NR
Edema peripheral – 24wk	Dichotomous	146	8	(5.5%)	141	4	(2.8%)		NR
Dropouts: Total dropouts – 24wkb	Dichotomous	155	32	(20.6%)	150	29	(19.3%)		
Dropout due to AEs – 24wk	Dichotomous	155	13b	(8.4%)	150	7c	(4.7%)		
Blood pressure: Systolic blood pressure (mmHg) – 24wk	Continuous	146		135 (SD 14)	142		137 (SD 15)		NS
Diastolic blood pressure (mmHg) – 24wk	Continuous	146		81 (SD 8)	142		81 (SD 9)		NS
Lipids: Total cholesterol (mmol/l) – 24wk	Continuous	146		5.37 (SD 1.31)	142		5.23 (SD 1.2)		
Total cholesterol (mmol/l) – 24wk	Mean change	146			142				NS
HDL cholesterol (mmol/l) – 24wk	Mean change	146		0.08 (SD 0.25)	142		-0.01 (SD 0.28)		<0.01
HDL cholesterol (mmol/l) – 24wk	Continuous	146		1.27 (SD 0.27)	142		1.2 (SD 0.25)		
Triglycerides (mmol/l) – 24wk	Mean change	146		-0.47 (SD 1.3)	142		-0.19 (SD 1.39)		NS
Triglycerides (mmol/l) – 24wk	Continuous	146		2.02 (SD 1.17)	142		2.17 (SD 1.29)		
LDL cholesterol (mmol/l) – 24wk	Mean change	146		0.25 (SD 0.9)	142		0.29 (SD 0.66)		NS
LDL cholesterol (mmol/l) – 24wk	Continuous	146		3.05 (SD 1.03)	142		2.97 (SD 0.88)		

[a] (Used in the analysis); Patient days estimated assuming dropout occurred halfway through trial
[b] Data derived from clinicaltrials.gov NCT00770653
[c] Adverse events include hypoglycaemia. Data derived from clinicaltrials.gov NCT00770653

The confirmatory inferential statistical evaluation of the primary target parameter ‘‘mean change of HDL cholesterol after 24 weeks of treatment in each treatment group’’ was performedwith the same test procedure as used for sample size calculation (i.e., the one-sided Student’s t test) using the
parameter estimates of a general model for analysis of covariance, with fixed effect factor for treatment group and with the baseline HDL cholesterol value as covariate

Table 27: Pratley et al. (2010)

General	**Phase:** ☐ monotherapy ☑ dual therapy ☐ triple therapy

	☐ insulin monotherapy ☐ insulin + oral **Parallel / crossover:** Parallel **Country:** 11 European countries (Croatia, Germany, Ireland, Italy, Netherlands, Romania, Serbia, Slovakia, Slovenia, Spain, and UK), the USA, and Canada **Authors' conclusions:** Liraglutide was superior to sitagliptin for reduction of HbA1c, and was well tolerated with minimum risk of hypoglycaemia. These findings support the use of liraglutide as an eff ective GLP-1 agent to add to metformin **Source of funding:** Novo Nordisk **Comments:** randomisation sequence was computer-generated, Consecutive allocation of the randomisation code to individual participants was concealed by use of a telephone-based (interactive voice response system) or web-based randomisation system. The study was open-label, but data were masked from the statistician until database release.
Number and characteristics of patients	**Total number of patients:** 665 **Inclusion criteria:** aged 18–80 years, had type 2 diabetes mellitus, had glycosylated haemoglobin (HbA1c) of 7·5–10·0%, had a body-mass index of 45·0 kg/m² or lower, and had been treated with metformin (=1500 mg daily) for 3 months or longer. **Exclusion criteria:** previous treatment with any antihyperglycaemic drug apart from metformin within 3 months of the trial; recurrent major hypoglycaemia or hypoglycaemic unawareness; present use of any drug except metformin that could affect glucose; contraindication to trial drugs; impaired renal or hepatic function; clinically significant cardiovascular disease; or cancer participants who did not tolerate trial treatment doses were withdrawn
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** all on oral hypoglycaemic drugs and/or insulin **Details of washout period:** All treated with metformin monotherapy at study entry
Lifestyle advice	NOT STATED
Follow-up	**Total follow-up (wks):** 52 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 52 **Frequency of monitoring appointments:** -
Arms	**(1) Metformin + Liraglutide (1.2mg)** N: 225 Treatment duration (wks): 26 Washout period (d): 0 Comments: All on metformin montherapy at baseline which continued throughout the study Treatment(s): (a) Metformin (Oral) Details of dosing regimen: background treatment with metformin remained stable (b) Liraglutide (Subcutaneous) – fixed-dose Set dose (mg/d):1.2 Details of dosing regimen: started at 0·6 mg/day and escalated by 0·6 mg/week to the allocated dose; injection was done subcutaneously with a pen device. **(2) Metformin + Liraglutide (1.8mg)** N: 221 Treatment duration (wks): 26 Washout period (d): 0 Comments: All on metformin montherapy at baseline which continued throughout the study Treatment(s): (a) Metformin (Oral) Details of dosing regimen: background treatment with metformin remained stable (b) Liraglutide (Subcutaneous) – fixed-dose Set dose (mg/d):1.8 **(3) Metformin + sitaglitin** N: 219 Treatment duration (wks): 26 Washout period (d): 0 Comments: All on metformin montherapy at baseline which continued throughout the study Treatment(s): (a) Metformin (Oral) Details of dosing regimen: background treatment with metformin remained stable (b) Sitagliptin (Oral) – fixed-dose Set dose (mg/d):100 Details of dosing regimen: Sitagliptin was started and maintained at 100 mg/day.

Outcomes

General

Primary efficacy analyses were done on the full analysis set (randomised

participants who were exposed to at least one dose of trial drug and with at least one HbA1c measurement taken after baseline) with missing values imputed by last observation carried forward, and on the per-protocol set.

At week 26, 52/225 (23%) patients in liraglutide 1.2mg group, 27/221 (12.2%) in liraglutide 1.8 mg and 25/219 (11.4%) in sitagliptin group discontinued the study. At week 52, 20/155 (8.9%) in liraglutide 1.2mg group, 26/176 (11.8%) in liraglutide 1.8mg group and 15/166 (6.8%) in sitagliptin group.

Outcomes not extracted in this evidence table include several measures of beta-cell function

Data from the 52 week extension trial are also reported in this evidence table Pratley (2011). Therefore data for adverse events were only extracted at the final study endpoint (52 weeks)

Blood glucose

HbA1c < 7% or <=7% (there was a composite endpoint Hba1c<7% with no weight gain and no confirmed major or minor hypoglycaemia)

Hypoglycaemic events

Minor (confirmed) hypoglycaemia (Minor hypoglycaemic episodes (plasma glucose <3·1 mmol/L) were self-treated)

Major/severe hypoglycaemic event (for major episodes, third-party assistance was needed, irrespective of glucose concentrations, and these episodes were recorded as adverse events)

Baseline characteristics

		Metformin + Liraglutide (1.2mg)			Metformin + Liraglutide (1.8mg)			Δ	p
		N	k	mean	N	k	mean		
Demographics:									
Age (years)	Continuous	225		55.9 (SD 9.6)	221		55 (SD 9.1)		
Sex (n male)	Dichotomous	225	116	(51.6%)	221	116	(52.5%)		
Duration of diabetes (yrs)	Continuous	225		6 (SD 4.5)	221		6.4 (SD 5.4)		
Full analysis set (FAS) or efficacy analysis pop									
Blood glucose:									
HbA1c (%) – 0wk	Continuous	225		8.4 (SD 0.8)	221		8.4 (SD 0.7)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	225		10.1 (SD 2.4)	221		9.9 (SD 2.4)		
Body weight:									
BMI (kg/m2)	Continuous	225		32.6 (SD 5.2)	221		33.1 (SD 5.1)		
Weight (kg) – 0wk	Continuous	225		93.7 (SD 18.4)	221		94.6 (SD 18.1)		
Blood pressure:									
Systolic blood pressure (mmHg) – 0wk	Continuous	225		131.2 (SD 14.4)	221		133.4 (SD 14.5)		
Diastolic blood pressure (mmHg) – 0wk	Continuous	225		80.3 (SD 9)	221		81.5 (SD 8.5)		

		Metformin + Liraglutide (1.2mg)			Metformin + sitaglitin			Δ	p
		N	k	mean	N	k	mean		
Demographics:									
Age (years)	Continuous	225		55.9 (SD 9.6)	219		55 (SD 9)		
Sex (n male)	Dichotomous	225	116	(51.6%)	219	120	(54.8%)		
Duration of diabetes (yrs)	Continuous	225		6 (SD 4.5)	219		6.3 (SD 5.4)		
Full analysis set (FAS) or efficacy analysis pop									
Blood glucose:									
HbA1c (%) – 0wk	Continuous	225		8.4 (SD 0.8)	219		8.5 (SD 0.7)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	225		10.1 (SD 2.4)	219		10 (SD 2)		

Body weight: BMI (kg/m2)	Continuous	225		32.6 (SD 5.2)	219		32.6 (SD 5.4)		
Weight (kg) – 0wk	Continuous	225		93.7 (SD 18.4)	219		93.1 (SD 18.9)		
Blood pressure: Systolic blood pressure (mmHg) – 0wk	Continuous	225		131.2 (SD 14.4)	219		132.1 (SD 14.8)		
Diastolic blood pressure (mmHg) – 0wk	Continuous	225		80.3 (SD 9)	219		81.9 (SD 9.1)		

		Metformin + Liraglutide (1.8mg)			**Metformin + sitaglitin**				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Demographics: Age (years)	Continuous	221		55 (SD 9.1)	219		55 (SD 9)		
Sex (n male)	Dichotomous	221	116	(52.5%)	219	120	(54.8%)		
Duration of diabetes (yrs)	Continuous	221		6.4 (SD 5.4)	219		6.3 (SD 5.4)		
Full analysis set (FAS) or efficacy analysis pop Blood glucose: HbA1c (%) – 0wk	Continuous	221		8.4 (SD 0.7)	219		8.5 (SD 0.7)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	221		9.9 (SD 2.4)	219		10 (SD 2)		
Body weight: BMI (kg/m2)	Continuous	221		33.1 (SD 5.1)	219		32.6 (SD 5.4)		
Weight (kg) – 0wk	Continuous	221		94.6 (SD 18.1)	219		93.1 (SD 18.9)		
Blood pressure: Systolic blood pressure (mmHg) – 0wk	Continuous	221		133.4 (SD 14.5)	219		132.1 (SD 14.8)		
Diastolic blood pressure (mmHg) – 0wk	Continuous	221		81.5 (SD 8.5)	219		81.9 (SD 9.1)		

Results

		Metformin + Liraglutide (1.2mg)			**Metformin + Liraglutide (1.8mg)**				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Dropouts: Total dropouts – 26wk	Dichotomous	225	56	(24.9%)	221	30	(13.6%)		
Total dropouts – 52wka	Dichotomous	225	90	(40.0%)	221	71	(32.1%)		
Dropout due to AEs – 26wk	Dichotomous	225	14	(6.2%)	221	15	(6.8%)		
Dropout due to AEs – 52wka	Dichotomous	225	19	(8.4%)	221	25	(11.3%)		
Full analysis set (FAS) or efficacy analysis pop Blood glucose: HbA1c (%) – 12wkb	Continuous	221		7.12 (SD 1.19)	218		7.01 (SD 1.18)		
HbA1c (%) – 26wkb	Continuous	221		7.23 (SD 1.09)	218		7 (SD 1.33)		
HbA1c (%) – 26wkb	Mean change	221		-1.24 (SD 0.995)	218		-1.5 (SD 0.986)		

HbA1c (%) – 52wkc	Mean change	221		-1.29 (SD 1.06)	218		-1.51 (SD 1.05)		
HbA1c < 7% or <=7% – 26wkb	Dichotomous	221	95	(43.0%)	218	120	(55.0%)		
HbA1c < 7% or <=7% – 52wk	Dichotomous	221	111d	(50.2%)	218	109e	(50.0%)		
HbA1c < 7% or <=7% – 52wke	Dichotomous	221	85	(38.5%)	218	109	(50.0%)		
HbA1c < 7% or <=7% – 52wk	Dichotomous	221	85e	(38.5%)	218	138	(63.3%)		
HbA1c < 7% or <=7% – 52wk	Dichotomous	221	111d	(50.2%)	218	138	(63.3%)		
Hba1c <6.5% – 26wkf	Dichotomous	221	50	(22.6%)	218	76	(34.9%)		
Hba1c <6.5% – 52wk	Dichotomous	221	54d	(24.4%)	218	88	(40.4%)		
Fasting plasma glucose (mmol/l) – 12wkb	Continuous	221		8.1 (SD 1.64)	218		7.95 (SD 2.95)		
Fasting plasma glucose (mmol/l) – 12wkb	Continuous	221		8.1 (SD 1.64)	218		9.15 (SD 2.95)		
Fasting plasma glucose (mmol/l) – 26wk	Mean change	221		-1.87 (SD 2.22)	218		-2.14 (SD 2.2)		
Fasting plasma glucose (mmol/l) – 26wkb	Continuous	221		8.3 (SD 2.68)	218		7.9 (SD 2.81)		
Fasting plasma glucose (mmol/l) – 52wk	Mean change	221		-1.71 (SD 2.5)	218		-2.04 (SD 2.49)		
Body weight: Weight (kg) – 12wkb	Mean change	221		-2.6 (SD 2.97)	218		-2.65 (SD 5.91)		
Weight (kg) – 26wkb	Mean change	221		-2.7 (SD 5.95)	218		-3.3 (SD 7.38)		
Weight (kg) – 26wk	Mean change	221		-2.86 (SD 4.06)	218		-3.38 (SD 4.02)		
Weight (kg) – 26wk	Mean change	221		-2.86 (SD 4.06)	218		-3.3 (SD 7.38) b		
Weight (kg) – 26wk	Mean change	221		-2.7 (SD 5.95) b	218		-3.38 (SD 4.02)		
Weight (kg) – 52wkc	Mean change	221		-2.78 (SD 4.63)	221		-3.68 (SD 4.6)		0.03
Weight (kg) – 52wkc	Mean change	221		-2.78 (SD 4.63)	218		-3.68 (SD 4.6)		0.03
Waist circumference (cms) – 26wk	Mean change	221		-2.69 (SD 5.28)	218		-2.63 (SD 5.31)		
Waist circumference (cms) – 52wk	Mean change	221		-2.36 (SD 5.61)	218		-3.02 (SD 5.57)		
Waist/hip ratio – 26wk	Mean change	221		-0.01 (SD 0)	218		-0.01 (SD 0.0758)		
Hypoglycaemic events: Minor (confirmed) hypoglycaemia – 26wk	Dichotomous	221	0.178g	(0.1%)	218	11h	(5.0%)		
Minor (confirmed) hypoglycaemia – 26wk	Dichotomous	221	12h	(5.4%)	218	0.37g	(0.2%)		

Minor (confirmed) hypoglycaemia – 26wkh	Dichotomous	221	12	(5.4%)	218	11	(5.0%)		
Minor (confirmed) hypoglycaemia – 26wkg	Dichotomous	221	0.178	(0.1%)	218	0.37	(0.2%)		
Minor (confirmed) hypoglycaemia – 26wki	Count	35854	17		37492	38			
Minor (confirmed) hypoglycaemia – 52wkj	Count	65520	26		67522	68			
Major/severe hypoglycaemic event – 26wk	Dichotomous	221	1	(0.5%)	218	0	(0.0%)		
Major/severe hypoglycaemic event – 52wk	Dichotomous	221	0	(0.0%)	218	0	(0.0%)		
Adverse events:									
GI: nausea – 26wk	Dichotomous	221	46	(20.8%)	218	59	(27.1%)		
GI: nausea – 52wk	Dichotomous	221	48	(21.7%)	218	60	(27.5%)		
Any adverse event(s) – 26wk	Dichotomous	221	146	(66.1%)	218	159	(72.9%)		
Any serious adverse event(s) – 26wk	Dichotomous	221	6	(2.7%)	218	6	(2.8%)		
Any serious adverse event(s) – 52wk	Dichotomous	221	10	(4.5%)	218	13	(6.0%)		
cardiovascular AE – 52wkk	Dichotomous	221	2	(0.9%)	218	1	(0.5%)		
Death – 26wk	Dichotomous	221	0	(0.0%)	218	1	(0.5%)		
Death – 52wkk	Dichotomous	221	0	(0.0%)	218	1	(0.5%)		
Dyspepsia – 26wk	Dichotomous	221	7	(3.2%)	218	14	(6.4%)		
Dyspepsia – 52wk	Dichotomous	221	8	(3.6%)	218	15	(6.9%)		
Gastrointestinal disorders (any) – 26wk	Dichotomous	221	73	(33.0%)	218	88	(40.4%)		
Gastrointestinal disorders (any) – 52wkk	Dichotomous	221	4	(1.8%)	218	5	(2.3%)		
Gastrointestinal disorders (any) – 52wk	Dichotomous	221	4k	(1.8%)	218	94	(43.1%)		
Gastrointestinal disorders (any) – 52wk	Dichotomous	221	80	(36.2%)	218	94	(43.1%)		
Gastrointestinal disorders (any) – 52wk	Dichotomous	221	80	(36.2%)	218	5k	(2.3%)		
GI: diarrhoea – 26wk	Dichotomous	221	16	(7.2%)	218	25	(11.5%)		
GI: diarrhoea – 52wk	Dichotomous	221	20	(9.0%)	218	27	(12.4%)		
GI: vomiting – 26wk	Dichotomous	221	17	(7.7%)	218	21	(9.6%)		
GI: vomiting – 52wk	Dichotomous	221	18	(8.1%)	218	23	(10.6%)		
GI: constipation – 26wk	Dichotomous	221	10	(4.5%)	218	11	(5.0%)		
GI: constipation – 52wk	Dichotomous	221	10	(4.5%)	218	13	(6.0%)		
Headache – 26wk	Dichotomous	221	20	(9.0%)	218	25	(11.5%)		
Headache – 52wk	Dichotomous	221	21	(9.5%)	218	29	(13.3%)		
Infection (upper airway or other common) – 26wk	Dichotomous	221	62	(28.1%)	218	1l	(0.5%)		
Infection (upper airway or other common) – 26wk	Dichotomous	221	1l	(0.5%)	218	59	(27.1%)		
Infection (upper airway or other common) – 26wkl	Dichotomous	221	1	(0.5%)	218	1	(0.5%)		
Infection (upper airway or other common) – 26wk	Dichotomous	221	62	(28.1%)	218	59	(27.1%)		

Infection (upper airway or other common) – 52wkk	Dichotomous	221	3	(1.4%)	218	3	(1.4%)		
Infection (upper airway or other common) – 52wk	Dichotomous	221	74	(33.5%)	218	77	(35.3%)		
Infection (upper airway or other common) – 52wk	Dichotomous	221	74	(33.5%)	218	3k	(1.4%)		
Infection (upper airway or other common) – 52wk	Dichotomous	221	3k	(1.4%)	218	77	(35.3%)		
Injection site – 26wk	Dichotomous	221	26	(11.8%)	218	32m	(14.7%)		
Injection site – 26wk	Dichotomous	221	31m	(14.0%)	218	26	(11.9%)		
Injection site – 26wkm	Dichotomous	221	31	(14.0%)	218	32	(14.7%)		
Injection site – 26wk	Dichotomous	221	26	(11.8%)	218	26	(11.9%)		
Musculoskeletal and connective tissue disorders – 26wk	Dichotomous	221	2l	(0.9%)	218	45	(20.6%)		
Musculoskeletal and connective tissue disorders – 26wk	Dichotomous	221	39	(17.6%)	218	1l	(0.5%)		
Musculoskeletal and connective tissue disorders – 26wk	Dichotomous	221	39	(17.6%)	218	45	(20.6%)		
Musculoskeletal and connective tissue disorders – 26wkl	Dichotomous	221	2	(0.9%)	218	1	(0.5%)		
Musculoskeletal and connective tissue disorders – 52wkk	Dichotomous	221	3	(1.4%)	218	1	(0.5%)		
Nasopharyngitis – 26wk	Dichotomous	221	21	(9.5%)	218	28	(12.8%)		
Nasopharyngitis – 52wk	Dichotomous	221	27	(12.2%)	218	32	(14.7%)		
Nervous system disorders – 52wkk	Dichotomous	221	0	(0.0%)	218	0	(0.0%)		
Nervous system disorders – 52wk	Dichotomous	221	40	(18.1%)	218	48	(22.0%)		
Nervous system disorders – 52wk	Dichotomous	221	40	(18.1%)	218	0k	(0.0%)		
Nervous system disorders – 52wk	Dichotomous	221	0k	(0.0%)	218	48	(22.0%)		
renal or urinary disorder – 26wkl	Dichotomous	221	0	(0.0%)	218	0	(0.0%)		
renal or urinary disorder – 52wkk	Dichotomous	221	0	(0.0%)	218	0	(0.0%)		
Skin reaction – 26wk	Dichotomous	221	22	(10.0%)	218	20	(9.2%)		
Skin reaction – 26wk	Dichotomous	221	16	(7.2%)	218	20	(9.2%)		
Skin reaction – 26wk	Dichotomous	221	16	(7.2%)	218	12	(5.5%)		
Skin reaction – 26wk	Dichotomous	221	22	(10.0%)	218	12	(5.5%)		
Temperature/influenza – 26wk	Dichotomous	221	13	(5.9%)	218	2	(0.9%)		
Temperature/influenza – 52wk	Dichotomous	221	13	(5.9%)	218	4	(1.8%)		
Vascular disorder – 26wk	Dichotomous	221	16	(7.2%)	218	15	(6.9%)		
Blood pressure: Systolic blood pressure (mmHg) – 26wk	Mean change	221		-0.55 (SD 13.4)	218		-0.72 (SD 13.3)		
Systolic blood pressure (mmHg) – 52wk	Mean change	221		-0.37 (SD 13.8)	218		-2.55 (SD 13.6)		

Diastolic blood pressure (mmHg) – 26wk	Mean change	221		-0.71 (SD 8.95)	218		0.07 (SD 8.87)		
Diastolic blood pressure (mmHg) – 52wk	Mean change	221		-0.53 (SD 8.5)	218		-0.87 (SD 8.44)		
Lipids: Total cholesterol (mmol/l) – 26wk	Mean change	221		-0.03 (SD 0.842)	218		-0.17 (SD 0.834)		
Total cholesterol (mmol/l) – 52wk	Mean change	221		-0.01 (SD 0.91)	218		-0.09 (SD 0.904)		
HDL cholesterol (mmol/l) – 26wk	Mean change	221		0 (SD 0.153)	218		0 (SD 0.152)		
HDL cholesterol (mmol/l) – 52wk	Mean change	221		0.01 (SD 0.152)	218		0.02 (SD 0.151)		
Triglycerides (mmol/l) – 26wk	Mean change	221		-0.19 (SD 1.45)	218		-0.43 (SD 1.37)		
Triglycerides (mmol/l) – 52wk	Mean change	221		-0.1 (SD 1.52)	218		-0.32 (SD 1.51)		
LDL cholesterol (mmol/l) – 26wk	Mean change	221		0.08 (SD 0.689)	218		0.05 (SD 0.683)		
LDL cholesterol (mmol/l) – 52wk	Mean change	221		0.09 (SD 0.758)	218		0.09 (SD 0.753)		
Blood glucose: HbA1c < 7% or <=7% – 52wk	Dichotomous	218			225			OR=1.560 (CI: 21.016, 0.116)	0.03

[a] (Used in the analysis)
[b] estimated from graph
[c] SD estimated from 95% CI
[d] approximated to nearest integer (percentages only presented in text)
[e] composite (no weight gain or hypos); approximated to nearest integer (percentages only presented in text)
[f] estimated from graph; approximated to nearest integer (percentages only presented in text)
[g] episodes per patient year
[h] No patients
[i] Event rate (events/patient year) and patient days calculated assuming dropouts occurred halfway through the study were used to calculate number of events
[j] (Used in the analysis); Adjusted event rate (events/patient years with outliers removed) and patient days calculated assuming dropouts occurred halfway through the study were used to calculate number of events
[k] SAE
[l] severe
[m] general disorder and administration site

		Metformin + Liraglutide (1.2mg)			**Metformin + sitaglitin**				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Dropouts: Total dropouts – 26wk	Dichotomous	225	56	(24.9%)	219	25	(11.4%)		
Total dropouts – 52wka	Dichotomous	225	90	(40.0%)	219	68	(31.1%)		
Dropout due to AEs – 26wk	Dichotomous	225	14	(6.2%)	219	4	(1.8%)		
Dropout due to AEs – 52wka	Dichotomous	225	19	(8.4%)	219	7	(3.2%)		
Full analysis set (FAS) or efficacy analysis pop Blood glucose: HbA1c (%) – 12wkb	Continuous	221		7.12 (SD 1.19)	219		7.5 (SD 1.18)		

	HbA1c (%) – 26wkb	Continuous	221		7.23 (SD 1.09)	219		7.6 (SD 1.48)		
	HbA1c (%) – 26wkb	Mean change	221		-1.24 (SD 0.995)	219		-0.9 (SD 0.982)	MD=-0.340 (CI: -0.510, -0.170)	
	HbA1c (%) – 52wkc	Mean change	221		-1.29 (SD 1.06)	219		-0.88 (SD 1.06)	MD=-0.400 (CI: -0.590, -0.210)	<0.0001
	HbA1c < 7% or <=7% – 26wk	Dichotomous	221	95b	(43.0%)	219	48d	(21.9%)	OR=2.750 (CI: 10.916, 0.693)	
	HbA1c < 7% or <=7% – 52wk	Dichotomous	221	111e	(50.2%)	219	41f	(18.7%)	OR=2.800 (CI: 9.340, 0.839)	<0.0001g
	HbA1c < 7% or <=7% – 52wkf	Dichotomous	221	85	(38.5%)	219	41	(18.7%)	OR=2.800 (CI: 9.340, 0.839)	<0.0001g
	HbA1c < 7% or <=7% – 52wke	Dichotomous	221	111	(50.2%)	219	59	(26.9%)	OR=2.800 (CI: 9.340, 0.839)	<0.0001g
	HbA1c < 7% or <=7% – 52wk	Dichotomous	221	85f	(38.5%)	219	59e	(26.9%)	OR=2.800 (CI: 9.340, 0.839)	<0.0001g
	Hba1c <6.5% – 26wk	Dichotomous	221	50d	(22.6%)	219	24b	(11.0%)	OR=2.110 (CI: 10.366, 0.429)	
	Hba1c <6.5% – 52wke	Dichotomous	221	54	(24.4%)	219	37	(16.9%)		
	Fasting plasma glucose (mmol/l) – 26wk	Mean change	221		-1.87 (SD 2.22)	219		-0.83 (SD 2.27)	MD=-1.040 (CI: -1.430, -0.650)	
	Fasting plasma glucose (mmol/l) – 26wkb	Continuous	221		8.3 (SD 2.68)	219		9.2 (SD 3.26)		
	Fasting plasma glucose (mmol/l) – 52wk	Mean change	221		-1.71 (SD 2.5)	219		-0.59 (SD 2.49)	MD=-1.130 (CI: -1.570, -0.690)	<0.0001
	Body weight: Weight (kg) – 12wkb	Mean change	221		-2.6 (SD 2.97)	219		-0.55 (SD 2.96)		
	Weight (kg) – 26wkb	Mean change	221		-2.7 (SD 5.95)	219		-0.8 (SD 4.88)	MD=-1.900 (CI: -2.610, -1.190)	
	Weight (kg) – 26wk	Mean change	221		-2.86 (SD 4.06)	219		-0.96 (SD 4.08)	MD=-1.900 (CI: -2.610, -1.190)	
	Weight (kg) – 26wk	Mean change	221		-2.86 (SD 4.06)	219		-0.8 (SD 4.88) b	MD=-1.900 (CI: -2.610, -1.190)	
	Weight (kg) – 26wk	Mean change	221		-2.7 (SD 5.95) b	219		-0.96 (SD 4.08)	MD=-1.900 (CI: -2.610, -1.190)	

Weight (kg) – 52wkc	Mean change	221		-2.78 (SD 4.63)	219		-1.16 (SD 4.61)	MD=-1.620 (CI: -2.430, -0.810)	<0.0001
Waist circumference (cms) – 26wk	Mean change	221		-2.69 (SD 5.28)	219		-1.12 (SD 5.29)	MD=-1.570 (CI: -2.500, -0.640)	0.001
Waist circumference (cms) – 52wk	Mean change	221		-2.36 (SD 5.61)	219		-1.23 (SD 5.59)	MD=-1.130 (CI: -2.120, -0.140)	0.03
Waist/hip ratio – 26wk	Mean change	221		-0.01 (SD 0)	219		0 (SD 0.0755)	MD=0.000 (CI: -0.010, 0.010)	0.87
Hypoglycaemic events:									
Minor (confirmed) hypoglycaemia – 26wkh	Count	35854	17		37583	11			
Minor (confirmed) hypoglycaemia – 26wki	Dichotomous	221	0.178	(0.1%)	219	0.106	(0.0%)		
Minor (confirmed) hypoglycaemia – 26wk	Dichotomous	221	12j	(5.4%)	219	0.106 i	(0.0%)		
Minor (confirmed) hypoglycaemia – 26wk	Dichotomous	221	0.178 i	(0.1%)	219	10j	(4.6%)		
Minor (confirmed) hypoglycaemia – 26wkj	Dichotomous	221	12	(5.4%)	219	10	(4.6%)		
Minor (confirmed) hypoglycaemia – 52wkk	Count	65520	26		67340	25			
Major/severe hypoglycaemic event – 26wk	Dichotomous	221	1	(0.5%)	219	0	(0.0%)		
Major/severe hypoglycaemic event – 52wk	Dichotomous	221	0	(0.0%)	219	0	(0.0%)		
Adverse events:									
GI: nausea – 26wk	Dichotomous	221	46	(20.8%)	219	10	(4.6%)		
GI: nausea – 52wk	Dichotomous	221	48	(21.7%)	219	12	(5.5%)		
Any adverse event(s) – 26wk	Dichotomous	221	146	(66.1%)	219	127	(58.0%)		
Any serious adverse event(s) – 26wk	Dichotomous	221	6	(2.7%)	219	4	(1.8%)		
Any serious adverse event(s) – 52wk	Dichotomous	221	10	(4.5%)	219	12	(5.5%)		
cardiovascular AE – 52wkl	Dichotomous	221	2	(0.9%)	219	1	(0.5%)		
Death – 26wk	Dichotomous	221	0	(0.0%)	219	1	(0.5%)		
Death – 52wkl	Dichotomous	221	0	(0.0%)	219	2	(0.9%)		
Dyspepsia – 26wk	Dichotomous	221	7	(3.2%)	219	5	(2.3%)		
Dyspepsia – 52wk	Dichotomous	221	8	(3.6%)	219	5	(2.3%)		
Gastrointestinal disorders (any) – 26wk	Dichotomous	221	73	(33.0%)	219	46	(21.0%)		

Gastrointestinal disorders (any) – 52wk	Dichotomous	221	80	(36.2%)	219	52	(23.7%)		
Gastrointestinal disorders (any) – 52wk	Dichotomous	221	80	(36.2%)	219	4l	(1.8%)		
Gastrointestinal disorders (any) – 52wkl	Dichotomous	221	4	(1.8%)	219	4	(1.8%)		
Gastrointestinal disorders (any) – 52wk	Dichotomous	221	4l	(1.8%)	219	52	(23.7%)		
GI: diarrhoea – 26wk	Dichotomous	221	16	(7.2%)	219	10	(4.6%)		
GI: diarrhoea – 52wk	Dichotomous	221	20	(9.0%)	219	14	(6.4%)		
GI: vomiting – 26wk	Dichotomous	221	17	(7.7%)	219	9	(4.1%)		
GI: vomiting – 52wk	Dichotomous	221	18	(8.1%)	219	11	(5.0%)		
GI: constipation – 26wk	Dichotomous	221	10	(4.5%)	219	6	(2.7%)		
GI: constipation – 52wk	Dichotomous	221	10	(4.5%)	219	8	(3.7%)		
Headache – 26wk	Dichotomous	221	20	(9.0%)	219	22	(10.0%)		
Headache – 52wk	Dichotomous	221	21	(9.5%)	219	27	(12.3%)		
Infection (upper airway or other common) – 26wkm	Dichotomous	221	1	(0.5%)	219	1	(0.5%)		
Infection (upper airway or other common) – 26wk	Dichotomous	221	62	(28.1%)	219	1m	(0.5%)		
Infection (upper airway or other common) – 26wk	Dichotomous	221	62	(28.1%)	219	63	(28.8%)		
Infection (upper airway or other common) – 26wk	Dichotomous	221	1m	(0.5%)	219	63	(28.8%)		
Infection (upper airway or other common) – 52wkl	Dichotomous	221	3	(1.4%)	219	3	(1.4%)		
Infection (upper airway or other common) – 52wk	Dichotomous	221	74	(33.5%)	219	75	(34.2%)		
Infection (upper airway or other common) – 52wk	Dichotomous	221	74	(33.5%)	219	3l	(1.4%)		
Infection (upper airway or other common) – 52wk	Dichotomous	221	3l	(1.4%)	219	75	(34.2%)		
Injection site – 26wk	Dichotomous	221	26	(11.8%)	219	8	(3.7%)		
Injection site – 26wk	Dichotomous	221	31n	(14.0%)	219	8	(3.7%)		
Injection site – 26wkn	Dichotomous	221	31	(14.0%)	219	13	(5.9%)		
Injection site – 26wk	Dichotomous	221	26	(11.8%)	219	13n	(5.9%)		
Musculoskeletal and connective tissue disorders – 26wk	Dichotomous	221	39	(17.6%)	219	45	(20.5%)		
Musculoskeletal and connective tissue disorders – 26wk	Dichotomous	221	39	(17.6%)	219	1m	(0.5%)		

	Musculoskeletal and connective tissue disorders – 26wkm	Dichotomous	221	2	(0.9%)	219	1	(0.5%)		
	Musculoskeletal and connective tissue disorders – 26wk	Dichotomous	221	2m	(0.9%)	219	45	(20.5%)		
	Musculoskeletal and connective tissue disorders – 52wkl	Dichotomous	221	3	(1.4%)	219	1	(0.5%)		
	Nasopharyngitis – 26wk	Dichotomous	221	21	(9.5%)	219	26	(11.9%)		
	Nasopharyngitis – 52wk	Dichotomous	221	27	(12.2%)	219	31	(14.2%)		
	Nervous system disorders – 52wk	Dichotomous	221	40	(18.1%)	219	2l	(0.9%)		
	Nervous system disorders – 52wkl	Dichotomous	221	0	(0.0%)	219	2	(0.9%)		
	Nervous system disorders – 52wk	Dichotomous	221	40	(18.1%)	219	44	(20.1%)		
	Nervous system disorders – 52wk	Dichotomous	221	0l	(0.0%)	219	44	(20.1%)		
	renal or urinary disorder – 26wkm	Dichotomous	221	0	(0.0%)	219	1	(0.5%)		
	renal or urinary disorder – 52wkl	Dichotomous	221	0	(0.0%)	219	1	(0.5%)		
	Skin reaction – 26wk	Dichotomous	221	22	(10.0%)	219	22	(10.0%)		
	Skin reaction – 26wk	Dichotomous	221	16	(7.2%)	219	12	(5.5%)		
	Skin reaction – 26wk	Dichotomous	221	16	(7.2%)	219	22	(10.0%)		
	Skin reaction – 26wk	Dichotomous	221	22	(10.0%)	219	12	(5.5%)		
	Temperature/influenza – 26wk	Dichotomous	221	13	(5.9%)	219	5	(2.3%)		
	Temperature/influenza – 52wk	Dichotomous	221	13	(5.9%)	219	8	(3.7%)		
	Vascular disorder – 26wk	Dichotomous	221	16	(7.2%)	219	10	(4.6%)		
	Blood pressure: Systolic blood pressure (mmHg) – 26wk	Mean change	221		-0.55 (SD 13.4)	219		-0.94 (SD 13.2)	MD=0.390 (CI: -1.960, 2.740)	0.75
	Systolic blood pressure (mmHg) – 52wk	Mean change	221		-0.37 (SD 13.8)	219		-1.03 (SD 13.7)	MD=0.660 (CI: -1.790, 3.110)	0.6
	Diastolic blood pressure (mmHg) – 26wk	Mean change	221		-0.71 (SD 8.95)	219		-1.78 (SD 8.83)	MD=1.070 (CI: -0.500, 2.640)	0.18
	Diastolic blood pressure (mmHg) – 52wk	Mean change	221		-0.53 (SD 8.5)	219		-1.47 (SD 8.46)	MD=0.940 (CI: -0.570, 2.450)	0.22
	Lipids: Total cholesterol (mmol/l) – 26wk	Mean change	221		-0.03 (SD 0.842)	219		-0.02 (SD 0.831)	MD=-0.010 (CI: -0.160, 0.140)	0.85
	Total cholesterol (mmol/l) – 52wk	Mean change	221		-0.01 (SD 0.91)	219		0.03 (SD 1.36)	MD=-0.040 (CI: -0.200, 0.120)	0.61

HDL cholesterol (mmol/l) – 26wk	Mean change	221		0 (SD 0.153)	219		0 (SD 0.151)	MD=0.000 (CI: -0.030, 0.030)	0.95
HDL cholesterol (mmol/l) – 52wk	Mean change	221		0.01 (SD 0.152)	219		0.01 (SD 0.151)	MD=0.000 (CI: -0.030, 0.030)	0.92
Triglycerides (mmol/l) – 26wk	Mean change	221		-0.19 (SD 1.45)	219		-0.4 (SD 1.36)	MD=0.210 (CI: -0.040, 0.460)	0.096
Triglycerides (mmol/l) – 52wk	Mean change	221		-0.1 (SD 1.52)	219		-0.23 (SD 1.51)	MD=0.120 (CI: -0.130, 0.370)	0.34
LDL cholesterol (mmol/l) – 26wk	Mean change	221		0.08 (SD 0.689)	219		0.13 (SD 0.68)	MD=-0.050 (CI: -0.170, 0.070)	0.44
LDL cholesterol (mmol/l) – 52wk	Mean change	221		0.09 (SD 0.758)	219		0.17 (SD 0.755)	MD=-0.080 (CI: -0.200, 0.040)	0.25

[a] (Used in the analysis)
[b] estimated from graph
[c] SD estimated from 95% CI
[d] estimated from graph; approximated to nearest integer (percentages only presented in text)
[e] approximated to nearest integer (percentages only presented in text)
[f] composite (no weight gain or hypos); approximated to nearest integer (percentages only presented in text)
[g] composite endpoint (no weight gain or hypoglycaemia)
[h] Event rate (events/patient year) and patient days calculated assuming dropouts occurred halfway through the study were used to calculate number of events
[i] episodes per patient year
[j] No patients
[k] (Used in the analysis); Adjusted event rate (events/patient years with outliers removed) and patient days calculated assuming dropouts occurred halfway through the study were used to calculate number of events
[l] SAE
[m] severe
[n] general disorder and administration site

		Metformin + Liraglutide (1.8mg)			**Metformin + sitaglitin**				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Dropouts:									
Total dropouts – 26wk	Dichotomous	221	30	(13.6%)	219	25	(11.4%)		
Total dropouts – 52wka	Dichotomous	221	71	(32.1%)	219	68	(31.1%)		
Dropout due to AEs – 26wk	Dichotomous	221	15	(6.8%)	219	4	(1.8%)		
Dropout due to AEs – 52wka	Dichotomous	221	25	(11.3%)	219	7	(3.2%)		
Full analysis set (FAS) or efficacy analysis pop									
Blood glucose:									
HbA1c (%) – 12wkb	Continuous	218		7.01 (SD 1.18)	219		7.5 (SD 1.18)		
HbA1c (%) – 26wkb	Continuous	218		7 (SD 1.33)	219		7.6 (SD 1.48)		
HbA1c (%) – 26wkb	Mean change	218		-1.5 (SD 0.986)	219		-0.9 (SD 0.982)	MD=-0.600 (CI: -0.770, -0.430)	

	HbA1c (%) – 52wkc	Mean change	218		-1.51 (SD 1.05)	219		-0.88 (SD 1.06)	MD=-0.630 (CI: -0.810, -0.450)	<0.0001
	HbA1c < 7% or <=7% – 26wk	Dichotomous	218	120 b	(55.0%)	219	48d	(21.9%)	OR=4.500 (CI: 6.698, 3.023)	
	HbA1c < 7% or <=7% – 52wk	Dichotomous	218	109 e	(50.0%)	219	59f	(26.9%)	OR=4.370 (CI: 6.272, 3.045)	<0.0001 g
	HbA1c < 7% or <=7% – 52wke	Dichotomous	218	109	(50.0%)	219	41	(18.7%)	OR=4.370 (CI: 6.272, 3.045)	<0.0001 g
	HbA1c < 7% or <=7% – 52wk	Dichotomous	218	138	(63.3%)	219	59f	(26.9%)	OR=4.370 (CI: 6.272, 3.045)	<0.0001 g
	HbA1c < 7% or <=7% – 52wk	Dichotomous	218	138	(63.3%)	219	41e	(18.7%)	OR=4.370 (CI: 6.272, 3.045)	<0.0001 g
	Hba1c <6.5% – 26wk	Dichotomous	218	76d	(34.9%)	219	24b	(11.0%)	OR=4.250 (CI: 5.617, 3.216)	
	Hba1c <6.5% – 52wk	Dichotomous	218	88	(40.4%)	219	37f	(16.9%)		
	Fasting plasma glucose (mmol/l) – 26wk	Mean change	218		-2.14 (SD 2.2)	219		-0.83 (SD 2.27)	MD=-1.310 (CI: -1.700, -0.920)	
	Fasting plasma glucose (mmol/l) – 26wkb	Continuous	218		7.9 (SD 2.81)	219		9.2 (SD 3.26)		
	Fasting plasma glucose (mmol/l) – 52wk	Mean change	218		-2.04 (SD 2.49)	219		-0.59 (SD 2.49)	MD=-1.450 (CI: -1.890, -1.010)	<0.0001
	Body weight: Weight (kg) – 12wkb	Mean change	218		-2.65 (SD 5.91)	219		-0.55 (SD 2.96)		
	Weight (kg) – 26wkb	Mean change	218		-3.3 (SD 7.38)	219		-0.8 (SD 4.88)	MD=-2.420 (CI: -3.140, -1.700)	
	Weight (kg) – 26wk	Mean change	218		-3.38 (SD 4.02)	219		-0.96 (SD 4.08)	MD=-2.420 (CI: -3.140, -1.700)	
	Weight (kg) – 26wk	Mean change	218		-3.38 (SD 4.02)	219		-0.8 (SD 4.88) b	MD=-2.420 (CI: -3.140, -1.700)	
	Weight (kg) – 26wk	Mean change	218		-3.3 (SD 7.38) b	219		-0.96 (SD 4.08)	MD=-2.420 (CI: -3.140, -1.700)	
	Weight (kg) – 52wkc	Mean change	218		-3.68 (SD 4.6)	219		-1.16 (SD 4.61)	MD=-2.530 (CI: -3.330, -1.730)	<0.0001
	Waist circumference (cms) – 26wk	Mean change	218		-2.63 (SD 5.31)	219		-1.12 (SD 5.29)	MD=-1.500 (CI: -2.440, -0.560)	0.002

	Waist circumference (cms) – 52wk	Mean change	218		-3.02 (SD 5.57)	219		-1.23 (SD 5.59)	MD=-1.790 (CI: -2.780, -0.800)	<0.001
	Waist/hip ratio – 26wk	Mean change	218		-0.01 (SD 0.0758)	219		0 (SD 0.0755)	MD=0.000 (CI: -0.010, 0.010)	0.3
	Hypoglycaemic events: Minor (confirmed) hypoglycaemia – 26wkh	Count	37492	38		37583	11			
	Minor (confirmed) hypoglycaemia – 26wki	Dichotomous	218	0.37	(0.2%)	219	0.106	(0.0%)		
	Minor (confirmed) hypoglycaemia – 26wk	Dichotomous	218	11j	(5.0%)	219	0.106i	(0.0%)		
	Minor (confirmed) hypoglycaemia – 26wk	Dichotomous	218	0.37i	(0.2%)	219	10j	(4.6%)		
	Minor (confirmed) hypoglycaemia – 26wkj	Dichotomous	218	11	(5.0%)	219	10	(4.6%)		
	Minor (confirmed) hypoglycaemia – 52wkk	Count	67522	68		67340	25			
	Major/severe hypoglycaemic event – 26wk	Dichotomous	218	0	(0.0%)	219	0	(0.0%)		
	Major/severe hypoglycaemic event – 52wk	Dichotomous	218	0	(0.0%)	219	0	(0.0%)		
	Adverse events: GI: nausea – 26wk	Dichotomous	218	59	(27.1%)	219	10	(4.6%)		
	GI: nausea – 52wk	Dichotomous	218	60	(27.5%)	219	12	(5.5%)		
	Any adverse event(s) – 26wk	Dichotomous	218	159	(72.9%)	219	127	(58.0%)		
	Any serious adverse event(s) – 26wk	Dichotomous	218	6	(2.8%)	219	4	(1.8%)		
	Any serious adverse event(s) – 52wk	Dichotomous	218	13	(6.0%)	219	12	(5.5%)		
	cardiovascular AE – 52wkl	Dichotomous	218	1	(0.5%)	219	1	(0.5%)		
	Death – 26wk	Dichotomous	218	1	(0.5%)	219	1	(0.5%)		
	Death – 52wkl	Dichotomous	218	1	(0.5%)	219	2	(0.9%)		
	Dyspepsia – 26wk	Dichotomous	218	14	(6.4%)	219	5	(2.3%)		
	Dyspepsia – 52wk	Dichotomous	218	15	(6.9%)	219	5	(2.3%)		
	Gastrointestinal disorders (any) – 26wk	Dichotomous	218	88	(40.4%)	219	46	(21.0%)		
	Gastrointestinal disorders (any) – 52wk	Dichotomous	218	94	(43.1%)	219	52	(23.7%)		
	Gastrointestinal disorders (any) – 52wk	Dichotomous	218	94	(43.1%)	219	4l	(1.8%)		
	Gastrointestinal disorders (any) – 52wkl	Dichotomous	218	5	(2.3%)	219	4	(1.8%)		

Gastrointestinal disorders (any) – 52wk	Dichotomous	218	5l	(2.3%)	219	52	(23.7%)		
GI: diarrhoea – 26wk	Dichotomous	218	25	(11.5%)	219	10	(4.6%)		
GI: diarrhoea – 52wk	Dichotomous	218	27	(12.4%)	219	14	(6.4%)		
GI: vomiting – 26wk	Dichotomous	218	21	(9.6%)	219	9	(4.1%)		
GI: vomiting – 52wk	Dichotomous	218	23	(10.6%)	219	11	(5.0%)		
GI: constipation – 26wk	Dichotomous	218	11	(5.0%)	219	6	(2.7%)		
GI: constipation – 52wk	Dichotomous	218	13	(6.0%)	219	8	(3.7%)		
Headache – 26wk	Dichotomous	218	25	(11.5%)	219	22	(10.0%)		
Headache – 52wk	Dichotomous	218	29	(13.3%)	219	27	(12.3%)		
Infection (upper airway or other common) – 26wkm	Dichotomous	218	1	(0.5%)	219	1	(0.5%)		
Infection (upper airway or other common) – 26wk	Dichotomous	218	59	(27.1%)	219	1m	(0.5%)		
Infection (upper airway or other common) – 26wk	Dichotomous	218	59	(27.1%)	219	63	(28.8%)		
Infection (upper airway or other common) – 26wk	Dichotomous	218	1m	(0.5%)	219	63	(28.8%)		
Infection (upper airway or other common) – 52wkl	Dichotomous	218	3	(1.4%)	219	3	(1.4%)		
Infection (upper airway or other common) – 52wk	Dichotomous	218	77	(35.3%)	219	75	(34.2%)		
Infection (upper airway or other common) – 52wk	Dichotomous	218	77	(35.3%)	219	3l	(1.4%)		
Infection (upper airway or other common) – 52wk	Dichotomous	218	3l	(1.4%)	219	75	(34.2%)		
Injection site – 26wk	Dichotomous	218	26	(11.9%)	219	8	(3.7%)		
Injection site – 26wk	Dichotomous	218	32n	(14.7%)	219	8	(3.7%)		
Injection site – 26wkn	Dichotomous	218	32	(14.7%)	219	13	(5.9%)		
Injection site – 26wk	Dichotomous	218	26	(11.9%)	219	13n	(5.9%)		
Musculoskeletal and connective tissue disorders – 26wk	Dichotomous	218	45	(20.6%)	219	45	(20.5%)		
Musculoskeletal and connective tissue disorders – 26wk	Dichotomous	218	45	(20.6%)	219	1m	(0.5%)		
Musculoskeletal and connective tissue disorders – 26wkm	Dichotomous	218	1	(0.5%)	219	1	(0.5%)		
Musculoskeletal and connective tissue disorders – 26wk	Dichotomous	218	1m	(0.5%)	219	45	(20.5%)		
Musculoskeletal and connective tissue disorders – 52wkl	Dichotomous	218	1	(0.5%)	219	1	(0.5%)		

	Nasopharyngitis – 26wk	Dichotomous	218	28	(12.8%)	219	26	(11.9%)		
	Nasopharyngitis – 52wk	Dichotomous	218	32	(14.7%)	219	31	(14.2%)		
	Nervous system disorders – 52wk	Dichotomous	218	48	(22.0%)	219	2l	(0.9%)		
	Nervous system disorders – 52wkl	Dichotomous	218	0	(0.0%)	219	2	(0.9%)		
	Nervous system disorders – 52wk	Dichotomous	218	48	(22.0%)	219	44	(20.1%)		
	Nervous system disorders – 52wk	Dichotomous	218	0l	(0.0%)	219	44	(20.1%)		
	renal or urinary disorder – 26wkm	Dichotomous	218	0	(0.0%)	219	1	(0.5%)		
	renal or urinary disorder – 52wkl	Dichotomous	218	0	(0.0%)	219	1	(0.5%)		
	Skin reaction – 26wk	Dichotomous	218	20	(9.2%)	219	22	(10.0%)		
	Skin reaction – 26wk	Dichotomous	218	12	(5.5%)	219	12	(5.5%)		
	Skin reaction – 26wk	Dichotomous	218	12	(5.5%)	219	22	(10.0%)		
	Skin reaction – 26wk	Dichotomous	218	20	(9.2%)	219	12	(5.5%)		
	Temperature/influenza – 26wk	Dichotomous	218	2	(0.9%)	219	5	(2.3%)		
	Temperature/influenza – 52wk	Dichotomous	218	4	(1.8%)	219	8	(3.7%)		
	Vascular disorder – 26wk	Dichotomous	218	15	(6.9%)	219	10	(4.6%)		
	Blood pressure:									
	Systolic blood pressure (mmHg) – 26wk	Mean change	218		-0.72 (SD 13.3)	219		-0.94 (SD 13.2)	MD=0.220 (CI: -2.120, 2.560)	0.85
	Systolic blood pressure (mmHg) – 52wk	Mean change	218		-2.55 (SD 13.6)	219		-1.03 (SD 13.7)	MD=-1.530 (CI: -3.970, 0.910)	0.22
	Diastolic blood pressure (mmHg) – 26wk	Mean change	218		0.07 (SD 8.87)	219		-1.78 (SD 8.83)	MD=1.850 (CI: 0.280, 3.420)	0.02
	Diastolic blood pressure (mmHg) – 52wk	Mean change	218		-0.87 (SD 8.44)	219		-1.47 (SD 8.46)	MD=0.600 (CI: -0.900, 2.100)	0.43
	Lipids:									
	Total cholesterol (mmol/l) – 26wk	Mean change	218		-0.17 (SD 0.834)	219		-0.02 (SD 0.831)	MD=-0.160 (CI: -0.300, -0.020)	0.03
	Total cholesterol (mmol/l) – 52wk	Mean change	218		-0.09 (SD 0.904)	219		0.03 (SD 1.36)	MD=-0.120 (CI: -0.280, 0.040)	0.12
	HDL cholesterol (mmol/l) – 26wk	Mean change	218		0 (SD 0.152)	219		0 (SD 0.151)	MD=0.000 (CI: -0.030, 0.030)	0.92
	HDL cholesterol (mmol/l) – 52wk	Mean change	218		0.02 (SD 0.151)	219		0.01 (SD 0.151)	MD=0.010 (CI: -0.020, 0.040)	0.53
	Triglycerides (mmol/l) – 26wk	Mean change	218		-0.43 (SD 1.37)	219		-0.4 (SD 1.36)	MD=-0.030 (CI: -0.280, 0.220)	0.80

	Triglycerides (mmol/l) – 52wk	Mean change	218		-0.32 (SD 1.51)	219		-0.23 (SD 1.51)	MD=-0.090 (CI: -0.340, 0.160)	0.49
	LDL cholesterol (mmol/l) – 26wk	Mean change	218		0.05 (SD 0.683)	219		0.13 (SD 0.68)	MD=-0.080 (CI: -0.200, 0.040)	0.21
	LDL cholesterol (mmol/l) – 52wk	Mean change	218		0.09 (SD 0.753)	219		0.17 (SD 0.755)	MD=-0.080 (CI: -0.210, 0.050)	0.23

[a] (Used in the analysis)
[b] estimated from graph
[c] SD estimated from 95% CI
[d] estimated from graph; approximated to nearest integer (percentages only presented in text)
[e] composite (no weight gain or hypos); approximated to nearest integer (percentages only presented in text)
[f] approximated to nearest integer (percentages only presented in text)
[g] composite endpoint (no weight gain or hypoglycaemia)
[h] Event rate (events/patient year) and patient days calculated assuming dropouts occurred halfway through the study were used to calculate number of events
[i] episodes per patient year
[j] No patients
[k] (Used in the analysis); Adjusted event rate (events/patient years with outliers removed) and patient days calculated assuming dropouts occurred halfway through the study were used to calculate number of events
[l] SAE
[m] severe
[n] general disorder and administration site

Most endpoints were assessed by ANCOVA, with treatment and country as fixed eff ects, and baseline measure as a covariate. We used logistic regression to compare the proportions of participants achieving HbA1c targets and the composite endpoint, and generate odds ratios (ORs). Treatment was a fixed effect, and baseline. HbA1c was a covariate, with baseline weight as an additional covariate for the composite endpoint only.

Safety analyses were done on data from all patients who had been exposed to at least one dose of trial drug. Hypoglycaemic episodes were analysed by a general linear model with treatment as a fixed effect. P-values are not reported for adverse events

Table 28: Ristic et al. (2006)

General	**Phase:** ☐ monotherapy ☑ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin + oral **Parallel / crossover:** Parallel **Country:** five countries (France, Italy, Canada, Spain and Austria) **Authors' conclusions:** No significant difference was seen between nateglinide plus metformin and gliclazide plus metformin in terms of HbA1c . However, the nateglinide combination demonstrated better postprandial glucose control **Source of funding:** Novartis **Comments:** double-blind, double-dummy, parallel group, randomized study carried out over a period of 24 weeks. Randomization to treatment was by a computer-generated schedule via an interactive voice-responding system that assigned randomization on a study-centre basis with a block size of 4.
Number and characteristics of patients	**Total number of patients:** 262 **Inclusion criteria:** Patients were eligible if they had Type 2 diabetes for a minimum of 6 months and had received metformin monotherapy for at least 3 months; the patients also had to be on a minimum metformin dose of 1000 mg per day continuously for at least 2 months prior to study entry, but remain inadequately controlled by medication, diet and physical exercise. Other inclusion criteria were a baseline HbA1c 6.8–9.0%, and a body mass index (BMI) between 20 and 35 kg/m2. In the 8 weeks preceding the study, and throughout the study, patients remained on their individual maximally tolerated dose of metformin. **Exclusion criteria:** No details reported
Previous glucose-lowering	**Any participants previously taking glucose-lowering therapy?** all on oral hypoglycaemic drugs and/or insulin **Details of washout period:** All patients received metformin monotherapy at study and this was continued

therapy	throughout the trial
Lifestyle advice	-
Follow-up	**Total follow-up (wks):** 52 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 52 **Frequency of monitoring appointments:** -
Arms	**(1) Metformin + nateglinide** N: 133 Treatment duration (wks): 24 Washout period (d): 0 Treatment(s): (a) Metformin (Oral) Mean dose (mg/d): 1921 (b) nateglinide (Oral) – flexible-dose (dose-adjusted) Minimum dose (mg/d): 180 Maximum dose (mg/d): 540 Participants achieving full dose (n): 79 Details of dosing regimen: Treatment regimens of nateglinide and gliclazide were started at the lowest levels (60 mg three times a day before meals and 80 mg once per day, respectively) and were titrated to the next dose level on a monthly basis up to a maximum of 180 mg before meals and 240 mg per day, respectively, during the first 3 months. Dose levels of study medication were increased if the fasting plasma glucose (FPG) level was > 7 mmol/l, if the patient had not experienced any confirmed hypoglycaemic events (symptomatic and/or asymptomatic events with plasma glucose concentration = 4.0 mmol/l) and if the patient had not experienced more than three hypoglycaemic events in the past month. 59.4% were titrated up to the highest dose level (180 mg tid) **(2) Metformin + gliclazide** N: 129 Treatment duration (wks): 52 Washout period (d): 0 Treatment(s): (a) Metformin (Oral) Mean dose (mg/d): 1812 (b) Sulfonylurea (Oral) – flexible-dose (dose-adjusted) Minimum dose (mg/d): 80 Maximum dose (mg/d): 240 Details of dosing regimen: 35.7% were titrated up to the highest dose level (240 mg/day)
Outcomes	**General** Efficacy analyses used the intent-to-treat population which included all randomized patients with at least one post-baseline efficacy evaluation, and safety was assessed for all randomized patients with a post-baseline safety assessment. After 24 weeks,13/133 patients in the nateglinide group and 20/129 in the gliclazide group discontinued the study 52 week outcomes from the extension study Ristic (2007) are also reported in this evidence table **Hypoglycaemic events** confirmed hypoglycaemia (An event was considered as confirmed if the self-monitored plasma glucose value obtained at the time of the event was = 4.0 mmol/l (corresponding to blood glucose value of = 3.6 mmol/l) or if hypoglycaemia was classified as grade 2 (i.e. an episode with sufficient neurological impairment that the patient was unable to initiate self-treatment and required assistance or hospitalization))
Baseline characteristics	

		Metformin + nateglinide			Metformin + gliclazide				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Demographics: Age (years)	Continuous	133		62 (SD 11)	129		61.6 (SD 10.1)		
Sex (n male)	Dichotomous	133	72	(54.1%)	129	65	(50.4%)		

	Duration of diabetes (yrs)	Continuous	133		7.16 (SD 6.3)	129		6.7 (SD 5.55)	
	Blood glucose: HbA1c (%) – 0wk	Continuous	133		7.67 (SD 0.59)	129		7.6 (SD 0.58)	
	Fasting plasma glucose (mmol/l) – 0wk	Continuous	133		8.95 (SD 1.49)	129		8.73 (SD 1.48)	
	Body weight: BMI (kg/m2)	Continuous	133		28.5 (SD 3.5)	129		29.5 (SD 3.6)	
	Weight (kg)	Continuous	133			129			
	ITT Blood glucose: HbA1c (%) – 0wk	Continuous	129		7.66 (SD 0.59)	118		7.57 (SD 0.57)	
	Fasting plasma glucose (mmol/l) – 0wk	Continuous	129		8.49 (SD 1.49)	118		8.65 (SD 1.49)	
	Data from 52 week extension Blood glucose: HbA1c (%) – 24wk	Continuous	112		7.65 (SD 0.6)	101		7.55 (SD 0.57)	
	Fasting plasma glucose (mmol/l) – 24wk	Continuous	112		9.04 (SD 1.53)	101		8.54 (SD 1.45)	
	Body weight: BMI (kg/m2)	Continuous	112		28.6 (SD 3.5)	101		30 (SD 3.2)	
	Weight (kg) a	Continuous	112		80.72064 (SD 9.88)	101		84.672 (SD 9.03)	

[a] estimated from BMI assuming mean height of 1.68m

Results

		Metformin + nateglinide			Metformin + gliclazide				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c reduction >=0.5% – 0wk	Dichotomous	133			129				NR
HbA1c < 7% or <=7% – 0wk	Dichotomous	133			129				NR
Hypoglycaemic events: All hypoglycaemic events (no events) – 24wka	Count	21252	110		19992	188			
Adverse events: Asthenia – 0wk	Dichotomous	133			129				NR
Death – 0wk	Dichotomous	133			129				NR
Tremor – 0wk	Dichotomous	133			129				NR
Dropouts: Total dropouts – 24wk	Dichotomous	133	13	(9.8%)	129	20	(15.5%)		
Dropout due to AEs – 0wk	Dichotomous	133			129				NR
Dropout due to AEs – 24wk	Dichotomous	130	2	(1.5%)	126	8	(6.3%)		
ITT Blood glucose: HbA1c (%) – 24wk	Mean change	133		-0.41 (SD 0.909)	129		-0.57 (SD 0.869)	MD=0.170 (CI: -0.026, 0.366)	0.099
HbA1c (%) – 24wk	Mean change	129		-0.41 (SD 0.909)	118		-0.57 (SD 0.869)	MD=0.170 (CI: -0.026, 0.366)	0.099
HbA1c reduction >=0.5% – 24wk	Dichotomous	129	63	(48.8%)	118	58	(49.2%)		
HbA1c < 7% or <=7% – 24wk	Dichotomous	129	45	(34.9%)	118	55	(46.6%)		
HbA1c < 7% or <=7% – 52wk	Dichotomous	110	44	(40.0%)	99	47	(47.5%)		

Fasting plasma glucose (mmol/l) – 24wk	Mean change	129		-0.63 (SD 1.93)	118		-0.82 (SD 1.96)	MD=0.190 (CI: -0.222, 0.602)	0.375
Fasting plasma glucose (mmol/l) – 24wk	Mean change	133		-0.63 (SD 1.93)	129		-0.82 (SD 1.96)	MD=0.190 (CI: -0.222, 0.602)	0.375
Fasting plasma glucose (mmol/l) – 52wk	Mean change	110			99			MD=0.490 (CI: -0.078, 1.058)	0.096
Safety population									
Hypoglycaemic events:									
All hypoglycaemic events (no patients) – 24wk	Dichotomous	130	13b	(10.0%)	126	32	(25.4%)		
All hypoglycaemic events (no patients) – 24wk	Dichotomous	130	32	(24.6%)	126	17b	(13.5%)		
All hypoglycaemic events (no patients) – 24wk	Dichotomous	130	32	(24.6%)	126	32	(25.4%)		
All hypoglycaemic events (no patients) – 24wkb	Dichotomous	130	13	(10.0%)	126	17	(13.5%)		
All hypoglycaemic events (no patients) – 52wk	Dichotomous	112	19c	(17.0%)	101	16d	(15.8%)		
confirmed hypoglycaemia – 24wk	Dichotomous	130	12e	(9.2%)	126	28f	(22.2%)		
confirmed hypoglycaemia – 24wk	Dichotomous	130	28f	(21.5%)	126	16e	(12.7%)		
confirmed hypoglycaemia – 24wkf	Dichotomous	130	28	(21.5%)	126	28	(22.2%)		
confirmed hypoglycaemia – 24wke	Dichotomous	130	12	(9.2%)	126	16	(12.7%)		
confirmed hypoglycaemia – 52wk	Dichotomous	112	7e	(6.3%)	101	15	(14.9%)		
confirmed hypoglycaemia – 52wk	Dichotomous	112	17	(15.2%)	101	7e	(6.9%)		
confirmed hypoglycaemia – 52wke	Dichotomous	112	7	(6.3%)	101	7	(6.9%)		
confirmed hypoglycaemia – 52wk	Dichotomous	112	17	(15.2%)	101	15	(14.9%)		
Adverse events:									
Death – 24wk	Dichotomous	130	0	(0.0%)	126	0	(0.0%)		
Data from 52 week extension									
Blood glucose:									
HbA1c (%) – 52wkg	Continuous	110		7.53 (SD 1.13)	99		7.35 (SD 1.3)		
Fasting plasma glucose (mmol/l) – 52wkh	Mean change	110		-0.2 (SD 2.31)	99		-0.69 (SD 2.29)		
Dropouts:									
Total dropouts – 52wki	Dichotomous	112	4	(3.6%)	101	3	(3.0%)		
Dropout due to AEs – 52wki	Dichotomous	112	1	(0.9%)	101	2	(2.0%)		

[a] (Used in the analysis); Patient days estimated assuming dropouts occurred halfway through the study and event rates derived from reported event rate (events/100 patients/month)
[b] Patients with >=3 events suggestive of hypo
[c] at least one event sugegstive of hypo
[d] at least one event suggestive of hypo
[e] patients with >= 3 events confirmed as hypoglycaemia
[f] No patients
[g] SD estimated from assumed SE in graph

	[h] SD estimated from SE [i] (Used in the analysis)
	An ANCOVA model was used to test the null hypothesis that nateglinide plus metformin combination therapy was as effective as gliclazide plus metformin combination therapy. The primary ANCOVA model included effects for treatment, study centre, baseline HbA1c and treatment by baseline HbA1c interaction

Table 29: Rosenstock et al. (2013)

General	**Phase:** ☐ monotherapy ☑ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin + oral **Parallel / crossover:** Parallel **Country:** Multinational- 122 centres across 18 countries (Argentina, Austria, Brazil, Colombia, Denmark, Finland, Germany, Greece, Hungary, Italy the Netherlands, Norway, Poland, Puerto Rico, Russian Federation, Spain, Sweden, USA) **Authors' conclusions:** Add on lixisenatide once daily in TTD inadequately controlled with metformin demonstrated noninferior improvements in HbA1c with slightly lower mean weight loss, lower incidence of hypoglycaemia, and better gastrointestinal tolerability compared with exenatide twice daily. **Source of funding:** The study was funded by Sanofi, the manufacturer of lixisenatide and were responsible for study design, protocol, statistical analysis plans, analysis and reporting of results **Comments:** Open label
Number and characteristics of patients	**Total number of patients:** 639 **Inclusion criteria:** men and women aged 21 to 84 years with TTD receiving 1500mg/d metformin or more, with HbA1c 7-10% **Exclusion criteria:** Use of oral or injectable glucose lowering agents other than metformin within 3 months before the time of screening; FPG >13.9mmol/l, history of unexplained pancreatitis, chronic pancreatitis, pancreatectomy, stomach/gastric surgery, inflammatory bowel disease; history of metabolic acidosis including diabetic ketoacidosis within 1 year before screening, history within the previous 6 months of MI, stroke or heart failure requiring hospitalisation; clinically relevant history of gastrointesitnal disease, with prolonged nausea and vomiting during the previous 6 months. Pre-randomisation phase: Not stated. Screening period lasted 2 weeks. Unclear what this involved
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** all on oral hypoglycaemic drugs and/or insulin **Details of washout period:** All patients were on metformin which was continued.
Lifestyle advice	not stated
Follow-up	**Total follow-up (wks):** 24 **Length of titration period (wks):** 2 **Length of maintenance period (wks):** 22 **Frequency of monitoring appointments:** 24 week study followed by a 52 week extension Stepwise dose increases were used lixisenitide: 10microg for 1 week, 15 microg for 1 week, 20microg thereafter Exenatide: 10migrog for 4 weeks, 20microg thereafter
Arms	**(1) Metformin + Lixisenatide** N: 318 Treatment duration (wks): 24 Washout period (d): - Treatment(s): (a) Metformin – fixed-dose Mean dose (mg/d): 2020 Minimum dose (mg/d): 1500 (b) Lixisenatide – fixed-dose Set dose (mg/d):0.02 Minimum dose (mg/d): 0.01 Maximum dose (mg/d): 0.02 Frequency of dosing: once a day Details of dosing regimen: Lixisenatide 10 migrog was given once daily for one week, then 15microg once daily for one week, and then 20microg for the rest of the trial **(2) Metformin + exenatide**

N: 316
Treatment duration (wks): -
Washout period (d): -
Treatment(s): (a) Metformin – fixed-dose
Mean dose (mg/d): 2058
Minimum dose (mg/d): 1500
(b) Exenatide – fixed-dose
Set dose (mg/d):0.02
Minimum dose (mg/d): 0.01
Maximum dose (mg/d): 0.02
Frequency of dosing: twice a day
Details of dosing regimen: Exenatide 5microg was given twice dialy for 4 weeks, and then 10migrog twice daily.

Outcomes

General

All efficacy parameters were assessed in a modified ITT population- all randomised participants who received at least one dose of open label investigational prodict and had both a baseline assessment and one post baseline assessment for any primary or secondary efficacy variables. The primary efficacy end point was change in HbA1c. The secondary efficacy measures were percentage of participants achieving HbA1c <7% or <=6.5%, changes in FPG and changes in body weight.

Safety population comprised participants exposed to one dose of the investigational product

The primary end point was analysed using ANCOVA with treatment group, screening strata for HbA1c and BMI, and country as fixed effects.

LOCF was used to handle missing data or early discontinuation from the study.

Hypoglycaemic events

Major/severe hypoglycaemic event (Defined as symptomatic hypoglycaemia in which the subject required the assistance of another person and that was associated with either plasma glucose level <2.0 mmol/l or if no plasma glucose measurement was available, prompt recovery with intravenous glucose, glucagon or oral carbohydrate administered by a 3rd party.)

Symptomatic hypoglycaemia (symptoms consistent with hypoglycaemia, with accompanying blood glucose <3.3 mmol/l and/or prompt recovery with oral carbohydrate, glucagon or intravenous glucose.)

Baseline characteristics

		Metformin + Lixisenatide			Metformin + exenatide				
		N	k	mean	N	k	mean	Δ	p
Demographics:									
Age (years)	Continuous	318		57.3 (SD 9.2)	316		57.6 (SD 10.7)		
Sex (n male)	Dichotomous	318			316				
Duration of diabetes (yrs)	Continuous	318		6.8 (SD 5.5)	316		6.8 (SD 4.9)		
Ethnicity-White	Dichotomous	318			316				
Ethnicity-Black	Dichotomous	318			316				
Ethnicity-Asian	Dichotomous	318			316				
Ethnicity-Other	Dichotomous	318			316				
Blood glucose:									
HbA1c (%) – 0wk	Continuous	318		8.03 (SD 0.8)	316		8.02 (SD 0.8)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	318		9.6913476 (SD 2)	316		9.6913476 (SD 2.3)		
Body weight:									
BMI (kg/m2)	Continuous	318		33.7 (SD 6.3)	316		33.5 (SD 6.5)		
Weight (kg) – 0wk	Continuous	318		94 (SD 19.6)	316		96.1 (SD 22.5)		

Results

		Metformin + Lixisenatide			Metformin + exenatide				
		N	k	mean	N	k	mean	Δ	p
Blood glucose:									
HbA1c (%) – 12wka	Continuous	315		7.25 (SD 0.887)	315		7 (SD 0.887)		
HbA1c (%) – 24wk	Mean change	318		-0.79 (SD 0.892)	316		-0.96 (SD 0.889)		

HbA1c (%) – 24wk	Continuous	318		7.17 (SD 0.96)	316		7.01 (SD 0.88)	MD=0.170	b
HbA1c < 7% or <=7% – 24wk	Dichotomous	318	154	(48.4%)	316	157	(49.7%)		
Hba1c <6.5% – 24wk	Dichotomous	318	91	(28.6%)	316	111	(35.1%)		
Fasting plasma glucose (mmol/l) – 12wka	Continuous	315		8.5 (SD 1.77)	315		8.3 (SD 1.77)		
Fasting plasma glucose (mmol/l) – 24wk	Continuous	315		8.3925072 (SD 2)	315		8.1926856 (SD 2.1)	MD=0.230	c
Body weight:									
Weight (kg) – 12wka	Mean change	315		-2 (SD 1.77)	315		-2.5 (SD 1.77)		
Weight (kg) – 24wk	Continuous	315		91.7 (SD 18.9)	315		92.9 (SD 22.3)	MD=1.020	d
Weight (kg) – 24wk	Mean change	315		-2.96 (SD 4.08)	315		-3.98 (SD 4.08)		
Hypoglycaemic events:									
Major/severe hypoglycaemic event – 24wk	Dichotomous	318	0	(0.0%)	316	0	(0.0%)		
Symptomatic hypoglycaemia – 24wke	Count	49980	8		49308	48			
Symptomatic hypoglycaemia – 24wkf	Dichotomous	318	8	(2.5%)	316	25	(7.9%)		
Adverse events:									
GI: nausea – 24wk	Dichotomous	318	78	(24.5%)	316	111	(35.1%)		
Any adverse event(s) – 24wk	Dichotomous	318	221	(69.5%)	316	228	(72.2%)		
Any serious adverse event(s) – 24wk	Dichotomous	318	9	(2.8%)	316	7	(2.2%)		
Death – 24wk	Dichotomous	318	1	(0.3%)	316	1	(0.3%)		
Gastrointestinal disorders (any) – 24wk	Dichotomous	318	137	(43.1%)	316	160	(50.6%)		
GI: diarrhoea – 24wk	Dichotomous	318	33	(10.4%)	316	42	(13.3%)		
GI: vomiting – 24wk	Dichotomous	318	32	(10.1%)	316	42	(13.3%)		
Dropouts:									
Total dropouts – 24wk	Dichotomous	318	41	(12.9%)	316	45	(14.2%)		
Dropout due to AEs – 24wk	Dichotomous	318	33	(10.4%)	316	41	(13.0%)		

[a] graph
[b] LS mean change 95% CI= 0.033 to 0.297
[c] LS mean change 95% CI= -0.052 to 0.522
[d] LS mean change 95% CI= 0.456 to 1.581
[e] (Used in the analysis); Patient days estimated assuming dropouts occurred halfway through the study
[f] number of patients

Table 30: Srivastava et al. (2012)

General

Phase:
☐ monotherapy
☑ dual therapy
☐ triple therapy
☐ insulin monotherapy
☐ insulin + oral

Parallel / crossover: Parallel

Country: India

Authors' conclusions: In this study addition of sitagliptin and glimepiride to metformin monotherapy, produced significan improvement in glycaemic control. Benefits were more with glimepiride in comparison to sitagliptin. Sitagliptin was well tolerated, with lower risk of hypoglycaemia than glimepiride, and produced weight loss as compared to weight gain with glimepiride.

	Source of funding: Unclear **Comments:** Subjectes were allocated randomly by computer generated random number table.
Number and characteristics of patients	**Total number of patients:** 50 **Inclusion criteria:** Patients with type 2 diabetes, aged 18 years and over, who were using only metformin as antidiabetic agent at least for the last 3 months and with inadequate glycaemic control (Hba1c >7 and <10%) **Exclusion criteria:** Patients with type 1 diabetes, evidence of cardiac failure, evidence of hepatic or renal insufficiency or other terminal illness were excluded
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** all on oral hypoglycaemic drugs and/or insulin **Details of washout period:** All patients were taking metformin monotherapy at study start and this was continued
Lifestyle advice	-
Follow-up	**Total follow-up (wks):** 18 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 18 **Frequency of monitoring appointments:** -
Arms	**(1) Metformin + sitagliptin** N: 25 Treatment duration (wks): 18 Washout period (d): 0 Treatment(s): (a) Metformin (Oral) Details of dosing regimen: Dose of metformin was kept constant throughout the study and no other antihyperglyacemic agent was added (b) Sitagliptin (Oral) – flexible-dose (dose-adjusted) Minimum dose (mg/d): 50 Maximum dose (mg/d): 200 Details of dosing regimen: Starting dose of sitagliptin was 50/100 mg per day. Doses were adjusted after every 4 weeks if glycaemic control was not reached. The maximum permitted dose was 200 mg/day **(2) Metformin + glimepiride** N: 25 Treatment duration (wks): 18 Washout period (d): 0 Treatment(s): (a) Metformin (Oral) Details of dosing regimen: Dose of metformin was kept constant throughout the study and no other antihyperglyacemic agent was added (b) Sulfonylurea (Oral) Details of dosing regimen: Starting dose was 1/2 mg per day. Dosesw ere adjusted after every 4 weeks if glycaemic control was not reached. The max dose was 4 mg/day.
Outcomes	**General** Details of statistical analysis were not reported and neither were patient detils of patients characteristics such as age and sex. Patients who discontinued the study were not reported All outcomes apart from postprandial blood glucose levels were extracted into this evidence table
Baseline characteristics	

		Metformin + sitagliptin			Metformin + glimepiride				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 0wk	Continuous	25		8.28 (SD 0.42)	25		8.248 (SD 0.57)		
Fasting plasma glucose (mmol/l) – 0wka	Continuous	25		10.229977824 (SD 0.62)	25		9.922030536 (SD 0.74)		
Body weight: BMI (kg/m2) – 0wk	Continuous	25		25.265 (SD 2.52)	25		26.487 (SD 3.97)		

[a] converted from mg/dl to mmol/l

Results

		Metformin + sitagliptin			Metformin + glimepiride			Δ	p
		N	k	mean	N	k	mean		
Blood glucose: HbA1c (%) – 12wka	Continuous	25		7.784 (SD 0.42)	25		7.48 (SD 0.4)		
HbA1c (%) – 18wka	Continuous	25		7.644 (SD 0.42)	25		7.076 (SD 0.36)		<0.001
HbA1c (%) – 18wka	Mean change	25		-0.636 (SD 0.99)	25		-1.172 (SD 0.25)		
HbA1c < 7% or <=7% – 18wk	Dichotomous	25	3	(12.0%)	25	9	(36.0%)		NR
Fasting plasma glucose (mmol/l) – 12wka	Continuous	25		9.545477832 (SD 0.61)	25		8.69668008 (SD 0.68)		
Fasting plasma glucose (mmol/l) – 18wka	Continuous	25		9.370300896 (SD 0.59)	25		8.26595352 (SD 0.61)		<0.001
Fasting plasma glucose (mmol/l) – 18wka	Mean change	25		-0.859676928 (SD 0.13)	25		-1.65574398 (SD 0.25)		
Body weight: BMI (kg/dl) – 12wka	Continuous	25		25.239 (SD 2.52)	25		26.498 (SD 3.97)		
BMI (kg/dl) – 18wka	Continuous	25		25.226 (SD 2.52)	25		26.506 (SD 3.97)		<0.01
BMI (kg/dl) – 18wka	Mean change	25		-0.039 (SD 0.58)	25		0.184 (SD 0.6)		

[a] assumed SD's reported but this is unclear

Assumed SD are reported

Table 31: Umpierrez et al. (2006)

General

Phase:

☐ monotherapy
☑ dual therapy
☐ triple therapy
☐ insulin monotherapy
☐ insulin + oral

Parallel / crossover: Parallel

Country: Multicentre in USA

Authors' conclusions: In patients with type two diabetes inadequately controlled on metformin monotherapy, add on glimepiride or pioglitazone results in similar overall improvements in glycaemic control. Compared with pioglitazone, glimepiride is associated with faster glycaemic control, lower total and LDL cholesterol levels and reduced short term healthcare costs.

Source of funding: Sanofi Aventis

Comments: -

Number and characteristics of patients

Total number of patients: 203

Inclusion criteria: Males and females aged 18 to 79 years with a diagnosis of TTD for at least 6 months, and who were taking stable doses of metformin 1 to 2.5 g/day, or extended release metformin 0.5 to 2g/day as their only OAD for at least 2 months prior to the study. All participants had BMI=>24, HbA1c 7/5 to 10%, FPG 126 to 235mg/dl, and evidence of insulin secretory capacity as defined by fasting Cpeptide concentration =>0.27nmol/l during the stabilization period.

Exclusion criteria: People treated with insulin, thiazolidinediones or sulfonylurea within 3 months prior to study enrolment; history of substance abuse; severe hypoglycaemia; acute metabolic complications; clinically significant abnormal baseline laboratory haemotology, blood chemistry or urinalysis values.

Pre-randomisation phase: The study included a 2 week stabilisation period in subjects treated with metformin or modified metformin

Previous glucose-lowering therapy

Any participants previously taking glucose-lowering therapy? all on oral hypoglycaemic drugs and/or insulin

Details of washout period: All were on metformin or modified release metformin and continued these throughout the trial

Lifestyle advice

Not stated

Follow-up

Total follow-up (wks): 28
Length of titration period (wks): 0
Length of maintenance period (wks): 26
Frequency of monitoring appointments: 6, 12, 20, 26, 28 weeks

Arms

(1) Metformin + Glimepiride
N: 96
Treatment duration (wks): 28
Washout period (d): 0
Treatment(s): (a) Metformin (Oral) – fixed-dose
Mean dose (mg/d): 1.47
Details of dosing regimen: Mean doses of metformin remained stable Baseline= 1.47 g/day Endpoint= 1.49g/d
Metformin and modified metformin were available
(b) Sulfonylurea (Oral) – forced titration
Minimum dose (mg/d): 2
Maximum dose (mg/d): 8
Frequency of dosing: once a day
Details of dosing regimen: Starting dose was 2mg and increased during weeks 1 to 6 to a maximum of 8mg day, or until the mean of 3 daily self monitored blood glucose values was <120mg/dl/

(2) Metformin + Pioglitazone
N: 107
Treatment duration (wks): 28
Washout period (d): 0
Treatment(s): (a) Metformin (Oral) – fixed-dose
Mean dose (mg/d): 1.54
Details of dosing regimen: Does of metformin remained stable during trial Baselie=1.54g/d Endpont= 1.57g/d
Metformin and modified metformin were available.
(b) Pioglitazone (Oral) – forced titration
Minimum dose (mg/d): 30
Maximum dose (mg/d): 45
Frequency of dosing: once a day
Details of dosing regimen: Dose was started at 30mg day and was increased to a maximum of 45mg/d at week 12 if mean self monitored blood glucose over the prior 3 days was >120mg/dl or HbA1c was >= 8%

Outcomes

General
Analysis was done on ITT population- defined as all randomised subjects who took at least one dose of study medications and who had at least one HbA1c result while on treatment.

Baseline characteristics

		Metformin + Glimepiride			Metformin + Pioglitazone				
		N	k	mean	N	k	mean	Δ	p
Demographics:									
Age (years)	Continuous	96		51.6 (SD 11.8)	107		55.7 (SD 9.7)		
Sex (n male)	Dichotomous	96	53	(55.2%)	107	56	(52.3%)		
Duration of diabetes (yrs)	Continuous	96		4.9 (SD 3.8)	107		5.9 (SD 6.1)		
Ethnicity-White	Dichotomous	96	76	(79.2%)	107	84	(78.5%)		
Ethnicity-Black	Dichotomous	96	13	(13.5%)	107	17	(15.9%)		
Ethnicity-Asian	Dichotomous	96	1	(1.0%)	107	4	(3.7%)		
Ethnicity-Hispanic	Dichotomous	96	5	(5.2%)	107	2	(1.9%)		
Ethnicity-Other	Dichotomous	96	1	(1.0%)	107	0	(0.0%)		
Blood glucose:									
HbA1c (%) – 0wk	Continuous	96		8.4 (SD 0.72)	107		8.31 (SD 0.77)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	96		10.0132824 (SD 2.15)	107		10.2242052 (SD 2.34)		
Body weight:									
BMI (kg/m2) – 0wk	Continuous	96		34.54 (SD 6.68)	107		33.81 (SD 6.62)		

Weight (kg) – 0wka	Continuous	96		97.485696 (SD 18.9)	107		95.425344 (SD 18.7)		
Lipids: Total cholesterol (mmol/l) – 0wk	Continuous	96		5.047872 (SD 1.07)	107		4.996152 (SD 1.01)		
HDL cholesterol (mmol/l) – 0wk	Continuous	96		1.132668 (SD 0.33)	107		1.109394 (SD 0.264)		
Triglycerides (mmol/l) – 0wk	Continuous	96		1.048841 (SD 0.64)	107		1.272383 (SD 1.15)		
LDL cholesterol (mmol/l) – 0wk	Continuous	96		2.92218 (SD 0.988)	107		2.80581 (SD 0.824)		

[a] estimated from BMI assuming mean height of 1.68m

Results

		Metformin + Glimepiride			Metformin + Pioglitazone				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 26wk	Mean change	96		-1.3 (SD 0.754)	107		-1.23 (SD 0.755)		
HbA1c < 7% or <=7% – 26wk	Dichotomous	96	54	(56.3%)	107	59	(55.1%)		
Fasting plasma glucose (mmol/l) – 26wk	Mean change	96		-1.8927546 (SD 1.97)	107		-2.2035882 (SD 1.96)		
Body weight: BMI (kg/m2) – 26wk	Mean change	96		0.57 (SD 1.37)	107		0.69 (SD 1.34)		
Weight (kg) – 26wk	Mean change	96		1.74 (SD 4.02)	107		1.85 (SD 3.93)		
Hypoglycaemic events: All hypoglycaemic events (no patients) – 26wka	Dichotomous	96	32	(33.3%)	107	1	(0.9%)		
Major/severe hypoglycaemic event – 26wk	Dichotomous	96	0	(0.0%)	107	0	(0.0%)		
Adverse events: Any serious adverse event(s) – 26wk	Dichotomous	96	7	(7.3%)	107	7	(6.5%)		
Edema peripheral – 26wk	Dichotomous	96	1	(1.0%)	107	4	(3.7%)		
Dropouts: Total dropouts – 26wk	Dichotomous	101	13	(12.9%)	109	16	(14.7%)		
Dropout due to AEs – 26wk	Dichotomous	101	1	(1.0%)	109	4	(3.7%)		
Lipids: Total cholesterol (mmol/l) – 26wk	Mean change	93		-0.09051 (SD 0.803)	107		0.315492 (SD 0.8)		
HDL cholesterol (mmol/l) – 26wk	Mean change	93		-0.015516 (SD 0.175)	105		0.124128 (SD 0.177)		
Triglycerides (mmol/l) – 26wk	Mean change	96		-0.047418 (SD 0.781)	107		-0.160318 (SD 0.767)		
LDL cholesterol (mmol/l) – 26wk	Mean change	87		-0.002586 (SD 0.692)	93		0.21981 (SD 0.701)		

[a] (Used in the analysis)

Table 32: van der et al. (2009)

General

Phase:
☐ monotherapy
☑ dual therapy
☐ triple therapy
☐ insulin monotherapy
☐ insulin + oral

Parallel / crossover: Parallel

	Country: The Netherlands **Authors' conclusions:** in TTD patients, pioglitazone was associated with improvement in some measures of left ventricular diastolic function, myocarial glucose uptake, and whole body insulin sensitivity. The functional changes were not associated with miocardial substrate and high-energy phosphate metabolism. **Source of funding:** The investigator initiated study was supported by Eli Lilly which has a partnership with Takeda, the manufacturer of pioglitazone **Comments:** -
Number and characteristics of patients	**Total number of patients:** 78 **Inclusion criteria:** Men with uncomplicated TTD aged 45 to 65 years were eligible for inclusion. Inclusion cirteria were a glycohemoglobin level of 6.5% to 8.5% at screening, BMI of 25 to 32 kg/m2, and blood pressure not exceeding 150/85 mm/Hg (with or without the use of antihypertesnives). **Exclusion criteria:** Clinically significant hisotry or complaints of cardiovascular disease, liver disease or diabetes related complications; prior use of thiazolidinediones. Pre-randomisation phase: Participants underwent a 2 step screening procedure that consisted of medical history, physical examination, ECG, Ewing tests to exclude autonomic neuropathy, and fasting blood and urine analysis (screening visit 1), as well as dobutamine stress echocardiography the exclude cardiac ischaemia or arrythmias (screening visit 2). After successful screening participants entered a 10 week run in period during which their previous blood glucose lowering medication (metofrin mono 39.8%, sulfonylurea mono 25.6%, met + sulf combo 34.6%) were washed out. They were transferred onto glimepiride monotherapy which was titrated until a stable dose was reached during the 8 weeks before randomisation.
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** all on oral hypoglycaemic drugs and/or insulin **Details of washout period:** All baseline therapy was washed out and replaced with glimepiride during a 8-10 week screening period.
Lifestyle advice	Not stated
Follow-up	**Total follow-up (wks):** 24 **Length of titration period (wks):** - **Length of maintenance period (wks):** - **Frequency of monitoring appointments:** -
Arms	**(1) Glimepiride + Pioglitazone + placebo** N: 39 Treatment duration (wks): 24 Washout period (d): - Treatment(s): (a) Sulfonylurea (Oral) – flexible-dose (dose-adjusted) Details of dosing regimen: Glimepiride was titrated until a stable dose was reached during the 8 weeks before randomisation. If recurrent hypoglycaemia occurred glimepeiride dose was lowered in a step wise fashion to levels of non occurrence. Glimepiride dose adjustment was required in 4 patients in this gorup (b) Pioglitazone (Oral) – fixed-dose Set dose (mg/d):30 Minimum dose (mg/d): 15 Frequency of dosing: once a day Details of dosing regimen: 15mg was give once daily, then titrated to 30mg once daily after 2 weeks Back titration of pioglitazone 15mg daily was made if persistent study related side effects occurred **(2) Glimepiride + metformin + placebo** N: 0 Treatment duration (wks): - Washout period (d): - Treatment(s): (a) Sulfonylurea Details of dosing regimen: Glimepiride was titrated until a stable dose was reached during the 8 weeks before randomisation. If recurrent hypoglycaemia occurred glimepeiride dose was lowered in a step wise fashion to levels of non occurrence. Glimepiride dose adjustment was required in 3 patients (b) Metformin (Oral) – fixed-dose Set dose (mg/d):1000 Minimum dose (mg/d): 500 Frequency of dosing: twice a day Details of dosing regimen: Metformin was given twice a day in 500mg doses, that was titrated to 100mg doses Back titration to metformin 500mg twice daily was made if persistent study related side

	effects occurred 2 patients required metformin back titration.
Outcomes	

Baseline characteristics

		Glimepiride + Pioglitazone + placebo			Glimepiride + metformin + placebo				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Demographics: Age (years)	Continuous	39		56.8 (SD 6.24)	39		56.4 (SD 5.62)		
Sex (n male)	Dichotomous	39	39	(100.0%)	39	39	(100.0%)		
Blood glucose: HbA1c (%) – 0wk	Continuous	39		7.1 (SD 1.25)	39		7.1 (SD 0.624)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	39		med: 8.4 [rng 7.2–10.3]	39		med: 8.2 [rng 6.8–9.1]		
Body weight: BMI (kg/m2)	Continuous	39		28.2 (SD 3.12)	39		29.3 (SD 3.75)		
Weight (kg) – 0wk	Continuous	39		91 (SD 12.5)	39		92 (SD 12.5)		
Waist circumference (cms)	Continuous	39		103.8 (SD 9.37)	39		104.9 (SD 11.2)		
Blood pressure: Systolic blood pressure (mmHg) – 0wk	Continuous	39		130 (SD 12.5)	39		126 (SD 12.5)		
Diastolic blood pressure (mmHg) – 0wk	Continuous	39		77 (SD 6.24)	39		74 (SD 6.24)		
Lipids: Total cholesterol (mmol/l) – 0wk	Continuous	39		4.5 (SD 0.624)	39		4.9 (SD 1.25)		
HDL cholesterol (mmol/l) – 0wk	Continuous	39		med: 1.07 [rng 0.94–1.28]	39		med: 1.13 [rng 0.9–1.42]		
Triglycerides (mmol/l) – 0wk	Continuous	39		med: 1.4 [rng 1–2.2]	39		med: 1.5 [rng 0.9–2.1]		
LDL cholesterol (mmol/l) – 0wk	Continuous	39		2.5 (SD 0.624)	39		2.6 (SD 1.25)		

Results

		Glimepiride + Pioglitazone + placebo			Glimepiride + metformin + placebo				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Blood glucose: HbA1c (%) – 24wk	Continuous	34		6.5 (SD 0.583)	37		6.3 (SD 0.608)		
Fasting plasma glucose (mmol/l) – 24wk	Continuous	34		med: 7.6 [rng 6.7–9.4]	37		med: 6.8 [rng 5.8–7.4]		
Body weight: Weight (kg) – 24wk	Continuous	34		94 (SD 11.7)	37		92 (SD 18.2)		
Dropouts: Total dropouts – 24wk	Dichotomous	39	5	(12.8%)	39	2	(5.1%)		
Blood pressure: Systolic blood pressure (mmHg) – 24wk	Continuous	34		125 (SD 11.7)	37		121 (SD 12.2)		
Diastolic blood pressure (mmHg) – 24wk	Continuous	34		74 (SD 5.83)	37		73 (SD 6.08)		
Lipids: Total cholesterol (mmol/l) – 24wk	Continuous	34		4.6 (SD 1.17)	37		4.5 (SD 1.22)		
HDL cholesterol (mmol/l) – 24wk	Continuous	34		med: 1.23 [rng 0.99–1.46]	37		med: 1.02 [rng 0.86–1.26]		

	Triglycerides (mmol/l) – 24wk	Continuous	34		med: 1.4 [rng 0.9–2.3]	37		med: 1.7 [rng 0.9–2.3]		
	LDL cholesterol (mmol/l) – 24wk	Continuous	34		2.5 (SD 0.583)	37		2.6 (SD 1.22)		

Table 33: Wang et al. (2011)

General	**Phase:** ☐ monotherapy ☑ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin + oral **Parallel / crossover:** Parallel **Country:** Taiwan **Authors' conclusions:** - **Source of funding:** - **Comments:** -
Number and characteristics of patients	**Total number of patients:** 55 **Inclusion criteria:** Adults (aged 30-70 years) with T2DM, on 1 or 2 OADs for at least 3 months and HbA1c between 7 and 11% **Exclusion criteria:** - Pre-randomisation phase: 8 weeks of metformin monotherapy (1500mg/d)
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** all on oral hypoglycaemic drugs and/or insulin **Details of washout period:** 8 weeks of metformin monotherapy (1500mg/d)
Lifestyle advice	Details not reported
Follow-up	**Total follow-up (wks):** 24 **Length of titration period (wks):** - **Length of maintenance period (wks):** 16 **Frequency of monitoring appointments:** Data reported at baseline and post-treatment 8 weeks monotherapy, 16 weeks add on of acarbose or glibenclamide
Arms	**(1) Metformin + Acarbose** N: 29 Treatment duration (wks): 16 Washout period (d): 0 Comments: Patients received 8 weeks of metformin monotherapy, followed by 16 weeks of add on acarbose Treatment(s): (a) Metformin (Oral) – fixed-dose Set dose (mg/d):1500 (b) Acarbose (Oral) – flexible-dose (dose-adjusted) Minimum dose (mg/d): 150 Maximum dose (mg/d): 300 Frequency of dosing: three times a day Details of dosing regimen: First 4 weeks: 50mg 3x per day Next 12 weeks: 100mg 3x per day **(2) Metformin + Glibenclamide** N: 26 Treatment duration (wks): 16 Washout period (d): 0 Comments: Patients received 8 weeks of metformin monotherapy, followed by 16 weeks of add on glibenclamide Treatment(s): (a) Metformin (Oral) – fixed-dose Set dose (mg/d):1500 (b) Sulfonylurea (Oral) – flexible-dose (dose-adjusted) Minimum dose (mg/d): 7.5

Maximum dose (mg/d): 15
Frequency of dosing: three times a day
Details of dosing regimen: First 4 weeks: 2.5mg 3x per day
Next 12 weeks: 5mg 3x per day

Outcomes

Baseline characteristics

		Metformin + Acarbose		
		N	k	mean
Full analysis set (FAS) or efficacy analysis pop				
Demographics:				
Age (years)	Continuous	28		52.8 (SD 8.2)
Sex (n male)	Dichotomous	28	15	(53.6%)
Duration of diabetes (yrs)	Continuous	28		7.6
Blood glucose:				
HbA1c (%) – 16wk	Continuous	28		8.2 (SD 0.8)
HbA1c (%) – 16wk	Continuous	28		8.2 (SD 0.8)
Fasting plasma glucose (mmol/l)	Continuous	28		8.2 (SD 1.2)
Body weight:				
BMI (kg/m2)	Continuous	28		25.9 (SD 3)
Weight (kg) – 0wk	Continuous	28		73.10016 (SD 8.4672) a
Weight (kg) – 0wk	Continuous	28		73.10016 (SD 8.4672) a
Weight (kg) – 16wk	Continuous	28		69.8 (SD 9.9)
Weight (kg) – 16wk	Continuous	28		69.8 (SD 9.9)

[a] estimated from BMI assuming mean height of 1.68m

		Metformin + Glibenclamide		
		N	k	mean
Full analysis set (FAS) or efficacy analysis pop				
Demographics:				
Age (years)	Continuous	23		54.7 (SD 8.3)
Sex (n male)	Dichotomous	23	10	(43.5%)
Duration of diabetes (yrs)	Continuous	23		6
Blood glucose:				
HbA1c (%) – 16wk	Continuous	23		8.6 (SD 1.6)
HbA1c (%) – 16wk	Continuous	23		8.6 (SD 1.6)
Fasting plasma glucose (mmol/l)	Continuous	23		9 (SD 3)
Body weight:				
BMI (kg/m2)	Continuous	23		25.3 (SD 3.8)
Weight (kg) – 0wk	Continuous	23		71.40672 (SD 10.72512) a
Weight (kg) – 0wk	Continuous	23		71.40672 (SD 10.72512) a
Weight (kg) – 16wk	Continuous	23		66 (SD 15.4)
Weight (kg) – 16wk	Continuous	23		66 (SD 15.4)

[a] estimated from BMI assuming mean height of 1.68m

Results

		Metformin + Acarbose		
		N	k	mean
Hypoglycaemic events:				
All hypoglycaemic events (no patients) – 16wk	Dichotomous	29	0	(0.0%)
Dropouts:				
Total dropouts – 16wk	Dichotomous	29	1	(3.4%)
Dropout due to AEs – 16wk	Dichotomous	29	0	(0.0%)

Full analysis set (FAS) or efficacy analysis pop				
Blood glucose:				
HbA1c (%) – 16wk	Continuous	28		7.5 (SD 0.8)
HbA1c (%) – 16wk	Continuous	28		7.5 (SD 0.8)
Body weight:				
Weight (kg) – 16wk	Continuous	28		68.3 (SD 10.4)
Weight (kg) – 16wk	Continuous	28		68.3 (SD 10.4)

		Metformin + Glibenclamide		
		N	**k**	**mean**
Hypoglycaemic events:				
All hypoglycaemic events (no patients) – 16wk	Dichotomous	26	6	(23.1%)
Dropouts:				
Total dropouts – 16wk	Dichotomous	26	3	(11.5%)
Dropout due to AEs – 16wk	Dichotomous	26	1	(3.8%)
Full analysis set (FAS) or efficacy analysis pop				
Blood glucose:				
HbA1c (%) – 16wk	Continuous	23		7.4 (SD 1.2)
HbA1c (%) – 16wk	Continuous	23		7.4 (SD 1.2)
Body weight:				
Weight (kg) – 16wk	Continuous	23		66.8 (SD 16.3)
Weight (kg) – 16wk	Continuous	23		66.8 (SD 16.3)

Table 34: Yang et al. (2011)

General	**Phase:** ☐ monotherapy ☑ dual therapy ☐ triple therapy ☐ insulin monotherapy ☐ insulin + oral **Parallel / crossover:** Parallel **Country:** China (17 sites), South Korea (10 sites), India (24 sites) **Authors' conclusions:** In asian subjects with TTD, once daily liraglutide led to improvement in glycaemic control similar to that with glimepiride but with less frequent major and minor hypoglycaemia. Liraglutide also induced significant weight loss and reduced SBP and was generally well tolerated. The most frequent reported AE was transient nausea. The effects of liraglutide in this Asian population is comparable to the effects seen in caucasian, African-American and Hispanic populations in global liraglutide phase 3 trials. **Source of funding:** Novo Nordisk **Comments:** -
Number and characteristics of patients	**Total number of patients:** 929 **Inclusion criteria:** People with TTD treated with one or more oral antidiabetic drugs for at least 3 months, aged 18 to 80 (18 to 75 for Chinese patients) with HbA1c between 7 and 11% for people on monotherapy, and between 7 and 10% for people on combination therapy, with a BMI< or = 45kg/m2 **Exclusion criteria:** People treated with insulin within the last 3 months Pre-randomisation phase: Patients discontinued their pretrial OADs except metformin and entered a 3 week run in with forced escalation of metformin to 2000mg/day, followed by another 3 week metformin maintenance period. After completing the maintenance period, patients with FPG between 7 and 12.8mmol/l were randomised to the study medication. After randomisation metformin could, at the discretion of the investigator, be decreased to a minimum of 1500mg in case of unacceptable gastrointestinal adverse events. If doses less than 1500mg were required, the patient was withdrawn from the trial.

Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** all on oral hypoglycaemic drugs and/or insulin **Details of washout period:** Discontinued all drugs except metformin
Lifestyle advice	Not stated
Follow-up	**Total follow-up (wks):** 16 **Length of titration period (wks):** - **Length of maintenance period (wks):** - **Frequency of monitoring appointments:** 14, 16 weels
Arms	**(1) Metformin + Liraglutide 0.6mg + Placebo** N: 231 Treatment duration (wks): 16 Washout period (d): - Treatment(s): (a) Metformin – forced titration Set dose (mg/d):2000 Minimum dose (mg/d): 1500 (b) Liraglutide (Subcutaneous) – fixed-dose Set dose (mg/d):0.6 Frequency of dosing: once a day Details of dosing regimen: Injected once daily at any time of day. Participants also received placebo glimepiride tablets **(2) Metformin + Liraglutide 1.2mg + placebo** N: 233 Treatment duration (wks): - Washout period (d): - Treatment(s): (a) Metformin – fixed-dose Set dose (mg/d):2000 Minimum dose (mg/d): 1500 (b) Liraglutide (Subcutaneous) – forced titration Set dose (mg/d):1.2 Frequency of dosing: once a day Details of dosing regimen: Daily injection at any time of day. Initially all patients in this arm started on 0.6mg, and then progressed to the target 1.2 mg in steps of 0.6mg per day per week. Participants also received placebo glimepiride tablets. **(3) Metformin + liraglutide 1.8mg + placebo** N: 233 Treatment duration (wks): - Washout period (d): - Treatment(s): (a) Metformin (Oral) – fixed-dose Set dose (mg/d):2000 Minimum dose (mg/d): 1500 (b) Liraglutide (Subcutaneous) – forced titration Set dose (mg/d):1.8 Frequency of dosing: once a day Details of dosing regimen: Daily injection at any time of day All patients in this arm were started on 0.6mg per day, and this was increased to target 1.8 in weekly steps of 0.6mg per day per week. Participants also received placebo glimepiride tablets **(4) Metformin + glimepiride 4mg + placebo** N: 231 Treatment duration (wks): - Washout period (d): - Treatment(s): (a) Metformin (Oral) – fixed-dose Set dose (mg/d):2000 Minimum dose (mg/d): 1500 (b) Sulfonylurea (Oral) – forced titration Set dose (mg/d):4 Maximum dose (mg/d): 1 Details of dosing regimen: Participants were instructed to start dose escalation of glimepiride or glimepiride placebo by daily administration of a 1mg capsule. Further dose escalation took place over a 2 week period, incrementing to a maximum dose of 4mg per day. Participants also received placebo liraglutide injection

Outcomes

Baseline characteristics

		Metformin + Liraglutide 0.6mg + Placebo			Metformin + Liraglutide 1.2mg + placebo				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	231		53.5 (SD 9.5)	233		53.5 (SD 9.6)		
Sex (n male)	Dichotomous	231	125	(54.1%)	233	128	(54.9%)		
Duration of diabetes (yrs)	Continuous	231		7.4 (SD 5.4)	233		7.5 (SD 5.3)		
Blood glucose: HbA1c (%) – 0wk	Continuous	231		8.5 (SD 1.1)	233		8.6 (SD 1.1)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	231		9.8 (SD 2.4)	233		9.5 (SD 2.2)		
Body weight: BMI (kg/m2)	Continuous	231		25.9 (SD 4.2)	233		25.4 (SD 3.7)		
Weight (kg) – 0wk	Continuous	231		68.6 (SD 11.6)	233		67.4 (SD 11.3)		
Blood pressure: Systolic blood pressure (mmHg) – 0wk	Continuous	231		126 (SD 14.3)	233		127 (SD 14)		
Previous blood glucose lowering drugs: any monotherapy (1 previous OAD)	Dichotomous	231	72	(31.2%)	233	74	(31.8%)		
any dual therapy (2 previous OAD)	Dichotomous	231	159	(68.8%)	233	159	(68.2%)		

		Metformin + Liraglutide 0.6mg + Placebo			Metformin + liraglutide 1.8mg + placebo				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	231		53.5 (SD 9.5)	233		52.7 (SD 9.1)		
Sex (n male)	Dichotomous	231	125	(54.1%)	233	126	(54.1%)		
Duration of diabetes (yrs)	Continuous	231		7.4 (SD 5.4)	233		7.2 (SD 5.2)		
Blood glucose: HbA1c (%) – 0wk	Continuous	231		8.5 (SD 1.1)	233		8.6 (SD 1.1)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	231		9.8 (SD 2.4)	233		9.9 (SD 2.5)		
Body weight: BMI (kg/m2)	Continuous	231		25.9 (SD 4.2)	233		25.8 (SD 3.8)		
Weight (kg) – 0wk	Continuous	231		68.6 (SD 11.6)	233		68.2 (SD 11.9)		
Blood pressure: Systolic blood pressure (mmHg) – 0wk	Continuous	231		126 (SD 14.3)	233		126 (SD 14.1)		
Previous blood glucose lowering drugs: any monotherapy (1 previous OAD)	Dichotomous	231	72	(31.2%)	233	75	(32.2%)		
any dual therapy (2 previous OAD)	Dichotomous	231	159	(68.8%)	233	159	(68.2%)		

	Metformin + Liraglutide 0.6mg + Placebo			Metformin + glimepiride 4mg + placebo				
	N	k	mean	N	k	mean	Δ	p

Demographics:									
Age (years)	Continuous	231		53.5 (SD 9.5)	231		53.6 (SD 9.7)		
Sex (n male)	Dichotomous	231	125	(54.1%)	231	135	(58.4%)		
Duration of diabetes (yrs)	Continuous	231		7.4 (SD 5.4)	231		7.8 (SD 6.1)		
Blood glucose:									
HbA1c (%) – 0wk	Continuous	231		8.5 (SD 1.1)	231		8.5 (SD 1.1)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	231		9.8 (SD 2.4)	231		9.6 (SD 2.4)		
Body weight:									
BMI (kg/m2)	Continuous	231		25.9 (SD 4.2)	231		25.3 (SD 3.7)		
Weight (kg) – 0wk	Continuous	231		68.6 (SD 11.6)	231		68.2 (SD 11.9)		
Blood pressure:									
Systolic blood pressure (mmHg) – 0wk	Continuous	231		126 (SD 14.3)	231		126 (SD 14.9)		
Previous blood glucose lowering drugs:									
any monotherapy (1 previous OAD)	Dichotomous	231	72	(31.2%)	231	68	(29.4%)		
any dual therapy (2 previous OAD)	Dichotomous	231	159	(68.8%)	231	163	(70.6%)		

		Metformin + Liraglutide 1.2mg + placebo			**Metformin + liraglutide 1.8mg + placebo**				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Demographics:									
Age (years)	Continuous	233		53.5 (SD 9.6)	233		52.7 (SD 9.1)		
Sex (n male)	Dichotomous	233	128	(54.9%)	233	126	(54.1%)		
Duration of diabetes (yrs)	Continuous	233		7.5 (SD 5.3)	233		7.2 (SD 5.2)		
Blood glucose:									
HbA1c (%) – 0wk	Continuous	233		8.6 (SD 1.1)	233		8.6 (SD 1.1)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	233		9.5 (SD 2.2)	233		9.9 (SD 2.5)		
Body weight:									
BMI (kg/m2)	Continuous	233		25.4 (SD 3.7)	233		25.8 (SD 3.8)		
Weight (kg) – 0wk	Continuous	233		67.4 (SD 11.3)	233		68.2 (SD 11.9)		
Blood pressure:									
Systolic blood pressure (mmHg) – 0wk	Continuous	233		127 (SD 14)	233		126 (SD 14.1)		
Previous blood glucose lowering drugs:									
any monotherapy (1 previous OAD)	Dichotomous	233	74	(31.8%)	233	75	(32.2%)		
any dual therapy (2 previous OAD)	Dichotomous	233	159	(68.2%)	233	159	(68.2%)		

		Metformin + Liraglutide 1.2mg + placebo			**Metformin + glimepiride 4mg + placebo**				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Demographics:									
Age (years)	Continuous	233		53.5 (SD 9.6)	231		53.6 (SD 9.7)		
Sex (n male)	Dichotomous	233	128	(54.9%)	231	135	(58.4%)		
Duration of diabetes (yrs)	Continuous	233		7.5 (SD 5.3)	231		7.8 (SD 6.1)		
Blood glucose:									
HbA1c (%) – 0wk	Continuous	233		8.6 (SD 1.1)	231		8.5 (SD 1.1)		

Fasting plasma glucose (mmol/l) – 0wk	Continuous	233		9.5 (SD 2.2)	231		9.6 (SD 2.4)	
Body weight: BMI (kg/m2)	Continuous	233		25.4 (SD 3.7)	231		25.3 (SD 3.7)	
Weight (kg) – 0wk	Continuous	233		67.4 (SD 11.3)	231		68.2 (SD 11.9)	
Blood pressure: Systolic blood pressure (mmHg) – 0wk	Continuous	233		127 (SD 14)	231		126 (SD 14.9)	
Previous blood glucose lowering drugs: any monotherapy (1 previous OAD)	Dichotomous	233	74	(31.8%)	231	68	(29.4%)	
any dual therapy (2 previous OAD)	Dichotomous	233	159	(68.2%)	231	163	(70.6%)	

		Metformin + liraglutide 1.8mg + placebo			Metformin + glimepiride 4mg + placebo			Δ	p
		N	k	mean	N	k	mean		
Demographics: Age (years)	Continuous	233		52.7 (SD 9.1)	231		53.6 (SD 9.7)		
Sex (n male)	Dichotomous	233	126	(54.1%)	231	135	(58.4%)		
Duration of diabetes (yrs)	Continuous	233		7.2 (SD 5.2)	231		7.8 (SD 6.1)		
Blood glucose: HbA1c (%) – 0wk	Continuous	233		8.6 (SD 1.1)	231		8.5 (SD 1.1)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	233		9.9 (SD 2.5)	231		9.6 (SD 2.4)		
Body weight: BMI (kg/m2)	Continuous	233		25.8 (SD 3.8)	231		25.3 (SD 3.7)		
Weight (kg) – 0wk	Continuous	233		68.2 (SD 11.9)	231		68.2 (SD 11.9)		
Blood pressure: Systolic blood pressure (mmHg) – 0wk	Continuous	233		126 (SD 14.1)	231		126 (SD 14.9)		
Previous blood glucose lowering drugs: any monotherapy (1 previous OAD)	Dichotomous	233	75	(32.2%)	231	68	(29.4%)		
any dual therapy (2 previous OAD)	Dichotomous	233	159	(68.2%)	231	163	(70.6%)		

Results

		Metformin + Liraglutide 0.6mg + Placebo			Metformin + Liraglutide 1.2mg + placebo			Δ	p
		N	k	mean	N	k	mean		
Blood glucose: HbA1c (%) – 12wk	Continuous	231		7.65a	233		7.4b		
HbA1c (%) – 16wkc	Mean change	231		-1.14 (SD 1.16)	233		-1.36 (SD 1.09)		
Composite end point (HbA1c <7, no hypo, no weight gain) – 16wk	Dichotomous	231	67d	(29.0%)	233	91e	(39.1%)		
Body weight: Weight (kg) – 16wk	Mean change	231		-1.8 (SD 2.2)	233		-2.3 (SD 2.4)		
Hypoglycaemic events: Major/severe hypoglycaemic event – 16wk	Dichotomous	231	0	(0.0%)	233	0	(0.0%)		

Symptomatic hypoglycaemia – 16wkf	Count	24248	12		23520	11			
Adverse events: Pancreatitis – 16wk	Dichotomous	231	0	(0.0%)	233	0	(0.0%)		
Dropouts: Total dropouts – 16wk	Dichotomous	231	29	(12.6%)	233	46	(19.7%)		
Dropout due to AEs – 16wk	Dichotomous	231	9	(3.9%)	233	22	(9.4%)		

[a] 0.1 (value defined as as 1.96 x standard error) read from graph
[b] 0.08 (value defined as as 1.96 x standard error) read from graph
[c] SD estimated from SE in graph
[d] 29%
[e] 39%
[f] (Used in the analysis); Patient days estimated assuming dropouts occurred halfway through the study, event rates (events/subject year) estimated from graph and used to calculate number of events

		Metformin + Liraglutide 0.6mg + Placebo			Metformin + liraglutide 1.8mg + placebo				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 12wk	Continuous	231		7.65a	234		7.25b		
HbA1c (%) – 16wkc	Mean change	231		-1.14 (SD 1.16)	234		-1.45 (SD 1.17)		
Composite end point (HbA1c <7, no hypo, no weight gain) – 16wk	Dichotomous	231	67d	(29.0%)	234	96e	(41.0%)		
Body weight: Weight (kg) – 16wk	Mean change	231		-1.8 (SD 2.2)	234		-2.4 (SD 2.6)		
Hypoglycaemic events: Major/severe hypoglycaemic event – 16wk	Dichotomous	231	0	(0.0%)	234	0	(0.0%)		
Symptomatic hypoglycaemia – 16wkf	Count	24248	12		22960	9			
Adverse events: Pancreatitis – 16wk	Dichotomous	231	0	(0.0%)	234	0	(0.0%)		
Dropouts: Total dropouts – 16wk	Dichotomous	231	29	(12.6%)	234	58	(24.8%)		
Dropout due to AEs – 16wk	Dichotomous	231	9	(3.9%)	234	30	(12.8%)		

[a] 0.1 (value defined as as 1.96 x standard error) read from graph
[b] 0.05 (value defined as as 1.96 x standard error) read from graph
[c] SD estimated from SE in graph
[d] 29%
[e] 41%
[f] (Used in the analysis); Patient days estimated assuming dropouts occurred halfway through the study, event rates (events/subject year) estimated from graph and used to calculate number of events

		Metformin + Liraglutide 0.6mg + Placebo			Metformin + glimepiride 4mg + placebo				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 12wk	Continuous	231		7.65a	231		7.4b		
HbA1c (%) – 16wkc	Mean change	231		-1.14 (SD 1.16)	231		-1.39 (SD 1.16)		
Composite end point (HbA1c <7, no hypo, no weight gain) – 16wk	Dichotomous	231	67d	(29.0%)	231	39e	(16.9%)		
Body weight: Weight (kg) – 16wk	Mean change	231		-1.8 (SD 2.2)	231		0.08 (SD 2.33) c		
Hypoglycaemic events: Major/severe hypoglycaemic event – 16wk	Dichotomous	231	0	(0.0%)	231	2	(0.9%)		

Symptomatic hypoglycaemia – 16wkf	Count	24248	12		24976	84			
Adverse events: Pancreatitis – 16wk	Dichotomous	231	0	(0.0%)	231	0	(0.0%)		
Dropouts: Total dropouts – 16wk	Dichotomous	231	29	(12.6%)	231	16	(6.9%)		
Dropout due to AEs – 16wk	Dichotomous	231	9	(3.9%)	231	3	(1.3%)		

[a] 0.1 (value defined as as 1.96 x standard error) read from graph
[b] 0.08 (value defined as as 1.96 x standard error) read from graph
[c] SD estimated from SE in graph
[d] 29%
[e] 17%
[f] (Used in the analysis); Patient days estimated assuming dropouts occurred halfway through the study, event rates (events/subject year) estimated from graph and used to calculate number of events

		Metformin + Liraglutide 1.2mg + placebo			Metformin + liraglutide 1.8mg + placebo				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 12wk	Continuous	233		7.4a	234		7.25b		
HbA1c (%) – 16wkc	Mean change	233		-1.36 (SD 1.09)	234		-1.45 (SD 1.17)		
Composite end point (HbA1c <7, no hypo, no weight gain) – 16wk	Dichotomous	233	91d	(39.1%)	234	96e	(41.0%)		
Body weight: Weight (kg) – 16wk	Mean change	233		-2.3 (SD 2.4)	234		-2.4 (SD 2.6)		
Hypoglycaemic events: minor hypoglycaemic events – 16wk	Dichotomous	233	0f	(0.0%)	234	4g	(1.7%)		
Major/severe hypoglycaemic event – 16wk	Dichotomous	233	0	(0.0%)	234	0	(0.0%)		
Symptomatic hypoglycaemia – 16wkh	Count	23520	11		22960	9			
Adverse events: Pancreatitis – 16wk	Dichotomous	233	0	(0.0%)	234	0	(0.0%)		
Dropouts: Total dropouts – 16wk	Dichotomous	233	46	(19.7%)	234	58	(24.8%)		
Dropout due to AEs – 16wk	Dichotomous	233	22	(9.4%)	234	30	(12.8%)		

[a] 0.08 (value defined as as 1.96 x standard error) read from graph
[b] 0.05 (value defined as as 1.96 x standard error) read from graph
[c] SD estimated from SE in graph
[d] 39%
[e] 41%
[f] 0%
[g] 1.7%
[h] (Used in the analysis); Patient days estimated assuming dropouts occurred halfway through the study, event rates (events/subject year) estimated from graph and used to calculate number of events

		Metformin + Liraglutide 1.2mg + placebo			Metformin + glimepiride 4mg + placebo				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 12wka	Continuous	233		7.4	231		7.4		
HbA1c (%) – 16wkb	Mean change	233		-1.36 (SD 1.09)	231		-1.39 (SD 1.16)		
HbA1c (%) – 16wk	Continuous	233			231			MD=0.030	c

Composite end point (HbA1c <7, no hypo, no weight gain) – 16wk	Dichotomous	233	91d	(39.1%)	231	39e	(16.9%)		
Body weight: Weight (kg) – 16wk	Mean change	233		-2.3 (SD 2.4)	231		0.08 (SD 2.33) b		
Hypoglycaemic events: minor hypoglycaemic events – 16wk	Dichotomous	233	0f	(0.0%)	231	44g	(19.0%)		
Major/severe hypoglycaemic event – 16wk	Dichotomous	233	0	(0.0%)	231	2	(0.9%)		
Symptomatic hypoglycaemia – 16wkh	Count	23520	11		24976	84			
Adverse events: Pancreatitis – 16wk	Dichotomous	233	0	(0.0%)	231	0	(0.0%)		
Dropouts: Total dropouts – 16wk	Dichotomous	233	46	(19.7%)	231	16	(6.9%)		
Dropout due to AEs – 16wk	Dichotomous	233	22	(9.4%)	231	3	(1.3%)		

[a] 0.08 (value defined as as 1.96 x standard error) read from graph
[b] SD estimated from SE in graph
[c] CI= -0.14 to 0.20
[d] 39%
[e] 17%
[f] 0%
[g] 19%
[h] (Used in the analysis); Patient days estimated assuming dropouts occurred halfway through the study, event rates (events/subject year) estimated from graph and used to calculate number of events

		Metformin + liraglutide 1.8mg + placebo			**Metformin + glimepiride 4mg + placebo**				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Blood glucose: HbA1c (%) – 12wk	Continuous	234		7.25a	231		7.4b		
HbA1c (%) – 16wkc	Mean change	234		-1.45 (SD 1.17)	231		-1.39 (SD 1.16)		
HbA1c (%) – 16wk	Continuous	233			231			MD=-0.060	d
Composite end point (HbA1c <7, no hypo, no weight gain) – 16wk	Dichotomous	234	96e	(41.0%)	231	39f	(16.9%)		
Body weight: Weight (kg) – 16wk	Mean change	234		-2.4 (SD 2.6)	231		0.08 (SD 2.33) c		
Hypoglycaemic events: minor hypoglycaemic events – 16wk	Dichotomous	234	4g	(1.7%)	231	44h	(19.0%)		
Major/severe hypoglycaemic event – 16wk	Dichotomous	234	0	(0.0%)	231	2	(0.9%)		
Symptomatic hypoglycaemia – 16wki	Count	22960	9		24976	84			
Adverse events: Pancreatitis – 16wk	Dichotomous	234	0	(0.0%)	231	0	(0.0%)		
Dropouts: Total dropouts – 16wk	Dichotomous	234	58	(24.8%)	231	16	(6.9%)		
Dropout due to AEs – 16wk	Dichotomous	234	30	(12.8%)	231	3	(1.3%)		

[a] 0.05 (value defined as as 1.96 x standard error) read from graph
[b] 0.08 (value defined as as 1.96 x standard error) read from graph
[c] SD estimated from SE in graph
[d] CI= -0.23 to 0.11
[e] 41%
[f] 17%
[g] 1.7%
[h] 19%

	[i] (Used in the analysis); Patient days estimated assuming dropouts occurred halfway through the study, event rates (events/subject year) estimated from graph and used to calculate number of events

E.1.3 Second intensification

Table 1: Aljabri et al. (2004)

General	**Phase:** ☐ monotherapy ☐ dual therapy ☑ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** Canada **Authors' conclusions:** Adding pioglitazone or bedtime insulin for 16 weeks improved glycaemic control in type 2 diabetic patients with secondary oral agent failure. Pioglitazone was associated with less hypoglycaemia and improved HDL cholesterol levels **Source of funding:** Elli Lilly **Comments:** Open label trial, randomisation using comouter-generated random numbers placed in opaque, sealed envelopes
Number and characteristics of patients	**Total number of patients:** 62 **Inclusion criteria:** Patients were 30-85 years old, had type 2 diabetes for more than 1 year and were taking maximally tolerated doses of an insulin secretagogue and metformin. All had received diabetes education and were performing SMBG. Their most recent Hba1c was >8% while undergoing stable diabetes treatment for >12 weeks **Exclusion criteria:** Previous use of insulin or thiazolidinedione, heart failure, myocardial infarction or stroke in the past 6 months, liver disease, serum creatinine >2 mg/dl, proliferative retinopathy, current glucocorticoid use, excess alcohol. Patients could be withdrawn if they had blood glucose levels that were considered dangerous, had intolerable side effects, or did not comply with the protocol Pre-randomisation phase: There was a 2 week run-in phase (to determine if patients would comply with the study requirements)
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** all on oral hypoglycaemic drugs and/or insulin **Details of washout period:** All taking metformin and sulfonylurea at study entry and these were continued
Lifestyle advice	-
Follow-up	**Total follow-up (wks):** 16 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 16 **Frequency of monitoring appointments:** Patients presented at weeks 4, 8 and 16
Arms	**(1) Pioglitazone + metformin + sulfonylurea** N: 30 Treatment duration (wks): 16 Washout period (d): 0 Comments: Continued previous metformin and sulfonylurea Treatment(s): (a) Pioglitazone (Oral) – flexible-dose (dose-adjusted) Mean dose (mg/d): 45 Details of dosing regimen: The goal in both groups was to achieve a FBG <108 mg/dl (same as the intensive arm in UKPDS). Pioglitazone was started at 30 mg/day in addition to their other hypoglycaemic agents. If FBG levels were not consistently <108 mg/dl after 4 weeks, the dose was increased to 45 mg/day. (b) Metformin (Oral) Mean dose (mg/d): 2050 (c) Sulfonylurea (Oral) Mean dose (mg/d): 20 **(2) NPH insulin + metformin + sulfonylurea** N: 28 Treatment duration (wks): 16 Washout period (d): 0 Comments: Continued previous metformin and sulfonylurea Treatment(s): (a) NPH insulin (Subcutaneous) – flexible-dose (dose-adjusted) Mean dose (mg/d): 31 Details of dosing regimen: Insulin patients were started on a dose of 0.3 units/kg in addition to their hypoglycaemic agents. They were instructed on how to increase the dose to achieve a FBG <108 mg/dl and were contacted weekly for help with insulin adjustment. (b) Metformin (Oral) Mean dose (mg/d): 2210 (c) Sulfonylurea (Oral)

	Mean dose (mg/d): 20
Outcomes	**General** Outcomes not extracted in this evidence table include diabetes satisfaction. 1/31 (3.2%) patients in pioglitazone group and 3/31 (9.7%) in the insulin group discontinued the study. No ITT analysis conducted **Hypoglycaemic events** Major/severe hypoglycaemic event (Severe hypoglycaemia was defined as low blood glucose levels resulting in loss of consciousness or requiring assistance for treatment) confirmed hypoglycaemia (Hypoglycaemia was defined as BG <68 mg/dl)

Baseline characteristics

		Pioglitazone + metformin + sulfonylurea			NPH insulin + metformin + sulfonylurea			Δ	p
		N	k	mean	N	k	mean		
Demographics: Age (years)	Continuous	30		59 (SD 9)	28		57 (SD 14)		
Sex (n male)	Dichotomous	30	18	(60.0%)	28	17	(60.7%)		
Duration of diabetes (yrs)	Continuous	30		9 (SD 6)	28		11 (SD 8)		
Blood glucose: HbA1c (%) – 0wk	Continuous	30		9.7 (SD 1.5)	28		10.1 (SD 1.4)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	30		10.213104 (SD 2.72)	28		11.212212 (SD 2.89)		
Body weight: BMI (kg/m2)	Continuous	30		26 (SD 9)	28		25 (SD 6)		
Weight (kg) – 0wk	Continuous	30		85.1 (SD 32)	28		86.5 (SD 22.4)		
Blood pressure: Systolic blood pressure (mmHg) – 0wk	Continuous	30		139 (SD 22)	28		138 (SD 22)		
Diastolic blood pressure (mmHg) – 0wk	Continuous	30		75 (SD 13)	28		76 (SD 12)		
Lipids: Total cholesterol (mmol/l) – 0wk	Continuous	30		5.14614 (SD 1.11)	28		5.40474 (SD 1.29)		
HDL cholesterol (mmol/l) – 0wk	Continuous	30		1.293 (SD 0.388)	28		1.11198 (SD 0.207)		
Triglycerides (mmol/l) – 0wk	Continuous	30		2.61928 (SD 2.72)	28		2.61928 (SD 1.31)		
LDL cholesterol (mmol/l) – 0wk	Continuous	30		2.89632 (SD 1.01)	28		3.20664 (SD 1.11)		
Renal function: serum creatinine	Continuous	30		0.8 (SD 0.3)	28		0.8 (SD 0.3)		
Microalbumin:creatinine – 0wk	Continuous	30		58.3 (SD 91.9)	28		178 (SD 493)		

Results

		Pioglitazone + metformin + sulfonylurea			NPH insulin + metformin + sulfonylurea			Δ	p
		N	k	mean	N	k	mean		
Blood glucose: HbA1c (%) – 16wka	Mean change	30		-1.9 (SD 1.5)	28		-2.3 (SD 1.5)	MD=0.400 (CI: -0.400, 1.200)	0.32
HbA1c < 7% or <=7% – 16wk	Dichotomous	30	7	(23.3%)	28	6	(21.4%)		0.86
Fasting plasma glucose (mmol/l) – 16wk	Mean change	30			28			MD=1.388 (CI: -0.056, 2.831)	0.07

Fasting plasma glucose (mmol/l) – 16wk	Continuous	30		-2.886312 (SD 2.72)	28		-4.273962 (SD 2.89)		
Body weight: Weight (kg) – 16wk	Mean change	30		2.6 (SD 4.3)	28		2.5 (SD 2.8)	MD=0.100 (CI: -1.200, 1.400)	0.97
Hypoglycaemic events: Major/severe hypoglycaemic event – 16wk	Dichotomous	30	0	(0.0%)	28	0	(0.0%)		NR
Major/severe hypoglycaemic event – 16wkb	Count	3416	0		3304	0			
confirmed hypoglycaemia – 16wk	Dichotomous	30	11c	(36.7%)	28	79d	(282.1%)	MD=31.000 (CI: 5.000, 57.000)	0.02
confirmed hypoglycaemia – 16wk	Dichotomous	30	11c	(36.7%)	28	79d	(282.1%)	MD=1.500 (CI: 0.800, 2.200)	<0.001e
confirmed hypoglycaemia – 16wk	Dichotomous	30	34d	(113.3%)	28	19c	(67.9%)	MD=1.500 (CI: 0.800, 2.200)	<0.001e
confirmed hypoglycaemia – 16wk	Dichotomous	30	34d	(113.3%)	28	19c	(67.9%)	MD=31.000 (CI: 5.000, 57.000)	0.02
confirmed hypoglycaemia – 16wkd	Dichotomous	30	34	(113.3%)	28	79	(282.1%)	MD=1.500 (CI: 0.800, 2.200)	<0.001e
confirmed hypoglycaemia – 16wkd	Dichotomous	30	34	(113.3%)	28	79	(282.1%)	MD=31.000 (CI: 5.000, 57.000)	0.02
confirmed hypoglycaemia – 16wkf	Count	3416	34		3220	79			
confirmed hypoglycaemia – 16wkc	Dichotomous	30	11	(36.7%)	28	19	(67.9%)	MD=1.500 (CI: 0.800, 2.200)	<0.001e
confirmed hypoglycaemia – 16wkc	Dichotomous	30	11	(36.7%)	28	19	(67.9%)	MD=31.000 (CI: 5.000, 57.000)	0.02
Adverse events: Injection site – 16wk	Dichotomous	30	0g	(0.0%)	28	5	(17.9%)		
Dropouts: Total dropouts – 16wk	Dichotomous	31	1	(3.2%)	31	3	(9.7%)		
Dropout due to AEs – 16wk	Dichotomous	31	0	(0.0%)	31	0	(0.0%)		
Blood pressure: Systolic blood pressure (mmHg) – 16wk	Mean change	30		-8 (SD 22)	28		-6 (SD 21)	MD=-2.000 (CI: -14.000, 10.000)	0.72
Diastolic blood pressure (mmHg) – 16wk	Mean change	30		-5 (SD 10)	28		-1 (SD 10)	MD=-4.000 (CI: -9.000, 1.000)	0.14
Lipids: Total cholesterol (mmol/l) – 16wk	Mean change	30		0.20688 (SD 1.11)	28		-0.31032 (SD 1.11)	MD=0.000	
HDL cholesterol (mmol/l) – 16wk	Mean change	30		0.10344 (SD 0.207)	28		0 (SD 0.103)	MD=0.103 (CI: 0.000, 0.207)	0.02
Triglycerides (mmol/l) – 16wk	Mean change	30		-0.9032 (SD 1.72)	28		-0.71127 (SD 1.11)	MD=0.203 (CI: -0.305, 0.711)	0.62

	LDL cholesterol (mmol/l) – 16wk	Mean change	30		-0.20688 (SD 0.931)	28		-0.10344 (SD 1.01)	MD=0.103 (CI: -0.310, 0.517)	0.69
	Renal function: Microalbumin:creatinine – 16wk	Mean change	30			28			MD=32.700 (CI: -8.800, 74.200)	0.13
	Microalbumin:creatinine – 16wk	Continuous	30		-25.6 (SD 63.6)	28		-58.3 (SD 91.9)		

[a] trial reports SD
[b] No of patients; person days estimated assuming dropout halfway through trial
[c] No patients
[d] No events (reported as total SMBG measurements indicating hypo)
[e] total measurements indicating hypos
[f] No of events; person days estimated assuming dropout halfway through trial where data not provided
[g] Pioglitazone taken orally

	Unpaired two-tailed t tests were used for between group comparisons of continuous variables and paired t tests were used for within group comparisons

Table 2: Bergenstal et al. (2009)

General	**Phase:** ☐ monotherapy ☐ dual therapy ☑ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** USA **Authors' conclusions:** BIAsp 30 was more efficacious in helping patients with high baseline Hba1c achieve glycaemic goals. **Source of funding:** Novo Nordisk **Comments:** randomisation performed centrally using a telephone interactive voice response system andor interactive web based system
Number and characteristics of patients	**Total number of patients:** 372 **Inclusion criteria:** type 2 diabetes for >6 months, aged 18-80 years, Hba1c >=8%, were insulin naïve and had received therapy with metformin (al least 1500 mg/day) and a sulfonylurea (at least half the max dose) for 3 months before screening **Exclusion criteria:** Significant cardiac disease within 12 months prior to the study, hepatic or renal insufficiency, use of thiazolidinediones, alpha glucosidase inhibitors or meglitinides within the 6 months prior to the study or were receiving a weight reducing diet
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** all on oral hypoglycaemic drugs and/or insulin **Details of washout period:** All taking metformin and sulfonylurea- doses were fixed during study (no washout phase)
Lifestyle advice	Participants were asked not to make any significant dietary or exercise modifications for the purpose of weight loss during the trial
Follow-up	**Total follow-up (wks):** 24 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 24 **Frequency of monitoring appointments:** Visits occurred at weeks 1,2,3,4,5,8,12,16,20 and 24
Arms	**(1) Metformin + sulfonylurea + exenatide** N: 124 Treatment duration (wks): 24 Washout period (d): 0 Treatment(s): (a) Metformin (Oral) Details of dosing regimen: Doses were remained fixed (no further details reported)

(b) Sulfonylurea (Oral)
Details of dosing regimen: Doses were remained fixed (no further details reported)
(c) Exenatide (Subcutaneous) – fixed-dose
Set dose (mg/d):10
Frequency of dosing: twice a day
Details of dosing regimen: exenatide was started at 5 µg bid for 4 weeks and 10 µg bid thereafter

(2) Metformin + sulfonylurea +BIAsp 30 qd

N: 124

Treatment duration (wks): 24
Washout period (d): 0

Treatment(s): (a) Metformin (Oral)
Details of dosing regimen: Doses were remained fixed (no further details reported)
(b) Sulfonylurea (Oral)
Details of dosing regimen: Doses were remained fixed (no further details reported)
(c) Biphasic insulin aspart (Subcutaneous) – flexible-dose (dose-adjusted)
Mean dose (mg/d): 44.9
Frequency of dosing: once a day
Details of dosing regimen: insulin therapy wa started with 12 U before supper. Patients were instructed to adjust their insulin dose every 3-4 days based on titration algorithm. Dose titration was based on the average SMBG results for the 3 days preceeding the visit, unless hypoglycaemia occurred.
Final daily insulin dose was 44.9 ± 27.1 U/day (pre-supper)

(3) Metformin +BIAsp 30 bid

N: 124

Treatment duration (wks): 24
Washout period (d): 0

Treatment(s): (a) Metformin (Oral)
Details of dosing regimen: Doses were remained fixed (no further details reported)
(b) Biphasic insulin aspart (Subcutaneous) – fixed-dose
Mean dose (mg/d): 96.1
Frequency of dosing: twice a day
Details of dosing regimen: patients started insulin therapy with 12 U were divided equally between pre-breakfast and pre-supper. Patients were instructed to adjust their insulin dose every 3-4 days based on an insulin titration algorithm. Dose titration was based on the average SMBG results for the 3 days preceeding the visit, unless hypoglycaemia occurred. Total daily dose could not be increased by more than 10 U at any time. After visit 2 doses were titrated weekly for the first 12 weeks and then every 2 weeks thereafter according to the titration algorithm.
Final daily insulin dose was 96.1 ± 42.2 U/day (pre-supper)

Outcomes

General

Per protocol population (PP), defined as participants who completed the study without protocol violations, were used to evaluate the primary efficacy analysis. The ITT population, defined as participants who were exposed to at least one dose of study medication and had one post-dosing and post-baseline primary efficacy measurement, was used to evaluate primary and secondary analyses. The safety population comprised all participants randomised.

29.8% of patients in exenatide group, 16.1% in BIAsp 30 qd group and 19.4% in the BIAsp 30 bid group discontinued the study

Outcomes not reported in this evidence table include SMBG

Hypoglycaemic events

Minor (confirmed) hypoglycaemia (Minor hypoglycaemia was defined as any symptom of hypoglycaemia with a confirmed blood glucose meter reading (3.1 mmol/l) or any asymptomatic reading <3.1 mmol/l which was handled by the participant themselves)

Major/severe hypoglycaemic event (Major hypoglycaemia was defined as symptoms associated with a BG reading <3.1 mmol/l and requiring third party assistance)

Baseline characteristics

		Metformin + sulfonylurea + exenatide			Metformin + sulfonylurea +BIAsp 30 qd				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Demographics:									
Age (years)	Continuous	124		52.5 (SD 10.6)	124		51.8 (SD 10.9)		
Sex (n male)	Dichotomous	124	60	(48.4%)	124	60	(48.4%)		
Duration of diabetes (yrs)	Continuous	124		8.6 (SD 5.9)	124		8.4 (SD 6.3)		

Blood glucose: HbA1c (%) – 0wk	Continuous	124		10.2 (SD 1.52)	124		10.1 (SD 1.79)	
Fasting plasma glucose (mmol/l) – 0wk	Continuous	124		11.711766 (SD 3.77)	124		10.934682 (SD 3.72)	
Body weight: BMI (kg/m2)	Continuous	124		34.2 (SD 7.1)	124		33.7 (SD 7.1)	
Weight (kg) – 0wk	Continuous	124		96.6 (SD 24)	124		96.9 (SD 25)	

		Metformin + sulfonylurea + exenatide			Metformin +BIAsp 30 bid				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	124		52.5 (SD 10.6)	124		53.4 (SD 9.96)		
Sex (n male)	Dichotomous	124	60	(48.4%)	124	59	(47.6%)		
Duration of diabetes (yrs)	Continuous	124		8.6 (SD 5.9)	124		9.9 (SD 5.6)		
Blood glucose: HbA1c (%) – 0wk	Continuous	124		10.2 (SD 1.52)	124		10.3 (SD 1.92)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	124		11.711766 (SD 3.77)	124		11.156706 (SD 4.16)		
Body weight: BMI (kg/m2)	Continuous	124		34.2 (SD 7.1)	124		33.5 (SD 7.4)		
Weight (kg) – 0wk	Continuous	124		96.6 (SD 24)	124		93.8 (SD 24)		

		Metformin + sulfonylurea +BIAsp 30 qd			Metformin +BIAsp 30 bid				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	124		51.8 (SD 10.9)	124		53.4 (SD 9.96)		
Sex (n male)	Dichotomous	124	60	(48.4%)	124	59	(47.6%)		
Duration of diabetes (yrs)	Continuous	124		8.4 (SD 6.3)	124		9.9 (SD 5.6)		
Blood glucose: HbA1c (%) – 0wk	Continuous	124		10.1 (SD 1.79)	124		10.3 (SD 1.92)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	124		10.934682 (SD 3.72)	124		11.156706 (SD 4.16)		
Body weight: BMI (kg/m2)	Continuous	124		33.7 (SD 7.1)	124		33.5 (SD 7.4)		
Weight (kg) – 0wk	Continuous	124		96.9 (SD 25)	124		93.8 (SD 24)		

Results

		Metformin + sulfonylurea + exenatide			Metformin + sulfonylurea +BIAsp 30 qd				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 24wk	Mean change	124			124			MD=-0.670 (CI: -0.990, -0.350)	<0.001
HbA1c < 7% or <=7% – 24wk	Dichotomous	124			124				NS
HbA1c <= 6.5% – 24wk	Dichotomous	124			124				NS

Fasting plasma glucose (mmol/l) – 12wka	Continuous	124		9.71355 (SD 2.47)	124		7.937358 (SD 1.24)		
Fasting plasma glucose (mmol/l) – 24wkb	Mean change	124		-1.1878284 (SD 0.332)	124		-2.9085144 (SD 0.32)		0.0002
Body weight:									
Weight (kg) – 24wk	Mean change	124		-1.9 (SD 3.8)	124		2.8 (SD 3.6)		
Weight (kg) – 24wk	Continuous	124		94.92 (SD 23.7)	124		99.2 (SD 24.1)		NR
Hypoglycaemic events:									
All hypoglycaemic events (no patients) – 24wk	Dichotomous	124	36c	(29.0%)	124	69d	(55.6%)		
Minor (confirmed) hypoglycaemia – 24wke	Count	17724	62		19152	212			<0.0001
Minor (confirmed) hypoglycaemia – 24wke	Count	124	62		124	212			<0.0001
Minor (confirmed) hypoglycaemia – 24wkf	Continuous	124		1.28	124		4.02		
Major/severe hypoglycaemic event – 24wkc	Dichotomous	124	0	(0.0%)	124	4	(3.2%)		
Adverse events:									
GI: nausea – 24wk	Dichotomous	124	36	(29.0%)	124	11g	(8.9%)		
Any serious adverse event(s) – 24wkh	Dichotomous	124			124				
Dropouts:									
Total dropouts – 24wk	Dichotomous	124	37	(29.8%)	124	20	(16.1%)		
Dropout due to AEs – 24wk	Dichotomous	124	9	(7.3%)	124	1	(0.8%)		
Drop out due to unsatisfactory effect – 24wk	Dichotomous	124	4	(3.2%)	124	1	(0.8%)		
Dropout due to hypoglycaemia – 24wk	Dichotomous	124	0	(0.0%)	124	0	(0.0%)		
PP									
Blood glucose:									
HbA1c (%) – 16wki	Continuous	87		8.05 (SD 0.933)	104		7.7 (SD 0.102)		
HbA1c (%) – 24wk	Mean change	87		-1.75 (SD 1.57)	104		-2.34 (SD 1.51)		
HbA1c (%) – 24wk	Continuous	87		8.46 (SD 1.72)	104		7.75 (SD 1.09)		
HbA1c < 7% or <=7% – 24wkg	Dichotomous	114	23	(20.2%)	116	30	(25.9%)		
HbA1c <= 6.5% – 24wk	Dichotomous	114	9g	(7.9%)	116	14	(12.1%)		

[a] estimated from graph
[b] converted from mg/dl (SD reported)
[c] No of patients
[d] approximated to nearest integer (percentages only presented in text); No of patients
[e] Person days estimated assuming dropout halfway through trial and no of events calculated using reported rate
[f] events per patient year; No 95% confidence interval reported
[g] approximated to nearest integer (percentages only presented in text)
[h] NR

[i] estimated from graph (SE converted)

		Metformin + sulfonylurea + exenatide			Metformin +BIAsp 30 bid				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 24wk	Mean change	124			124			MD=-0.910 (CI: -1.230, -0.590)	<0.001
HbA1c < 7% or <=7% – 24wk	Dichotomous	124			124				0.006
HbA1c <= 6.5% – 24wk	Dichotomous	124			124				0.0004
Fasting plasma glucose (mmol/l) – 12wka	Continuous	124		9.71355 (SD 2.47)	124		7.21578 (SD 1.24)		
Fasting plasma glucose (mmol/l) – 24wkb	Mean change	124		-1.1878284 (SD 0.332)	124		-3.4802262 (SD 0.315)		<0.0001
Body weight: Weight (kg) – 24wk	Mean change	124		-1.9 (SD 3.8)	124		4.1 (SD 5.4)		
Weight (kg) – 24wk	Continuous	124		94.92 (SD 23.7)	124		97.75 (SD 24)		NR
Hypoglycaemic events: All hypoglycaemic events (no patients) – 24wk	Dichotomous	124	36c	(29.0%)	124	76d	(61.3%)		
Minor (confirmed) hypoglycaemia – 24wke	Count	17724	62		18816	271			<0.0001
Minor (confirmed) hypoglycaemia – 24wke	Count	124	62		124	271			<0.0001
Minor (confirmed) hypoglycaemia – 24wkf	Continuous	124		1.28	124		5.25		
Major/severe hypoglycaemic event – 24wkc	Dichotomous	124	0	(0.0%)	124	6	(4.8%)		
Adverse events: GI: nausea – 24wk	Dichotomous	124	36	(29.0%)	124	10g	(8.1%)		
Any serious adverse event(s) – 24wk	Dichotomous	124	h		124	2c			
Dropouts: Total dropouts – 24wk	Dichotomous	124	37	(29.8%)	124	24	(19.4%)		
Dropout due to AEs – 24wk	Dichotomous	124	9	(7.3%)	124	6	(4.8%)		
Drop out due to unsatisfactory effect – 24wk	Dichotomous	124	4	(3.2%)	124	0	(0.0%)		
Dropout due to hypoglycaemia – 24wk	Dichotomous	124	0	(0.0%)	124	0	(0.0%)		
PP Blood glucose: HbA1c (%) – 16wki	Continuous	87		8.05 (SD 0.933)	99		7.4 (SD 0.0995)		

HbA1c (%) – 24wk	Mean change	87		-1.75 (SD 1.57)	99		-2.76 (SD 1.79)		
HbA1c (%) – 24wk	Continuous	87		8.46 (SD 1.72)	99		7.61 (SD 1.37)		
HbA1c < 7% or <=7% – 24wkj	Dichotomous	114	23	(20.2%)	120	44	(36.7%)		
HbA1c <= 6.5% – 24wk	Dichotomous	114	9j	(7.9%)	120	30	(25.0%)		

[a] estimated from graph
[b] converted from mg/dl (SD reported)
[c] No of patients
[d] approximated to nearest integer (percentages only presented in text); No of patients
[e] Person days estimated assuming dropout halfway through trial and no of events calculated using reported rate
[f] events per patient year; No 95% confidence interval reported
[g] approximated to nearest integer (percentages only presented in text);
[h] NR
[i] estimated from graph (SE converted)
[j] approximated to nearest integer (percentages only presented in text)

		Metformin + sulfonylurea +BIAsp 30 qd			Metformin +BIAsp 30 bid				
		N	k	mean	N	k	mean	Δ	p
Blood glucose:									
Fasting plasma glucose (mmol/l) – 12wka	Continuous	124		7.937358 (SD 1.24)	124		7.21578 (SD 1.24)		
Fasting plasma glucose (mmol/l) – 24wkb	Mean change	124		-2.9085144 (SD 0.32)	124		-3.4802262 (SD 0.315)		
Body weight:									
Weight (kg) – 24wk	Mean change	124		2.8 (SD 3.6)	124		4.1 (SD 5.4)		
Weight (kg) – 24wk	Continuous	124		99.2 (SD 24.1)	124		97.75 (SD 24)		
Hypoglycaemic events:									
All hypoglycaemic events (no patients) – 24wkc	Dichotomous	124	69	(55.6%)	124	76	(61.3%)		
Minor (confirmed) hypoglycaemia – 24wkd	Count	19152	212		18816	271			
Minor (confirmed) hypoglycaemia – 24wke	Continuous	124		4.02	124		5.25		
Major/severe hypoglycaemic event – 24wkf	Dichotomous	124	4	(3.2%)	124	6	(4.8%)		
Adverse events:									
GI: nausea – 24wk	Dichotomous	124	11g	(8.9%)	124	10h	(8.1%)		
Any serious adverse event(s) – 24wk	Dichotomous	124	i		124	2f			
Dropouts:									
Total dropouts – 24wk	Dichotomous	124	20	(16.1%)	124	24	(19.4%)		
Dropout due to AEs – 24wk	Dichotomous	124	1	(0.8%)	124	6	(4.8%)		
Drop out due to unsatisfactory effect – 24wk	Dichotomous	124	1	(0.8%)	124	0	(0.0%)		
Dropout due to hypoglycaemia – 24wk	Dichotomous	124	0	(0.0%)	124	0	(0.0%)		
PP									
Blood glucose:									
HbA1c (%) – 16wkj	Continuous	104		7.7 (SD 0.102)	99		7.4 (SD 0.0995)		
HbA1c (%) – 24wk	Mean change	104		-2.34 (SD 1.51)	99		-2.76 (SD 1.79)		
HbA1c (%) – 24wk	Continuous	104		7.75 (SD 1.09)	99		7.61 (SD 1.37)		
HbA1c < 7% or <=7% – 24wkg	Dichotomous	116	30	(25.9%)	120	44	(36.7%)		

	HbA1c <= 6.5% – 24wk	Dichotomous	116	14	(12.1%)	120	30	(25.0%)		

[a] estimated from graph
[b] converted from mg/dl (SD reported)
[c] approximated to nearest integer (percentages only presented in text); No of patients
[d] Person days estimated assuming dropout halfway through trial and no of events calculated using reported rate
[e] events per patient year; No 95% confidence interval reported
[f] No of patients
[g] approximated to nearest integer (percentages only presented in text)
[h] approximated to nearest integer (percentages only presented in text);
[i] NR
[j] estimated from graph (SE converted)

Assumed PP analyses were conducted on hba1c data as reported in methods section

Missing data were imputed using LOCF. A linear statistical model with the change in hba1c from baseline to end of the study as the dependent variable and treatment as the fixed factor was used to perform between group comparisons. Baseline values were included in the model as a covariate. Fischers exact test was used to assess chievement of Hba1c goals and log-linear Poisson regression model with treatment as a factor was used to analyse hypoglycaemic episodes.

Table 3: Civera et al. (2008)

General

Phase:
☐ monotherapy
☐ dual therapy
☑ triple therapy
☐ insulin monotherapy
☐ insulin+oral

Parallel / crossover: Parallel

Country: Spain

Authors' conclusions: The combination of repaglinide, metformin and bedtime NPH is safe and effective and it provides better postprandial blood glucose control. The association of metformin and a dose of NPH does not obtain suitable control in patients with a long evolution who have already receievd two or more Oads

Source of funding: Unclear

Comments: Open label study

Number and characteristics of patients

Total number of patients: 37

Inclusion criteria: patients with type 2 diabetes, with secondary failure of combined OAD for at least 3 months. Patients were between 40 and 70 years with over 3 years evolution and Hba1c >8%

Exclusion criteria: pregnancy, BMI >40 kg/m2, renal or hepatic failure, pulmonary or cardiac disease which would contrindicate the use of metformin or intolerance and any severe systemic disease

Previous glucose-lowering therapy

Any participants previously taking glucose-lowering therapy? all on oral hypoglycaemic drugs and/or insulin

Details of washout period: All were having secondary failure on combined OAD but other OADs were stopped

Lifestyle advice

Patients were instructed not to modify their diet or life habits despite the insulin treatment during the entire study

Follow-up

Total follow-up (wks): 24

Length of titration period (wks): 0

Length of maintenance period (wks): 24

Frequency of monitoring appointments: There were 7 visits during the 6 month study

Arms

(1) Repaglinide + metformin + NPH insulin

N: 12

Treatment duration (wks): 24
Washout period (d): 0
Comments: All remaining OADs were stopped

Treatment(s): (a) repaglinide (Oral) – fixed-dose
Set dose (mg/d):12
Frequency of dosing: three times a day
Details of dosing regimen: 2 mg before meals. This was increased to 4 mg at week 12

before the meal at which point postprandial glucose levels were

(b) Metformin (Oral) – fixed-dose

Set dose (mg/d):1700
Frequency of dosing: twice a day
Details of dosing regimen: metformin 850 mg was given after breakfast and dinner

(c) NPH insulin (Subcutaneous)

Frequency of dosing: once a day
Details of dosing regimen: NPH insulin was given before dinner. The initial insulin dose in the baseline visit was calculated by multiplying bodyweight in kg by 0.2 IU/day for a single injection and by 0.3 IU/day for two injections. The insulin doses were modified in visits 2,3 and 4 according to criterion of the endocrinologist in charge according to the self-tests and hypoglycaemia, but no specific algorithm was used. The main objective was to obtain basal blood glucose <110 mg/dl and <120 mg/dl before dinner for the group taking two doses of NPH

(2) Metformin + NPH insulin

N: 12

Treatment duration (wks): 24
Washout period (d): 0
Comments: All remaining OADs were stopped

Treatment(s): (a) Metformin (Oral) – fixed-dose

Set dose (mg/d):1700
Frequency of dosing: twice a day
Details of dosing regimen: metfomin 850 mg after breakfast and dinner

(b) NPH insulin (Subcutaneous) – flexible-dose (dose-adjusted)

Details of dosing regimen: NPH given before dinner

(3) NPH insulin

N: 13

Treatment duration (wks): 24
Washout period (d): 0
Comments: All remaining OADs were stopped

Treatment(s): NPH insulin (Subcutaneous) – flexible-dose (dose-adjusted)

Frequency of dosing: twice a day
Details of dosing regimen: NPH given before breakfast and dinner

Outcomes

General

Outcomes not extracted into this evidence table inculde SMBG levels

No details of drop outs were reported

No details of ITT analysis reported

Hypoglycaemic events

Major/severe hypoglycaemic event (required assistance from another person)

confirmed hypoglycaemia (Only hypoglycaemia defined by BG <60 mg/dl and the presence of typical clinical values to prevent subjectivity in identifying symptoms were reported)

Baseline characteristics

		Repaglinide + metformin + NPH insulin			Metformin + NPH insulin				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	12		60.3 (SD 7.7)	12		61.6 (SD 9.2)		
Sex (n male)	Dichotomous	12	6	(50.0%)	12	7	(58.3%)		
Duration of diabetes (yrs)	Continuous	12		8 (SD 5.7)	12		7.9 (SD 3.3)		
Blood glucose: HbA1c (%) – 0wk	Continuous	12		9.6 (SD 0.6)	12		9.6 (SD 0.7)		
Body weight: BMI (kg/m2)	Continuous	12		30.6 (SD 4.8)	12		27.9 (SD 3.8)		
Weight (kg) – 0wk	Continuous	12		75.4 (SD 13.4)	12		74.7 (SD 8)		
Waist circumference (cms)	Continuous	12		102.3 (SD 10.3)	12		99.4 (SD 8)		
Waist/hip ratio	Continuous	12		0.97 (SD 0.1)	12		0.97 (SD 0.05)		

		Repaglinide + metformin + NPH insulin			NPH insulin			Δ	p
		N	k	mean	N	k	mean		
Demographics: Age (years)	Continuous	12		60.3 (SD 7.7)	13		61.8 (SD 10.2)		
Sex (n male)	Dichotomous	12	6	(50.0%)	13	7	(53.8%)		
Duration of diabetes (yrs)	Continuous	12		8 (SD 5.7)	13		11.1 (SD 6.7)		
Blood glucose: HbA1c (%) – 0wk	Continuous	12		9.6 (SD 0.6)	13		9.8 (SD 1.1)		
Body weight: BMI (kg/m2)	Continuous	12		30.6 (SD 4.8)	13		27.4 (SD 4.8)		
Weight (kg) – 0wk	Continuous	12		75.4 (SD 13.4)	13		68.8 (SD 14.7)		
Waist circumference (cms)	Continuous	12		102.3 (SD 10.3)	13		96.3 (SD 14)		
Waist/hip ratio	Continuous	12		0.97 (SD 0.1)	13		0.98 (SD 0.09)		

		Metformin + NPH insulin			NPH insulin			Δ	p
		N	k	mean	N	k	mean		
Demographics: Age (years)	Continuous	12		61.6 (SD 9.2)	13		61.8 (SD 10.2)		
Sex (n male)	Dichotomous	12	7	(58.3%)	13	7	(53.8%)		
Duration of diabetes (yrs)	Continuous	12		7.9 (SD 3.3)	13		11.1 (SD 6.7)		
Blood glucose: HbA1c (%) – 0wk	Continuous	12		9.6 (SD 0.7)	13		9.8 (SD 1.1)		
Body weight: BMI (kg/m2)	Continuous	12		27.9 (SD 3.8)	13		27.4 (SD 4.8)		
Weight (kg) – 0wk	Continuous	12		74.7 (SD 8)	13		68.8 (SD 14.7)		
Waist circumference (cms)	Continuous	12		99.4 (SD 8)	13		96.3 (SD 14)		
Waist/hip ratio	Continuous	12		0.97 (SD 0.05)	13		0.98 (SD 0.09)		

Results

		Repaglinide + metformin + NPH insulin			Metformin + NPH insulin			Δ	p
		N	k	mean	N	k	mean		
Blood glucose: HbA1c (%) – 24wk	Continuous	12		7.2 (SD 0.7)	12		8.8 (SD 1)		
HbA1c (%) – 24wk	Mean change	12		-2.4 (SD 1.1)	12		-0.7 (SD 1.2)		0.01
HbA1c < 7% or <=7% – 24wk	Dichotomous	12	4	(33.3%)	12	1	(8.3%)		NR
Body weight: Weight (kg) – 24wk	Continuous	12		78.3 (SD 14.7)	12		76.1 (SD 8)		
Weight (kg) – 24wk	Mean change	12		2.9 (SD 2.8)	12		1.7 (SD 2.6)		NS
Hypoglycaemic events: Major/severe hypoglycaemic event – 24wka	Dichotomous	12	0	(0.0%)	12	0	(0.0%)		NR
Major/severe hypoglycaemic event – 24wk	Count	2016	0		2016	0			

confirmed hypoglycaemia – 24wkb	Count	2016	10		2016	6			
confirmed hypoglycaemia – 24wkc	Continuous	12		0.8 (SD 1.48)	12		0.5 (SD 0.93)		
confirmed hypoglycaemia – 24wk	Dichotomous	12			12				NS
Dropouts:									
Total dropouts – 24wk	Dichotomous	12	1	(8.3%)	12	0	(0.0%)		
Dropout due to AEs – 24wk	Dichotomous	12	1	(8.3%)	12	0	(0.0%)		
Insulin:									
Total daily dose (U) – 24wk	Continuous	12		18.2 (SD 5.3)	12		21.4 (SD 5.3)		<0.001
Total daily dose (U/kg) – 24wk	Continuous	12		0.23 (SD 0.06)	12		0.28 (SD 0.07)		<0.001

[a] No of patients
[b] patient day estimated assuming no drop outs and no events calculated using mean number of hypos in each treatment group
[c] hypoglycaemia per patient (mean SD)

		Repaglinide + metformin + NPH insulin			NPH insulin				
		N	k	mean	N	k	mean	Δ	p
Blood glucose:									
HbA1c (%) – 24wk	Continuous	12		7.2 (SD 0.7)	13		8.4 (SD 1.2)		NS
HbA1c (%) – 24wk	Mean change	12		-2.4 (SD 1.1)	13		-1.4 (SD 1.6)		
HbA1c < 7% or <=7% – 24wk	Dichotomous	12	4	(33.3%)	13	2a	(15.4%)		NR
Body weight:									
Weight (kg) – 24wk	Continuous	12		78.3 (SD 14.7)	13		73.3 (SD 15.6)		NS
Weight (kg) – 24wk	Mean change	12		2.9 (SD 2.8)	13		3 (SD 2.8)		
Hypoglycaemic events:									
Major/severe hypoglycaemic event – 24wkb	Dichotomous	12	0	(0.0%)	13	0	(0.0%)		NR
Major/severe hypoglycaemic event – 24wk	Count	2016	0		2184	0			
confirmed hypoglycaemia – 24wkc	Count	2016	10		2184	12			
confirmed hypoglycaemia – 24wkd	Continuous	12		0.8 (SD 1.48)	13		0.9 (SD 0.29)		
confirmed hypoglycaemia – 24wk	Dichotomous	12			13				NSe
Dropouts:									
Total dropouts – 24wk	Dichotomous	12	1	(8.3%)	13	1	(7.7%)		
Dropout due to AEs – 24wk	Dichotomous	12	1	(8.3%)	13	0	(0.0%)		
Insulin:									
Total daily dose (U) – 24wk	Continuous	12		18.2 (SD 5.3)	13		39.2 (SD 12.9)		<0.001
Total daily dose (U/kg) – 24wk	Continuous	12		0.23 (SD 0.06)	13		0.55 (SD 0.19)		<0.001

[a] approximated to nearest integer (percentages only presented in text); approximated to nearest integer (percentages only presented in text)
[b] No of patients
[c] patient day estimated assuming no drop outs and no events calculated using mean number of hypos in each treatment group
[d] hypoglycaemia per patient (mean SD)
[e] across all groups

	Metformin + NPH insulin			NPH insulin				
	N	k	mean	N	k	mean	Δ	p

Blood glucose: HbA1c (%) – 24wk	Continuous	12		8.8 (SD 1)	13		8.4 (SD 1.2)		
HbA1c (%) – 24wk	Mean change	12		-0.7 (SD 1.2)	13		-1.4 (SD 1.6)		NS
HbA1c < 7% or <=7% – 24wk	Dichotomous	12	1	(8.3%)	13	2a	(15.4%)		NR
Body weight: Weight (kg) – 24wk	Continuous	12		76.1 (SD 8)	13		73.3 (SD 15.6)		NS
Weight (kg) – 24wk	Mean change	12		1.7 (SD 2.6)	13		3 (SD 2.8)		
Hypoglycaemic events: Major/severe hypoglycaemic event – 24wkb	Dichotomous	12	0	(0.0%)	13	0	(0.0%)		NRc
Major/severe hypoglycaemic event – 24wk	Count	2016	0		2184	0			
confirmed hypoglycaemia – 24wkd	Count	2016	6		2184	12			
confirmed hypoglycaemia – 24wke	Continuous	12		0.5 (SD 0.93)	13		0.9 (SD 0.29)		
confirmed hypoglycaemia – 24wk	Dichotomous	12			13				NS
Dropouts: Total dropouts – 24wk	Dichotomous	12	0	(0.0%)	13	1	(7.7%)		
Dropout due to AEs – 24wk	Dichotomous	12	0	(0.0%)	13	0	(0.0%)		
Insulin: Total daily dose (U) – 24wk	Continuous	12		21.4 (SD 5.3)	13		39.2 (SD 12.9)		<0.001
Total daily dose (U/kg) – 24wk	Continuous	12		0.28 (SD 0.07)	13		0.55 (SD 0.19)		<0.001

[a] approximated to nearest integer (percentages only presented in text); approximated to nearest integer (percentages only presented in text)
[b] No of patients
[c] no events
[d] patient day estimated assuming no drop outs and no events calculated using mean number of hypos in each treatment group
[e] hypoglycaemia per patient (mean SD)

Comparisons between pairs of treatment was carried out by Mann-Whitney test (quantitative variables) or chi sqaured for qualitative variables using a corrected significance levelfor three contrasts (Bonferroni's correction, p<0.017)

Table 4: Derosa et al. (2009)

General

Phase:
☐ monotherapy
☐ dual therapy
☑ triple therapy
☐ insulin monotherapy
☐ insulin+oral

Parallel / crossover: Crossover

Country: Italy

Authors' conclusions: In addition to having a similar effect to repaglinide on PPG, acarbose appeared to have a more comprehensive positive effect on glucose metabolism compared with repaglinide in this relatively small sample of type 2 diabetic patients when used as add on therapy to sulfonylureas and metformin

Source of funding: Funding from the University of Pavia

Comments: Multicentre, double-blind, cross over trial. Randomisation was carried out using envelopes containing randomisation codes prepared by a statistician. A copy of the code was provided to the person responsible for data analysis. Study drugs were supplied as matching opaque capsules in coded bottles.

Number and characteristics of patients

Total number of patients: 103

Inclusion criteria: type 2 diabetes for at least 6 months, did not have glycaemia control with diet and oral agents such as sulfonlyurea and metformin (Hba1c >=6.5% and PPG >=160 mg/dl)

Exclusion criteria: Patients with a history of ketoacidosis, unstable or rapidly progressive diabetic

	retinopathy, nephropathy, neuropathy, impaired hepatic function, impaired renal function, severe anaemia and patients with serious cardiovascular or cerebrovascular conditions within 6 months before study enrollment. Women who were pregnant, breastfeeding or were of child bearing age and no taking adequate contraceptive precautions were also excluded Pre-randomisation phase: There was a 4 week run-in period during which metformin and sulfonylurea were taken
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** all on oral hypoglycaemic drugs and/or insulin **Details of washout period:** patients were being treated with sulfonylurea + metformin combination therapy
Lifestyle advice	Participants began a controlled energy diet based on ADA recommendations. Standard diet advice was given by a dietician and/or specialist doctor.
Follow-up	**Total follow-up (wks):** 27 **Length of titration period (wks):** 15 **Length of maintenance period (wks):** 12 **Frequency of monitoring appointments:** There was a 4 week run-in period during which metformin and sulfonylurea were taken. After the treatment cross over, drugs were directly administered at the maximum dosage from the beginning of the 16th week, since patients were already compensated for on-going treatment.
Arms	**(1) Metformin + sulfonylurea + repaglinide** N: 51 Treatment duration (wks): 27 Washout period (d): 0 Comments: No specific washout period before cross-over was reported Treatment(s): (a) Metformin (Oral) Mean dose (mg/d): 2500 (b) Sulfonylurea (Oral) Details of dosing regimen: Doses of sulfonylurea at start of the study were: Gliburide 10 ± 2.5 Gliclazide 160 ± 40 Glimepiride 5 ± 1 (c) repaglinide (Oral) – forced titration Set dose (mg/d):6 Details of dosing regimen: 6 mg/day (2 mg three times a day) **(2) Metformin + sulfonylurea +acarbose** N: 52 Treatment duration (wks): 27 Washout period (d): 0 Comments: No specific washout period before cross-over was reported Treatment(s): (a) Metformin (Oral) Mean dose (mg/d): 2000 (b) Sulfonylurea (Oral) Details of dosing regimen: Doses of sulfonylurea at start of the study were: Gliburide 12.5 ± 2.5 Gliclazide 160 ± 80 Glimepiride 5 ± 1 (c) Acarbose (Oral) – forced titration Set dose (mg/d):300 Frequency of dosing: three times a day Details of dosing regimen: 100 mg given three times a day
Outcomes	**General** An ITT analysis was conducted in patients who had received >=1 dose of the study and had subsequent efficacy observation. Patients were included in the safety analysis if they had received >=1 dose of trial medication and had undergone subsequent tolerability observation. Outcomes were only extracted for week 17 (i.e. the first cross-over period) 7 patients did not complete the study (5/52 in the acarbose group and 2/51 in the repaglinide group)
Baseline characteristics	

	Metformin + sulfonylurea + repaglinide			Metformin + sulfonylurea +acarbose				
	N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**

Demographics: Age (years)	Continuous	51		53 (SD 9)	52		55 (SD 11)		
Sex (n male)	Dichotomous	51	25	(49.0%)	52	24	(46.2%)		
Duration of diabetes (yrs)	Continuous	51		3.3 (SD 1.5)	52		3.7 (SD 1.9)		
ITT Blood glucose: HbA1c (%) – 0wk	Continuous	51		8 (SD 0.8)	52		8.2 (SD 0.9)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	51		7.548816 (SD 0.444)	52		7.77084 (SD 0.555)		
Body weight: BMI (kg/m2) – 0wk	Continuous	51		27.2 (SD 0.9)	52		26.7 (SD 0.7)		
Weight (kg) – 0wk	Continuous	51		74.8 (SD 7.5)	52		73.7 (SD 7)		
Blood pressure: Systolic blood pressure (mmHg) – 0wk	Continuous	51		135 (SD 5)	52		136 (SD 6)		
Diastolic blood pressure (mmHg) – 0wk	Continuous	51		90 (SD 5)	52		88 (SD 3)		
Lipids: Total cholesterol (mmol/l) – 0wk	Continuous	51		5.35302 (SD 0.414)	52		5.19786 (SD 0.31)		
HDL cholesterol (mmol/l) – 0wk	Continuous	51		1.08612 (SD 0.181)	52		1.0344 (SD 0.129)		
Triglycerides (mmol/l) – 0wk	Continuous	51		1.5806 (SD 0.361)	52		1.50157 (SD 0.294)		
LDL cholesterol (mmol/l) – 0wk	Continuous	51		3.54282 (SD 0.259)	52		3.46524 (SD 0.181)		

Results

		Metformin + sulfonylurea + repaglinide			**Metformin + sulfonylurea +acarbose**				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Blood glucose: HbA1c (%) – 17wk	Continuous	51			52				NS
Fasting plasma glucose (mmol/l) – 17wk	Continuous	51			52				NS
Body weight: BMI (kg/m2) – 17wk	Continuous	51			52				NS
Weight (kg) – 17wk	Continuous	51			52				NS
Dropouts: Total dropouts – 15wk	Dichotomous	51	1	(2.0%)	52	3	(5.8%)		
Dropout due to AEs – 15wk	Dichotomous	51	1	(2.0%)	52	2	(3.8%)		
Blood pressure: Systolic blood pressure (mmHg) – 17wk	Continuous	51			52				NS
Diastolic blood pressure (mmHg) – 17wk	Continuous	51			52				NS
Lipids: Total cholesterol (mmol/l) – 17wk	Continuous	51			52				NS
HDL cholesterol (mmol/l) – 17wk	Continuous	51			52				NS
Triglycerides (mmol/l) – 17wk	Continuous	51			52				NS
LDL cholesterol (mmol/l) – 17wk	Continuous	51			52				NS
ITT Blood glucose: HbA1c (%) – 15wk	Continuous	50		6.9 (SD 0.4)	49		6.8 (SD 0.3)		

	Fasting plasma glucose (mmol/l) – 15wk	Continuous	50		6.827238 (SD 0.222)	49		6.93825 (SD 0.278)		
	Body weight:									
	BMI (kg/m2) – 15wk	Continuous	50		28.1 (SD 1.3)	49		25.6 (SD 0.4)		
	Weight (kg) – 15wk	Continuous	50		76.5 (SD 8.2)	49		72.3 (SD 6.5)		
	Blood pressure:									
	Systolic blood pressure (mmHg) – 15wk	Continuous	50		134 (SD 4)	49		135 (SD 5)		
	Diastolic blood pressure (mmHg) – 15wk	Continuous	50		90 (SD 5)	49		88 (SD 3)		
	Lipids:									
	Total cholesterol (mmol/l) – 15wk	Continuous	50		5.12028 (SD 0.259)	49		5.01684 (SD 0.207)		
	HDL cholesterol (mmol/l) – 15wk	Continuous	50		1.11198 (SD 0.207)	49		1.11198 (SD 0.207)		
	Triglycerides (mmol/l) – 15wk	Continuous	50		1.44512 (SD 0.26)	49		1.4677 (SD 0.271)		
	LDL cholesterol (mmol/l) – 15wk	Continuous	50		3.33594 (SD 0.129)	49		3.2325 (SD 0.103)		
	As there was no washout period, only data from the first cross-over were extracted ANOVA and ANCOVA were used to test whether change from baseline in outcomes at the end of the 15 and 27 weeks differed between repaglinide and acarbose.									

Table 5: Derosa et al. (2010)

General	**Phase:** ☐ monotherapy ☐ dual therapy ☑ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** Italy **Authors' conclusions:** Pioglitazone reduces the inflammatory response to a glucose challenge more than acarbose in type diabetic patients, already treated with maximal doses of sulfonylurea and metformin **Source of funding:** Unclear funding **Comments:** Multicentre trial. Randomisation by drawing envelopes containing randomisation codes prepared by statistician.
Number and characteristics of patients	**Total number of patients:** 473 **Inclusion criteria:** Eligible patients were taking sulfonlyureas and metformin at various dosages, caucasian type 2 diabetic patients aged 18 years or over, with poor glycaemic control (Hba1c >6.5%). Patients were undergoing dietary control and exercise and were taking oral hypoglycaemic agents. No patients were treated with insulin. **Exclusion criteria:** history of ketoacidosis, unstable or rapidly progressive diabetic retinopathy, nephropathy, neuropathy, impaired hepatic function, impaired renal function, severe anaemia and patients with serious cardiovascular or cerebrovascular conditions within 6 months before study enrollment. Women who were pregnant, breastfeeding or were of child bearing age and no taking adequate contraceptive precautions were also excluded Pre-randomisation phase: 3 month run-in on metformin and sulfonylurea therapy
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** all on oral hypoglycaemic drugs and/or insulin **Details of washout period:** Eligible patients were taking sulfonlyureas and metformin at various dosages (see arm details)
Lifestyle advice	Patients began a controlled eneregy diet based on ADA recommendations. Each centres standard diet advice was given by a dietitian, who provided instruction on dietary intake-recording as part of a behaviour modification program each monthduring the titration period and then every 3 months. Patients were also

	encouraged to increase physical activity by walking briskly or riding a stationary bicycle for 20-30 mins 3-5 times per week.
Follow-up	**Total follow-up (wks):** 38 **Length of titration period (wks):** 12 **Length of maintenance period (wks):** 26 **Frequency of monitoring appointments:** Assessments were made at start of titration, after 3 months, 6 months and at study end
Arms	**(1) Metformin + sulfonylurea + pioglitazone** N: 175 Treatment duration (wks): 38 Washout period (d): 0 Treatment(s): (a) Metformin (Oral) Mean dose (mg/d): 1500 (b) Sulfonylurea (Oral) Details of dosing regimen: mean dose of sulfonylureas were: Gliburide 12.5 ± 2.5 Gliclazide 160 ± 80 Glimepiride 5 ± 1 (c) Pioglitazone (Oral) – forced titration Set dose (mg/d):45 Frequency of dosing: three times a day Details of dosing regimen: Titrated up to 45 mg/day, this was forced upwards over 3 months independently from glycaemic control unless side effects were unacceptable **(2) Metformin + sulfonylurea +acarbose** N: 175 Treatment duration (wks): 38 Washout period (d): 0 Treatment(s): (a) Metformin (Oral) Mean dose (mg/d): 2000 (b) Sulfonylurea (Oral) Details of dosing regimen: mean dose of sulfonylureas were: Gliburide 10.0 ± 2.5 Gliclazide 160 ± 40 Glimepiride 4 ± 1 (c) Acarbose (Oral) – forced titration Set dose (mg/d):300 Details of dosing regimen: Titrated up to 300 mg/day, this was forced upwards over 3 months independently from glycaemic control unless side effects were unacceptable
Outcomes	**General** An ITT analysis was conducted in patients who had received >=1 dose of the study and had subsequent efficacy observation. Patients were included in the tolerability analysis if they had received >=1 dose of trial medication and had undergone subsequent tolerability observation. Outcomes not extracted in this evidence table include measures of insulin resistance, postprandial blood glucose, c-reactive protein, TNF-alpha, sICAM-1, sICAM-1, IL-6 37 (21%) patients discontinued the study in the pioglitazone group and 39 (22%) in the acarbose group
Baseline characteristics	

		Metformin + sulfonylurea + pioglitazone			Metformin + sulfonylurea +acarbose				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Demographics:									
Age (years)	Continuous	175		55 (SD 8)	175		57 (SD 6)		
Sex (n male)	Dichotomous	175	86	(49.1%)	175	87	(49.7%)		
Blood glucose:									
HbA1c (%) – 0wk	Continuous	175		7.9 (SD 0.5)	175		8 (SD 0.6)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	175		7.437804 (SD 0.722)	175		7.326792 (SD 0.666)		
Body weight:									
BMI (kg/m2) – 0wk	Continuous	175		26.18 (SD 0.6)	175		26.97 (SD 0.8)		
Weight (kg) – 0wk	Continuous	175		74.9 (SD 7)	175		75.6 (SD 7.4)		

Blood pressure: Systolic blood pressure (mmHg) – 0wk	Continuous	175		133 (SD 5)	175		135 (SD 6)			
Diastolic blood pressure (mmHg) – 0wk	Continuous	175		86 (SD 4)	175		85 (SD 3)			
Lipids: Total cholesterol (mmol/l) – 0wk	Continuous	175		5.0427 (SD 0.207)	175		5.06856 (SD 0.233)			
HDL cholesterol (mmol/l) – 0wk	Continuous	175		1.13784 (SD 0.129)	175		1.11198 (SD 0.129)			
Triglycerides (mmol/l) – 0wk	Continuous	175		1.30964 (SD 0.294)	175		1.3548 (SD 0.316)			
LDL cholesterol (mmol/l) – 0wk	Continuous	175		3.25836 (SD 0.233)	175		3.28422 (SD 0.259)			

Results

		Metformin + sulfonylurea + pioglitazone			**Metformin + sulfonylurea +acarbose**				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Blood glucose: HbA1c (%) – 12wka	Continuous	175		7.1 (SD 0.3)	175		7.5 (SD 0.4)		
HbA1c (%) – 38wka	Continuous	175		6.5 (SD 0.2)	175		7.1 (SD 0.3)		<0.05
HbA1c (%) – 38wka	Continuous	138		6.5 (SD 0.2)	136		7.1 (SD 0.3)		<0.05
Fasting plasma glucose (mmol/l) – 12wk	Continuous	175		6.993756 (SD 0.555)	175		7.160274 (SD 0.611)		
Fasting plasma glucose (mmol/l) – 38wk	Continuous	138		6.549708 (SD 0.389)	136		6.827238 (SD 0.5)		NS
Fasting plasma glucose (mmol/l) – 38wk	Continuous	175		6.549708 (SD 0.389)	175		6.827238 (SD 0.5)		NS
Body weight: BMI (kg/m2) – 12wk	Continuous	175		26.85 (SD 0.7)	175		26.57 (SD 0.7)		
BMI (kg/m2) – 38wk	Continuous	175		27.13 (SD 0.8)	175		26.14 (SD 0.6)		<0.05
BMI (kg/m2) – 38wk	Continuous	138		27.13 (SD 0.8)	136		26.14 (SD 0.6)		<0.05
Weight (kg) – 12wk	Continuous	175		75.8 (SD 7.5)	175		75 (SD 7.2)		
Weight (kg) – 38wk	Continuous	138		76.3 (SD 7.8)	136		74.4 (SD 6.6)		<0.05
Weight (kg) – 38wk	Continuous	175		76.3 (SD 7.8)	175		74.4 (SD 6.6)		<0.05
Dropouts: Total dropouts – 38wk	Dichotomous	175	37	(21.1%)	175	39	(22.3%)		
Dropout due to AEs – 38wkb	Dichotomous	175	16	(9.1%)	175	16	(9.1%)		
Dropout due to hypoglycaemia – 38wk	Dichotomous	175	7	(4.0%)	175	5	(2.9%)		
drop out due to other GI event – 38wkc	Dichotomous	175	7	(4.0%)	175	7	(4.0%)		
Blood pressure: Systolic blood pressure (mmHg) – 12wk	Continuous	175		132 (SD 5)	175		134 (SD 6)		
Systolic blood pressure (mmHg) – 38wk	Continuous	175		131 (SD 4)	175		134 (SD 6)		NS
Systolic blood pressure (mmHg) – 38wk	Continuous	138		131 (SD 4)	136		134 (SD 6)		NS
Diastolic blood pressure (mmHg) – 12wk	Continuous	175		85 (SD 4)	175		85 (SD 3)		
Diastolic blood pressure (mmHg) – 38wk	Continuous	175		83 (SD 3)	175		84 (SD 4)		NS
Diastolic blood pressure (mmHg) – 38wk	Continuous	138		83 (SD 3)	136		84 (SD 4)		NS

Lipids:									
Total cholesterol (mmol/l) – 12wk	Continuous	175		4.96512 (SD 0.207)	175		5.12028 (SD 0.259)		
Total cholesterol (mmol/l) – 38wk	Continuous	138		4.9134 (SD 0.181)	136		5.0427 (SD 0.233)		NS
Total cholesterol (mmol/l) – 38wk	Continuous	175		4.9134 (SD 0.181)	175		5.0427 (SD 0.233)		NS
HDL cholesterol (mmol/l) – 12wk	Continuous	175		1.1637 (SD 0.129)	175		1.11198 (SD 0.129)		
HDL cholesterol (mmol/l) – 38wk	Continuous	138		1.18956 (SD 0.181)	136		1.13784 (SD 0.129)		NS
HDL cholesterol (mmol/l) – 38wk	Continuous	175		1.18956 (SD 0.181)	175		1.13784 (SD 0.129)		NS
Triglycerides (mmol/l) – 12wk	Continuous	175		1.23061 (SD 0.26)	175		1.33222 (SD 0.305)		
Triglycerides (mmol/l) – 38wk	Continuous	138		1.09513 (SD 0.215)	136		1.2419 (SD 0.237)		NS
Triglycerides (mmol/l) – 38wk	Continuous	175		1.09513 (SD 0.215)	175		1.2419 (SD 0.237)		NS
LDL cholesterol (mmol/l) – 12wk	Continuous	175		3.2325 (SD 0.207)	175		3.31008 (SD 0.259)		
LDL cholesterol (mmol/l) – 38wk	Continuous	138		3.18078 (SD 0.155)	136		3.28422 (SD 0.233)		NS
LDL cholesterol (mmol/l) – 38wk	Continuous	175		3.18078 (SD 0.155)	175		3.28422 (SD 0.233)		NS

[a] trial reported SD
[b] Any AE including hypo and GI event
[c] GI event

Baseline values were exatracted from the beginning of titration. SD is reported.

Continuous variables were compared using ANOVA. Intervention effects were adjusted for additional potential confounders using ANCOVA. Where data was not normally distributed, Kolmogorov-Smirnov test was used.

Table 6: Diamant et al. (2010)

General

Phase:
☐ monotherapy
☐ dual therapy
☑ triple therapy
☐ insulin monotherapy
☐ insulin+oral

Parallel / crossover: Parallel

Country: USA, Europe, Russia, Australia, Korea, Taiwan and Mexico

Authors' conclusions: Once weekly exenatide is an important therapeutic option for patients for whom risk of hypoglycaemia, weight loss and convenience are particular concerns

Source of funding: Amylin Pharmaceuticals and Eli Lily

Comments: Open label study. Random assignment was achieved with a computer-generated randomisation sequence thatwas administered by the sponsor via an automated voice response system. Study participants and clinical investigators were not masked to treatment assignment, but investigators analysing data were

Number and characteristics of patients

Total number of patients: 456

Inclusion criteria: type 2 diabetes aged 18 years and over with suboptimum glycaemic control despite maximum tolerated doses of metformin and sulfonylurea for 3 months or longer. Hba1c between 7.1 and 11%, BMI between 25 and 45 kg/m2 and a stable bodyweight for 3 months or more. Participants had to have been treated with a stable dose of metformin of 1500 mg or more per day for 8 or more weeks before screening

Exclusion criteria: more than 3 episodes of major hypoglycaemia within 6 months of screening, treatment within 4 weeks with systemic glucocorticoids, treatment for longer than 2 weeks with insulin, thiazolidinediones, alpha-glucosidase inhibitors, meglitinides, exenatide twice a day formulation, DPP-4s or pramlintide within 3 months of screening

Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** all on oral hypoglycaemic drugs and/or insulin **Details of washout period:** All patients were taking metformin with or without sulfonylurea-subgroup analyses were extracted for those taking metformin + sulfonylurea
Lifestyle advice	-
Follow-up	**Total follow-up (wks):** 84 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 84 **Frequency of monitoring appointments:** -
Arms	**(1) Metformin + sulfonylurea + exenatide (once weekly)** N: 233 Treatment duration (wks): 84 Washout period (d): 0 Treatment(s): (a) Metformin (Oral) Details of dosing regimen: Pre-study doses of metformin and sulfonylurea not reported (b) Sulfonylurea (Oral) Details of dosing regimen: Pre-study doses of metformin and sulfonylurea not reported (c) Exenatide (once weekly) (Subcutaneous) – fixed-dose Set dose (mg/d):2 Frequency of dosing: once weekly Details of dosing regimen: 2mg dose was injected into abdominal subcutaneous tissue at randomisation and once a week (within 2 days of date of first injection) thereafter **(2) Metformin + sulfonylurea + insulin glargine** N: 223 Treatment duration (wks): 84 Washout period (d): 0 Treatment(s): (a) Metformin (Oral) Details of dosing regimen: Patients continued their stable metformin dosing until week 26 (no dosing reported) (b) Sulfonylurea (Oral) (c) Insulin glargine (Subcutaneous) – flexible-dose (dose-adjusted) Details of dosing regimen: The 26-week treatment duration allowed for implementation of the INITIATE (Initiate Insulin by Aggressive Titration and Education) dosing algorithm for insulin glargine. Patients started insulin glargine treatment with 10 IU per day, measured fastingblood glucose concentrations every morning, and were instructed to adjust insulin doses to achieve a target glucose of 4·0–5·5 mmol/L. Patients and investigators were asked to adhere to titration targets; however, there was no central supervision to enforce titration. Insulin glargine was injected at the same time every day, preferably at bedtime.
Outcomes	**General** Outcomes that were reported in patients on metformin and sulfonylurea combined (not metformin alone) were extracted. No outcomes from the original 26 week trial reported outcomes in this way and so no outcomes for this time point were extracted. For the extension study (Diamant 2012), data collected after any treatment regimen changes at 48 weeks or after (other then insulin glargine titration) were excluded from the analyses 60 (25.8%) patients discontinued before week 84 in the exenatide arm and 61 (27.4%) patients in the insulin arm discontinued **Hypoglycaemic events** Minor (confirmed) hypoglycaemia (defined minor hypoglycaemia as any time a patient felt that they had a sign or symptom, associated with concurrent blood glucose lower than 3·0 mmol/L, that was either selftreated by the patient or resolved independently.) Major/severe hypoglycaemic event (Major hypoglycaemia was classifi ed as any episode with symptoms resulting in loss of consciousness or seizure that showed prompt recovery after administration of glucose, or documented blood glucose lower than 3·0 mmol/L necessitating the assistance of another person because of severe impairment in consciousness or behaviour) symptomatic (unconfirmed) hypoglycaemia (Symptoms of hypoglycaemia were defined as any sign or symptom reported by the patient, but not confi rmed with a blood glucose measurement)
Baseline characteristics	

	Metformin + sulfonylurea + exenatide (once weekly)			Metformin + sulfonylurea + insulin glargine				
	N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**

Demographics:										
Age (years)	Continuous	233		58 (SD 10)	223		58 (SD 9)			
Duration of diabetes (yrs)	Continuous	233		8 (SD 6)	223		7.8 (SD 6)			
Blood glucose:										
HbA1c (%)	Continuous	233		8.3 (SD 1.1)	223		8.3 (SD 1)			
Fasting plasma glucose (mmol/l)	Continuous	233		9.9 (SD 2.5)	223		9.7 (SD 2.7)			
Body weight:										
BMI (kg/m2)	Continuous	233		32 (SD 5)	223		32 (SD 5)			
Weight (kg)	Continuous	233		91.2 (SD 18.6)	223		90.6 (SD 16.4)			
Previous blood glucose lowering drugs:										
Metformin	Dichotomous	233	164	(70.4%)	223	157	(70.4%)			
Metformin + Sulfonylurea	Dichotomous	233	69	(29.6%)	223	66	(29.6%)			

Results

		Metformin + sulfonylurea + exenatide (once weekly)			Metformin + sulfonylurea + insulin glargine				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Metformin + sulfonylurea									
Hypoglycaemic events:									
Minor (confirmed) hypoglycaemia – 84wka	Dichotomous	69	17	(24.6%)	66	36	(54.5%)		<0.001
Major/severe hypoglycaemic event – 84wk	Dichotomous	69	0	(0.0%)	66	0	(0.0%)		b
symptomatic (unconfirmed) hypoglycaemia – 84wka	Dichotomous	69	25	(36.2%)	66	37	(56.1%)		0.025
Nocturnal hypoglycaemia – 84wka	Dichotomous	69	9	(13.0%)	66	31	(47.0%)		<0.001

[a] Data extracted from table in Diamant (2012); No of patients
[b] NR

Table 7: Duran et al. (2009)

General	**Phase:** ☐ monotherapy ☐ dual therapy ☑ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** Turkey **Authors' conclusions:** Repaglinide and acarbose were equally effective when combined with insulin glargine for obese type 2 diabetic patients controlled inadequately with OAD alone. Furthermore acarbose seems to have advantages over repaglinide concerning weight gain and severe hypoglycaemic attacks **Source of funding:** Not reported **Comments:** Single-centre, open labelled, randomised trial
Number and characteristics	**Total number of patients:** 40 **Inclusion criteria:** type 2 diabetes, 18-65 years with a BMI 27-35 kg/m2, FBG>=7.7 mmol/l, Hba1c >=9%

of patients	despite maximal OAD combination therapy **Exclusion criteria:** type 1 or gestational diabetes, pregnancy, lactation, hypoglycaemia unawareness, hepatic impairment, heart failure, renal impairment, alcohol abuse, gastric surgery, lactose intolerance, taking any medications that may affect glycaemic control and allergy to trial medication Pre-randomisation phase: There was a 2 week run-in period and 13 week maintenance period
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** all on oral hypoglycaemic drugs and/or insulin **Details of washout period:** All taking maximal OAD therapy with inadequate control, during the 2 week lead in period all participants continued taking their previous OADs. Patients were included if they had FBG>=7.7 mmol/l at the end of the run-in period despite OAD combination therapies and regular exercise
Lifestyle advice	-
Follow-up	**Total follow-up (wks):** 13 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 13 **Frequency of monitoring appointments:** Patients were invited for visits 3 and 4 at monthly intervals where they were questioned about dietary adaption and exercise capacities
Arms	**(1) Insulin glargine + repaglinide** N: 20 Treatment duration (wks): 13 Washout period (d): 0 Comments: Patients were randomised after discontinuing previous OAD therapy Treatment(s): (a) Insulin glargine (Subcutaneous) – flexible-dose (dose-adjusted) Mean dose (mg/d): 0.34 Frequency of dosing: once a day Details of dosing regimen: insulin glargine once per day. The target for FBG was 4.4-6.6 mmol/l. Insulin dose was increased 2 units for every 1.1 mmol/l above 6. mmol/l until 10 mmol/l. If over 10 mmol/l, 8 extra units were prescribed. If BG<4.4 mmol/l, a 2 unit decrement was offered. Titrations were done every other day Insulin dose was 0.34 ± 0.12 IU/kg (b) repaglinide (Oral) – fixed-dose Set dose (mg/d):6 Frequency of dosing: three times a day Details of dosing regimen: 2 mg tid **(2) Insulin glargine + acarbose** N: 18 Treatment duration (wks): 13 Washout period (d): 0 Comments: Patients were randomised after discontinuing previous OAD therapy Treatment(s): (a) Insulin glargine (Subcutaneous) – flexible-dose (dose-adjusted) Mean dose (mg/d): 0.32 Frequency of dosing: once a day Details of dosing regimen: See insulin + repaglinide for dosing details Insulin dose was 0.32 ± 0.17 IU/kg (b) Acarbose (Oral) – fixed-dose Set dose (mg/d):300 Frequency of dosing: three times a day Details of dosing regimen: 100 mg tid
Outcomes	**General** Outcomes not extracted in this evidence table include SMBG levels (8 point profiles). 2 patients in the insulin + acarbose group withdrew from the study No details of ITT analysis (assumed analysis conducted in all those completed) **Hypoglycaemic events** **symptomatic hypoglycaemia was defined as BG <3 mmol/l with symptoms** Major/severe hypoglycaemic event (Severe hypoglycaemia was defined as BG <2.2 mmol/l with or without symptoms or requiring third party assistance)
Baseline characteristics	

	Insulin glargine + repaglinide			Insulin glargine + acarbose				
	N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**

Demographics:										
Age (years)	Continuous	20		53.5 (SD 5.9)	18		55.1 (SD 7.2)			
Sex (n male)	Dichotomous	20	12	(60.0%)	18	8	(44.4%)			
Duration of diabetes (yrs)	Continuous	20		10.8 (SD 5.4)	18		9.6 (SD 4.5)			
Blood glucose:										
HbA1c (%) – 0wk	Continuous	20		10.9 (SD 1.4)	18		11 (SD 1.4)			
Fasting plasma glucose (mmol/l)	Continuous	20		11.9 (SD 2.7)	18		11.1 (SD 2.5)			
Body weight:										
BMI (kg/m2)	Continuous	20		30.5 (SD 2.6)	18		30.5 (SD 2.6)			
Weight (kg) – 0wka	Continuous	20		86.0832 (SD 7.34)	18		86.0832 (SD 7.34)			
Blood pressure:										
Systolic blood pressure (mmHg)	Continuous	20		131 (SD 15.5)	18		132.2 (SD 19.8)			
Diastolic blood pressure (mmHg)	Continuous	20		79 (SD 9.1)	18		80 (SD 10.8)			
Insulin:										
Total daily dose (U/kg) – 0wk	Continuous	20		0.34 (SD 0.12)	18		0.32 (SD 0.17)			

[a] estimated from BMI assuming mean height of 1.68m

Results

		Insulin glargine + repaglinide			Insulin glargine + acarbose				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Blood glucose:									
HbA1c (%) – 0wk	Continuous	20			18				NS
HbA1c (%) – 13wk	Continuous	20		7.7 (SD 1.1)	18		8.1 (SD 1.4)		
Body weight:									
Weight (kg) – 0wk	Continuous	20			18				NR
Weight (kg) – 13wk	Mean change	20		2.9 (SD 4.2)	18		0.8 (SD 3.2)		
Hypoglycaemic events:									
All hypoglycaemic events (no events) – 0wk	Dichotomous	20			18				NR
All hypoglycaemic events (no events) – 13wka	Count	1820	14		1729	14			
All hypoglycaemic events (no events) – 13wkb	Continuous	20		0.68 (SD 0.76)	18		0.77 (SD 1.12)		
Major/severe hypoglycaemic event – 0wk	Dichotomous	20			18				NR
Major/severe hypoglycaemic event – 13wkc	Dichotomous	20	2	(10.0%)	18	0	(0.0%)		
Adverse events:									
Flatulence – 0wk	Dichotomous	20			18				NR
Flatulence – 13wk	Dichotomous	20	3	(15.0%)	18	12	(66.7%)		
Injection site – 0wk	Dichotomous	20			18				NR
Injection site – 13wk	Dichotomous	20	5	(25.0%)	18	4	(22.2%)		
Dropouts:									
Total dropouts – 13wk	Dichotomous	20	0	(0.0%)	20	2	(10.0%)		
Insulin:									
Total daily dose (U/kg) – 0wk	Continuous	20			18				NS
Total daily dose (U/kg) – 13wk	Continuous	20		0.33 (SD 0.13)	18		0.36 (SD 0.18)		

[a] Person days estimated assuming dropout halfway through study and no of events calculated using mean hypos per month
[b] episodes per month
[c] No of patients

	Kruskal wallis and Mann Whitney U tests were used for statistical analysis. Wilcoxon test was used for intragroup comparisons, chi squared and Fischers test was used to compare categorical data.

Table 8: Eliaschewitz et al. (2006)

General	**Phase:** ☐ monotherapy ☐ dual therapy ☑ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** 56 centres in Argentina, Brazil, Chile, Colombia, Guatemala, Mexico, Paraguay, Peru, Uruguay and Venezuela **Authors' conclusions:** In patients with type 2 diabetes, inadequately controlled on OADs, once daily insulin glargine + glimepiride is effective in improving metabolic control with a reduced incidence of nocturnal hypoglycaemia compared with NPH insulin **Source of funding:** Study was supported by Sanofi-Aventis **Comments:** Open label, randomised, multicentre trial
Number and characteristics of patients	**Total number of patients:** 481 **Inclusion criteria:** men and women aged <=75 years with a BMI <=35 kg/m2 were enrolled if they had type 2 diabetes and had failed to achieve adequate control on OADs (Hba1c >=7.5% and <=10.5%). Patients were required to have been receiveing OADs (any sulfonylureas or a combination of sulfonylureas with other OADs) for at least 6 months. The previous doses were required to have been at least equivalent to glimepiride 3 mg. Patients also had to be willing to receive tight antidiabetic therapy **Exclusion criteria:** previous treatment with any insulin in the 3 months before the study, pregnant or breastfeeding, likely to require treatment with drugs not permitted by the study protocol (e.g. beta blockers), had been enrolled in a previous study, had received the study drug within 3 months of the study or had a history of alchohol abuse Pre-randomisation phase: There was a 4 week screening phase and a 24 week treatment period
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** all on oral hypoglycaemic drugs and/or insulin **Details of washout period:** During screening, patients stayed on their previous OAD until confirmtaion of meeting study inclusion criteria at which point they were switched to glimepiride
Lifestyle advice	-
Follow-up	**Total follow-up (wks):** 28 **Length of titration period (wks):** 6 **Length of maintenance period (wks):** 24 **Frequency of monitoring appointments:** -
Arms	**(1) Insulin glargine +glimepiride** N: 231 Treatment duration (wks): 24 Washout period (d): 0 Comments: During screening, patients stayed on their previous OAD until confirmtaion of meeting study inclusion criteria at which point they were switched to glimepiride Treatment(s): (a) Insulin glargine (Subcutaneous) – flexible-dose (dose-adjusted) Mean dose (mg/d): 16.2 Frequency of dosing: once a day Details of dosing regimen: Bedtime injection. Insulin doses were titrated during the first 6 weeks of treatment to achieve FBG <= 5.5 mmol/l (b) Sulfonylurea (Oral) – fixed-dose Set dose (mg/d):4 Frequency of dosing: once a day Details of dosing regimen: 4 mg od this dose was kept stable throughout the study **(2) Insulin NPH +glimepiride** N: 250 Treatment duration (wks): 24 Washout period (d): 0 Treatment(s): (a) NPH insulin (Subcutaneous) – flexible-dose (dose-adjusted) Mean dose (mg/d): 14.9

Frequency of dosing: once a day
Details of dosing regimen: see insulin glargine + glimepiride for dosing details

(b) Sulfonylurea (Oral) – fixed-dose

Set dose (mg/d):4
Frequency of dosing: once a day
Details of dosing regimen: 4 mg od this dose was kept stable throughout the study

Outcomes

General

Outcomes not extracted in this evidence table include satisfaction

13/231 (5.6%) patients in the glargine group and 6/250 (2.4%) in the NPH group discontinued the study

Analyses were conducted in the full analysis population which included all randomised patients who received at least one dose of the study medication and had at least one primary or secondary efficacy outcome value recorded during the treatment phase. The per protocol analysis included all patients from the full set except those with major protocol deviations. The safety population included all patients randomised who received at least one dose of study medication.

Hypoglycaemic events

Major/severe hypoglycaemic event (severe events were defined as symptoms consistent with hypoglycaemia requiring assistance from another person and associated with BG <2.8 mmol/l or with prompt recovery after oral carbohydrate or IV glucose/glucagons))

Symptomatic hypoglycaemia (symptomatic events were categorised as mild (BG 2.8-4.2 mmol/l), moderate (BG <2.8 mmol/l) or severe. Symptomatic confirmed events were those associated with FBG <=4.2 mmol/l)

Nocturnal (symptomatic) (symptomatic nocturnal hypoglycaemia was defined as an event that occurred while the patient was asleep between bedtime and getting up in the morning)

Baseline characteristics

		Insulin glargine +glimepiride			Insulin NPH +glimepiride				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	231		56.1 (SD 9.9)	250		57.1 (SD 9.6)		
Sex (n male)	Dichotomous	231	99	(42.9%)	250	95	(38.0%)		
Duration of diabetes (yrs)	Continuous	231		10.3 (SD 6.4)	250		10.8 (SD 6.4)		
Blood glucose: HbA1c (%) – 0wk	Continuous	231		9.1 (SD 1)	250		9.2 (SD 0.9)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	231		11.4 (SD 3.2)	250		10.7 (SD 3.1)		
Body weight: BMI (kg/m2)	Continuous	231		27.3 (SD 3.7)	250		27.2 (SD 4)		
Insulin: Total daily dose (U) – 0wk	Continuous	231		16.2 (SD 8.3)	250		14.9 (SD 7.2)		

Results

		Insulin glargine +glimepiride			Insulin NPH +glimepiride				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 24wk	Continuous	231		7.65 (SD 1.3)	250		7.78 (SD 1.29)		
HbA1c (%) – 24wk	Mean change	231		-1.38 (SD 1.32)	250		-1.44 (SD 1.33)	MD=-0.047 (CI: -0.267, 0.173)	a
HbA1c (%) – 24wk	Mean change	231		-1.38 (SD 1.32)	250		-1.44 (SD 1.33)	MD=-0.029 (CI: -0.245, 0.187)	b
Fasting plasma glucose (mmol/l) – 24wk	Continuous	231		6.4164936 (SD 2)	250		6.632967 (SD 2.45)		NS

Fasting plasma glucose (mmol/l) – 24wkc	Continuous	231		6.4 (SD 2)	250		6.6 (SD 2.5)		NS
Fasting plasma glucose (mmol/l) – 24wk	Continuous	231		6.4 (SD 2) c	250		6.632967 (SD 2.45)		NS
Fasting plasma glucose (mmol/l) – 24wk	Mean change	231		-4.8 (SD 3.7)	250		-4.1 (SD 3.7)		
Fasting plasma glucose (mmol/l) – 24wk	Continuous	231		6.4164936 (SD 2)	250		6.6 (SD 2.5) c		NS
Hba1c<=7.5% – 24wk	Dichotomous	231	115	(49.8%)	250	118	(47.2%)		NS
FBG <=100 mg/dl – 24wk	Dichotomous	231	96	(41.6%)	250	98	(39.2%)		NS
Hypoglycaemic events:									
Major/severe hypoglycaemic event – 24wkd	Continuous	231		0.1	250		0.2		
Major/severe hypoglycaemic event – 24wke	Dichotomous	231	6	(2.6%)	250	11	(4.4%)	RR=1.020 (CI: 3682.845, 0.000)	0.303
Major/severe hypoglycaemic event – 24wkf	Count	37716	10		41496	23			
Symptomatic hypoglycaemia – 24wke	Dichotomous	231	122	(52.8%)	250	157	(62.8%)	RR=1.270 (CI: 77.869, 0.021)	0.042
Symptomatic hypoglycaemia – 24wkf	Count	37716	517		41496	819			
Symptomatic hypoglycaemia – 24wkd	Continuous	231		5	250		7.2		
Nocturnal (confirmed) – 24wkd	Continuous	231		0.8	250		2.3		
Nocturnal (confirmed) – 24wke	Dichotomous	231	39	(16.9%)	250	75	(30.0%)	RR=1.190 (CI: 283.867, 0.005)	<0.01
Nocturnal (confirmed) – 24wkf	Count	37716	83		41496	262			
Nocturnal (symptomatic) – 24wkd	Continuous	231		1.1	250		3.1		
Nocturnal (symptomatic) – 24wke	Dichotomous	231	47	(20.3%)	250	87	(34.8%)	RR=1.220 (CI: 248.768, 0.006)	<0.001
Nocturnal (symptomatic) – 24wkf	Count	37716	114		41496	353			
Adverse events:									
Any adverse event(s) – 24wkg	Dichotomous	231	137	(59.3%)	250	150	(60.0%)		NR
Any serious adverse event(s) – 24wkg	Dichotomous	231	10	(4.3%)	250	10	(4.0%)		NR
Study drug-related adverse event – 24wkg	Dichotomous	231	39	(16.9%)	250	31	(12.4%)		NR

	Injection site – 24wk	Dichotomous	231	19	(8.2%)	250	17	(6.8%)		NR
	Dropouts: Total dropouts – 24wk	Dichotomous	231	13	(5.6%)	250	6	(2.4%)		
	Dropout due to AEs – 24wk	Dichotomous	231	2	(0.9%)	250	0	(0.0%)		
	Insulin: Total daily dose (U) – 24wk	Continuous	231		32.6 (SD 17)	250		31.2 (SD 16.4)		NS

[a] per protocol analysis
[b] full analysis population
[c] reported in paper
[d] events per patient year; no SD reported
[e] No of patients
[f] person days estimated assuming dropout halfway through trial and no of events calculated using reported rates
[g] No patients

The primary analysis (Hba1c) was anlysed using ANCOVA with treatment and country as fixed effects and baseline values as a covariate. Catergorical variables were analysed using Cochran-Mantel-Haenzel tests. P-values for between group comparisons for adverse events were not reported.

Table 9: Fritsche A,Schweitzer MA,Haring (2003)

General	**Phase:** ☐ monotherapy ☐ dual therapy ☑ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** 13 European countries **Authors' conclusions:** The risk for nocturnal hypoglycemia was lower with glimepiride in combination with morning and bedtime insulin glargine than with glimepiride in combination with bedtime NPH insulin in patients with type 2 diabetes. Morning insulin glargine provided better glycemic control than did bedtime insulin glargine or bedtime NPH insulin **Source of funding:** Aventis Pharma **Comments:** open-label, randomized, controlled, multinational, multicenter, parallel-group clinical trial. The randomisation schedule generated by the sponsor, eligible patients were linked sequentially to treatment codes allocated at random.
Number and characteristics of patients	**Total number of patients:** 700 **Inclusion criteria:** Criteria for study inclusion were as follows: 1) type 2 diabetes, 2) age younger than 75 years, 3) body mass index less than 35 kg/m2, and 4) previous oral therapy with any sulfonylurea as monotherapy or in combination with metformin or acarbose. Furthermore, the fasting blood glucose level had to be 6.7 mmol/L or greater, and the HbA1c level had to be between 7.5% and 10.5% **Exclusion criteria:** Main exclusion criteria were as follows: 1) pregnancy or breast-feeding, 2) pretreatment with insulin or any investigational drugs within the previous 3 months, or 3) presence of any clinically relevant somatic or mental diseases. Pre-randomisation phase: Patients with type 2 diabetes who did not achieve good metabolic control while receiving oral antidiabetic drugs had their oral agents replaced by 3 mg of glimepiride for 4 weeks and were then randomly assigned
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** all on oral hypoglycaemic drugs and/or insulin **Details of washout period:** Before starting the study patients discontinued use of their previous oral antidiabetic drug treatment and received 3 mg of glimepiride in the morning
Lifestyle advice	-
Follow-up	**Total follow-up (wks):** 28 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 24

Frequency of monitoring appointments: During the treatment phase, patients visited the investigation sites 1, 2, 3, 4, 6, 8, 12, 16, 20, and 24 weeks after randomisation.

Arms

(1) NPH insulin (bedtime) + glimepiride

N: 234

Treatment duration (wks): 24
Washout period (d): 0
Comments: Before starting the study patients discontinued use of their previous oral antidiabetic drug treatment and received 3 mg of glimepiride in the morning

Treatment(s): (a) NPH insulin (Subcutaneous) – flexible-dose (dose-adjusted)
Details of dosing regimen: When combination therapy was initiated, insulin glargine or NPH insulin was injected subcutaneously once daily. The insulin dose for the first day of the treatment phase was calculated according to the formula of Holman and Turner. During the treatment phase, the insulin dose was titrated every visit by using a predefined regimen: If the fasting blood glucose level was greater than 5.6, 6.7, 7.8, or 8.9 mmol/L (>100, 120, 140, 160 mg/dL) for at least 1 of 2 consecutive days before the visit with no hypoglycemia, the insulin dose was increased by 2, 4, 6, or 8 units, respectively
(b) Sulfonylurea (Oral) – fixed-dose
Set dose (mg/d):3
Details of dosing regimen: Doses of glimepiride remained unchanged throughout the study.

(2) Insulin glargine (bedtime) + glimepiride

N: 229

Treatment duration (wks): 24
Washout period (d): 0

Treatment(s): (a) Insulin glargine (Subcutaneous) – flexible-dose (dose-adjusted)
Details of dosing regimen: see NPH + glimepiride for details of dosing
(b) Sulfonylurea (Subcutaneous) – fixed-dose
Set dose (mg/d):3
Details of dosing regimen: Doses of glimepiride remained unchanged throughout the study.

(3) Insulin glargine (morning) + glimepiride

N: 237

Treatment duration (wks): 24
Washout period (d): 0

Treatment(s): (a) Insulin glargine (Subcutaneous) – flexible-dose (dose-adjusted)
Details of dosing regimen: see NPH + glimepiride for details of dosing
(b) Sulfonylurea (Oral) – fixed-dose
Set dose (mg/d):3
Details of dosing regimen: Doses of glimepiride remained unchanged throughout the study.

Outcomes

General

Outcomes not extracted in this evidence table include diurnal glucose profiles

Analyses were completed in the ITT (full analysis) set

2/234 in the NPH group, 2/229 in the bedtime glargine and 1/237 were not included in the full analysis set. 27/234, 17/229 and 11/237 discontinued the intervention.

Total drop out rates have not been extracted as they do not correlate with the attrition rates due to adverse events.

Hypoglycaemic events

Major/severe hypoglycaemic event (Severe hypoglycemia was defined as an event with symptoms consistent with hypoglycemia that required the assistance of another person and that was associated with a blood glucose level less than 2.8 mmol/L or that was followed by prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration.)

Symptomatic hypoglycaemia (Hypoglycemia was defined as symptomatic or asymptomatic (blood glucose level < 4.2 mmol/L [<75mg/dL]))

Nocturnal hypoglycaemia (Nocturnal hypoglycemia was defined as hypoglycemia that occurs while the patient is asleep—between bedtime after the evening injection and before the patient awakes in the morning)

Baseline characteristics

		NPH insulin (bedtime) + glimepiride			Insulin glargine (bedtime) + glimepiride			Δ	p
		N	k	mean	N	k	mean		
Full analysis set (FAS) or efficacy analysis pop									
Demographics:									
Age (years)	Continuous	232		62 (SD 9)	227		60 (SD 9)		
Sex (n male)	Dichotomous	232	119	(51.3%)	227	132	(58.1%)		

Duration of diabetes (yrs)	Continuous	232		med: 9.3 [rng 1–39]	227		med: 8.2 [rng 1–51]		
Blood glucose:									
HbA1c (%) – 0wk	Continuous	232		9.1 (SD 1.1)	227		9.1 (SD 1)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	232		12.2 (SD 3.2)	227		12 (SD 2.9)		
Body weight:									
BMI (kg/m2) – 0wk	Continuous	232		28.9 (SD 3.9)	227		28.7 (SD 3.9)		
Weight (kg) – 0wk	Continuous	232		81 (SD 14.9)	227		82.1 (SD 13.6)		
Insulin:									
Total daily dose (U) – 0wk	Continuous	232		19 (SD 11)	227		20 (SD 11)		

		NPH insulin (bedtime) + glimepiride			Insulin glargine (morning) + glimepiride			Δ	p
		N	k	mean	N	k	mean		
Full analysis set (FAS) or efficacy analysis pop									
Demographics:									
Age (years)	Continuous	232		62 (SD 9)	236		61 (SD 9)		
Sex (n male)	Dichotomous	232	119	(51.3%)	236	122	(51.7%)		
Duration of diabetes (yrs)	Continuous	232		med: 9.3 [rng 1–39]	236		med: 9 [rng 0–38]		
Blood glucose:									
HbA1c (%) – 0wk	Continuous	232		9.1 (SD 1.1)	236		9.1 (SD 1)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	232		12.2 (SD 3.2)	236		12.1 (SD 3)		
Body weight:									
BMI (kg/m2) – 0wk	Continuous	232		28.9 (SD 3.9)	236		28.6 (SD 4.5)		
Weight (kg) – 0wk	Continuous	232		81 (SD 14.9)	236		80.7 (SD 15.8)		
Insulin:									
Total daily dose (U) – 0wk	Continuous	232		19 (SD 11)	236		19 (SD 11)		

		Insulin glargine (bedtime) + glimepiride			Insulin glargine (morning) + glimepiride			Δ	p
		N	k	mean	N	k	mean		
Full analysis set (FAS) or efficacy analysis pop									
Demographics:									
Age (years)	Continuous	227		60 (SD 9)	236		61 (SD 9)		
Sex (n male)	Dichotomous	227	132	(58.1%)	236	122	(51.7%)		
Duration of diabetes (yrs)	Continuous	227		med: 8.2 [rng 1–51]	236		med: 9 [rng 0–38]		
Blood glucose:									
HbA1c (%) – 0wk	Continuous	227		9.1 (SD 1)	236		9.1 (SD 1)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	227		12 (SD 2.9)	236		12.1 (SD 3)		
Body weight:									
BMI (kg/m2) – 0wk	Continuous	227		28.7 (SD 3.9)	236		28.6 (SD 4.5)		
Weight (kg) – 0wk	Continuous	227		82.1 (SD 13.6)	236		80.7 (SD 15.8)		
Insulin:									
Total daily dose (U) – 0wk	Continuous	227		20 (SD 11)	236		19 (SD 11)		

Results

		NPH insulin (bedtime) + glimepiride			Insulin glargine (bedtime) + glimepiride				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: Hba1c<=7.5% – 24wk	Dichotomous	234			229				0.022a
Hypoglycaemic events: All hypoglycaemic events (no events) – 24wk	Dichotomous	234			229				>0.2a
Major/severe hypoglycaemic event – 24wk	Dichotomous	234			229				>0.2a
Major/severe hypoglycaemic event – 24wk	Count	39144	6		38304	13			
Symptomatic hypoglycaemia – 24wk	Dichotomous	234			229				0.002a
Nocturnal hypoglycaemia – 24wk	Dichotomous	234			229				<0.001a
Adverse events: Any adverse event(s) – 24wkb	Count	39144	423		38304	414			
Full analysis set (FAS) or efficacy analysis pop									
Blood glucose: HbA1c (%) – 24wk	Mean change	232		-0.84 (SD 1.09)	227		-0.96 (SD 1.08)		
HbA1c (%) – 24wk	Continuous	232		8.3 (SD 1.3)	227		8.1 (SD 1.3)		
Fasting plasma glucose (mmol/l) – 24wk	Continuous	232		6.9 (SD 1.9)	227		6.8 (SD 1.9)		
Hba1c<=7.5% – 24wk	Dichotomous	232	74	(31.9%)	227	75	(33.0%)		
Body weight: Weight (kg) – 24wk	Mean change	232		2.9 (SD 4.3)	227		3.7 (SD 3.6)		
Hypoglycaemic events: All hypoglycaemic events (no patients) – 24wkc	Dichotomous	232	173	(74.6%)	227	155	(68.3%)		
Major/severe hypoglycaemic event – 24wkc	Dichotomous	232	6	(2.6%)	227	4	(1.8%)		
Major/severe hypoglycaemic event – 24wkd	Continuous	232		12.2	227		3.8		
Symptomatic hypoglycaemia – 24wkc	Dichotomous	232	135	(58.2%)	227	98	(43.2%)		
Nocturnal hypoglycaemia – 24wkc	Dichotomous	232	89	(38.4%)	227	52	(22.9%)		
Adverse events: Any adverse event(s) – 24wke	Dichotomous	232	423	(182.3%)	227	414	(182.4%)		
Death – 24wkc	Dichotomous	232	1	(0.4%)	227	2	(0.9%)		
Dropouts: Dropout due to AEs – 24wk	Dichotomous	232	7	(3.0%)	227	4	(1.8%)		
Insulin: Total daily dose (U) – 24wk	Continuous	232		37 (SD 22)	227		39 (SD 21)		

[a] p-value overall
[b] No of events, reviewer estimated person time at risk
[c] No of patients

[d] per 100 person years; No 95% CI reported
[e] No of events

		NPH insulin (bedtime) + glimepiride			Insulin glargine (morning) + glimepiride				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 24wk	Mean change	234			237			MD=0.400 (CI: 0.230, 0.570)	<0.001
Fasting plasma glucose (mmol/l) – 24wk	Continuous	234			237				>0.2a
Body weight: Weight (kg) – 24wk	Continuous	234			237				NSa
Hypoglycaemic events: Major/severe hypoglycaemic event – 24wk	Count	39144	6		39732	4			
Adverse events: Any adverse event(s) – 24wkb	Count	39144	423		39732	403			
Insulin: Total daily dose (U) – 24wk	Mean change	234			237				0.06a
Full analysis set (FAS) or efficacy analysis pop Blood glucose: HbA1c (%) – 24wk	Mean change	232		-0.84 (SD 1.09)	236		-1.24 (SD 1.1)		
HbA1c (%) – 24wk	Continuous	232		8.3 (SD 1.3)	236		7.8 (SD 1.2)		
Fasting plasma glucose (mmol/l) – 24wk	Continuous	232		6.9 (SD 1.9)	236		7 (SD 1.9)		
Hba1c<=7.5% – 24wk	Dichotomous	232	74	(31.9%)	236	102	(43.2%)		
Body weight: Weight (kg) – 24wk	Mean change	232		2.9 (SD 4.3)	236		3.9 (SD 4.5)		
Hypoglycaemic events: All hypoglycaemic events (no patients) – 24wkc	Dichotomous	232	173	(74.6%)	236	175	(74.2%)		
Major/severe hypoglycaemic event – 24wkc	Dichotomous	232	6	(2.6%)	236	5	(2.1%)		
Major/severe hypoglycaemic event – 24wkd	Continuous	232		12.2	236		5.5		
Symptomatic hypoglycaemia – 24wkc	Dichotomous	232	135	(58.2%)	236	133	(56.4%)		
Nocturnal hypoglycaemia – 24wkc	Dichotomous	232	89	(38.4%)	236	39	(16.5%)		
Adverse events: Any adverse event(s) – 24wke	Dichotomous	232	423	(182.3%)	236	403	(170.8%)		
Death – 24wkc	Dichotomous	232	1	(0.4%)	236	0	(0.0%)		

Dropouts: Dropout due to AEs – 24wk	Dichotomous	232	7	(3.0%)	236	5	(2.1%)		
Insulin: Total daily dose (U) – 24wk	Continuous	232		37 (SD 22)	236		40 (SD 24)		

[a] p-value overall
[b] No of events, reviewer estimated person time at risk
[c] No of patients
[d] per 100 person years; No 95% CI reported
[e] No of events

		Insulin glargine (bedtime) + glimepiride			Insulin glargine (morning) + glimepiride				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Blood glucose: HbA1c (%) – 24wk	Mean change	229			237			MD=0.280 (CI: 0.077, 0.483)	0.008
Hypoglycaemic events: Major/severe hypoglycaemic event – 24wk	Count	38304	13		39732	4			
Adverse events: Any adverse event(s) – 24wka	Count	38304	414		39732	403			
Full analysis set (FAS) or efficacy analysis pop Blood glucose: HbA1c (%) – 24wk	Mean change	227		-0.96 (SD 1.08)	236		-1.24 (SD 1.1)		
HbA1c (%) – 24wk	Continuous	227		8.1 (SD 1.3)	236		7.8 (SD 1.2)		
Fasting plasma glucose (mmol/l) – 24wk	Continuous	227		6.8 (SD 1.9)	236		7 (SD 1.9)		
Hba1c<=7.5% – 24wk	Dichotomous	227	75	(33.0%)	236	102	(43.2%)		
Body weight: Weight (kg) – 24wk	Mean change	227		3.7 (SD 3.6)	236		3.9 (SD 4.5)		
Hypoglycaemic events: All hypoglycaemic events (no patients) – 24wkb	Dichotomous	227	155	(68.3%)	236	175	(74.2%)		
Major/severe hypoglycaemic event – 24wkb	Dichotomous	227	4	(1.8%)	236	5	(2.1%)		
Major/severe hypoglycaemic event – 24wkc	Continuous	227		3.8	236		5.5		
Symptomatic hypoglycaemia – 24wkb	Dichotomous	227	98	(43.2%)	236	133	(56.4%)		
Nocturnal hypoglycaemia – 24wkb	Dichotomous	227	52	(22.9%)	236	39	(16.5%)		
Adverse events: Any adverse event(s) – 24wkd	Dichotomous	227	414	(182.4%)	236	403	(170.8%)		
Death – 24wkb	Dichotomous	227	2	(0.9%)	236	0	(0.0%)		

	Dropouts: Dropout due to AEs – 24wk	Dichotomous	227	4	(1.8%)	236	5	(2.1%)		
	Insulin: Total daily dose (U) – 24wk	Continuous	227		39 (SD 21)	236		40 (SD 24)		

[a] No of events, reviewer estimated person time at risk
[b] No of patients
[c] per 100 person years; No 95% CI reported
[d] No of events

An analysis of covariance was performed to compare the changes in HbA1c values; treatment and country were fixed effects, and HbA1c baseline values were covariates. Categoric secondary variables were analyzed for treatment differences by using Cochran–Mantel–Haenszel tests, stratified by country. P-values for adverse events were not reported.

Table 10: Furlong et al. (2002)

General	**Phase:** ☐ monotherapy ☐ dual therapy ☑ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** UK **Authors' conclusions:** Combined with bedtime NPH insulin, metformin provides superior glycemic control to repaglinide with less weight gain and improved diabetes treatment satisfaction **Source of funding:** supported by an unrestricted educational grant from Novo Nordisk Pharmaceuticals **Comments:** single center open-label randomized parallel group study. Subjects were then individually randomized by way of concealed random numbers in sequenced envelopes
Number and characteristics of patients	**Total number of patients:** 80 **Inclusion criteria:** Men and women >18 years of age with type 2 diabetes treated with 850 or 1,000 mg t.i.d. (maximum tolerated dose) metformin combined with bedtime NPH insulin, were included **Exclusion criteria:** type 1 diabetes, pregnancy or lactation, hypoglycemic unawareness, recurrent severe hypoglycemia (four or more episodes in the previous year), hepatic impairment, renal impairment, decompensated heart failure, unstable angina, known or suspected allergy to any trial medications, or a known or suspected history of alcohol or drug abuse. Subjects were also excluded if they were taking other medications likely to affect glycemic control or drugs known to interact with trial medication Pre-randomisation phase: There was a 4 week run-in (screening) period where patients continued their previous OAD therapy unchanged
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** all on oral hypoglycaemic drugs and/or insulin **Details of washout period:** Patients included were treated with 850 or 1,000 mg t.i.d. (maximum tolerated dose) metformin combined with bedtime NPH insulin. The use of other oral hypoglycemic agents (including sulfonylureas or thiazolidinediones) was not permitted
Lifestyle advice	All subjects received dietetic and lifestyle advice regarding hypoglycemia prevention
Follow-up	**Total follow-up (wks):** 13 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 13 **Frequency of monitoring appointments:** Subjects were seen by the trial investigator at 2, 4, 6, and 13 weeks after randomization
Arms	**(1) Metformin + NPH insulin (bedtime)** N: 41 Treatment duration (wks): 13 Washout period (d): 0 Treatment(s): (a) Metformin (Oral)

Mean dose (mg/d): 2824
Details of dosing regimen: Metformin was administered with meals and dose was unchanged

(b) NPH insulin (Subcutaneous) – flexible-dose (dose-adjusted)

Frequency of dosing: once a day
Details of dosing regimen: the bedtime insulin dose was increased to >=0.5 units/kg body wt (providing no risk of hypoglycemia as judged by the study coordinator) and

subsequently increased after 1 week to >=0.7 units/kg providing no (risk of) hypoglycemi. Insulin doses were then titrated at the clinician's discretion at each subsequent visit (with increments typically between 4 and 20 units), aiming for a target FBG of 4.0–6.0 mmol/l.

(2) Repaglinide +NPH insulin (bedtime)

N: 39

Treatment duration (wks): 13
Washout period (d): 0

Treatment(s): (a) repaglinide (Oral) – fixed-dose

Set dose (mg/d):12
Frequency of dosing: three times a day
Details of dosing regimen: 4 mg tid, administered 15 mins preprandially

(b) NPH insulin (Subcutaneous) – flexible-dose (dose-adjusted)

Frequency of dosing: once a day
Details of dosing regimen: see metformin + insulin for dosing details

Outcomes

General

Outcomes not extracted in this evidence table include satisfaction and wellbeing measures and 7 point blood glucose profiles (SMBG).

All data were summarized using an intention-to-treat analysis (all subjects

who received at least one dose of the study medication and returned for at least one visit after randomization.) The end point was defined as the last measurement available during the treatment phase

2/41 in the metformin + insulin group and 3/39 in the repaglinide + insulin group discontinued the study

Hypoglycaemic events

Major/severe hypoglycaemic event (Severe hypoglycemia was defined as that requiring third-party assistance)

confirmed hypoglycaemia (Hypoglycemia was defined as a blood glucose reading <3.5 mmol/l with or

without symptoms.)

Nocturnal hypoglycaemia (Nocturnal hypoglycemia was defined as that occurring while the subject was asleep between bedtime after the injection of insulin and before prebreakfast blood glucose determination.)

Baseline characteristics

		Metformin + NPH insulin (bedtime)			Repaglinide +NPH insulin (bedtime)			Δ	p
		N	k	mean	N	k	mean		
Demographics: Age (years)	Continuous	41		61.6 (SD 10.2)	39		57.4 (SD 9.99)		
Sex (n male)	Dichotomous	41	15	(36.6%)	39	24	(61.5%)		
Duration of diabetes (months)	Continuous	41		med: 120 [rng 9–306]	39		med: 120 [rng 10–240]		
Blood glucose: HbA1c (%) – 0wk	Continuous	41		8.4 (SD 1.28)	39		8.1 (SD 1.25)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	41		7.6 (SD 2.56)	39		7.6 (SD 3.12)		
Body weight: BMI (kg/m2)	Continuous	41		33 (SD 4.48)	39		33.7 (SD 6.24)		
Weight (kg) – 0wk	Continuous	41		91.2 (SD 17.9)	39		97.5 (SD 21.9)		
Insulin: Total daily dose (U/kg) – 0wka	Continuous	41		0.47 (SD 0.192)	39		0.5 (SD 0.187)		

[a] assumed daily

Results

	Metformin + NPH insulin (bedtime)			Repaglinide +NPH insulin (bedtime)			Δ	p
	N	k	mean	N	k	mean		

Blood glucose: HbA1c (%) – 13wka	Continuous	41		8.1 (SD 1.34)	39		8.6 (SD 1.31)		0.005
Fasting plasma glucose (mmol/l) – 13wka	Continuous	41		6.6 (SD 1.28)	39		7.9 (SD 2.5)		0.04
Body weight: Weight (kg) – 13wkb	Mean change	41		0.9 (SD 2.56)	39		2.7 (SD 2.5)		
Weight (kg) – 13wk	Continuous	41			39				0.002
Hypoglycaemic events: Major/severe hypoglycaemic event – 13wkc	Count	3640	0		3412.5	0			
Major/severe hypoglycaemic event – 13wk	Dichotomous	41	0	(0.0%)	39	0	(0.0%)		NR
confirmed hypoglycaemia – 13wkd	Count	3609	64		3381	38			
confirmed hypoglycaemia – 13wke	Continuous	41		1.56 (SD 2.56)	39		0.97 (SD 1.62)		NS
confirmed hypoglycaemia – 13wk	Dichotomous	41	22f	(53.7%)	39	16g	(41.0%)		
Nocturnal hypoglycaemia – 13wkh	Dichotomous	41	0	(0.0%)	39	5	(12.8%)		
Nocturnal hypoglycaemia – 13wkc	Count	3640	0		3412.5	5			
Adverse events: Any adverse event(s) – 13wkc	Count	3640	43		3412.5	50			
Any adverse event(s) – 13wkh	Dichotomous	41	43	(104.9%)	39	50	(128.2%)		NR
Any serious adverse event(s) – 13wkc	Count	3640	0		3412.5	5			
Any serious adverse event(s) – 13wkh	Dichotomous	41	0	(0.0%)	39	5	(12.8%)		NR
Dropouts: Total dropouts – 13wk	Dichotomous	41	2	(4.9%)	39	3	(7.7%)		
Insulin: Total daily dose (U/kg) – 13wk	Continuous	41			39				NS
Total daily dose (U/kg) – 13wk	Mean change	41		0.19 (SD 0.192)	39		0.21 (SD 0.187)		

[a] SE estimated from graph
[b] SD calculated from reported SE
[c] person days estimated assuming dropout halfway during trial
[d] person days estimated assuming dropout halfway during trial or data where available and no of events calculated using reported rate
[e] mean no episodes per patient (assumed that SE reported and converted to SD)
[f] No patients (data presented as number of patients free from hypoglycaemia, assumed total sample)
[g] No patients (data presented as number of patients free from hypoglycaemia, assumed total sample)
[h] No of events

For parametric data, withinpatient comparisons were made using paired two-tailed t tests and betweengroup comparisons two-tailed unpaired t

tests. For nonparametric data, within withinpatient comparisons were made using Wilcoxon's signed-rank test; betweengroup comparisons were made using the Mann-Whitney U test. The chi squared test was used for analyzing proportions of discontinuous variables.

Table 11: Furlong et al. (2003)

General	**Phase:** ☐ monotherapy

	☐ dual therapy ☑ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** UK **Authors' conclusions:** Over 13 weeks, both repglinide and gliclazide, when combined with bedtime NPH insulin produce similar significant improvements in glycaemic control (-1%) and similar weight gain **Source of funding:** supported by an unrestricted educational grant from Novo Nordisk Pharmaceuticals **Comments:** single center open-label randomized parallel group study. Subjects were then individually randomized by way of concealed random numbers in sequenced envelopes
Number and characteristics of patients	**Total number of patients:** 80 **Inclusion criteria:** Men and women >18 years of age with type 2 diabetes and inadequate glycaemic control despite maximal oral therapy **Exclusion criteria:** type 1 diabetes, pregnancy or lactation, hypoglycemic unawareness, recurrent severe hypoglycemia (four or more episodes in the previous year), hepatic impairment, renal impairment, decompensated heart failure, unstable angina, known or suspected allergy to any trial medications, or a known or suspected history of alcohol or drug abuse. Subjects were also excluded if they were taking other medications likely to affect glycemic control or drugs known to interact with trial medication Pre-randomisation phase: There was a 4 week run-in (screening) period where patients continued their previous OAD therapy unchanged
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** all on oral hypoglycaemic drugs and/or insulin **Details of washout period:** All participants had inadequate control on maximal oral therapy (these were discontinued when assigned to treatment groups)
Lifestyle advice	-
Follow-up	**Total follow-up (wks):** 13 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 13 **Frequency of monitoring appointments:** Participants were seen at 2,4,6 and 13 weeks after randomisation
Arms	**(1) Gliclazide + NPH insulin (bedtime)** N: 39 Treatment duration (wks): 13 Washout period (d): 0 Comments: All OADs were discontinued when assigned to treatment groups Treatment(s): (a) Sulfonylurea (Oral) – fixed-dose Set dose (mg/d):320 Frequency of dosing: twice a day Details of dosing regimen: Administered 15 mins preprandially. All participants received their OHA in maximum dose (b) NPH insulin (Subcutaneous) – flexible-dose (dose-adjusted) Frequency of dosing: once a day Details of dosing regimen: Bedtime insulin was started at a dose of 0.5 U/kg (provising no risk of hypoglycaemia judged by the co-ordinator) then increased after 1 week to 0.7 units/kg providing no (risk of) hypoglycemi. Insulin doses were then titrated at the clinician's discretion at each subsequent visit (with increments typically between 4 and 20 units), aiming for a target FBG of 4.0–6.0 mmol/l. **(2) Repaglinide + NPH insulin (bedtime)** N: 41 Treatment duration (wks): 13 Washout period (d): 0 Comments: All OADs were discontinued when assigned to treatment groups Treatment(s): (a) repaglinide (Oral) – fixed-dose Set dose (mg/d):12 Details of dosing regimen: 4 mg tid. All participants received their OHA in maximum dose (b) NPH insulin (Subcutaneous) – flexible-dose (dose-adjusted) Details of dosing regimen: Bedtime insulin (see sulfonylurea + insulin for dosing details)
Outcomes	**General** Outcomes not extracted in this evidence table include satisfaction and wellbeing measures and 7 point blood glucose profiles (SMBG). All data were summarized using an intention-to-treat analysis (all subjects who received at least one dose of the study medication and returned for at least one visit after

randomization.) The end point was defined as the last measurement available during the treatment phase

0/39 patients in the insulin + gliclazide group and 6/41 in the insulin + repaglinide group discontinued the study

Hypoglycaemic events

Major/severe hypoglycaemic event (Severe hypoglycemia was defined as that requiring third-party assistance)

confirmed hypoglycaemia (Hypoglycemia was defined as a blood glucose reading <3.5 mmol/l with or without symptoms.)

Nocturnal hypoglycaemia (Nocturnal hypoglycemia was defined as that occurring while the subject was asleep between bedtime after the injection of insulin and before prebreakfast blood glucose determination.)

Baseline characteristics

		Gliclazide + NPH insulin (bedtime)			Repaglinide + NPH insulin (bedtime)			Δ	p
		N	k	mean	N	k	mean		
Demographics:									
Age (years)	Continuous	39		59 (SD 12.5)	41		59 (SD 12.8)		
Sex (n male)	Dichotomous	39	21	(53.8%)	41	21	(51.2%)		
Duration of diabetes (months)	Continuous	39		med: 97 [rng 5–301]	41		med: 85 [rng 7–241]		
Blood glucose:									
HbA1c (%) – 0wk	Continuous	39		9.2 (SD 1.87)	41		9.4 (SD 1.92)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	39		10.1 (SD 2.5)	41		10 (SD 3.2)		
Body weight:									
BMI (kg/m2)	Continuous	39		31.5 (SD 4.37)	41		31.9 (SD 7.68)		
Weight (kg) – 0wk	Continuous	39		90.8 (SD 17.5)	41		91.4 (SD 24.3)		
Previous blood glucose lowering drugs:									
Sulfonylurea	Dichotomous	39	7	(17.9%)	41	8	(19.5%)		
Metformin + Sulfonylurea	Dichotomous	39	30	(76.9%)	41	27	(65.9%)		
Sulfonylurea + rosiglitazone	Dichotomous	39	0	(0.0%)	41	1	(2.4%)		

Results

		Gliclazide + NPH insulin (bedtime)			Repaglinide + NPH insulin (bedtime)			Δ	p
		N	k	mean	N	k	mean		
Blood glucose:									
HbA1c (%) – 13wka	Continuous	39		8.2 (SD 1.31)	41		8.5 (SD 1.6)		NS
Fasting plasma glucose (mmol/l) – 13wka	Continuous	39		6.7 (SD 1.56)	41		7.1 (SD 1.6)		NS
Body weight:									
Weight (kg) – 13wkb	Mean change	39		4.1 (SD 3.12)	41		3.4 (SD 2.56)		
Weight (kg) – 13wk	Continuous	39			41				NS
Hypoglycaemic events:									
Major/severe hypoglycaemic event – 13wkc	Dichotomous	39	1	(2.6%)	41	0	(0.0%)		NR
confirmed hypoglycaemia – 13wkd	Continuous	39		2.95 (SD 5.12)	41		2.3 (SD 3.33)		
confirmed hypoglycaemia – 13wke	Dichotomous	39	20	(51.3%)	41	25	(61.0%)		NR
confirmed hypoglycaemia – 13wk	Count	3549	115		3458	94			
Nocturnal hypoglycaemia – 13wk	Count	3549	25		3458	17			
Nocturnal hypoglycaemia – 13wkf	Dichotomous	39	8	(20.5%)	41	8	(19.5%)		NR

Adverse events:										
Any adverse event(s) – 13wkg	Dichotomous	39	38	(97.4%)	41	32	(78.0%)		NR
Any adverse event(s) – 13wk	Count	3549	38		3458	32			
Any serious adverse event(s) – 13wkg	Dichotomous	39	4	(10.3%)	41	2	(4.9%)		NR
Any serious adverse event(s) – 13wk	Count	3549	4		3458	2			
Dropouts:										
Total dropouts – 13wk	Dichotomous	39	0	(0.0%)	41	6	(14.6%)		
Insulin:										
Total daily dose (U/kg) – 13wkh	Continuous	39		0.54 (SD 0.187)	41		0.51 (SD 0.192)		

[a] Assumed SE estimated from graph
[b] SD calculated from SE
[c] No of patients
[d] SD calculated from assumed reported SE; mean number of hypoglycaemia episodes per patient
[e] No of patients (data presented as number of patients free from hypoglycaemia, assumed total sample)
[f] approximated to nearest integer (percentages only presented in text); No of events
[g] No of events
[h] assumed daily

Error bars in graph not labelled but assumed to be SE

For parametric data, withinpatient comparisons were made using paired two-tailed t tests and betweengroup comparisons two-tailed unpaired t

tests. For nonparametric data, within withinpatient comparisons were made using Wilcoxon's signed-rank test; betweengroup comparisons were made using the Mann-Whitney U test. The chi squared test was used for analyzing proportions of discontinuous variables.

Table 12: Goudswaard et al. (2004)

General	**Phase:** ☐ monotherapy ☐ dual therapy ☑ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** Netherlands **Authors' conclusions:** Bedtime NPH insulin added to maximal therapy with sulfonylurea and metformin is an effective, simple, well-tolerated approach for patients with uncontrolled type 2 diabetes **Source of funding:** Unclear **Comments:** This was an open-label, parallel group trial. Randomisation was performed by a telephone call to an independent trial center that used a computer-generated random assignment.
Number and characteristics of patients	**Total number of patients:** 69 **Inclusion criteria:** younger than 76 years, had HbA1c =7.0% despite treatment with both sulfonylurea and metformin in maximally tolerated dosages, were willing to start insulin therapy, and were deemed by their family physician to be candidates for more tight glycemic control. **Exclusion criteria:** Exclusion criteria were severe comorbidity (ie, an illness that surpasses the impact of diabetes or was associated with a short life expectancy) and insufficient understanding of spoken Dutch to follow instructions.
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** all on oral hypoglycaemic drugs and/or insulin **Details of washout period:** all taking metformin and sulfonylurea at study start
Lifestyle advice	After randomization, patients were referred to the diabetes nurse of their family practice to receive usual education for patients starting on insulin therapy. This included information on diabetes (eg, symptoms of hypoglycemia) and dietary counseling
Follow-up	**Total follow-up (wks):** 52 **Length of titration period (wks):** 0

	Length of maintenance period (wks): 52 **Frequency of monitoring appointments:** Practice visits with the diabetes nurse or the family physician (according to local policy) were scheduled for 3, 6, 9, and 12 months after start of treatment.
Arms	**(1) Metformin + sulfonylurea + NPH bedtime (insulin combination group)** N: 33 Treatment duration (wks): 52 Washout period (d): 0 Treatment(s): (a) Metformin (Oral) Details of dosing regimen: Patients continued current treatment with metformin and sulfonylurea (no further details reported) (b) Sulfonylurea (Oral) Details of dosing regimen: Patients continued current treatment with metformin and sulfonylurea (no further details reported) (c) NPH insulin (Subcutaneous) – flexible-dose (dose-adjusted) Frequency of dosing: once a day Details of dosing regimen: NPH insulin at bedtime (Insulatard; Novo Nordisk, Copenhagen, Denmark) was given in addition to current treatment with sulfonylurea and metformin (insulin combination [IC] group). Insulin therapy was initiated with 8 IU before bedtime in the IC group.Insulin dosages were adjusted twice weekly by telephone contact with the diabetes nurse (adjusting phase), aiming for a target fasting blood glucose of 4.0–7.0 mmol/L and a target postprandial glucose of 4.0–10.0 mmol/L. When these targets were achieved and had proved stable, the insulin dose was fixed. Treatment failure was declared for patients in the IC group if glucose targets were not reached with a maximum daily dose of 40 IU NPH insulin. **(2) NPH 70/30 (insulin monotherapy group, IM)** N: 31 Treatment duration (wks): 52 Washout period (d): 0 Treatment(s): NPH insulin mix 70/30 (Subcutaneous) – flexible-dose (dose-adjusted) Frequency of dosing: twice a day Details of dosing regimen: Insulin therapy was initiated with 12 and 6 IU before breakfast and dinner in the IM group. In the IM group, no ceiling was set for the insulin dose, but treatment was declared a failure when patients were switched to other treatment regimens due to unsatisfactory diurnal blood glucose profiles.
Outcomes	**General** In the IC group, 8 patients (24%) experienced a treatment failure because glucose targets were not reached with a daily dose of 40 IU NPH insulin. Analyses were based on intention to treat, and missing data were fitted by the last observation-carried-forward principle. Last available measurements were used for patients reaching a study end point before 12 months of follow-up. Outcomes not extracted in this evidence table include satisfaction and other quality of life measures 5/69 patients did not start the intervention (no further details reported)
Baseline characteristics	

		Metformin + sulfonylurea + NPH bedtime (insulin combination group)			NPH 70/30 (insulin monotherapy group, IM)			Δ	p
		N	k	mean	N	k	mean		
Demographics: Age (years)	Continuous	33		58.6 (SD 8.6)	31		58.3 (SD 11.3)		
Sex (n male)	Dichotomous	33	18a	(54.5%)	31	13	(41.9%)		
Duration of diabetes (yrs)	Continuous	33		7.2 (SD 3.9)	31		7.7 (SD 4.8)		
Blood glucose: HbA1c (%) – 0wk	Continuous	33		8.3 (SD 0.9)	31		8.8 (SD 1.5)		
Body weight: BMI (kg/m2)	Continuous	33		33.2 (SD 6.4)	31		28.5 (SD 3.8)		
Weight (kg) – 0wk	Continuous	33		96.3 (SD 19.4)	31		81 (SD 14.3)		

[a] approximated to nearest integer (percentages only presented in text)

Results

		Metformin + sulfonylurea + NPH bedtime (insulin combination group)			NPH 70/30 (insulin monotherapy group, IM)				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 0wk	Mean change	33			31			MD=0.140 (CI: -0.720, 1.000)	NS
HbA1c (%) – 52wk	Mean change	33		-0.8 (SD 1.3)	31		-1.2 (SD 1.2)		
HbA1c (%) – 52wk	Continuous	33		7.6 (SD 1.3)	31		7.6 (SD 1.1)		
HbA1c < 7% or <=7% – 0wk	Dichotomous	33			31				NS
HbA1c < 7% or <=7% – 52wk	Dichotomous	33	12a	(36.4%)	31	13	(41.9%)		
Body weight: Weight (kg) – 0wk	Mean change	33			31			MD=3.000 (CI: 0.680, 5.320)	0.01
Weight (kg) – 52wk	Mean change	33		1.3 (SD 3.9)	31		4.2 (SD 4.3)		
Hypoglycaemic events: All hypoglycaemic events (no events) – 0wk	Dichotomous	33			31				0.02
All hypoglycaemic events (no events) – 52wkb	Count	12012	89		11284	133			
All hypoglycaemic events (no events) – 52wkc	Continuous	33		2.7 (SD 5.2)	31		4.3 (SD 4.3)		
Major/severe hypoglycaemic event – 52wkd	Dichotomous	33	0	(0.0%)	31	1	(3.2%)		
Major/severe hypoglycaemic event – 52wk	Dichotomous	33	0e	(0.0%)	31	1d	(3.2%)		
Major/severe hypoglycaemic event – 52wke	Dichotomous	33	0	(0.0%)	31	2	(6.5%)		
Major/severe hypoglycaemic event – 52wkf	Count	12012	0		11284	2			
Major/severe hypoglycaemic event – 52wk	Dichotomous	33	0d	(0.0%)	31	2e	(6.5%)		
confirmed hypoglycaemia – 52wkc	Continuous	33		2.4 (SD 5.2)	31		2.7 (SD 3.5)		
confirmed hypoglycaemia – 52wkb	Count	12012	79		11284	84			
Insulin: Total daily dose (U/kg) – 0wk	Continuous	33			31				NR
Total daily dose (U/kg) – 52wk	Continuous	33		0.27 (SD 0.13)	31		0.86 (SD 0.37)		

[a] approximated to nearest integer (percentages only presented in text)
[b] person days estimated assuming no dropouts and no of events calculated using reported mean number of episodes
[c] mean no events per patient
[d] No of patients

	[e] No of events [f] person days estimated assuming no dropouts
	Outcome measurements were compared between the 2 intervention groups by either analyses of covariance (ANCOVA) adjusting for baseline values,12 unpaired t tests, or Mann-Whitney U test.

Table 13: Gram et al. (2011)

General	**Phase:** ☐ monotherapy ☐ dual therapy ☑ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** Denmark **Authors' conclusions:** Insulin treatment of postprandial hyperglycemia results in lower A1C than treatment of fasting hyperglycemia, at the expense of higher body weight and hypoglycemic episodes. However, insulin therapy has to be combined with treatment of both peripheral and liver insulin resistance to normalize blood glucose, and in this case, the insulin regimen is less important. **Source of funding:** The counties of southern Denmark and the Danish Medical Research Council are acknowledged for financial support. Novo Nordisk is acknowledged for supplying insulin and financial support for data management and statistical expertise, and GlaxoSmithKline is acknowledged for providing blinded tablets containing rosiglitazone/placebo and metformin/placebo **Comments:** Statistical analysis was performed by an independent statistician. The statistical analysis plan was completed before the database was locked and unblinded. The randomization code was developed by an independent statistician using a computer random number generator to select random blocks of eight. Randomization to insulin type was open, whereas allocation to other treatments was double-blinded.
Number and characteristics of patients	**Total number of patients:** 371 **Inclusion criteria:** BMI >25 kg/m2 and fasting plasma C-peptide >300 pmol/l, treatment for at least 3 months with stable doses of oral antidiabetic medications and/or insulin, and A1C>7.0%. Prior insulin treatment could be any insulin regimen, but most subjects were treated with long-acting insulin **Exclusion criteria:** congestive heart failure, impaired renal function, and known intolerance to metformin or rosiglitazone and/or treatment with glitazones <30 days before randomisation.
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** all on oral hypoglycaemic drugs and/or insulin **Details of washout period:** all prioir OADs were stopped prior to starting the intervention
Lifestyle advice	-
Follow-up	**Total follow-up (wks):** 104 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 104 **Frequency of monitoring appointments:** Hba1c was measured every 3 months
Arms	**(1) Metformin + NPH insulin** N: 45 Treatment duration (wks): 104 Washout period (d): 0 Treatment(s): (a) Metformin (Oral) – fixed-dose Set dose (mg/d):2000 Frequency of dosing: twice a day Details of dosing regimen: Metformin or placebo was given from the start of the study as one tablet of 500 mg twice daily during the first 4 weeks succeeded by two tablets twice daily. (b) NPH insulin (Subcutaneous) – flexible-dose (dose-adjusted) Mean dose (mg/d): 80.1 Frequency of dosing: once a day Details of dosing regimen: received a starting dose of 12 IU at bedtime. Patients already on insulin received 50% of their prior total daily dose. In a treat-to-target algorithm, insulin dose was increased by 2 IU if FBG was >5.6 mmol/l, 4 IU if FBG was >8.mmol/l, and 6 IU if

FBG was >12.0mmol/l on 3 consecutive days until FBG was <=5.5 mmol/l and A1C was <6.5%,provided no unacceptable hypoglycemic episodes.

(2) Metformin + insulin aspart

N: 45

Treatment duration (wks): 104
Washout period (d): 0

Treatment(s): (a) Metformin (Oral) – fixed-dose
Set dose (mg/d):2000
Frequency of dosing: twice a day
Details of dosing regimen: see insulin NPH + metformin

(b) Insulin aspart (short acting) (Subcutaneous) – flexible-dose (dose-adjusted)
Mean dose (mg/d): 61.2
Frequency of dosing: three times a day
Details of dosing regimen: received a starting dose of 4 IU just before each main meal. Patients already on insulin received 50% of their prior total daily dose divided into three doses. In a treat-to-target algorithm, insulin dose at each meal was increased by 1 IU if postprandial blood glucose was >=7.5 mmol/l, 2 IU if postprandial blood glucose was >=9.0 mmol/l, 3 IU if postprandialblood glucose was >=11.0mmol/l on 3 consecutive days until postprandial blood glucose was<7.5 mmol/land A1C was<6.5%, provided no limiting hypoglycemic episodes

(3) NPH insulin

N: 46

Treatment duration (wks): 104
Washout period (d): 0

Treatment(s): NPH insulin (Subcutaneous) – flexible-dose (dose-adjusted)
Details of dosing regimen: See metformin + NPH for dosing details

(4) Insulin aspart

N: 48

Treatment duration (wks): 104
Washout period (d): 0

Treatment(s): Insulin aspart (short acting) (Subcutaneous) – flexible-dose (dose-adjusted)
Details of dosing regimen: See metformin + aspart for dosing details

Outcomes

General

Statistical analysis was on an intention-totreat basis and last observation carried forward. A per-protocol analysis for the primary end point was also performed.

Only data from 4/8 arms were extracted as these involved rosiglitazone treatment.

Outcomes not extracted in this evidence table include SMBG and adverse events (these were not reported for each treatment group)

8/45 (18%) in metformin + NPH group and 7/45 (15.5%) in insulin aspart + metformin group discontinued the study

Hypoglycaemic events

symptomatic (unconfirmed) hypoglycaemia (mild hypoglycaemia (blood glucose <2.8 mmol/l and symptoms consistent with hypoglycemia))

Moderate/severe (moderate hypoglycaemia (blood glucose <2.8 mmol/l with or without symptoms) and serious hypoglycemia was defined as any hypoglycemic episode requiring assistance)

Baseline characteristics

		Metformin + NPH insulin			Metformin + insulin aspart				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	45		55.4 (SD 8.5)	45		56.1 (SD 8.2)		
Sex (n male)	Dichotomous	45	26	(57.8%)	45	28	(62.2%)		
Duration of diabetes (yrs)	Continuous	45		8.2 (SD 4)	45		8.7 (SD 4.5)		
Blood glucose: HbA1c (%) – 0wk	Continuous	45		8.9 (SD 1.2)	45		8.5 (SD 1.2)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	45		11.3 (SD 2.8)	45		10 (SD 2.3)		
Body weight: BMI (kg/m2)	Continuous	45		35.7 (SD 6.4)	45		33.7 (SD 6.1)		
Weight (kg) – 0wk	Continuous	45		105.1 (SD 17.7)	45		100.5 (SD 17.9)		

Previous blood glucose lowering drugs:									
Metformin	Dichotomous	45	38a	(84.4%)	45	31	(68.9%)		
Sulfonylurea	Dichotomous	45	26	(57.8%)	45	13	(28.9%)		
Insulin therapy	Dichotomous	45	14	(31.1%)	45	24a	(53.3%)		

[a] approximated to nearest integer (percentages only presented in text)

		Metformin + NPH insulin			NPH insulin				
		N	k	mean	N	k	mean	Δ	p
Demographics:									
Age (years)	Continuous	45		55.4 (SD 8.5)	46		55.8 (SD 7.7)		
Sex (n male)	Dichotomous	45	26	(57.8%)	46	33	(71.7%)		
Duration of diabetes (yrs)	Continuous	45		8.2 (SD 4)	46		7.3 (SD 4.3)		
Blood glucose:									
HbA1c (%) – 0wk	Continuous	45		8.9 (SD 1.2)	46		8.7 (SD 1.3)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	45		11.3 (SD 2.8)	46		11.2 (SD 2.6)		
Body weight:									
BMI (kg/m2)	Continuous	45		35.7 (SD 6.4)	46		34 (SD 6)		
Weight (kg) – 0wk	Continuous	45		105.1 (SD 17.7)	46		100.2 (SD 19.8)		
Previous blood glucose lowering drugs:									
Metformina	Dichotomous	45	38	(84.4%)	46	36	(78.3%)		
Sulfonylurea	Dichotomous	45	26	(57.8%)	46	30	(65.2%)		
Insulin therapy	Dichotomous	45	14	(31.1%)	46	13a	(28.3%)		

[a] approximated to nearest integer (percentages only presented in text)

		Metformin + NPH insulin			Insulin aspart				
		N	k	mean	N	k	mean	Δ	p
Demographics:									
Age (years)	Continuous	45		55.4 (SD 8.5)	48		57.1 (SD 8.5)		
Sex (n male)	Dichotomous	45	26	(57.8%)	48	23	(47.9%)		
Duration of diabetes (yrs)	Continuous	45		8.2 (SD 4)	48		9.1 (SD 5.5)		
Blood glucose:									
HbA1c (%) – 0wk	Continuous	45		8.9 (SD 1.2)	48		8.5 (SD 1.2)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	45		11.3 (SD 2.8)	48		10.7 (SD 2.5)		
Body weight:									
BMI (kg/m2)	Continuous	45		35.7 (SD 6.4)	48		33.7 (SD 5)		
Weight (kg) – 0wk	Continuous	45		105.1 (SD 17.7)	48		98.3 (SD 16.6)		
Previous blood glucose lowering drugs:									
Metformin	Dichotomous	45	38a	(84.4%)	48	34	(70.8%)		
Sulfonylurea	Dichotomous	45	26	(57.8%)	48	23	(47.9%)		
Insulin therapy	Dichotomous	45	14	(31.1%)	48	23	(47.9%)		

[a] approximated to nearest integer (percentages only presented in text)

	Metformin + insulin aspart			NPH insulin				
	N	k	mean	N	k	mean	Δ	p

Demographics: Age (years)	Continuous	45		56.1 (SD 8.2)	46		55.8 (SD 7.7)		
Sex (n male)	Dichotomous	45	28	(62.2%)	46	33	(71.7%)		
Duration of diabetes (yrs)	Continuous	45		8.7 (SD 4.5)	46		7.3 (SD 4.3)		
Blood glucose: HbA1c (%) – 0wk	Continuous	45		8.5 (SD 1.2)	46		8.7 (SD 1.3)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	45		10 (SD 2.3)	46		11.2 (SD 2.6)		
Body weight: BMI (kg/m2)	Continuous	45		33.7 (SD 6.1)	46		34 (SD 6)		
Weight (kg) – 0wk	Continuous	45		100.5 (SD 17.9)	46		100.2 (SD 19.8)		
Previous blood glucose lowering drugs: Metformin	Dichotomous	45	31	(68.9%)	46	36a	(78.3%)		
Sulfonylurea	Dichotomous	45	13	(28.9%)	46	30	(65.2%)		
Insulin therapya	Dichotomous	45	24	(53.3%)	46	13	(28.3%)		

[a] approximated to nearest integer (percentages only presented in text)

		Metformin + insulin aspart			Insulin aspart				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	45		56.1 (SD 8.2)	48		57.1 (SD 8.5)		
Sex (n male)	Dichotomous	45	28	(62.2%)	48	23	(47.9%)		
Duration of diabetes (yrs)	Continuous	45		8.7 (SD 4.5)	48		9.1 (SD 5.5)		
Blood glucose: HbA1c (%) – 0wk	Continuous	45		8.5 (SD 1.2)	48		8.5 (SD 1.2)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	45		10 (SD 2.3)	48		10.7 (SD 2.5)		
Body weight: BMI (kg/m2)	Continuous	45		33.7 (SD 6.1)	48		33.7 (SD 5)		
Weight (kg) – 0wk	Continuous	45		100.5 (SD 17.9)	48		98.3 (SD 16.6)		
Previous blood glucose lowering drugs: Metformin	Dichotomous	45	31	(68.9%)	48	34	(70.8%)		
Sulfonylurea	Dichotomous	45	13	(28.9%)	48	23	(47.9%)		
Insulin therapy	Dichotomous	45	24a	(53.3%)	48	23	(47.9%)		

[a] approximated to nearest integer (percentages only presented in text)

		NPH insulin			Insulin aspart				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	46		55.8 (SD 7.7)	48		57.1 (SD 8.5)		
Sex (n male)	Dichotomous	46	33	(71.7%)	48	23	(47.9%)		
Duration of diabetes (yrs)	Continuous	46		7.3 (SD 4.3)	48		9.1 (SD 5.5)		
Blood glucose: HbA1c (%) – 0wk	Continuous	46		8.7 (SD 1.3)	48		8.5 (SD 1.2)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	46		11.2 (SD 2.6)	48		10.7 (SD 2.5)		
Body weight: BMI (kg/m2)	Continuous	46		34 (SD 6)	48		33.7 (SD 5)		
Weight (kg) – 0wk	Continuous	46		100.2 (SD 19.8)	48		98.3 (SD 16.6)		

Previous blood glucose lowering drugs:								
Metformin	Dichotomous	46	36a	(78.3%)	48	34	(70.8%)	
Sulfonylurea	Dichotomous	46	30	(65.2%)	48	23	(47.9%)	
Insulin therapy	Dichotomous	46	13a	(28.3%)	48	23	(47.9%)	

[a] approximated to nearest integer (percentages only presented in text)

Results

		Metformin + NPH insulin			Metformin + insulin aspart				
		N	k	mean	N	k	mean	Δ	p
Blood glucose:									
HbA1c (%) – 12wka	Continuous	45		8.1 (SD 0.939)	45		7.3 (SD 0.671)		
HbA1c (%) – 26wka	Continuous	45		7.4 (SD 0.671)	45		6.9 (SD 0.671)		
HbA1c (%) – 52wka	Continuous	45		7.5 (SD 0.738)	45		7.2 (SD 0.671)		
HbA1c (%) – 104wkb	Continuous	45		7.6 (SD 1.3)	45		7.3 (SD 1.1)		
HbA1c < 7% or <=7% – 104wk	Dichotomous	45	19c	(42.2%)	45	23	(51.1%)		
Fasting plasma glucose (mmol/l) – 104wk	Continuous	45		6.6 (SD 2)	45		9.6 (SD 3.1)		
Body weight:									
Weight (kg) – 104wk	Continuous	45		108 (SD 19.6)	45		104.4 (SD 19.2)		
Hypoglycaemic events:									
All hypoglycaemic events (no patients) – 104wk	Dichotomous	45	33	(73.3%)	45	36	(80.0%)		
symptomatic (unconfirmed) hypoglycaemia – 52wkd	Continuous	45		1 (SD 2.7)	45		9.1 (SD 10.5)		
Moderate/severe – 52wkd	Continuous	45		0.3 (SD 1.1)	45		2.9 (SD 4.9)		
Moderate/severe – 104wkd	Continuous	45		0.1 (SD 0.4)	45		1.5 (SD 2.6)		
Nocturnal (mild) – 52wke	Continuous	45		2.8 (SD 4.8)	45		1.4 (SD 3.1)		
Nocturnal (mild) – 104wke	Continuous	45		1.5 (SD 2.8)	45		0.7 (SD 3)		
Nocturnal (moderate/severe) – 52wke	Continuous	45		0.4 (SD 1.2)	45		0.2 (SD 0.6)		
Nocturnal (moderate/severe) – 104wke	Continuous	45		0.5 (SD 1.3)	45		0.2 (SD 0.7)		
Dropouts:									
Total dropouts – 104wk	Dichotomous	45	8	(17.8%)	45	7	(15.6%)		
Dropout due to AEs – 104wk	Dichotomous	45	5	(11.1%)	45	2	(4.4%)		

[a] estimated from graph; SE converted
[b] SD reported
[c] approximated to nearest integer (percentages only presented in text)
[d] daytime; number per person per year
[e] number per person per year

		Metformin + NPH insulin			NPH insulin				
		N	k	mean	N	k	mean	Δ	p
Blood glucose:									
HbA1c (%) – 12wka	Continuous	45		8.1 (SD 0.939)	46		8.5 (SD 1.15)		
HbA1c (%) – 26wka	Continuous	45		7.4 (SD 0.671)	46		8.3 (SD 1.22)		
HbA1c (%) – 52wka	Continuous	45		7.5 (SD 0.738)	46		8.2 (SD 1.29)		

HbA1c (%) – 104wkb	Continuous	45		7.6 (SD 1.3)	46		8.3 (SD 1.4)		
HbA1c < 7% or <=7% – 104wkc	Dichotomous	45	19	(42.2%)	46	9	(19.6%)		
Fasting plasma glucose (mmol/l) – 104wk	Continuous	45		6.6 (SD 2)	46		7.3 (SD 2.5)		
Body weight: Weight (kg) – 104wk	Continuous	45		108 (SD 19.6)	46		105.5 (SD 20.2)		
Hypoglycaemic events: All hypoglycaemic events (no patients) – 104wk	Dichotomous	45	33	(73.3%)	46	35	(76.1%)		
symptomatic (unconfirmed) hypoglycaemia – 52wkd	Continuous	45		1 (SD 2.7)	46		2.3 (SD 8.2)		
symptomatic (unconfirmed) hypoglycaemia – 104wkd	Continuous	45		1.1 (SD 2.9)	46		2.6 (SD 8.1)		
Moderate/severe – 52wkd	Continuous	45		0.3 (SD 1.1)	46		0.4 (SD 1.4)		
Moderate/severe – 104wkd	Continuous	45		0.1 (SD 0.4)	46		0.3 (SD 0.9)		
Nocturnal (mild) – 52wke	Continuous	45		2.8 (SD 4.8)	46		2.8 (SD 6.1)		
Nocturnal (mild) – 104wke	Continuous	45		1.5 (SD 2.8)	46		2.8 (SD 4.5)		
Nocturnal (moderate/severe) – 52wke	Continuous	45		0.4 (SD 1.2)	46		0.5 (SD 1.9)		
Nocturnal (moderate/severe) – 104wke	Continuous	45		0.5 (SD 1.3)	46		1.1 (SD 2.9)		
Dropouts: Total dropouts – 104wk	Dichotomous	45	8	(17.8%)	46	6	(13.0%)		
Dropout due to AEs – 104wk	Dichotomous	45	5	(11.1%)	46	0	(0.0%)		

[a] estimated from graph; SE converted
[b] SD reported
[c] approximated to nearest integer (percentages only presented in text)
[d] daytime; number per person per year
[e] number per person per year

		Metformin + NPH insulin			Insulin aspart				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 12wka	Continuous	45		8.1 (SD 0.939)	48		7.5 (SD 0.693)		
HbA1c (%) – 26wka	Continuous	45		7.4 (SD 0.671)	48		7.6 (SD 0.693)		
HbA1c (%) – 52wka	Continuous	45		7.5 (SD 0.738)	48		7.8 (SD 0.693)		
HbA1c (%) – 104wkb	Continuous	45		7.6 (SD 1.3)	48		7.9 (SD 1.2)		
HbA1c < 7% or <=7% – 104wkc	Dichotomous	45	19	(42.2%)	48	12	(25.0%)		
Fasting plasma glucose (mmol/l) – 104wk	Continuous	45		6.6 (SD 2)	48		12.2 (SD 3.9)		
Body weight: Weight (kg) – 104wk	Continuous	45		108 (SD 19.6)	48		104.4 (SD 18.3)		
Hypoglycaemic events: All hypoglycaemic events (no patients) – 104wk	Dichotomous	45	33	(73.3%)	48	43	(89.6%)		
symptomatic (unconfirmed) hypoglycaemia – 52wkd	Continuous	45		1 (SD 2.7)	48		10.1 (SD 12.2)		
symptomatic (unconfirmed) hypoglycaemia – 104wkd	Continuous	45		1.1 (SD 2.9)	48		7.2 (SD 9.7)		
symptomatic (unconfirmed) hypoglycaemia – 104wkd	Continuous	45		1.1 (SD 2.9)	45		4.1 (SD 5.5)		

Moderate/severe – 52wkd	Continuous	45		0.3 (SD 1.1)	48		3.1 (SD 6.3)		
Moderate/severe – 104wkd	Continuous	45		0.1 (SD 0.4)	48		2.5 (SD 4.4)		
Nocturnal (mild) – 52wke	Continuous	45		2.8 (SD 4.8)	48		1.4 (SD 3.1)		
Nocturnal (mild) – 104wke	Continuous	45		1.5 (SD 2.8)	48		0.5 (SD 2)		
Nocturnal (moderate/severe) – 52wke	Continuous	45		0.4 (SD 1.2)	48		0.3 (SD 1.2)		
Nocturnal (moderate/severe) – 104wke	Continuous	45		0.5 (SD 1.3)	48		0.2 (SD 0.6)		
Dropouts:									
Total dropouts – 104wk	Dichotomous	45	8	(17.8%)	48	15	(31.3%)		
Dropout due to AEs – 104wk	Dichotomous	45	5	(11.1%)	48	3	(6.3%)		

[a] estimated from graph; SE converted
[b] SD reported
[c] approximated to nearest integer (percentages only presented in text)
[d] daytime; number per person per year
[e] number per person per year

		Metformin + insulin aspart			NPH insulin				
		N	k	mean	N	k	mean	Δ	p
Blood glucose:									
HbA1c (%) – 12wka	Continuous	45		7.3 (SD 0.671)	46		8.5 (SD 1.15)		
HbA1c (%) – 26wka	Continuous	45		6.9 (SD 0.671)	46		8.3 (SD 1.22)		
HbA1c (%) – 52wka	Continuous	45		7.2 (SD 0.671)	46		8.2 (SD 1.29)		
HbA1c (%) – 104wkb	Continuous	45		7.3 (SD 1.1)	46		8.3 (SD 1.4)		
HbA1c < 7% or <=7% – 104wk	Dichotomous	45	23	(51.1%)	46	9c	(19.6%)		
Fasting plasma glucose (mmol/l) – 104wk	Continuous	45		9.6 (SD 3.1)	46		7.3 (SD 2.5)		
Body weight:									
Weight (kg) – 104wk	Continuous	45		104.4 (SD 19.2)	46		105.5 (SD 20.2)		
Hypoglycaemic events:									
All hypoglycaemic events (no patients) – 104wk	Dichotomous	45	36	(80.0%)	46	35	(76.1%)		
symptomatic (unconfirmed) hypoglycaemia – 52wkd	Continuous	45		9.1 (SD 10.5)	46		2.3 (SD 8.2)		
Moderate/severe – 52wkd	Continuous	45		2.9 (SD 4.9)	46		0.4 (SD 1.4)		
Moderate/severe – 104wkd	Continuous	45		1.5 (SD 2.6)	46		0.3 (SD 0.9)		
Nocturnal (mild) – 52wke	Continuous	45		1.4 (SD 3.1)	46		2.8 (SD 6.1)		
Nocturnal (mild) – 104wke	Continuous	45		0.7 (SD 3)	46		2.8 (SD 4.5)		
Nocturnal (moderate/severe) – 52wke	Continuous	45		0.2 (SD 0.6)	46		0.5 (SD 1.9)		
Nocturnal (moderate/severe) – 104wke	Continuous	45		0.2 (SD 0.7)	46		1.1 (SD 2.9)		
Dropouts:									
Total dropouts – 104wk	Dichotomous	45	7	(15.6%)	46	6	(13.0%)		
Dropout due to AEs – 104wk	Dichotomous	45	2	(4.4%)	46	0	(0.0%)		

[a] estimated from graph; SE converted
[b] SD reported
[c] approximated to nearest integer (percentages only presented in text)
[d] daytime; number per person per year
[e] number per person per year

		Metformin + insulin aspart			Insulin aspart				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 12wka	Continuous	45		7.3 (SD 0.671)	48		7.5 (SD 0.693)		
HbA1c (%) – 26wka	Continuous	45		6.9 (SD 0.671)	48		7.6 (SD 0.693)		
HbA1c (%) – 52wka	Continuous	45		7.2 (SD 0.671)	48		7.8 (SD 0.693)		
HbA1c (%) – 104wkb	Continuous	45		7.3 (SD 1.1)	48		7.9 (SD 1.2)		
HbA1c < 7% or <=7% – 104wk	Dichotomous	45	23	(51.1%)	48	12c	(25.0%)		
Fasting plasma glucose (mmol/l) – 104wk	Continuous	45		9.6 (SD 3.1)	48		12.2 (SD 3.9)		
Body weight: Weight (kg) – 104wk	Continuous	45		104.4 (SD 19.2)	48		104.4 (SD 18.3)		
Hypoglycaemic events: All hypoglycaemic events (no patients) – 104wk	Dichotomous	45	36	(80.0%)	48	43	(89.6%)		
symptomatic (unconfirmed) hypoglycaemia – 52wkd	Continuous	45		9.1 (SD 10.5)	48		10.1 (SD 12.2)		
Moderate/severe – 52wkd	Continuous	45		2.9 (SD 4.9)	48		3.1 (SD 6.3)		
Moderate/severe – 104wkd	Continuous	45		1.5 (SD 2.6)	48		2.5 (SD 4.4)		
Nocturnal (mild) – 52wke	Continuous	45		1.4 (SD 3.1)	48		1.4 (SD 3.1)		
Nocturnal (mild) – 104wke	Continuous	45		0.7 (SD 3)	48		0.5 (SD 2)		
Nocturnal (moderate/severe) – 52wke	Continuous	45		0.2 (SD 0.6)	48		0.3 (SD 1.2)		
Nocturnal (moderate/severe) – 104wke	Continuous	45		0.2 (SD 0.7)	48		0.2 (SD 0.6)		
Dropouts: Total dropouts – 104wk	Dichotomous	45	7	(15.6%)	48	15	(31.3%)		
Dropout due to AEs – 104wk	Dichotomous	45	2	(4.4%)	48	3	(6.3%)		

[a] estimated from graph; SE converted
[b] SD reported
[c] approximated to nearest integer (percentages only presented in text)
[d] daytime; number per person per year
[e] number per person per year

		NPH insulin			Insulin aspart				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 12wka	Continuous	46		8.5 (SD 1.15)	48		7.5 (SD 0.693)		
HbA1c (%) – 26wka	Continuous	46		8.3 (SD 1.22)	48		7.6 (SD 0.693)		
HbA1c (%) – 52wka	Continuous	46		8.2 (SD 1.29)	48		7.8 (SD 0.693)		
HbA1c (%) – 104wkb	Continuous	46		8.3 (SD 1.4)	48		7.9 (SD 1.2)		
HbA1c < 7% or <=7% – 104wkc	Dichotomous	46	9	(19.6%)	48	12	(25.0%)		
Fasting plasma glucose (mmol/l) – 104wk	Continuous	46		7.3 (SD 2.5)	48		12.2 (SD 3.9)		
Body weight: Weight (kg) – 104wk	Continuous	46		105.5 (SD 20.2)	48		104.4 (SD 18.3)		

Hypoglycaemic events:										
All hypoglycaemic events (no patients) – 104wk	Dichotomous	46	35	(76.1%)	48	43	(89.6%)		
symptomatic (unconfirmed) hypoglycaemia – 52wkd	Continuous	46		2.3 (SD 8.2)	48		10.1 (SD 12.2)		
symptomatic (unconfirmed) hypoglycaemia – 104wkd	Continuous	46		2.6 (SD 8.1)	48		7.2 (SD 9.7)		
symptomatic (unconfirmed) hypoglycaemia – 104wkd	Continuous	46		2.6 (SD 8.1)	45		4.1 (SD 5.5)		
Moderate/severe – 52wkd	Continuous	46		0.4 (SD 1.4)	48		3.1 (SD 6.3)		
Moderate/severe – 104wkd	Continuous	46		0.3 (SD 0.9)	48		2.5 (SD 4.4)		
Nocturnal (mild) – 52wke	Continuous	46		2.8 (SD 6.1)	48		1.4 (SD 3.1)		
Nocturnal (mild) – 104wke	Continuous	46		2.8 (SD 4.5)	48		0.5 (SD 2)		
Nocturnal (moderate/severe) – 52wke	Continuous	46		0.5 (SD 1.9)	48		0.3 (SD 1.2)		
Nocturnal (moderate/severe) – 104wke	Continuous	46		1.1 (SD 2.9)	48		0.2 (SD 0.6)		
Dropouts:									
Total dropouts – 104wk	Dichotomous	46	6	(13.0%)	48	15	(31.3%)		
Dropout due to AEs – 104wk	Dichotomous	46	0	(0.0%)	48	3	(6.3%)		

[a] estimated from graph; SE converted
[b] SD reported
[c] approximated to nearest integer (percentages only presented in text)
[d] daytime; number per person per year
[e] number per person per year

The efficacy analysis (A1C) was performed by ANCOVA on changes from baseline to the mean of A1C for 12–24 months (inclusive) with the three treatments and center as fixed main effects and baseline A1C value as a covariate. The patient was a random effect in the model. First-order interactions and each of the following baseline covariates were also included as fixed effects in the statistical model: fasting plasma C-peptide, interaction between fasting plasma C-peptide and treatment, and previous insulin use. Treatment differences in the number of patients with A1C <7.0% were tested using logistic linear regression, with the three treatments and their interactions included in the model. Hypoglycemic

episodes were analyzed using a generalized linear model based on the negative binomial distribution. The number of patients experiencing at least one

hypoglycemic episode was compared with the groups using the Fisher exact test. P-values for all comparison groups were not reported.

Table 14: Haak et al. (2005)

General

Phase:
☐ monotherapy
☐ dual therapy
☑ triple therapy
☐ insulin monotherapy
☐ insulin+oral

Parallel / crossover: Parallel

Country: five European countries

Authors' conclusions: Patients with type 2 diabetes, treated for 26 weeks with insulin detemir plus insulin aspart at mealtimes, experienced comparable glycaemic control but significantly lower within-subject variability and less weight gain compared to patients treated with NPH insulin and insulin aspart. Insulin detemir was well tolerated and had a similar safety profile to NPH insulin.

Source of funding: Unclear

Comments: -

Number and characteristics of patients

Total number of patients: 505

Inclusion criteria: patients with type 2 diabetes of >=12 months duration, aged>=35 years, HbA1c <=12.0% and who had received insulin treatment for at least 2 months (basal insulin dose >=30% of the total daily

	insulin dose) were included in the trial **Exclusion criteria:** Patients were excluded if they had received OADs within 2 months of the trial, were pregnant or breast feeding, suffered from proliferative retinopathy, uncontrolled hypertension, recurrent major hypoglycaemia, impaired renal or hepatic function, cardiac problems, or if they received a total daily basal insulin dose >100 IU/day
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** all on oral hypoglycaemic drugs and/or insulin **Details of washout period:** All taking insulin monotherapy at study start (no OADs were taken in the previous 2 months)
Lifestyle advice	-
Follow-up	**Total follow-up (wks):** 29 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 26 **Frequency of monitoring appointments:** -
Arms	**(1) Insulin detemir + aspart** N: 341 Treatment duration (wks): 26 Washout period (d): 0 Comments: All taking insulin monotherapy at study start Treatment(s): (a) Insulin detemir (Subcutaneous) – flexible-dose (dose-adjusted) Details of dosing regimen: Patients receiving more than one basal insulin injection per day prior to the trial received twice-daily (before breakfast and at bedtime) injections following randomisation. All other patients, including those receiving biphasic (premixed insulin) prior to the trial, received a once-daily basal insulin injection (at bedtime). Throughout the trial, basal insulin doses were optimised according to self-measured blood glucose (SMBG) values. Patients randomised to insulin detemir were initiated on 50% of their pretrial basal insulin dose.During the trial, patients were instructed to aim for the following SMBG levels: prebreakfast, 4–7 mmol/l; nocturnal (02 : 00–04 : 00), 4–7 mmol/l; postprandial (90 min after meal), <10 mmol/l. If a patient did not reach these SMBG targets on a once-daily basal insulin regimen (either with insulin detemir or NPH insulin), and further dose escalations were inadvisable, they were transferred to a twice-daily basal insulin regimen with appropriate dose adjustments. (b) Insulin aspart (short acting) (Subcutaneous) – flexible-dose (dose-adjusted) Frequency of dosing: three times a day Details of dosing regimen: For all patients, insulin aspart was administered immediately prior to each main meal **(2) Insulin NPH + aspart** N: 164 Treatment duration (wks): 26 Washout period (d): 0 Comments: All taking insulin monotherapy at study start Treatment(s): (a) NPH insulin (Subcutaneous) – flexible-dose (dose-adjusted) Details of dosing regimen: Patients randomised to NPH insulin continued with their pretrial basal insulin dose. (b) Insulin aspart (short acting) (Subcutaneous) – flexible-dose (dose-adjusted)
Outcomes	**General** All analyses were based on the intention-to-treat (ITT) analysis set, which included all patients randomised and exposed to at least one dose of study drug. 26/341 (7.6%) patients in the detemir group and 8/164 (4.9%) in the NPH group discontinued the study. Outcomes not extracted in this evidence table include 9 point glucose profiles **Hypoglycaemic events** Minor (confirmed) hypoglycaemia (defined as minor if blood glucose concentration was <2.8 mmol/l but no assistance was required) Major/severe hypoglycaemic event (Hypoglycaemic episodes were classified as major when a subject was unable to treat him/herself) symptomatic (unconfirmed) hypoglycaemia (defined as symptoms only if the episode was not confirmed by a blood glucose measurement) Nocturnal hypoglycaemia (Nocturnal hypoglycaemia was defined as any hypoglycaemic episode that occurred between the hours of 23:00 and 06:00)
Baseline characteristics	

	Insulin detemir + aspart	Insulin NPH + aspart	Δ	p

			N	k	mean	N	k	mean		
Demographics: Age (years)		Continuous	341		60.6 (SD 8.7)	164		60 (SD 8.4)		
Sex (n male)		Dichotomous	341	165	(48.4%)	164	93	(56.7%)		
Duration of diabetes (yrs)		Continuous	341		12.9 (SD 7.4)	164		13.7 (SD 8)		
Blood glucose: HbA1c (%) – 0wk		Continuous	341		7.9 (SD 1.3)	164		7.8 (SD 1.3)		
Fasting plasma glucose (mmol/l) – 0wk		Continuous	341		10.1 (SD 3.32)	164		10.4 (SD 3.42)		
Body weight: BMI (kg/m2)		Continuous	341		30.1 (SD 5)	164		31.1 (SD 5.8)		
Weight (kg) – 0wk		Continuous	341		85.7 (SD 14.9)	164		89.3 (SD 17.5)		
Insulin: Total daily dose (U) a		Continuous	341		33.6 (SD 19.2)	164		34.8 (SD 19.9)		
Total daily dose (U) b		Continuous	341		27.8 (SD 14.7)	164		28 (SD 15.4)		
Total daily dose (U)		Continuous	341		33.6 (SD 19.2) a	164		28 (SD 15.4) b		
Total daily dose (U)		Continuous	341		27.8 (SD 14.7) b	164		34.8 (SD 19.9) a		

[a] bolus
[b] basal

Results

		Insulin detemir + aspart			Insulin NPH + aspart				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 26wka	Continuous	341		7.6 (SD 1.77)	164		7.5 (SD 1.24)	MD=0.160 (CI: 0.003, 0.317)	
HbA1c (%) – 26wka	Continuous	315		7.6 (SD 1.77)	155		7.5 (SD 1.24)	MD=0.160 (CI: 0.003, 0.317)	
Fasting plasma glucose (mmol/l) – 26wkb	Continuous	341		9.7 (SD 3.69)	164		9.6 (SD 3.84)	MD=0.110 (CI: -0.400, 0.620)	NS
Body weight: Weight (kg) – 26wk	Continuous	341			164			MD=-0.790 (CI: -1.440, -0.140)	0.017c
Weight (kg) – 26wk	Mean change	341		1	164		1.8		
Hypoglycaemic events: All hypoglycaemic events (no events) – 26wkd	Dichotomous	341	1218	(357.2%)	164	708	(431.7%)	RR=0.840 (CI: 29.306, 0.024)	0.48
All hypoglycaemic events (no events) – 26wke	Count	59696	1218		29120	708			
All hypoglycaemic events (no patients) – 26wkf	Dichotomous	341	152	(44.6%)	164	80	(48.8%)		
Minor (confirmed) hypoglycaemia – 26wkg	Dichotomous	341			164				NR
Major/severe hypoglycaemic event – 26wkg	Dichotomous	341			164				NR

	symptomatic (unconfirmed) hypoglycaemia – 26wkg	Dichotomous	341			164				NR
	Nocturnal hypoglycaemia – 26wk	Dichotomous	341	166h	(48.7%)	164	38f	(23.2%)	RR=1.020 (CI: 16.752, 0.062)	0.95
	Nocturnal hypoglycaemia – 26wk	Dichotomous	341	52f	(15.2%)	164	80h	(48.8%)	RR=1.020 (CI: 16.752, 0.062)	0.95
	Nocturnal hypoglycaemia – 26wkh	Dichotomous	341	166	(48.7%)	164	80	(48.8%)	RR=1.020 (CI: 16.752, 0.062)	0.95
	Nocturnal hypoglycaemia – 26wkf	Dichotomous	341	52	(15.2%)	164	38	(23.2%)	RR=1.020 (CI: 16.752, 0.062)	0.95
	Nocturnal hypoglycaemia – 26wke	Count	59696	166		29120	80			
	Adverse events:									
	Any serious adverse event(s) – 26wki	Dichotomous	341	0	(0.0%)	164	1	(0.6%)		NR
	Death – 26wk	Dichotomous	341	1	(0.3%)	164	0	(0.0%)		NR
	Dropouts:									
	Total dropouts – 26wk	Dichotomous	241	26	(10.8%)	164	8	(4.9%)		

[a] SD calculated from SE
[b] unclear if this was conducted in ITT population
[c] adjusted for baseline weight
[d] No of events
[e] person day estimated assuming dropout halfway through the study
[f] No of patients
[g] Not reported
[h] No episodes
[i] related to study drug; no of events

The primary endpoint, HbA1c (%) after 26 weeks of treatment, was evaluated by an analysis of variance (ANOVA) model, with treatment and country as fixed effects and covariate adjustment for baseline values. Change in body weight (both with and without adjustment for change in HbA1c concentration) and FPG levels following 26 weeks of treatment were analysed using a similar ANOVA model to that used for the primary endpoint. To estimate the relative risk of hypoglycaemia, all hypoglycaemic episodes occurring during the maintenance period were analysed as recurrent events using a gamma frailty model with treatment group as covariate. Nocturnal hypoglycaemic episodes were analysed separately

Table 15: Hartemann-Heurtier et al. (2009)

General

Phase:
☐ monotherapy
☐ dual therapy
☑ triple therapy
☐ insulin monotherapy
☐ insulin+oral

Parallel / crossover: Parallel

Country: France

Authors' conclusions: 24 week treatment with pioglitazone or bed-time insulin has a similar impact on intra-abdominal fat mass and systemic low-grade inflammation

Source of funding: Public funds from Assistance Publique des Hopitaux de Paris

Comments: Randomisation was made by reference to a statistical series whose details were unknown to the investigators and were contained in a set of sealed envelopes

Number and characteristics of patients	**Total number of patients:** 28 **Inclusion criteria:** type 2 diabetes aged 18-80 years, BMI>=26 kg/m2 with Hba1c between 7.5 and 9.5% and treated with maximally tolerated and stable doses of sulfonylurea and metformin for >=6 months **Exclusion criteria:** prior use of insulin or glitazones, use of other affecting glycaemic control agents, ASAT ot ALAT >2.5 fold the ypper limit of normal, eGFR <60 ml/min, heart failure >=grade 2, haemaglobin <10 g/dl
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** all on oral hypoglycaemic drugs and/or insulin **Details of washout period:** all patients were treated with maximally tolerated and stable doses of sulfonylurea and metformin
Lifestyle advice	-
Follow-up	**Total follow-up (wks):** 24 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 24 **Frequency of monitoring appointments:** Data was measured at enrollment and at 24 weeks
Arms	**(1) Metformin + sulfonylurea + pioglitazone** N: 14 Treatment duration (wks): 24 Washout period (d): 0 Treatment(s): (a) Metformin (Oral) Details of dosing regimen: Metformin and sulfonylurea were contiuned but specific doses were not reported (b) Sulfonylurea (Oral) Details of dosing regimen: Metformin and sulfonylurea were contiuned but specific doses were not reported (c) Pioglitazone (Oral) – flexible-dose (dose-adjusted) Details of dosing regimen: At the follow up visits (2 and 4 months) pioglitazone was increased from 30 to 45 mg/day if Hba1c had not decreased by at least 1%, in the presence of lower limb oedema, the investigator could decrease the dose to 15 mg/day. At the end of the study, 57% received 30 mg, 36% received 45 mg and 7% received 15 mg **(2) Metformin + sulfonylurea +human NPH insulin** N: 13 Treatment duration (wks): 24 Washout period (d): 0 Treatment(s): (a) Metformin (Oral) Details of dosing regimen: Metformin and sulfonylurea were contiuned but specific doses were not reported (b) Sulfonylurea (Oral) Details of dosing regimen: Metformin and sulfonylurea were continued but specific doses were not reported (c) NPH insulin (Subcutaneous) – flexible-dose (dose-adjusted) Mean dose (mg/d): 0.3 Frequency of dosing: once a day Details of dosing regimen: Human NPH insulin was given at 0.2 IU/kg/day at bedtime for 24 weeks. Patients were contacted weekly by phone to discuss dosage changes. Target FPG was <6.1 mmol/l
Outcomes	**General** Outcomes not extracted in this evidence table include free fatty acids (FFAs), adiponectin concentrations, serum inflammation markers, ferritin 1 patient from each group withdrew from the study (although the one from the pioglitazone group was still included in the analysis)

Baseline characteristics

		Metformin + sulfonylurea + pioglitazone			Metformin + sulfonylurea +human NPH insulin			Δ	p
		N	k	mean	N	k	mean		
Demographics:									
Age (years)	Continuous	14		62 (SD 10)	13		58 (SD 10)		
Sex (n male)	Dichotomous	14	9	(64.3%)	13	7	(53.8%)		
Duration of diabetes (yrs)	Continuous	14		12 (SD 4.5)	13		12 (SD 6)		

Blood glucose: HbA1c (%) – 0wk	Continuous	14		8.3 (SD 0.5)	13		8.6 (SD 0.5)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	14		8.5 (SD 2.2)	13		9.5 (SD 2.6)		
Body weight: BMI (kg/m2)	Continuous	14		30 (SD 5)	13		32 (SD 4)		
Weight (kg) – 0wk	Continuous	14		85 (SD 13)	13		90 (SD 14)		
Waist circumference (cms)	Continuous	14		106 (SD 12)	13		110 (SD 11)		

Results

		Metformin + sulfonylurea + pioglitazone			Metformin + sulfonylurea +human NPH insulin				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Blood glucose: HbA1c (%) – 24wka	Mean change	14		-1.2 (SD 0.7)	13		-1.6 (SD 0.5)		
HbA1c (%) – 24wk	Continuous	14		7.1 (SD 0.6)	13		7 (SD 0.5)		NS
Fasting plasma glucose (mmol/l) – 24wka	Mean change	14		-0.02 (SD 0.08)	13		-0.11 (SD 0.06)		
Fasting plasma glucose (mmol/l) – 24wk	Continuous	14		7.7 (SD 2.2)	13		5.5 (SD 1.6)		<0.01
Body weight: Weight (kg) – 24wka	Mean change	14		3.7 (SD 3.5)	13		2.4 (SD 1.7)		
Weight (kg) – 24wk	Continuous	14		89 (SD 15)	13		92 (SD 14)		NS
Hypoglycaemic events: Symptomatic hypoglycaemia – 24wk	Dichotomous	14	6	(42.9%)	13	10	(76.9%)		
Dropouts: Total dropouts – 24wk	Dichotomous	14	1b	(7.1%)	14	1c	(7.1%)		
Dropout due to AEs – 24wk	Dichotomous	14	1	(7.1%)	14	1	(7.1%)		

[a] SD reported
[b] Person dropped out because of weight gain after 4 months (data included in analysis)
[c] Person dropped out because of hypoglycaemia (data not included in analysis)

Comparisons between baseline and final parameter values were performed using sign rank test and comparisons between groups were assessed using Fisher's exact test for qualitative variables and two sample Wilcoxon tests for quantitative ones

Table 16: Heine et al. (2005)

General

Phase:
☐ monotherapy
☐ dual therapy
☑ triple therapy
☐ insulin monotherapy
☐ insulin+oral

Parallel / crossover: Parallel

Country: 13 countries

Authors' conclusions: Exenatide and insulin glargine achieved similar improvements in overall glycaemic control in patients with type 2 diabetes that was suboptimally controlled with oral combination therapy. Exenatide was associated with weight reduction and had a higher incidence of gastrointestinal adverse effects than insulin glargine

Source of funding: Eli Lilly and Amylin Pharmaceuticals

Comments: Open label trial. Central randomisation table was generated by the sponsor and administrered by an automated interactive voice response system

Number and characteristics of patients	**Total number of patients:** 551 **Inclusion criteria:** 30 to 75 years and were treated with stable and maximally effective doses of metformin and a sulfonylurea for at least 3 months before screening. Hba1c level from 7 to 10%, BMI from 25 to 45 kg/m2, a history of stable body weight **Exclusion criteria:** participated in a research study within 30 days before screening, had more than 3 episodes of severe hypoglycaemia within 6 months, therapy for skin cancer, had cardiac disease, serum creatinine >135 µmol/L for men or >110 µmol/L for women, signs and symptoms of liver disease, long term systemic glucocorticoid therapy, use of prescription drugs for weight loss, treated with insulin within 3 months, thiazolidinediones within 4 months, alpha glucosidase within 3 months or meglitinides within 3 months before screening
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** all on oral hypoglycaemic drugs and/or insulin **Details of washout period:** All patients were treated with stable and maximally effective dose sof metformin and sulfonylurea for at least 3 months prior to screening
Lifestyle advice	-
Follow-up	**Total follow-up (wks):** 26 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 26 **Frequency of monitoring appointments:** Hba1c was measured at screening, week 12 and week 26
Arms	**(1) Metformin + sulfonylurea + exenatide** N: 282 Treatment duration (wks): 26 Washout period (d): 0 Treatment(s): (a) Metformin (Oral) Details of dosing regimen: Metformin doses were fixed at pre-study levels unless the patient experienced hypoglycaemia (b) Sulfonylurea (Oral) Details of dosing regimen: Sulfonylurea doses were fixed at pre-study levels unless the patient experienced hypoglycaemia, in which case a 50% dose reduction was recommended in sulfonylurea. (c) Exenatide (Subcutaneous) – forced titration Set dose (mg/d):10 Frequency of dosing: twice a day Details of dosing regimen: Exenatide (before morning and evening meal) was added to current therapy. For 4 weeks 5 µg bid was given and then this was increased to 10 µg for the remainder of the study **(2) Metformin + sulfonylurea + insulin glargine** N: 267 Treatment duration (wks): 26 Washout period (d): 0 Treatment(s): (a) Metformin (Oral) Details of dosing regimen: Metformin doses were fixed at pre-study levels unless the patient experienced hypoglycaemia (b) Sulfonylurea (Oral) Details of dosing regimen: Sulfonylurea doses were fixed at pre-study levels unless the patient experienced hypoglycaemia, in which case a 50% dose reduction was recommended in sulfonylurea. (c) Insulin glargine (Subcutaneous) – flexible-dose (dose-adjusted) Mean dose (mg/d): 25 Details of dosing regimen: Insulin glargine was started at 10 U/d, then using a fixed dose algorithm to adjust the dose, patients self-titrated the dose in 2 U increments every 3 days to achieve FBG <5.6 mmol/l on daily glucose monitoring. At week 26 the average dose of insulin glargine was 25.0 U/d
Outcomes	**General** Outcomes not extracted in this evidence table include SMBG, postprandial BG 54 (19%) in the exenatide group and 25 (9.4%) in the insulin glargine group were withdrawn from the study ITT analysis was defined as any patient who had at least 1 postbaseline measurement of Hba1c. The PP analysis was defined as patients who had at least 12 weeks exposure to study medication, had no violations at screening and did not discontinue the study Data from Matyjaszek-Matuszek (2013) for patients from poland as a subgroup of the overall study population are also included in this evidence table **Hypoglycaemic events** Major/severe hypoglycaemic event (hypoglycaemia episode in which the patient required assistance from

	another person and had a blood glucose < 2.8 mmol/L or had promptly recovered after oral carbohydrate or glucagon injection or IV glucose) Symptomatic hypoglycaemia (BG <3.4 mmol/L or hypoglycaemia accompanied by symptoms such as sweating, shaking, pounding heart or confusion)

Baseline characteristics

		Metformin + sulfonylurea + exenatide			Metformin + sulfonylurea + insulin glargine			Δ	p
		N	k	mean	N	k	mean		
Demographics: Age (years)	Continuous	282		59.8 (SD 8.8)	267		58 (SD 9.5)		
Sex (n male) a	Dichotomous	282	155	(55.0%)	267	151	(56.6%)		
Duration of diabetes (yrs)	Continuous	282		9.9 (SD 6)	267		9.2 (SD 5.7)		
Blood glucose: HbA1c (%) – 0wk	Continuous	282		8.2 (SD 1)	267		8.3 (SD 1)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	282		10.1 (SD 2.6)	267		10.4 (SD 2.9)		
Body weight: BMI (kg/m2)	Continuous	282		31.4 (SD 4.4)	267		31.3 (SD 4.6)		
Weight (kg) – 0wk	Continuous	282		87.5 (SD 16.9)	267		88.3 (SD 17.9)		

[a] approximated to nearest integer (percentages only presented in text)

Results

		Metformin + sulfonylurea + exenatide			Metformin + sulfonylurea + insulin glargine			Δ	p
		N	k	mean	N	k	mean		
Hypoglycaemic events: All hypoglycaemic events (no events) – 0wk	Count	282			267				a
All hypoglycaemic events (no events) – 26wkb	Continuous	282		7.3	267		6.3		
All hypoglycaemic events (no events) – 26wkc	Count	46410	928		46319	799			
Major/severe hypoglycaemic event – 0wk	Count	282			267				d
Major/severe hypoglycaemic event – 26wke	Dichotomous	282	4	(1.4%)	267	4	(1.5%)		
Symptomatic hypoglycaemia – 26wkd	Dichotomous	282			267				
Nocturnal hypoglycaemia – 0wk	Count	282			267				a
Nocturnal hypoglycaemia – 26wkc	Count	46410	115		46501	307			
Nocturnal hypoglycaemia – 26wkb	Continuous	282		0.9	267		2.4		
Adverse events: GI: nausea – 0wk	Dichotomous	282			267				<0.001
GI: nausea – 26wkf	Dichotomous	282	161	(57.1%)	267	23	(8.6%)		
Asthenia – 0wk	Dichotomous	282			267				NS
Asthenia – 26wkf	Dichotomous	282	6	(2.1%)	267	7	(2.6%)		
Arthralgia – 0wk	Dichotomous	282			267				NS

Arthralgia – 26wkf	Dichotomous	282	9	(3.2%)	267	10	(3.7%)		
Back pain – 26wkf	Dichotomous	282	17	(6.0%)	267	8	(3.0%)		
Bronchitis – 0wk	Dichotomous	282			267				NS
Bronchitis – 26wkf	Dichotomous	282	5	(1.8%)	267	7	(2.6%)		
Chest pain – 0wk	Dichotomous	282			267				NS
Chest pain – 26wkf	Dichotomous	282	6	(2.1%)	267	3	(1.1%)		
Cough – 0wk	Dichotomous	282			267				NS
Cough – 26wkf	Dichotomous	282	11	(3.9%)	267	8	(3.0%)		
Dizziness – 0wk	Dichotomous	282			267				NS
Dizziness – 26wkf	Dichotomous	282	15	(5.3%)	267	6	(2.2%)		
Dyspepsia – 0wk	Dichotomous	282			267				0.011
Dyspepsia – 26wkf	Dichotomous	282	10	(3.5%)	267	1	(0.4%)		
GI: diarrhoea – 0wk	Dichotomous	282			267				0.006
GI: diarrhoea – 26wkf	Dichotomous	282	24	(8.5%)	267	8	(3.0%)		
GI: vomiting – 0wk	Dichotomous	282			267				<0.001
GI: vomiting – 26wkf	Dichotomous	282	49	(17.4%)	267	10	(3.7%)		
GI: abdominal pain – 0wk	Dichotomous	282			267				0.012
GI: abdominal pain – 26wkf	Dichotomous	282	12	(4.3%)	267	2	(0.7%)		
GI: constipation – 0wk	Dichotomous	282			267				0.011
GI: constipation – 26wkf	Dichotomous	282	10	(3.5%)	267	1	(0.4%)		
Headache – 0wk	Dichotomous	282			267				NS
Headache – 26wkf	Dichotomous	282	25	(8.9%)	267	23	(8.6%)		
Infection (upper airway or other common) – 0wk	Dichotomous	282			267				NS
Infection (upper airway or other common) – 26wkf	Dichotomous	282	15	(5.3%)	267	13	(4.9%)		
Nasopharyngitis – 0wk	Dichotomous	282			267				NS
Nasopharyngitis – 26wkf	Dichotomous	282	22	(7.8%)	267	24	(9.0%)		
Pain (extremity) – 0wk	Dichotomous	282			267				NS
Pain (extremity) – 26wkf	Dichotomous	282	11	(3.9%)	267	8	(3.0%)		
Rash – 0wk	Dichotomous	282			267				NS
Rash – 26wkf	Dichotomous	282	3	(1.1%)	267	6	(2.2%)		
Temperature/influenza – 0wk	Dichotomous	282			267				NS
Temperature/influenza – 26wkf	Dichotomous	282	7	(2.5%)	267	15	(5.6%)		
UTI – 0wk	Dichotomous	282			267				NS
UTI – 26wkf	Dichotomous	282	7	(2.5%)	267	3	(1.1%)		
Dropouts:									
Total dropouts – 26wk	Dichotomous	282	54	(19.1%)	267	25	(9.4%)		
Dropout due to AEs – 26wk	Dichotomous	282	27	(9.6%)	267	2	(0.7%)		
ITT									
Blood glucose:									
HbA1c (%) – 12wkg	Mean change	275		-1.24	260		-1.08	MD=-0.162 (CI: -0.301, -0.023)	
HbA1c (%) – 26wkh	Mean change	275		-1.11	260		-1.11	MD=0.017 (CI: -0.123, 0.157)	
Fasting plasma glucose (mmol/l) – 26wkg	Mean change	275		-1.4	260		-2.9	MD=1.500 (CI: 1.100, 1.900)	

Body weight: Weight (kg) – 12wki	Mean change	275		-1.4 (SD 1.66)	260		1.3 (SD 0.806)		
Weight (kg) – 26wki	Mean change	275		-2.3 (SD 3.65)	260		1.8 (SD 3.55)	MD=-4.100 (CI: -4.600, -3.600)	
Poland Blood glucose: HbA1c (%) – 26wk	Mean change	40		-0.72 (SD 0.759)	40		-0.64 (SD 0.759)	MD=-0.070 (CI: -0.403, 0.263)	
HbA1c < 7% or <=7% – 26wkj	Dichotomous	40	17	(42.5%)	40	15	(37.5%)		
Fasting plasma glucose (mmol/l) – 26wk	Mean change	40		-0.56 (SD 2.53)	40		-1.43 (SD 2.47)	MD=0.870 (CI: -0.240, 1.980)	
Body weight: Weight (kg) – 26wk	Mean change	40		-1.9 (SD 3.04)	40		1.6 (SD 3.04)	MD=-3.500 (CI: -4.833, -2.167)	
Hypoglycaemic events: All hypoglycaemic events (no events) – 26wk	Count	40			40				0.995
All hypoglycaemic events (no events) – 26wkk	Continuous	40		0.11	40		0.1		
Nocturnal hypoglycaemia – 26wk	Count	40			40				0.175
Nocturnal hypoglycaemia – 26wkk	Continuous	40		0	40		0.1		
Adverse events: GI: nausea – 26wkl	Dichotomous	40	22	(55.0%)	40	1	(2.5%)		
GI: nausea – 26wke	Dichotomous	40	17	(42.5%)	40	1	(2.5%)		
GI: nausea – 26wk	Dichotomous	40	22l	(55.0%)	40	1e	(2.5%)		
GI: nausea – 26wk	Dichotomous	40	17e	(42.5%)	40	1l	(2.5%)		
GI: vomiting – 26wk	Dichotomous	40	5l	(12.5%)	40	0e	(0.0%)		
GI: vomiting – 26wkl	Dichotomous	40	5	(12.5%)	40	0	(0.0%)		
GI: vomiting – 26wke	Dichotomous	40	4	(10.0%)	40	0	(0.0%)		
GI: vomiting – 26wk	Dichotomous	40	4e	(10.0%)	40	0l	(0.0%)		
GI: abdominal pain – 26wk	Dichotomous	40	3l	(7.5%)	40	0e	(0.0%)		
GI: abdominal pain – 26wk	Dichotomous	40	3e	(7.5%)	40	0l	(0.0%)		
GI: abdominal pain – 26wkl	Dichotomous	40	3	(7.5%)	40	0	(0.0%)		
GI: abdominal pain – 26wke	Dichotomous	40	3	(7.5%)	40	0	(0.0%)		
Headache – 26wk	Dichotomous	40	4e	(10.0%)	40	2l	(5.0%)		
Headache – 26wk	Dichotomous	40	8l	(20.0%)	40	2e	(5.0%)		
Headache – 26wke	Dichotomous	40	4	(10.0%)	40	2	(5.0%)		
Headache – 26wkl	Dichotomous	40	8	(20.0%)	40	2	(5.0%)		
Infection (upper airway or other common) – 26wkl	Dichotomous	40	2	(5.0%)	40	0	(0.0%)		
Infection (upper airway or other common) – 26wk	Dichotomous	40	2e	(5.0%)	40	0l	(0.0%)		
Infection (upper airway or other common) – 26wk	Dichotomous	40	2l	(5.0%)	40	0e	(0.0%)		
Infection (upper airway or other common) – 26wke	Dichotomous	40	2	(5.0%)	40	0	(0.0%)		

	Nasopharyngitis – 26wk	Dichotomous	40	4l	(10.0%)	40	2e	(5.0%)		
	Nasopharyngitis – 26wk	Dichotomous	40	4e	(10.0%)	40	2l	(5.0%)		
	Nasopharyngitis – 26wkl	Dichotomous	40	4	(10.0%)	40	2	(5.0%)		
	Nasopharyngitis – 26wke	Dichotomous	40	4	(10.0%)	40	2	(5.0%)		

[a] events per patient year
[b] events per patient year; 95% CI not reported
[c] Person days estimated assuming dropouts halfway through the trial and no of events calculated using reported rates
[d] NR
[e] no patients
[f] No of patients
[g] SE not reported
[h] percentage points; SE not reported
[i] estimated from graph; SE converted
[j] approximated to nearest integer (percentages only presented in text)
[k] events/patient/30 days; 95% CI not reported
[l] no events

Unclear graphs for Hba1c with unclear SEs and unclear denominators fpr per protocol analyses, therefore these were not extracted.

Mixed effect model repeated measures (MMRM) was used for the primary analyses. The model included change in Hba1c as the dependent variable, treatment, week of visit, treatment by week interaction, baseline value Hba1c and country as fixed effects and patient and error as random effects. There was no imputation of missing data. Categorical data were analysed using Fishers exact test to compare treatments.

Table 17: Heise et al. (2011)

General	**Phase:** ☐ monotherapy ☐ dual therapy ☑ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** five European countries (France, Germany, Norway, Romania, and Spain) **Authors' conclusions:** In this proof-of-concept trial, once-daily IDegAsp was safe, well tolerated, and provided comparable overall glycemic control to insulin glargine at similar low rates of hypoglycemia, but better postdinner plasma glucose control **Source of funding:** Novo Nordisk **Comments:** open-label, randomized, controlled 16-week trial. Randomization was carried out using a telephone- or web-based randomization system, with subjects stratified according to pretrial OAD treatment
Number and characteristics of patients	**Total number of patients:** 178 **Inclusion criteria:** Adults with type 2 diabetes were enrolled if they were 18–75 years of age, had an A1C of 7–11%, and had a BMI of 25–37 kg/m2. Subjects had to be insulin-naïve (no previous insulin treatment or insulin treatment for <=14 days in the 3 months prior to trial), and had to be treated with up to two OADs in the 2 months prior to trial at stable maximum doses or at least half maximum allowed doses **Exclusion criteria:** been treated with thiazolidinediones in the 3 months preceding the trial. Other exclusion criteria included cardiac disease within 12 months of the trial, severe hypertension (systolic blood pressure >=180 mmHg or sitting diastolic blood pressure >=100 mmHg), recurrent severe hypoglycemia or hypoglycemia unawareness, use of drugs likely to affect glycemia, impaired hepatic function, pregnancy, and breast-feeding Pre-randomisation phase: eligible subjects discontinued their pretrial OAD treatment and underwent a 2-week forced metformin titration period followed by a 1-week metformin maintenance period
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** all on oral hypoglycaemic drugs and/or insulin **Details of washout period:** All patients had to be treated with up to 2 OADs in the two months prior to trial. Patients were then required to undergo metformin forced titration for 2 weeks
Lifestyle advice	-

Follow-up	**Total follow-up (wks):** 18 **Length of titration period (wks):** 2 **Length of maintenance period (wks):** 16 **Frequency of monitoring appointments:** -
Arms	**(1) Metformin + insulin glargine** N: 60 Treatment duration (wks): 16 Washout period (d): 14 Comments: 2 week forced titration of metformin while discontinuing all other drugs Treatment(s): (a) Metformin (Oral) – forced titration Set dose (mg/d):2000 Frequency of dosing: twice a day Details of dosing regimen: 2-week forced metformin titration period (dose increased up to 2,000 mg/day: 1,000 mg each at breakfast and the evening meal) followed by a 1-week metformin maintenance period. Subjects taking metformin at enrollment could undergo a modified titration period or advance directly to the metformin maintenance period. Metformin could be decreased to aminimum of 1,500 mg/day in the case of unacceptable hypoglycemia or other adverse events. Subjects were eligible for randomization provided the maximum dailymetformin dose (2,000 mg) or maximum tolerated dose (1,500 mg) remained unchanged in the maintenance period and the median prebreakfast self-measured plasma glucose (SMPG) value (measured on the 3 days prior to randomization) was >=7.5 mmol/L (135 mg/dL). (b) Insulin glargine (Subcutaneous) – flexible-dose (dose-adjusted) Mean dose (mg/d): 0.45 Details of dosing regimen: The insulin starting dose was 10 units administered in the abdomen (IDegAsp, AF) or thigh (IGlar) before the evening meal. IDegAsp and AF were administered using a 3 mL FlexPen device; Iglar was administered using a 3 mL Optiset device. Based on SMPG levels before breakfast (lowest FPG value from 3 consecutive days), insulin doses were individually titrated once a week throughout the trial (by clinic or telephone contacts) aiming at an FPG level of 4.0–6.0 mmol/L (72– 108 mg/dL) **(2) Metformin + insulin (degludec 70% apart 30%)** N: 59 Treatment duration (wks): 16 Washout period (d): 14 Comments: 2 week forced titration of metformin while discontinuing all other drugs Treatment(s): (a) Metformin (Oral) – forced titration Set dose (mg/d):2000 Frequency of dosing: twice a day Details of dosing regimen: see arm 1 for details (b) Insulin degludec/aspart mix (Subcutaneous) – flexible-dose (dose-adjusted) Mean dose (mg/d): 0.38 Details of dosing regimen: see arm 1 for dosing information **(3) Metformin + insulin (55% degludec 45% aspart)** N: 59 Treatment duration (wks): 16 Washout period (d): 14 Comments: 2 week forced titration of metformin while discontinuing all other drugs Treatment(s): (a) Metformin (Oral) – forced titration Set dose (mg/d):2000 Frequency of dosing: twice a day Details of dosing regimen: see arm 1 for details (b) Insulin degludec/aspart mix (Subcutaneous) – flexible-dose (dose-adjusted) Mean dose (mg/d): 0.36 Details of dosing regimen: see arm 1 for details of dosing
Outcomes	**General** Outcomes not extracted in this eveidence table include SMBG levels and postprandial blood glucose. 5 (8%) patients in the glargine group, 4 (7%) in the degludec 70/aspart 30 group and 6 (10%) in the degludec 55/aspart 45 group discontinued the study The statistical evaluation of A1C, FPG, and 2-h postprandial plasma glucose increment was based on all randomized subjects following the intention-to-treat principle. Missing values for A1C and FPG were imputed using last observation carried forward.

Baseline characteristics

		Metformin + insulin glargine			Metformin + insulin (degludec 70% apart 30%)			Δ	p
		N	k	mean	N	k	mean		
Demographics: Age (years)	Continuous	60		58.4 (SD 8.4)	59		58.7 (SD 8.8)		
Sex (n male) a	Dichotomous	60	44	(73.3%)	59	37	(62.7%)		
Duration of diabetes (yrs)	Continuous	60		8.5 (SD 4.8)	59		9.1 (SD 8)		
Blood glucose: HbA1c (%) – 0wk	Continuous	60		8.4 (SD 1.3)	59		8.3 (SD 1.2)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	60		12.1 (SD 3.5)	59		11.1 (SD 3.3)		
Body weight: BMI (kg/m2)	Continuous	60		30.5 (SD 3.5)	59		30.2 (SD 3.4)		
Weight (kg) – 0wk	Continuous	60		86.8 (SD 11.3)	59		85.1 (SD 11.7)		
Previous blood glucose lowering drugs: Metformin + Sulfonylurea	Dichotomous	60	30	(50.0%)	59	28	(47.5%)		

[a] approximated to nearest integer (percentages only presented in text)

		Metformin + insulin glargine			Metformin + insulin (55% degludec 45% aspart)			Δ	p
		N	k	mean	N	k	mean		
Demographics: Age (years)	Continuous	60		58.4 (SD 8.4)	59		60.2 (SD 8.2)		
Sex (n male) a	Dichotomous	60	44	(73.3%)	59	34	(57.6%)		
Duration of diabetes (yrs)	Continuous	60		8.5 (SD 4.8)	59		9.5 (SD 5.8)		
Blood glucose: HbA1c (%) – 0wk	Continuous	60		8.4 (SD 1.3)	59		8.6 (SD 1.5)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	60		12.1 (SD 3.5)	59		11.5 (SD 3.2)		
Body weight: BMI (kg/m2)	Continuous	60		30.5 (SD 3.5)	59		30.3 (SD 4.3)		
Weight (kg) – 0wk	Continuous	60		86.8 (SD 11.3)	59		83.9 (SD 15.7)		
Previous blood glucose lowering drugs: Metformin + Sulfonylurea	Dichotomous	60	30	(50.0%)	59	29	(49.2%)		

[a] approximated to nearest integer (percentages only presented in text)

		Metformin + insulin (degludec 70% apart 30%)			Metformin + insulin (55% degludec 45% aspart)			Δ	p
		N	k	mean	N	k	mean		
Demographics: Age (years)	Continuous	59		58.7 (SD 8.8)	59		60.2 (SD 8.2)		
Sex (n male) a	Dichotomous	59	37	(62.7%)	59	34	(57.6%)		
Duration of diabetes (yrs)	Continuous	59		9.1 (SD 8)	59		9.5 (SD 5.8)		
Blood glucose: HbA1c (%) – 0wk	Continuous	59		8.3 (SD 1.2)	59		8.6 (SD 1.5)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	59		11.1 (SD 3.3)	59		11.5 (SD 3.2)		
Body weight: BMI (kg/m2)	Continuous	59		30.2 (SD 3.4)	59		30.3 (SD 4.3)		
Weight (kg) – 0wk	Continuous	59		85.1 (SD 11.7)	59		83.9 (SD 15.7)		

Previous blood glucose lowering drugs: Metformin + Sulfonylurea	Dichotomous	59	28	(47.5%)	59	29	(49.2%)				

[a] approximated to nearest integer (percentages only presented in text)

Results

		Metformin + insulin glargine			Metformin + insulin (degludec 70% apart 30%)			Δ	p
		N	k	mean	N	k	mean		
Blood glucose: HbA1c (%) – 16wk	Continuous	60		7.1 (SD 1.3)	59		7 (SD 1)		
HbA1c (%) – 16wk	Mean change	60		-1.3 (SD 1.1)	59		-1.3 (SD 1)	MD=-0.110 (CI: -0.410, 0.190)	
Fasting plasma glucose (mmol/l) – 16wk	Mean change	60		-5.1 (SD 3.9)	59		-4.3 (SD 3.5)	MD=-0.130 (CI: -1.030, 0.770)	
Fasting plasma glucose (mmol/l) – 16wk	Continuous	60		7 (SD 2.5)	59		6.8 (SD 2.5)		
Body weight: Weight (kg) – 16wk	Mean change	60		-0.1 (SD 3.2)	59		-0.4 (SD 2.3)		
Hypoglycaemic events: Major/severe hypoglycaemic event – 16wk	Dichotomous	60	0	(0.0%)	59	0	(0.0%)		
Major/severe hypoglycaemic event – 16wka	Count	6440	0		6384	0			
confirmed hypoglycaemia – 16wkb	Continuous	60		0.7	59		1.2		
confirmed hypoglycaemia – 16wkc	Count	6440	12		6384	20			
Nocturnal hypoglycaemia – 16wkc	Count	6440	3		6384	1			
Adverse events: GI: nausea – 16wk	Dichotomous	60	0	(0.0%)	59	0	(0.0%)		
Any serious adverse event(s) – 16wkd	Dichotomous	60	0	(0.0%)	59	2	(3.4%)		
Any serious adverse event(s) – 16wka	Count	6440	0		6384	2			
Dropouts: Total dropouts – 16wk	Dichotomous	60	5	(8.3%)	59	4	(6.8%)		
Dropout due to AEs – 16wk	Dichotomous	60	0	(0.0%)	59	1	(1.7%)		
Drop out due to unsatisfactory effect – 16wk	Dichotomous	60	2	(3.3%)	59	0	(0.0%)		

[a] person days estimated using reported rates for confirmed hypos
[b] events per patient year; 95% CI not reported
[c] reviewer estimated patient days (episodes)
[d] No of events

	Metformin + insulin glargine			Metformin + insulin (55% degludec 45% aspart)			Δ	p
	N	k	mean	N	k	mean		

Blood glucose: HbA1c (%) – 16wk	Continuous	60		7.1 (SD 1.3)	59		7.2 (SD 1)		
HbA1c (%) – 16wk	Mean change	60		-1.3 (SD 1.1)	59		-1.5 (SD 1.4)		
Fasting plasma glucose (mmol/l) – 16wk	Mean change	60		-5.1 (SD 3.9)	59		-4.1 (SD 3.1)		
Fasting plasma glucose (mmol/l) – 16wk	Continuous	60		7 (SD 2.5)	59		7.4 (SD 2.8)		
Body weight: Weight (kg) – 16wk	Mean change	60		-0.1 (SD 3.2)	59		0.3 (SD 2.2)		
Hypoglycaemic events: Major/severe hypoglycaemic event – 16wk	Dichotomous	60	0	(0.0%)	59	0	(0.0%)		
Major/severe hypoglycaemic event – 16wka	Count	6440	0		6272	0			
confirmed hypoglycaemia – 16wkb	Continuous	60		0.7	59		2.4		
confirmed hypoglycaemia – 16wkc	Count	6440	12		6272	41			
Nocturnal hypoglycaemia – 16wkc	Count	6440	3		6272	27			
Adverse events: GI: nausea – 16wk	Dichotomous	60	0	(0.0%)	59	1	(1.7%)		
Any serious adverse event(s) – 16wkd	Dichotomous	60	0	(0.0%)	59	1	(1.7%)		
Any serious adverse event(s) – 16wka	Count	6440	0		6272	1			
Dropouts: Total dropouts – 16wk	Dichotomous	60	5	(8.3%)	59	6	(10.2%)		
Dropout due to AEs – 16wk	Dichotomous	60	0	(0.0%)	59	0	(0.0%)		
Drop out due to unsatisfactory effect – 16wk	Dichotomous	60	2	(3.3%)	59	0	(0.0%)		

[a] person days estimated using reported rates for confirmed hypos
[b] events per patient year; 95% CI not reported
[c] reviewer estimated patient days (episodes)
[d] No of events

		Metformin + insulin (degludec 70% apart 30%)			**Metformin + insulin (55% degludec 45% aspart)**				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Blood glucose: HbA1c (%) – 16wk	Continuous	59		7 (SD 1)	59		7.2 (SD 1)		
HbA1c (%) – 16wk	Mean change	59		-1.3 (SD 1)	59		-1.5 (SD 1.4)	MD=0.080 (CI: -0.220, 0.380)	
Fasting plasma glucose (mmol/l) – 16wk	Mean change	59		-4.3 (SD 3.5)	59		-4.1 (SD 3.1)	MD=0.640 (CI: -0.250, 1.530)	
Fasting plasma glucose (mmol/l) – 16wk	Continuous	59		6.8 (SD 2.5)	59		7.4 (SD 2.8)		
Body weight: Weight (kg) – 16wk	Mean change	59		-0.4 (SD 2.3)	59		0.3 (SD 2.2)		
Hypoglycaemic events: Major/severe hypoglycaemic event – 16wk	Dichotomous	59	0	(0.0%)	59	0	(0.0%)		
Major/severe hypoglycaemic event – 16wka	Count	6384	0		6272	0			

	confirmed hypoglycaemia – 16wkb	Continuous	59		1.2	59		2.4	
	confirmed hypoglycaemia – 16wkc	Count	6384	20		6272	41		
	Nocturnal hypoglycaemia – 16wkc	Count	6384	1		6272	27		
	Adverse events:								
	GI: nausea – 16wk	Dichotomous	59	0	(0.0%)	59	1	(1.7%)	
	Any serious adverse event(s) – 16wkd	Dichotomous	59	2	(3.4%)	59	1	(1.7%)	
	Any serious adverse event(s) – 16wka	Count	6384	2		6272	1		
	Dropouts:								
	Total dropouts – 16wk	Dichotomous	59	4	(6.8%)	59	6	(10.2%)	
	Dropout due to AEs – 16wk	Dichotomous	59	1	(1.7%)	59	0	(0.0%)	
	Drop out due to unsatisfactory effect – 16wk	Dichotomous	59	0	(0.0%)	59	0	(0.0%)	

[a] person days estimated using reported rates for confirmed hypos
[b] events per patient year; 95% CI not reported
[c] reviewer estimated patient days (episodes)
[d] No of events

Treatment differences in A1C and FPG values after 16 weeks of treatment were estimated by a linear model, in which the estimates were adjusted

by country, sex, OAD therapy at screening, age, and baseline values. P-values for between group comparisons were not reported for adverse events, drop outs, body weight and hypoglycaemia

Table 18: Janka et al. (2005)

General

Phase:

☐ monotherapy
☐ dual therapy
☑ triple therapy
☐ insulin monotherapy
☐ insulin+oral

Parallel / crossover: Parallel

Country: 10 European countries

Authors' conclusions: Initiating insulin treatment by adding basal insulin glargine once daily to glimepiride plus metformin treatment was safer and more effective than beginning twice-daily injections of 70/30 and discontinuing OADs in type 2 diabetic patients inadequately controlled with OADs.

Source of funding: Aventis Pharma

Comments: Open label trial, A 1:1 randomisation schedule stratified by center sequentially assigned treatment codes to eligible patients, using a central randomisation service of the electronic case report form InForm

Number and characteristics of patients

Total number of patients: 364

Inclusion criteria: Male or female patients aged 35–75 years with a type 2 diabetes duration of at least 1 year and treated with a stable dose of sulfonylurea and metformin for at least 1 month were enrolled. Further inclusion criteria included BMI <=35 kg/m2, HbA1c levels between 7.5 and 10.5%, and fasting blood glucose (FBG) levels >=120 mg/dl (>=6.7 mmol/l)

Exclusion criteria: any additional use of other oral blood glucose–lowering agents, prior use of insulin exceeding 3 days, and a history of ketoacidosis

Pre-randomisation phase: There was a 1- to 4-week screening phase and a 24-week treatment phase

Previous glucose-lowering

Any participants previously taking glucose-lowering therapy? all on oral hypoglycaemic drugs and/or insulin

Details of washout period: All treated with metformin and sulfonylurea and this was continued in one arm

therapy	and discontinued in the other arm
Lifestyle advice	-
Follow-up	**Total follow-up (wks):** 24 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 24 **Frequency of monitoring appointments:** -
Arms	**(1) Insulin glargine + metformin + glimepiride** N: 177 Treatment duration (wks): 24 Washout period (d): 0 Comments: Taking metformin + sulfonylurea at study start Treatment(s): (a) Metformin (Oral) Mean dose (mg/d): 1895 Details of dosing regimen: Metformin (>=850 mg) during the study was provided and taken at the same dose as before study entry. The dosage of both metformin and sulfoylurea remained unchanged throughout the study. Mean 1922 mg ± 475.8 for subgroup of insulin naïve older adults (b) Sulfonylurea (Oral) Mean dose (mg/d): 3.4 Details of dosing regimen: Previous sulfonylurea therapies were replaced with 3 or 4 mg glimepiride during the screening phase. Mean 3.4 mg ± 0.5 mg for subgroup of insulin naïve older adults (c) Insulin glargine (Subcutaneous) – flexible-dose (dose-adjusted) Frequency of dosing: once a day Details of dosing regimen: insulin glargine was given once daily in the morning in combination with glimepiride and metformin (glargine plus OAD). The starting dose for insulin glargine was 10 IU (mean 9.9 IU) in the morning and, for premixed insulin, 10 IU before breakfast and 10 IU before dinner. These starting doses could be lowered if considered clinically necessary by the investigator. Insulin doses were adjusted by a forced titration regimen calling for weekly adjustments for 8 weeks and at 2-week intervals thereafter for both groups, according to daily self-monitored capillary whole blood glucose. For both groups, the FBG target was 100 mg/dl (5.6 mmol/l), and the before dinner blood glucose target for the 70/30 group was 100 mg/dl (5.6 mmol/l), with a stepwise increase of insulin depending on the blood glucose values **(2) NPH insulin** N: 187 Treatment duration (wks): 24 Washout period (d): 0 Comments: Taking metformin + sulfonylurea at study start Treatment(s): NPH insulin (Subcutaneous) – flexible-dose (dose-adjusted) Details of dosing regimen: human premixed insulin (30% regular, 70% NPH insulin) to be administered twice daily (before breakfast and dinner), while glimepiride and metformin were discontinued (70/30). The starting dose for insulin glargine was 10 IU in the morning and, for premixed insulin, 10 IU (mean 10.3 IU) before breakfast and 10 IU (mean 10.3 IU) before dinner. Target values before dinner for the 70/30 group was 100 mg/dl (5.6 mmol/l), with a stepwise increase of insulin depending on the blood glucose values
Outcomes	**General** Statistical analyses were performed on the intent-to-treat population, defined as randomised patients who received at least one injection of insulin. 7/177 (4%) patients on glargine plus metformin + sulfonylurea and 28/187 (15%) patients on 70/30 pre-mixed insulin discontinued the study Outcomes not extracted in this evidence table include 24 hours blood glucose levels. Outcomes reported in Janka (2007) relating to subgroup analyses for insulin naive older adults are also reported in this evidence table. **Hypoglycaemic events** **Hypoglycemia was confirmed by blood glucose <60 mg/dl** Major/severe hypoglycaemic event (Severe hypoglycemia was defined as an event with symptoms consistent with hypoglycemia during which the person required the assistance of another person and which was associated with a blood glucose level <36 mg/dl and/or with recovery after oral carbohydrate, intravenous glucose, or glucagon administration)

Baseline characteristics		**Insulin glargine + metformin + glimepiride**	**NPH insulin**	**Δ**	**p**

		N	k	mean	N	k	mean		
Demographics: Age (years)	Continuous	177		60.9 (SD 8.7)	187		60.4 (SD 9.1)		
Sex (n male)	Dichotomous	177	108	(61.0%)	187	107a	(57.2%)		
Duration of diabetes (yrs)	Continuous	177		9.9 (SD 7.3)	187		9.9 (SD 6.4)		
Blood glucose: HbA1c (%) – 0wk	Continuous	177		8.85 (SD 0.98)	187		8.83 (SD 0.87)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	177		9.5 (SD 1.9)	187		9.6 (SD 2.1)		
Body weight: BMI (kg/m2)	Continuous	177		29.5 (SD 3.6)	187		29.6 (SD 3.6)		
Weight (kg) – 0wk	Continuous	177		85.1 (SD 14.7)	187		84.6 (SD 14.2)		
Age >=65 years Blood glucose: Fasting plasma glucose (mmol/l) – 0wk	Continuous	67		9.2 (SD 1.8)	63		9.5 (SD 2.2)		
Insulin: Total daily dose (U) – 0wk	Continuous	67		9.8 (SD 2)	63		10.3 (SD 2.8) b		

[a] approximated to nearest integer (percentages only presented in text)
[b] pre-breakfast dose

Results

		Insulin glargine + metformin + glimepiride			NPH insulin				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 12wka	Continuous	177		7.35 (SD 0.9)	187		7.85 (SD 0.85)		
HbA1c (%) – 24wkb	Mean change	177		-1.64 (SD 0.92)	187		-1.31 (SD 0.94)	MD=-0.340 (CI: -0.520, -0.160)	0.0003
HbA1c (%) – 24wk	Continuous	177		7.15 (SD 0.9)	187		7.49 (SD 1.09)		
HbA1c < 7% or <=7% – 24wk	Dichotomous	177	87c	(49.2%)	187	53d	(28.3%)		0.0596
HbA1c < 7% or <=7% – 24wk	Dichotomous	177	81d	(45.8%)	187	73	(39.0%)		0.0596
HbA1c < 7% or <=7% – 24wk	Dichotomous	177	87c	(49.2%)	187	73	(39.0%)		0.0596
HbA1c < 7% or <=7% – 24wkd	Dichotomous	177	81	(45.8%)	187	53	(28.3%)		0.0596
Fasting plasma glucose (mmol/l) – 24wke	Continuous	177			187			MD=-0.900 (CI: -1.300, -0.500)	<0.0001
FBG <=100 mg/dl – 24wk	Dichotomous	177	56	(31.6%)	187	28	(15.0%)		
Body weight: Weight (kg) – 24wk	Mean change	177		1.4 (SD 3.4)	187		2.1 (SD 4.2)		
Weight (kg) – 24wk	Continuous	177			187				0.0805
Hypoglycaemic events: All hypoglycaemic events (no patients) – 24wk	Dichotomous	177	109	(61.6%)	187	127	(67.9%)		

Major/severe hypoglycaemic event – 24wk	Dichotomous	177			187				0.0702
Major/severe hypoglycaemic event – 24wkf	Continuous	177		0	187		0.05		
Major/severe hypoglycaemic event – 24wkg	Count	29148	0		29064	4			
symptomatic (confirmed) – 24wkg	Count	29148	210		29064	458			
symptomatic (confirmed) – 24wkf	Continuous	177		2.62	187		5.73		
symptomatic (confirmed) – 24wk	Dichotomous	177			187				0.0009
confirmed hypoglycaemia – 24wkg	Count	29148	326		29064	788			
confirmed hypoglycaemia – 24wkf	Continuous	177		4.07	187		9.87		
confirmed hypoglycaemia – 24wk	Dichotomous	177			187				<0.0001
Nocturnal (confirmed) – 24wk	Dichotomous	177			187				0.0449
Nocturnal (confirmed) – 24wkf	Continuous	177		0.51	187		1.04		
Nocturnal (confirmed) – 24wkg	Count	29148	41		29064	83			
Adverse events: Any adverse event(s) – 24wkh	Dichotomous	177	89	(50.3%)	187	92	(49.2%)		NR
Dropouts: Total dropouts – 24wk	Dichotomous	177	7	(4.0%)	187	28	(15.0%)		
Dropout due to AEs – 24wk	Dichotomous	177	1	(0.6%)	187	6	(3.2%)		NR
Insulin: Total daily dose (U) – 24wk	Continuous	177		28.2	187		64.5		NR
Age >=65 years Blood glucose: HbA1c (%) – 24wki	Mean change	67		-1.9 (SD 0.835)	63		-1.4 (SD 1.01)	MD=-0.460 (CI: -0.750, -0.170)	0.003
HbA1c < 7% or <=7% – 24wk	Dichotomous	67	41	(61.2%)	63	19j	(30.2%)		0.006j
HbA1c < 7% or <=7% – 24wkj	Dichotomous	67	37	(55.2%)	63	19	(30.2%)		0.006j
HbA1c < 7% or <=7% – 24wk	Dichotomous	67	18k	(26.9%)	63	19j	(30.2%)		0.006j
HbA1c < 7% or <=7% – 24wk	Dichotomous	67	18k	(26.9%)	63	24	(38.1%)		0.006j
HbA1c < 7% or <=7% – 24wk	Dichotomous	67	37j	(55.2%)	63	5k	(7.9%)		0.006j
HbA1c < 7% or <=7% – 24wk	Dichotomous	67	41	(61.2%)	63	24	(38.1%)		0.006j
HbA1c < 7% or <=7% – 24wk	Dichotomous	67	41	(61.2%)	63	5k	(7.9%)		0.006j
HbA1c < 7% or <=7% – 24wkk	Dichotomous	67	18	(26.9%)	63	5	(7.9%)		0.006j
HbA1c < 7% or <=7% – 24wk	Dichotomous	67	37j	(55.2%)	63	24	(38.1%)		0.006j

Fasting plasma glucose (mmol/l) – 24wk	Continuous	67		6.1 (SD 1.4)	63		7.2 (SD 2.2)		
Fasting plasma glucose (mmol/l) – 24wk	Mean change	67			63				0.002
Body weight:									
Weight (kg) – 24wk	Continuous	67			63				0.17
Weight (kg) – 24wk	Mean change	67		1.3 (SD 3)	63		2.2 (SD 3.9)		
Hypoglycaemic events:									
All hypoglycaemic events (no events) – 24wkl	Count	11172	171		10416	160			
All hypoglycaemic events (no events) – 24wk	Dichotomous	67			63				0.01
All hypoglycaemic events (no events) – 24wkm	Continuous	67		5.59	63		11.39		
Major/severe hypoglycaemic event – 24wk	Dichotomous	67			36				0.21
Major/severe hypoglycaemic event – 24wkm	Continuous	67		0	63		0.09		
symptomatic (confirmed) – 24wk	Dichotomous	67			63				0.06
symptomatic (confirmed) – 24wkm	Continuous	67		2.22	63		5.01		
confirmed hypoglycaemia – 24wk	Dichotomous	67			63				0.008
confirmed hypoglycaemia – 24wkm	Continuous	67		3.68	63		9.09		
Nocturnal (confirmed) – 24wk	Dichotomous	67			63				0.26
Nocturnal (confirmed) – 24wkm	Continuous	67		0.39	63		0.71		
Adverse events:									
Any adverse event(s) – 24wk	Dichotomous	67	32	(47.8%)	63	27	(42.9%)		
Gastrointestinal disorders (any) – 24wk	Dichotomous	67	11n	(16.4%)	63	4h	(6.3%)		
Gastrointestinal disorders (any) – 24wk	Dichotomous	67	9h	(13.4%)	63	8n	(12.7%)		
Gastrointestinal disorders (any) – 24wkn	Dichotomous	67	11	(16.4%)	63	8	(12.7%)		
Gastrointestinal disorders (any) – 24wkh	Dichotomous	67	9	(13.4%)	63	4	(6.3%)		
Nervous system disorders – 24wk	Dichotomous	67	4h	(6.0%)	63	18n	(28.6%)		
Nervous system disorders – 24wk	Dichotomous	67	6n	(9.0%)	63	10h	(15.9%)		
Nervous system disorders – 24wkn	Dichotomous	67	6	(9.0%)	63	18	(28.6%)		
Nervous system disorders – 24wkh	Dichotomous	67	4	(6.0%)	63	10	(15.9%)		

Respiratory disorders – 24wk	Dichotomous	67	8	(11.9%)	63	8	(12.7%)		
Dropouts: Dropout due to AEs – 24wk	Dichotomous	67	1	(1.5%)	63	2	(3.2%)		
Insulin: Total daily dose (U) – 24wk	Continuous	67		24.4 (SD 10.3)	63		34.9 (SD 20.3) o		

[a] estimated from graph
[b] adjusted change; SD calculated from 95% CI
[c] approximated to nearest integer (percentages only presented in text)
[d] without confirmed nocturnal hypo; approximated to nearest integer (percentages only presented in text)
[e] No SDs reported
[f] mean events per patient year; 95% CI not reported
[g] person days estimated assuming dropout halfway through trial and no of events calculated using reported rates
[h] No of patients
[i] SD calculated from 95% CI
[j] without nocturnal hypoglycaemia
[k] without confirmed hypoglycaemia
[l] person days estimated assuming dropout halfway through trial and no of events calculated using reported event rates/patient year
[m] per patient year; 95% CI not reported
[n] No of events
[o] pre-breakfast dose

ANCOVAs were performed to compare changes in HbA1c and secondary continuous variables between treatment groups. Adjusted means and corresponding two-sided 95% CIs were calculated. Categoric secondary variables were analysed using Cochran-Mantel-Haenszel tests

Table 19: Kilo et al. (2003)

General

Phase:
☐ monotherapy
☐ dual therapy
☑ triple therapy
☐ insulin monotherapy
☐ insulin+oral

Parallel / crossover: Parallel

Country: USA

Authors' conclusions: The results indicate that patients with type 2 diabetes can safely and effectively begin insulin therapy using once daily injections of insulin biphasic aspart 70/3, biphasic human insulin 70/30 or NPH in combination with metformin

Source of funding: Novo Nordisk

Comments: Open label trial

Number and characteristics of patients

Total number of patients: 140

Inclusion criteria: Men or women, aged 18 years aand older with type 2 diabetes and a body weight <=100 kg and BMI <=40 kg/m2. patients were naïve to insulin treatment and had inadquate glycaemic control (Hba1c >=7.5%) on a regimen of >= 3 months of metformin as monotherapy or in combination with a sulfonylurea or repaglinide

Exclusion criteria: significantly impaired hepatic or renal function or significant cardiac disease within 12 months

Pre-randomisation phase: There was a 4 week run-in period in which patients received metformin as monotherapy followed by 12 weeks of combination therapy. During the 4 week run-in, patients were treated with 500 to 2550 mg/day of metfomin divided into one of three doses. The dose was adjusted during the first 3 weeks to achieve and maintain a FBG 90-126 mg/dl or the maximally tolerated dose or a maximum daily dose of 2550 mg. The patients metformin dose was not changed after the fourth week of the run-in period, unless a dose reduction was necessary for clinical reasons. At the end of the run in period, patients who were not able to achieve FBG target of 90-126 mg/dl on metformin only were randomised to one of three insulin treatment regimens

Previous glucose-lowering

Any participants previously taking glucose-lowering therapy? all on oral hypoglycaemic drugs and/or insulin

Details of washout period: All taking metformin monotherapy or combination therapy (metformin

therapy	monotherapy was used during the run-in period)
Lifestyle advice	-
Follow-up	**Total follow-up (wks):** 16 **Length of titration period (wks):** 4 **Length of maintenance period (wks):** 8 **Frequency of monitoring appointments:** Blood samples were collected at baseline and at weeks 1,2,4,8,and 12
Arms	**(1) Metformin + biphasic insulin aspart od (70% protaminated aspart/30% soluble aspart)** N: 46 Treatment duration (wks): 12 Washout period (d): 0 Comments: All taking metformin monotherapy or combination therapy (metformin monotherapy was used during the run-in period) Treatment(s): (a) Metformin (Oral) Mean dose (mg/d): 2200 Details of dosing regimen: Metformin doses from the run-in period were maintained (this was approx 2200 mg in each group) (b) Biphasic insulin aspart (Subcutaneous) – flexible-dose (dose-adjusted) Minimum dose (mg/d): 0.16 Frequency of dosing: once a day Details of dosing regimen: The starting insulin dose was 0.16 U/kg for each insulin formulation. During the first 4 weeks of treatment, the insulin dosage was adjusted by 2-6 U to achieve FBG 90-126 mg/dl. The dose adjustments were based on twice weekly SMBG assessments. After the dose adjustment period, the insulin dose was maintained for the remaining 8 weeks of the study. **(2) Metformin + NPH (od)** N: 47 Treatment duration (wks): 12 Washout period (d): 0 Comments: All taking metformin monotherapy or combination therapy (metformin monotherapy was used during the run-in period) Treatment(s): (a) Metformin (Oral) Mean dose (mg/d): 2200 Details of dosing regimen: Metformin doses from the run-in period were maintained this was approx 2200 mg in each group) (b) NPH insulin (Subcutaneous) – flexible-dose (dose-adjusted) Minimum dose (mg/d): 0.16 Frequency of dosing: once a day **(3) Metformin + biphasic human insulin od (70% protaminated human insulin 30% soluble human insulin)** N: 47 Treatment duration (wks): 12 Washout period (d): 0 Comments: All taking metformin monotherapy or combination therapy (metformin monotherapy was used during the run-in period) Treatment(s): (a) Metformin (Oral) Mean dose (mg/d): 2200 Details of dosing regimen: Metformin doses from the run-in period were maintained this was approx 2200 mg in each group) (b) NPH insulin mix 70/30 (Subcutaneous) – flexible-dose (dose-adjusted) Frequency of dosing: once a day
Outcomes	**General** 4/46 patients in the metformin + biphasic aspart group, 4/47 in the metformin + NPH group and 1/47 in the biphasic human insulin group discontinued the study No details of ITT analysis reported. The LOCF method was used to calculate end of study results for blood glucose and Hba1c values **Hypoglycaemic events** Minor (confirmed) hypoglycaemia (Events were classed as minor if patients had symptoms of hypoglycaemia with a BG<50 mg/dl which the patient handled themselves) Major/severe hypoglycaemic event (Events were classed as major if patients had BG <50 mg/dl with severe CNS symptoms and the patient was unable to treat themselves) symptomatic (unconfirmed) hypoglycaemia (Events were classed as symptomatic only where there were symptoms of hypoglycaemia but this was not confirmed by a BG measurement)

Baseline characteristics

		Metformin + biphasic insulin aspart od (70% protaminated aspart/30% soluble aspart)			Metformin + NPH (od)				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	46		57.2 (SD 12.1)	47		55.1 (SD 12.6)		
Sex (n male)	Dichotomous	46	25	(54.3%)	47	19	(40.4%)		
Duration of diabetes (yrs)	Continuous	46		10.4 (SD 8.6)	47		10.7 (SD 7.3)		
Blood glucose: HbA1c (%) – 0wk	Continuous	46		9.5 (SD 1.8)	47		9.5 (SD 1.6)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	46		13.4213508 (SD 4.15)	47		13.4713062 (SD 3.87)		
Body weight: BMI (kg/m2)	Continuous	46		30.4 (SD 4.4)	47		30.4 (SD 3.9)		
Weight (kg) – 0wka	Continuous	46		85.80096 (SD 12.4)	47		85.80096 (SD 11)		
Previous blood glucose lowering drugs: Metformin	Dichotomous	46	10	(21.7%)	47	14	(29.8%)		
Combination therapy	Dichotomous	46	36	(78.3%)	47	33	(70.2%)		
Insulin: Total daily dose (U) – 0wk	Continuous	46		12	47		12		

[a] estimated from BMI assuming mean height of 1.68m

		Metformin + biphasic insulin aspart od (70% protaminated aspart/30% soluble aspart)			Metformin + biphasic human insulin od (70% protaminated human insulin 30% soluble human insulin)				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	46		57.2 (SD 12.1)	47		55.4 (SD 11)		
Sex (n male)	Dichotomous	46	25	(54.3%)	47	29	(61.7%)		
Duration of diabetes (yrs)	Continuous	46		10.4 (SD 8.6)	47		8.4 (SD 4.9)		
Blood glucose: HbA1c (%) – 0wk	Continuous	46		9.5 (SD 1.8)	47		9.3 (SD 1.4)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	46		13.4213508 (SD 4.15)	47		12.6109632 (SD 3.73)		
Body weight: BMI (kg/m2)	Continuous	46		30.4 (SD 4.4)	47		30.6 (SD 4.3)		
Weight (kg) – 0wka	Continuous	46		85.80096 (SD 12.4)	47		86.36544 (SD 12.1)		
Previous blood glucose lowering drugs: Metformin	Dichotomous	46	10	(21.7%)	47	14	(29.8%)		
Combination therapy	Dichotomous	46	36	(78.3%)	47	33	(70.2%)		
Insulin: Total daily dose (U) – 0wk	Continuous	46		12	47		12		

[a] estimated from BMI assuming mean height of 1.68m

		Metformin + NPH (od)			Metformin + biphasic human insulin od (70% protaminated human insulin 30% soluble human insulin)				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	47		55.1 (SD 12.6)	47		55.4 (SD 11)		
Sex (n male)	Dichotomous	47	19	(40.4%)	47	29	(61.7%)		
Duration of diabetes (yrs)	Continuous	47		10.7 (SD 7.3)	47		8.4 (SD 4.9)		
Blood glucose: HbA1c (%) – 0wk	Continuous	47		9.5 (SD 1.6)	47		9.3 (SD 1.4)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	47		13.4713062 (SD 3.87)	47		12.6109632 (SD 3.73)		
Body weight: BMI (kg/m2)	Continuous	47		30.4 (SD 3.9)	47		30.6 (SD 4.3)		
Weight (kg) – 0wka	Continuous	47		85.80096 (SD 11)	47		86.36544 (SD 12.1)		
Previous blood glucose lowering drugs: Metformin	Dichotomous	47	14	(29.8%)	47	14	(29.8%)		
Combination therapy	Dichotomous	47	33	(70.2%)	47	33	(70.2%)		
Insulin: Total daily dose (U) – 0wk	Continuous	47		12	47		12		

[a] estimated from BMI assuming mean height of 1.68m

Results

		Metformin + biphasic insulin aspart od (70% protaminated aspart/30% soluble aspart)			Metformin + NPH (od)				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 12wk	Continuous	46		8.3 (SD 1.36) a	47		-1.2b		NSc
HbA1c (%) – 12wka	Continuous	46		8.3 (SD 1.36)	47		8.25 (SD 1.03)		NSc
HbA1c (%) – 12wkb	Continuous	46		-1.3	47		-1.2		NSc
HbA1c (%) – 12wk	Continuous	46		-1.3b	47		8.25 (SD 1.03) a		NSc
Fasting plasma glucose (mmol/l) – 12wk	Continuous	46			47				NSc
Fasting plasma glucose (mmol/l) – 12wk	Mean change	46		-4.16295 (SD 4.01)	47		-5.051046 (SD 4)		
Body weight: Weight (kg) – 12wkb	Continuous	46		0.7	47		0.1		
Hypoglycaemic events: All hypoglycaemic events (no patients) – 12wkd	Dichotomous	46	20	(43.5%)	47	13	(27.7%)		0.245e
Minor (confirmed) hypoglycaemia – 12wkd	Dichotomous	46	11	(23.9%)	47	6	(12.8%)		NR
Major/severe hypoglycaemic event – 12wkd	Dichotomous	46	0	(0.0%)	47	0	(0.0%)		NR

symptomatic (unconfirmed) hypoglycaemia – 12wkd	Dichotomous	46	13	(28.3%)	47	10	(21.3%)		NR
Nocturnal hypoglycaemia – 12wkd	Dichotomous	46	7	(15.2%)	47	11	(23.4%)		NR
Dropouts:									
Total dropouts – 12wk	Dichotomous	46	4	(8.7%)	47	4	(8.5%)		
Dropout due to AEs – 12wk	Dichotomous	46	2	(4.3%)	47	0	(0.0%)		
Insulin:									
Total daily dose (U) – 12wk	Continuous	46		26 (SD 13.6)	47		28 (SD 15.8)		NR
FBG <126 mg/dl									
Hypoglycaemic events:									
All hypoglycaemic events (no patients) – 12wkd	Dichotomous	9	4	(44.4%)	9	2	(22.2%)		
Minor (confirmed) hypoglycaemia – 12wkd	Dichotomous	9	3	(33.3%)	9	1	(11.1%)		
symptomatic (unconfirmed) hypoglycaemia – 12wkd	Dichotomous	9	3	(33.3%)	9	2	(22.2%)		
Nocturnal hypoglycaemia – 12wkd	Dichotomous	9	0	(0.0%)	9	1	(11.1%)		

[a] estimated from graph
[b] No details of dispersion
[c] at any time point across groups
[d] No of patients
[e] across treatment groups

		Metformin + biphasic insulin aspart od (70% protaminated aspart/30% soluble aspart)			Metformin + biphasic human insulin od (70% protaminated human insulin 30% soluble human insulin)				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Blood glucose:									
HbA1c (%) – 12wk	Continuous	46		8.3 (SD 1.36) a	47		-1.1b		
HbA1c (%) – 12wka	Continuous	46		8.3 (SD 1.36)	47		8.2 (SD 0.754)		
HbA1c (%) – 12wkb	Continuous	46		-1.3	47		-1.1		
HbA1c (%) – 12wk	Continuous	46		-1.3b	47		8.2 (SD 0.754) a		
Fasting plasma glucose (mmol/l) – 12wk	Mean change	46		-4.16295 (SD 4.01)	47		-3.496878 (SD 4.78)		
Body weight:									
Weight (kg) – 12wkb	Continuous	46		0.7	47		1		
Hypoglycaemic events:									
All hypoglycaemic events (no patients) – 12wkc	Dichotomous	46	20	(43.5%)	47	15	(31.9%)		
Minor (confirmed) hypoglycaemia – 12wkc	Dichotomous	46	11	(23.9%)	47	9	(19.1%)		
Major/severe hypoglycaemic event – 12wkc	Dichotomous	46	0	(0.0%)	47	0	(0.0%)		

symptomatic (unconfirmed) hypoglycaemia – 12wkc	Dichotomous	46	13	(28.3%)	47	11	(23.4%)	
Nocturnal hypoglycaemia – 12wkc	Dichotomous	46	7	(15.2%)	47	11	(23.4%)	
Dropouts:								
Total dropouts – 12wk	Dichotomous	46	4	(8.7%)	47	1	(2.1%)	
Dropout due to AEs – 12wk	Dichotomous	46	2	(4.3%)	47	0	(0.0%)	
Insulin:								
Total daily dose (U) – 12wk	Continuous	46		26 (SD 13.6)	47		29 (SD 16.2)	
FBG <126 mg/dl								
Hypoglycaemic events:								
All hypoglycaemic events (no patients) – 12wkc	Dichotomous	9	4	(44.4%)	8	4	(50.0%)	
Minor (confirmed) hypoglycaemia – 12wkc	Dichotomous	9	3	(33.3%)	8	2	(25.0%)	
symptomatic (unconfirmed) hypoglycaemia – 12wkc	Dichotomous	9	3	(33.3%)	8	3	(37.5%)	
Nocturnal hypoglycaemia – 12wkc	Dichotomous	9	0	(0.0%)	8	3	(37.5%)	

[a] estimated from graph
[b] No details of dispersion
[c] No of patients

		Metformin + NPH (od)			Metformin + biphasic human insulin od (70% protaminated human insulin 30% soluble human insulin)			Δ	p
		N	k	mean	N	k	mean		
Blood glucose:									
HbA1c (%) – 12wk	Continuous	47		8.25 (SD 1.03) a	47		-1.1b		
HbA1c (%) – 12wka	Continuous	47		8.25 (SD 1.03)	47		8.2 (SD 0.754)		
HbA1c (%) – 12wkb	Continuous	47		-1.2	47		-1.1		
HbA1c (%) – 12wk	Continuous	47		-1.2b	47		8.2 (SD 0.754) a		
Fasting plasma glucose (mmol/l) – 12wk	Mean change	47		-5.051046 (SD 4)	47		-3.496878 (SD 4.78)		
Body weight:									
Weight (kg) – 12wkb	Continuous	47		0.1	47		1		
Hypoglycaemic events:									
All hypoglycaemic events (no patients) – 12wkc	Dichotomous	47	13	(27.7%)	47	15	(31.9%)		
Minor (confirmed) hypoglycaemia – 12wkc	Dichotomous	47	6	(12.8%)	47	9	(19.1%)		
Major/severe hypoglycaemic event – 12wkc	Dichotomous	47	0	(0.0%)	47	0	(0.0%)		
symptomatic (unconfirmed) hypoglycaemia – 12wkc	Dichotomous	47	10	(21.3%)	47	11	(23.4%)		

	Nocturnal hypoglycaemia – 12wkc	Dichotomous	47	11	(23.4%)	47	11	(23.4%)		
	Dropouts: Total dropouts – 12wk	Dichotomous	47	4	(8.5%)	47	1	(2.1%)		
	Dropout due to AEs – 12wk	Dichotomous	47	0	(0.0%)	47	0	(0.0%)		
	Insulin: Total daily dose (U) – 12wk	Continuous	47		28 (SD 15.8)	47		29 (SD 16.2)		
	FBG <126 mg/dl Hypoglycaemic events: All hypoglycaemic events (no patients) – 12wkc	Dichotomous	9	2	(22.2%)	8	4	(50.0%)		
	Minor (confirmed) hypoglycaemia – 12wkc	Dichotomous	9	1	(11.1%)	8	2	(25.0%)		
	symptomatic (unconfirmed) hypoglycaemia – 12wkc	Dichotomous	9	2	(22.2%)	8	3	(37.5%)		
	Nocturnal hypoglycaemia – 12wkc	Dichotomous	9	1	(11.1%)	8	3	(37.5%)		

[a] estimated from graph
[b] No details of dispersion
[c] No of patients

	Values for Hba1c, FBG and SMBG profiles were analysed using ANCOVA with the baseline measurement as the covariate and treatment and centre as fixed effects.

Table 20: Kokic et al. (2010)

General	**Phase:** ☐ monotherapy ☐ dual therapy ☑ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** - **Authors' conclusions:** - **Source of funding:** - **Comments:** -
Number and characteristics of patients	**Total number of patients:** 237 **Inclusion criteria:** Adults with T2DM between 5 and 15 years, HbA1c >=7.5%, BMI >=23, with no renal or liver dysfunction **Exclusion criteria:** - Pre-randomisation phase: Unclear randomisation method
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** - **Details of washout period:** Not stated. Unclear whether patients had previous AHA
Lifestyle advice	Not reported
Follow-up	**Total follow-up (wks):** 26 **Length of titration period (wks):** - **Length of maintenance period (wks):** 26

	Frequency of monitoring appointments: Assessments at baseline, 3 and 6 months
Arms	**(1) Glimepiride + Metformin + Acarbose** N: 79 Treatment duration (wks): 26 Washout period (d): 0 Treatment(s): (a) Sulfonylurea (Oral) Details of dosing regimen: No dose regimen details provided (b) Metformin (Oral) Details of dosing regimen: No dose regimen details provided (c) Acarbose (Oral) Details of dosing regimen: No dose regimen details provided **(2) Biphasic insulin (regular/NPH 30/70) + NPH** N: 79 Treatment duration (wks): 26 Washout period (d): 0 Treatment(s): (a) Biphasic human insulin (Subcutaneous) Details of dosing regimen: 2 doses - no other details provided (b) NPH insulin (Subcutaneous) Details of dosing regimen: 1 dose at bedtime **(3) Insulin lispro + Metformin** N: 79 Treatment duration (wks): 26 Washout period (d): 0 Treatment(s): (a) Insulin lispro (Subcutaneous) Details of dosing regimen: 3 doses before meals - no details provided (b) Metformin (Oral) Details of dosing regimen: 2 doses before meals - no details provided
Outcomes	
Baseline characteristics	

		Glimepiride + Metformin + Acarbose		
		N	**k**	**mean**
Demographics:				
Age (years)	Continuous	79		64.1 (SD 10.3)
Sex (n male)	Dichotomous	79	38	(48.1%)
Duration of diabetes (yrs)	Continuous	79		8.14 (SD 4.67)
Blood glucose:				
HbA1c (%) – 3mo	Continuous	79		8.9 (SD 1.9)
HbA1c (%) – 3mo	Continuous	79		8.9 (SD 1.9)
Fasting plasma glucose (mmol/l) – 3mo	Continuous	79		9.1 (SD 2.8)
Fasting plasma glucose (mmol/l) – 3mo	Continuous	79		9.1 (SD 2.8)
Body weight:				
BMI (kg/m2)	Continuous	79		28.9 (SD 4.3)
Weight (kg)	Continuous	79		81.56736 (SD 12.13632) a

[a] estimated from BMI assuming mean height of 1.68m

		Biphasic insulin (regular/NPH 30/70) + NPH		
		N	**k**	**mean**
Demographics:				
Age (years)	Continuous	79		66 (SD 12.7)
Sex (n male)	Dichotomous	79	27	(34.2%)
Duration of diabetes (yrs)	Continuous	79		10.03 (SD 6.2)
Blood glucose:				
HbA1c (%) – 3mo	Continuous	79		10.2 (SD 2.1)
HbA1c (%) – 3mo	Continuous	79		10.2 (SD 2.1)
Fasting plasma glucose (mmol/l) – 3mo	Continuous	79		11.2 (SD 3.7)
Fasting plasma glucose (mmol/l) – 3mo	Continuous	79		11.2 (SD 3.7)

Body weight:				
BMI (kg/m2)	Continuous	79		28.5 (SD 3.5)
Weight (kg)	Continuous	79		80.4384 (SD 9.8784) a

[a] estimated from BMI assuming mean height of 1.68m

		Insulin lispro + Metformin		
		N	k	mean
Demographics:				
Age (years)	Continuous	79		64.2 (SD 8.4)
Sex (n male)	Dichotomous	79	32	(40.5%)
Duration of diabetes (yrs)	Continuous	79		9.45 (SD 3.6)
Blood glucose:				
HbA1c (%) – 3mo	Continuous	79		9.5 (SD 2)
HbA1c (%) – 3mo	Continuous	79		9.5 (SD 2)
Fasting plasma glucose (mmol/l) – 3mo	Continuous	79		11.1 (SD 3.4)
Fasting plasma glucose (mmol/l) – 3mo	Continuous	79		11.1 (SD 3.4)
Body weight:				
BMI (kg/m2)	Continuous	79		28.9 (SD 3.5)
Weight (kg)	Continuous	79		81.56736 (SD 9.8784) a

[a] estimated from BMI assuming mean height of 1.68m

Results

		Glimepiride + Metformin + Acarbose		
		N	k	mean
Blood glucose:				
HbA1c (%) – 3mo	Continuous	79		8 (SD 1.4)
HbA1c (%) – 3mo	Continuous	79		8 (SD 1.4)
HbA1c (%) – 6mo	Continuous	79		7.6 (SD 0.9)
HbA1c (%) – 6mo	Continuous	79		7.6 (SD 0.9)
Fasting plasma glucose (mmol/l) – 3mo	Continuous	79		8.6 (SD 2)
Fasting plasma glucose (mmol/l) – 3mo	Continuous	79		8.6 (SD 2)
Fasting plasma glucose (mmol/l) – 6mo	Continuous	79		7.9 (SD 0.9)
Fasting plasma glucose (mmol/l) – 6mo	Continuous	79		7.9 (SD 0.9)
Hypoglycaemic events:				
All hypoglycaemic events (no events) – 6mo	Count	14378	18	

		Biphasic insulin (regular/NPH 30/70) + NPH		
		N	k	mean
Blood glucose:				
HbA1c (%) – 3mo	Continuous	79		8.5 (SD 1.3)
HbA1c (%) – 3mo	Continuous	79		8.5 (SD 1.3)
HbA1c (%) – 6mo	Continuous	79		8 (SD 0.9)
HbA1c (%) – 6mo	Continuous	79		8 (SD 0.9)
Fasting plasma glucose (mmol/l) – 3mo	Continuous	79		9.3 (SD 2.7)
Fasting plasma glucose (mmol/l) – 3mo	Continuous	79		9.3 (SD 2.7)
Fasting plasma glucose (mmol/l) – 6mo	Continuous	79		8.2 (SD 2)
Fasting plasma glucose (mmol/l) – 6mo	Continuous	79		8.2 (SD 2)
Hypoglycaemic events:				
All hypoglycaemic events (no events) – 6mo	Count	14378	25	

		Insulin lispro + Metformin		
		N	**k**	**mean**
Blood glucose:				
HbA1c (%) – 3mo	Continuous	79		7.5 (SD 1.1)
HbA1c (%) – 3mo	Continuous	79		7.5 (SD 1.1)
HbA1c (%) – 6mo	Continuous	79		6.9 (SD 0.7)
HbA1c (%) – 6mo	Continuous	79		6.9 (SD 0.7)
Fasting plasma glucose (mmol/l) – 3mo	Continuous	79		8.5 (SD 2)
Fasting plasma glucose (mmol/l) – 3mo	Continuous	79		8.5 (SD 2)
Fasting plasma glucose (mmol/l) – 6mo	Continuous	79		7.7 (SD 1.3)
Fasting plasma glucose (mmol/l) – 6mo	Continuous	79		7.7 (SD 1.3)
Hypoglycaemic events:				
All hypoglycaemic events (no events) – 6mo	Count	14378	10	

Table 21: Kvapil et al. (2006)

General	**Phase:** ☐ monotherapy ☐ dual therapy ☑ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** 11 countries (Croatia, Czech Republic, Denmark, France, Greece, Hungary, Norway, Poland, Portugal, Russia, Spain) **Authors' conclusions:** BIAsp 30 added to metformin could be an appropriate therapeutic option for achieving good glycaemic control, compared with the addition of a second oral agent, particularly where Hba1c >=9% **Source of funding:** Unclear **Comments:** Multinational, open-label, parallel group trial. Randomisation was carried out using a telephone system, which automatically assigns treatment according to a pre-defined randomisation list.
Number and characteristics of patients	**Total number of patients:** 341 **Inclusion criteria:** Patients had been receiving at least 850 mg metformin per day for at least one month (no further details reported) **Exclusion criteria:** significant medical problems such as proliferative retinopathy, impaired hepatic or renal function, recurrent severe hypoglycaemia, cardiac disease, anaemia or change in dose of medications known to interfere with glucose metabolism
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** all on oral hypoglycaemic drugs and/or insulin **Details of washout period:** All taking metformin at study start
Lifestyle advice	-
Follow-up	**Total follow-up (wks):** 16 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 16 **Frequency of monitoring appointments:** Blood glucose profiles were obtained at weeks 1,2,4,8,12 and 16
Arms	**(1) BIAsp 30 alone** N: 107 Treatment duration (wks): -

Washout period (d): -

Treatment(s): Biphasic insulin aspart (Subcutaneous) – flexible-dose (dose-adjusted)

Details of dosing regimen: The intial daily dose of BIAsp 30 was 0.3 U/kg body weight per day. Half the dose was injected immediately before breakfast and the other was injected immediately before the main evening meal. Total daily doses were titrated every 1-7 days in steps of 2-4 U per injection. The breakfast dose was adjusted on the basis of post-breakfast and pre-dinner blood glucose values (target range 5-8 mmol/l) while the evening dose was adjusted according to post-dinner, night time and pre-breakfast values (target range 5-8 mmol/l).

(2) Metformin + BIAsp 30

N: 108

Treatment duration (wks): -
Washout period (d): -

Treatment(s): (a) Metformin (Oral)

Mean dose (mg/d): 1660
Minimum dose (mg/d): 500
Maximum dose (mg/d): 3000
Details of dosing regimen: The mean total daily matromin dose was maintained at pre-trial dosing levels throughout the trial, approx. 1660 mg (range 500-3000mg). Metformin is usually titrated on the basis of individual maximum tolerated or maximum effective doses; the mean doses used int his trial were within the typically prescribed range.

(b) Biphasic insulin aspart (Subcutaneous) – flexible-dose (dose-adjusted)

Details of dosing regimen: The intial daily odse of BIAsp 30 was 0.2 U/kg body weight per day. See BIAsp 30 alone for titration details

Outcomes

General

Outcomes for 2/3 of the arms have been extracted in this evidence table. The arm relating to metformin + sulfonylurea was not used as it is outside the decision space for second intensification.

All analyses were based on the ITT dataset or subgroups of the ITT population. Adverse events were reported for the safety population (exposed patients), which was the same as the ITT population.

6/111 (5.4%) patients in the BIAsp alone group and 11/116 (9.5%) in the BIAsp + metformin group doscontinued the study

Outcomes not reported in this evidence table include 8 point BG profile

Hypoglycaemic events

Minor (confirmed) hypoglycaemia (Symptoms consistent with hypoglycaemia, confirmed with BG levels <2.8 mmol/l and handled by the patient, or any asymptomatic event with BG <2.8 mmol/l)

Major/severe hypoglycaemic event (requiring assistance, BG <2.8 mmol/l and requiring food intake or IV glucose)

Adverse events

Any adverse event(s) (An undesirable event that occurred during the trial)

Any serious adverse event(s) (Events causing or threatening to cause death or resulting in significant hospitalisation or incapacity)

Baseline characteristics

		BIAsp 30 alone			Metformin + BIAsp 30				
		N	k	mean	N	k	mean	Δ	p
ITT									
Demographics:									
Age (years)	Continuous	107		55.2 (SD 10.3)	108		56.4 (SD 9)		
Sex (n male)	Dichotomous	107	50	(46.7%)	108	53	(49.1%)		
Duration of diabetes (yrs)	Continuous	107		8.2 (SD 7.1)	108		6.7 (SD 5.7)		
Blood glucose:									
HbA1c (%) – 0wk	Continuous	107		9.6 (SD 1.5)	108		9.3 (SD 1.3)		
Body weight:									
BMI (kg/m2)	Continuous	107		30.9 (SD 4.5)	108		30.4 (SD 4)		
Weight (kg) – 0wk	Continuous	107		87.3 (SD 16.5)	108		85.1 (SD 15.1)		
Lipids:									
HDL cholesterol (mmol/l) – 0wk	Continuous	107		1.2 (SD 0.3)	108		1.2 (SD 0.3)		
Triglycerides (mmol/l) – 0wk	Continuous	107		2.6 (SD 2.5)	108		2.8 (SD 2.4)		
Insulin:									
Total daily dose (U/kg) – 0wk	Continuous	107		0.3	108		0.2		

Results

		BIAsp 30 alone			Metformin + BIAsp 30			Δ	p
		N	k	mean	N	k	mean		
Body weight: Weight (kg) – 16wka	Mean change	107		1.6	108		0.8		
Hypoglycaemic events: All hypoglycaemic events (no events) – 16wkb	Count	11648	62		11480	64			
Minor (confirmed) hypoglycaemia – 16wkb	Count	12108.11	20		12675.68	23			
Major/severe hypoglycaemic event – 16wkb	Count	12108.11	0		12675.68	0			
symptomatic (unconfirmed) hypoglycaemia – 16wkb	Count	12108.11	44		12675.68	44			
Dropouts: Total dropouts – 16wk	Dichotomous	107	6	(5.6%)	108	11	(10.2%)		
ITT Blood glucose: HbA1c (%) – 16wkc	Continuous	107		8.05 (SD 2.28)	108		7.5 (SD 2.08)		
HbA1c (%) – 16wk	Mean change	107			108			MD=-0.390 (CI: -0.684, -0.096)	<0.01
Body weight: Weight (kg) – 16wkd	Mean change	107			108			MD=-0.800 (CI: -1.604, 0.004)	0.051
Hypoglycaemic events: All hypoglycaemic events (no events) – 16wke	Continuous		0.037			0.039			
Minor (confirmed) hypoglycaemia – 16wkf	Dichotomous	107	10	(9.3%)	108	13	(12.0%)		d
Minor (confirmed) hypoglycaemia – 16wkg	Dichotomous	107	20	(18.7%)	108	23	(21.3%)		d
Minor (confirmed) hypoglycaemia – 16wk	Dichotomous	107	20g	(18.7%)	108	13f	(12.0%)		d
Minor (confirmed) hypoglycaemia – 16wk	Dichotomous	107	10f	(9.3%)	108	23g	(21.3%)		d
Major/severe hypoglycaemic event – 16wkf	Dichotomous	107	0	(0.0%)	108	0	(0.0%)		d

symptomatic (unconfirmed) hypoglycaemia – 16wk	Dichotomous	107	44g	(41.1%)	108	22f	(20.4%)		d
symptomatic (unconfirmed) hypoglycaemia – 16wkg	Dichotomous	107	44	(41.1%)	108	44	(40.7%)		d
symptomatic (unconfirmed) hypoglycaemia – 16wkf	Dichotomous	107	22	(20.6%)	108	22	(20.4%)		d
symptomatic (unconfirmed) hypoglycaemia – 16wk	Dichotomous	107	22f	(20.6%)	108	44g	(40.7%)		d
Adverse events: Any adverse event(s) – 16wk	Dichotomous	107	45f	(42.1%)	108	33h	(30.6%)		d
Any serious adverse event(s) – 16wki	Dichotomous	107			108				d
Dropouts: Dropout due to AEs – 16wk	Dichotomous	107	1	(0.9%)	108	2	(1.9%)		d
Lipids: HDL cholesterol (mmol/l) – 16wkd	Mean change	107			108			MD=0.010 (CI: -0.049, 0.069)	NS
Triglycerides (mmol/l) – 16wkd	Mean change	107			108			MD=0.230 (CI: -0.044, 0.504)	NS
Insulin: Total daily dose (U/kg) – 16wk	Continuous	107		0.51	108		0.3		d
Hba1c <=9.0% or <9% Blood glucose: HbA1c (%) – 16wk	Mean change	107			108			MD=-0.420 (CI: -0.812, -0.028)	<0.05
Body weight: Weight (kg) – 16wk	Mean change	107			108			MD=0.310 (CI: -0.846, 1.466)	NS
Lipids: HDL cholesterol (mmol/l) – 16wk	Mean change	107			108			MD=0.000 (CI: -0.098, 0.098)	NS
Triglycerides (mmol/l) – 16wk	Mean change	107			108			MD=0.090 (CI: -0.302, 0.482)	NS
baseline Hba1c >=9% Blood glucose: HbA1c (%) – 16wk	Mean change	107			108			MD=-0.390 (CI: -0.802, 0.022)	NS
Body weight: Weight (kg) – 16wk	Mean change	107			108			MD=-1.540 (CI: -2.657, -0.423)	<0.01

Lipids: HDL cholesterol (mmol/l) – 16wk	Mean change	107			108			MD=0.000 (CI: -0.059, 0.059)	NS
Triglycerides (mmol/l) – 16wk	Mean change	107			108			MD=0.220 (CI: -0.172, 0.612)	NS

[a] No details of dispersion
[b] person days calculated using rate reported for any hypo (assuming sum of minor and symptomatic hypos)
[c] SE assumed and estimated from graph, used to calculate SD
[d] NR
[e] events per patient per week; minor and symptoms only; reviewer estimated patient days at risk
[f] No patients
[g] No of events
[h] approximated to nearest integer (percentages only presented in text)
[i] unclear

Hba1c was analysed using ANOVA with treatment regimen and country as fixed effects, and with Hba1c value at baseline as a covariate. Other continuous variables were analysed using a repeated measures ANOVA including treatment regimen, visit, country and baseline value as a covariate. Hypoglycaemia events were analysed using a log linear Poisson regression model, with treatment and country as factors.

Table 22: Liu et al. (2013)

General	**Phase:** ☐ monotherapy ☐ dual therapy ☑ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** Taiwan **Authors' conclusions:** Pioglitazone and sitaglitin achieved similar improvements in overall glycaemic control in patients with type 2 diabetes inadequately controlled with metformin and a sulfonylurea. However, there were some difefrences in terms of FBG, hs-CRP, lipids, body weight and Aes. **Source of funding:** Supported by Mackay Memorial Hospital **Comments:** Open label trial. Randomisation was performed using an interactive voice response system
Number and characteristics of patients	**Total number of patients:** 120 **Inclusion criteria:** Males and females with type 2 diabetes (>20 years) who are taking stable doses of metformin (>=1500 mg/day) and a sulfonylurea (>= maximal dose, modified release gliclazide 60 to 120 mg daily or glimepiride 4 to 8mg daily) for at least 10 weeks prior to screening and had inadeqaute glycaemic control (Hba1c >=7 and <11%) **Exclusion criteria:** Type 1 diabetes, insulin use within 12 weeks, contraindications to pioglitazone or sitagliptin, impaired renal function, ALT or AST above the normal limit, current or planned pregnancy or lactation. Withdrawal criteria included pregnancy, Hba1c >11% after the first 12 weeks of treatment, ALT or AST >3 times the ULN, AEs unacceptable to the patient or serioud Aes (e.g. hepatic failure)
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** all on oral hypoglycaemic drugs and/or insulin **Details of washout period:** All patients were taking metformin and sulfonylurea at study entry
Lifestyle advice	Patients were instructed to continue the same lifestyle (including diet and exercise) they had maintained prior to study entry
Follow-up	**Total follow-up (wks):** 24 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 24 **Frequency of monitoring appointments:** -
Arms	**(1) Metformin + sulfonylurea + pioglitazone**

N: 60
Treatment duration (wks): 24
Washout period (d): 0
Comments: All patients were taking metformin + sulfonylurea at study entry
Treatment(s): (a) Metformin (Oral)
Mean dose (mg/d): 1713
Details of dosing regimen: No dose adjustments were made to metformin or sulfonylurea
(b) Sulfonylurea (Oral)
Mean dose (mg/d): 6.5
Details of dosing regimen: No dose adjustments were made to metformin or sulfonylurea
Mean dose of glimepiride 6.5 ± 1.3
Mean dose of gliclazide 90 ± 30
(c) Pioglitazone (Oral) – fixed-dose
Set dose (mg/d):30

(2) Metformin + sulfonylurea + sitagliptin

N: 60
Treatment duration (wks): 24
Washout period (d): 0
Comments: All patients were taking metformin + sulfonylurea at study entry
Treatment(s): (a) Metformin (Oral)
Mean dose (mg/d): 1717
Details of dosing regimen: No dose adjustments were made to metformin or sulfonylurea
(b) Sulfonylurea (Oral)
Mean dose (mg/d): 6.5
Details of dosing regimen: No dose adjustments were made to metformin or sulfonylurea
Mean dose of glimepiride 6.5 ± 1.5
Mean dose of gliclazide 95 ± 29.5
(c) Sitagliptin (Oral) – fixed-dose
Set dose (mg/d):100

Outcomes

General

An ITT analysis with LOCF was used to assess efficacy. The ITT population included all patients who had received at least one dose of the study medication and had Hba1c recorded at baseline and at least once after baseline.

Outcomes not extracted in this evidence table include measures of insulin resistance, fasting insulin

8/60 (13.3%) patients in the pioglitazone group and 6/60 (10%) in the sitagliptin group duiscontinued the study

Baseline characteristics

		Metformin + sulfonylurea + pioglitazone			Metformin + sulfonylurea + sitagliptin			Δ	p
		N	k	mean	N	k	mean		
Demographics: Age (years)	Continuous	60		58.1 (SD 8.3)	60		60.1 (SD 8.9)		
Sex (n male)	Dichotomous	60	23	(38.3%)	60	22	(36.7%)		
Duration of diabetes (yrs)	Continuous	60		7.8 (SD 3.9)	60		7.8 (SD 4.3)		
Blood glucose: HbA1c (%) – 0wk	Continuous	60		8.54 (SD 0.97)	60		8.27 (SD 0.86)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	60		10.1242944 (SD 2.11)	60		9.8134608 (SD 2.59)		
Body weight: BMI (kg/m2) – 0wk	Continuous	60		25.7 (SD 3.7)	60		26.6 (SD 4.6)		
Weight (kg) – 0wk	Continuous	60		65.4 (SD 10.4)	60		69.4 (SD 13.6)		
Adverse events: liver enzymes: abnormal ALT – 0wk	Continuous	60		28.5 (SD 15.5)	60		34.2 (SD 17.5)		
Blood pressure: Systolic blood pressure (mmHg) – 0wk	Continuous	60		128 (SD 11.4)	60		127.9 (SD 11)		
Diastolic blood pressure (mmHg) – 0wk	Continuous	60		72.9 (SD 6.6)	60		72.3 (SD 8.2)		

Lipids:										
Total cholesterol (mmol/l) – 0wk	Continuous	60		5.019426 (SD 0.861)	60		4.509984 (SD 0.804)			
HDL cholesterol (mmol/l) – 0wk	Continuous	60		1.109394 (SD 0.31)	60		1.093878 (SD 0.318)			
Triglycerides (mmol/l) – 0wk	Continuous	60		1.850431 (SD 0.828)	60		1.543343 (SD 0.833)			
LDL cholesterol (mmol/l) – 0wk	Continuous	60		2.87046 (SD 0.809)	60		2.645478 (SD 0.654)			
Previous blood glucose lowering drugs:										
Metformin	Continuous	60		1713 (SD 247)	60		1717 (SD 246)			
Sulfonylureaa	Continuous	60		6.5 (SD 1.3)	60		6.5 (SD 1.5)			

[a] glimepiride (mg/day)

Results

		Metformin + sulfonylurea + pioglitazone			Metformin + sulfonylurea + sitagliptin				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Blood glucose:									
HbA1c (%) – 24wk	Mean change	60			60				0.17
HbA1c < 7% or <=7% – 24wk	Dichotomous	60			60				NR
Fasting plasma glucose (mmol/l) – 24wk	Mean change	60			60				0.024
Body weight:									
Weight (kg) – 24wk	Mean change	60			60				<0.001
Hypoglycaemic events:									
minor hypoglycaemic events – 24wk	Dichotomous	60			60				NS
Major/severe hypoglycaemic event – 24wk	Dichotomous	60			60				NR
Adverse events:									
Any adverse event(s) – 24wk	Dichotomous	60			60				NS
Any serious adverse event(s) – 24wk	Dichotomous	60			60				NR
Edema peripheral – 24wk	Dichotomous	60			60				<0.001
Gastrointestinal disorders (any) – 24wk	Dichotomous	60			60				0.035
GI: nausea/vomiting – 24wk	Dichotomous	60			60				NR
GI: diarrhoea – 24wk	Dichotomous	60			60				NR
GI: abdominal pain – 24wk	Dichotomous	60			60				NR
GI: constipation – 24wk	Dichotomous	60			60				NR
liver enzymes: abnormal ALT – 24wk	Mean change	60			60				0.20
Nasopharyngitis – 24wk	Dichotomous	60			60				NS
Dropouts:									
Total dropouts – 24wk	Dichotomous	60	8	(13.3%)	60	6	(10.0%)		
Dropout due to AEs – 24wk	Dichotomous	60			60				NR
Blood pressure:									
Systolic blood pressure (mmHg) – 24wk	Mean change	60			60				0.65
Diastolic blood pressure (mmHg) – 24wk	Mean change	60			60				0.06

Lipids: Total cholesterol (mmol/l) – 24wk	Mean change	60			60					0.11
HDL cholesterol (mmol/l) – 24wk	Mean change	60			60					0.003
Triglycerides (mmol/l) – 24wk	Mean change	60			60					0.025
LDL cholesterol (mmol/l) – 24wk	Mean change	60			60					0.14
Men Blood glucose: HbA1c (%) – 24wk	Mean change	23		-0.65 (SD 0.815)	22		-1.11 (SD 0.844)			
Women Blood glucose: HbA1c (%) – 24wk	Mean change	36		-1.11 (SD 0.9)	38		-0.48 (SD 0.863)			
ITT Blood glucose: HbA1c (%) – 12wka	Mean change	59		-0.61 (SD 0.538)	60		-0.58 (SD 0.542)			
HbA1c (%) – 24wk	Mean change	59		-0.94 (SD 0.922)	60		-0.71 (SD 0.93)			
HbA1c < 7% or <=7% – 24wk	Dichotomous	59	17	(28.8%)	60	17	(28.3%)			
Fasting plasma glucose (mmol/l) – 12wka	Mean change	59		-1.998216 (SD 1.49)	60		-1.443156 (SD 1.72)			
Fasting plasma glucose (mmol/l) – 24wk	Mean change	59		-1.9871148 (SD 1.71)	60		-1.2655368 (SD 1.72)			
Body weight: Weight (kg) – 24wk	Mean change	59		1.34 (SD 2.46)	60		-0.26 (SD 2.48)			
Hypoglycaemic events: minor hypoglycaemic events – 24wkb	Dichotomous	59	5	(8.5%)	60	6	(10.0%)			
Major/severe hypoglycaemic event – 24wkb	Dichotomous	59	0	(0.0%)	60	0	(0.0%)			
Adverse events: Any adverse event(s) – 24wkb	Dichotomous	59	31	(52.5%)	60	26	(43.3%)			
Any serious adverse event(s) – 24wkb	Dichotomous	59	0	(0.0%)	60	0	(0.0%)			
Edema peripheral – 24wkb	Dichotomous	59	16	(27.1%)	60	0	(0.0%)			
Gastrointestinal disorders (any) – 24wkb	Dichotomous	59	4	(6.8%)	60	12	(20.0%)			
GI: nausea/vomiting – 24wkb	Dichotomous	59	2	(3.4%)	60	6	(10.0%)			
GI: diarrhoea – 24wkb	Dichotomous	59	0	(0.0%)	60	4	(6.7%)			
GI: abdominal pain – 24wkb	Dichotomous	59	3	(5.1%)	60	4	(6.7%)			
GI: constipation – 24wkb	Dichotomous	59	1	(1.7%)	60	1	(1.7%)			
liver enzymes: abnormal ALT – 24wk	Mean change	59		-4.5 (SD 18.4)	60		0 (SD 18.6)			
Nasopharyngitis – 24wkb	Dichotomous	59	11	(18.6%)	60	12	(20.0%)			
Dropouts: Dropout due to AEs – 24wk	Dichotomous	59	2	(3.4%)	60	1	(1.7%)			
Blood pressure: Systolic blood pressure (mmHg) – 24wk	Mean change	59		-0.5 (SD 6.91)	60		0 (SD 6.97)			
Diastolic blood pressure (mmHg) – 24wk	Mean change	59		-0.8 (SD 4.61)	60		0.9 (SD 4.65)			

	Lipids: Total cholesterol (mmol/l) – 24wk	Mean change	59		0.256014 (SD 0.795)	60		0.015516 (SD 0.781)		
	HDL cholesterol (mmol/l) – 24wk	Mean change	59		0.162918 (SD 0.238)	60		0.033618 (SD 0.24)		
	Triglycerides (mmol/l) – 24wk	Mean change	59		-0.269831 (SD 0.815)	60		0.071127 (SD 0.813)		
	LDL cholesterol (mmol/l) – 24wk	Mean change	59		0.170676 (SD 0.735)	60		-0.031032 (SD 0.741)		
	<59 years Blood glucose: HbA1c (%) – 24wk	Mean change	29		-0.91 (SD 0.915)	29		-0.6 (SD 0.915)		
	>=59 years Blood glucose: HbA1c (%) – 24wk	Mean change	30		-0.97 (SD 0.876)	31		-0.82 (SD 0.891)		
	<7 years diabetes duration Blood glucose: HbA1c (%) – 24wk	Mean change	26		-1.1 (SD 0.918)	28		-0.91 (SD 0.9)		
	>=7 years diabetes duration Blood glucose: HbA1c (%) – 24wk	Mean change	33		-0.81 (SD 0.862)	32		-0.53 (SD 0.905)		
	BMI <25.5 Blood glucose: HbA1c (%) – 24wk	Mean change	29		-0.81 (SD 0.915)	32		-0.86 (SD 0.962)		
	BMI>=25.5 Blood glucose: HbA1c (%) – 24wk	Mean change	31		-1.07 (SD 0.891)	32		-0.58 (SD 0.905)		
	< max dose of sulfonylurea Blood glucose: HbA1c (%) – 24wk	Mean change	37		-0.98 (SD 0.791)	33		-0.89 (SD 0.804)		
	on max dose sulfonylurea Blood glucose: HbA1c (%) – 24wk	Mean change	22		-0.85 (SD 0.985)	27		-0.51 (SD 0.987)		
	< Hba1c 8.2% Blood glucose: HbA1c (%) – 24wk	Mean change	23		-0.62 (SD 0.767)	33		-0.43 (SD 0.747)		
	>=Hba1c 8.2% Blood glucose: HbA1c (%) – 24wk	Mean change	36		-1.22 (SD 1.02)	27		-0.94 (SD 0.987)		
	<FBG 170mg/dl Blood glucose: HbA1c (%) – 24wk	Mean change	27		-0.94 (SD 0.8)	32		-0.77 (SD 0.792)		
	>=FBG 170mg/dl Blood glucose: HbA1c (%) – 24wk	Mean change	32		-0.94 (SD 0.962)	28		-0.64 (SD 1.01)		
	[a] estimated from graph [b] No of patients									
	Treatment groups were compared using ANCOVA with treatment and baseline value at covariates. Chi squared or Fisher's exact test were used for dichotomous parameters.									

Table 23: Lund et al. (2009)

General	**Phase:**

	☐ monotherapy ☐ dual therapy ☑ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** Denmark **Authors' conclusions:** In non-obese patients with type 2 diabetes and poor glycaemic regulation on oral hypoglycaemic agents, overall glycaemic regulation with insulin incombination with metformin was equivalent to that with insulin plus repaglinide. Weight gain seemed less with insulin plus metformin than with insulin plus repaglinide **Source of funding:** Novo Nordisk and the Clinical Development Foundation at Steno Diabetes Center co-sponsored the study financially **Comments:** single centre, prospective, randomised, double blind, double dummy, parallel trial. Active and placebo tablets were identical in appearance, taste, and smell. Random allocation was centrally performed in blocks of three and four, stratified by baseline levels of HbA1c and BMI.
Number and characteristics of patients	**Total number of patients:** 101 **Inclusion criteria:** Type 2 diabetes mellitus, defined as age at onset of diabetes =40 years; fasting serum C peptide =300 pmol/l or a non-fasting or glugacon stimulated serum C peptide =600 pmol/l (measured either during the screening or run-in period); and no history of persistent ketonuria or of ketoacidosis, BMI =27, Insulin naive patients: HbA1c =6.5% after a minimum of four months' treatment on oral hypoglycaemic agents as monotherapy or combination therapy, Insulin treated patients: HbA1c <9.5% at ongoing insulin therapy **Exclusion criteria:** Type 1 diabetes mellitus or secondary diabetes mellitus, Weight loss of more than 5.0 kg during the 6 months before enrolment, HbA1c <6.5% at baseline, BMI >27 at baseline, Contraindications for the use of the study drugs (for example, clinical signs of heart, kidney, or liver failure), Coexisting serious medical conditions, HbA1c >10.5% at two separate visits with =1 month interval a minimum of four months after initiation of the randomised study drugs Pre-randomisation phase: After the screening period, patients entered a four month run-in period. All patients received combination therapy with metformin (1000 mg twice a day) plus repaglinide (2 mg three times a day) and stopped prior glucose lowering treatments. Doses were adjusted by forced titration to reach maximum tolerated doses.
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** all on oral hypoglycaemic drugs and/or insulin **Details of washout period:** During the run-in period patients received metformin + repaglinide and stopped all other treatments
Lifestyle advice	Patients were asked not to make any lifestyle modifications during the trial.
Follow-up	**Total follow-up (wks):** 68 **Length of titration period (wks):** 16 **Length of maintenance period (wks):** 52 **Frequency of monitoring appointments:** -
Arms	**(1) Metformin + Biphasic insulin aspart (70/30)** N: 52 Treatment duration (wks): - Washout period (d): 0 Treatment(s): (a) Biphasic insulin aspart (Subcutaneous) – flexible-dose (dose-adjusted) Frequency of dosing: variable Details of dosing regimen: The starting dose of insulin was six units injected before dinner. Patients self adjusted insulin dose every third day according to a predefined algorithm, aiming for a fasting plasma glucose concentration of 4.0-6.0 mmol/l. The target HbA1c concentration was less than 6.5%. If glycaemic targets were not reached, patients intensified to two or three insulin injections a day at three, six, or nine months using prespecified criteria. Doses were reduced if adverse events with possible relation to either of the study medications occurred. Once adverse events had resolved, drug dose was increased again; if adverse events recurred, the lower dose was continued (b) Metformin (Oral) – forced titration Set dose (mg/d):2000 Mean dose (mg/d): 1771 Maximum dose (mg/d): 2000 Frequency of dosing: twice a day Details of dosing regimen: Maximum dose metformin 1000 mg twice a day (total daily dose: 2000 mg) **(2) Biphasic insulin aspart (70/30) + repaglinide** N: 49 Treatment duration (wks): - Washout period (d): 0

Treatment(s): (a) Biphasic insulin aspart (Subcutaneous) – flexible-dose (dose-adjusted)
Frequency of dosing: variable
Details of dosing regimen: see metfomin + insulin group for dosing details
(b) repaglinide (Oral) – forced titration
Set dose (mg/d):6
Mean dose (mg/d): 5.2
Maximum dose (mg/d): 6
Frequency of dosing: three times a day
Details of dosing regimen: The maximum dose of repaglinide was 2 mg three times a day (total daily dose: 6 mg)

Outcomes

General

For the primary outcome, the randomised population was analysed on an intention to treat basis, with last observation carried forward for missing values at the end of treatment. For HbA1c, the last observation was carried forward only if both measurements were missing at the end of treatment. Only values obtained a minimum of three months after randomisation were used for last observation carried forward (one patient).

1 (1.9%) patient in the met + insulin group and 3 (6.1%) patients in the insulin + repaglinide group discontinued the study

Outcomes not extracted in this evidence table include SMBG levels

Baseline characteristics

		Metformin + Biphasic insulin aspart (70/30)			Biphasic insulin aspart (70/30) + repaglinide				
		N	k	mean	N	k	mean	Δ	p
Demographics:									
Age (years)	Continuous	52		63 (SD 7.8)	49		63.7 (SD 7.9)		
Sex (n male)	Dichotomous	52	31	(59.6%)	49	31	(63.3%)		
Duration of diabetes (yrs)	Continuous	52		med: 8 [rng 1–30]	49		med: 12 [rng 2–25]		
Blood glucose:									
HbA1c (%) – 0wk	Continuous	52		7.8 (SD 0.97)	49		7.82 (SD 1.23)		
HbA1c (%) – 0wk	Continuous	52		7.8 (SD 0.97)	49		8.07 (SD 1.49) a		
HbA1c (%) – 0wk	Continuous	52		8.15 (SD 1.32) a	49		7.82 (SD 1.23)		
HbA1c (%) – 0wka	Continuous	52		8.15 (SD 1.32)	49		8.07 (SD 1.49)		
Body weight:									
BMI (kg/m2)	Continuous	52		24.53 (SD 2.33)	49		24.88 (SD 2.45)		
Weight (kg) – 0wk	Continuous	52		72.82 (SD 11.4)	49		73.84 (SD 10.6)		
Waist circumference (cms)	Continuous	52		92.21 (SD 8.83)	49		92.39 (SD 8.83)		
Hip circumference (cm)	Continuous	52		96.31 (SD 5.89)	49		96.96 (SD 5.81)		
Waist/hip ratio	Continuous	52		0.96 (SD 0.07)	49		0.95 (SD 0.07)		
Diabetic complications:									
Retinopathyb	Dichotomous	52	2	(3.8%)	49	3	(6.1%)		
Neuropathy	Dichotomous	52	42	(80.8%)	49	43	(87.8%)		
Macroangiopathy	Dichotomous	52	19	(36.5%)	49	16	(32.7%)		
Previous blood glucose lowering drugs:									
Diet alone (i.e. drug naïve)	Dichotomous	52	1	(1.9%)	49	0	(0.0%)		
Oral antidiabetic medicationc	Dichotomous	52	32	(61.5%)	49	29	(59.2%)		
Insulin therapy	Dichotomous	52	19	(36.5%)	49	20	(40.8%)		
Oral agents (any use)	Dichotomous	52	45	(86.5%)	49	38	(77.6%)		

[a] before treatment (used in analysis)
[b] proliferative
[c] oral agents only

Results

	Metformin + Biphasic insulin aspart (70/30)	Biphasic insulin aspart (70/30) + repaglinide	Δ	p

		N	k	mean	N	k	mean		
Blood glucose: HbA1c (%) – 13wka	Continuous	52		7.6 (SD 1.08)	49		7.5 (SD 1.05)		
HbA1c (%) – 26wka	Continuous	52		6.95 (SD 0.721)	49		7.1 (SD 0.7)		
HbA1c (%) – 52wk	Continuous	52		6.72 (SD 0.66)	49		6.9 (SD 0.68)		
HbA1c (%) – 52wkb	Mean change	52		-1.42 (SD 0.649)	49		-1.23 (SD 0.7)	MD=-0.180 (CI: -0.450, 0.090)	0.177
Hba1c <6.5% – 52wk	Dichotomous	52	22	(42.3%)	49	14	(28.6%)		0.169
Body weight: Weight (kg) – 13wka	Continuous	52		73.5 (SD 12.3)	49		76 (SD 11.9)		
Weight (kg) – 26wka	Continuous	52		74.5 (SD 13.7)	49		77.5 (SD 14)		
Weight (kg) – 52wk	Continuous	52		74.45 (SD 12.3)	49		77.66 (SD 12.1)		
Weight (kg) – 52wkb	Mean change	52		2.22 (SD 3.89)	49		4.73 (SD 3.99)	MD=-2.510 (CI: -4.070, -0.950)	0.002
Hypoglycaemic events: minor hypoglycaemic events – 52wk	Dichotomous	52			49			RR=0.780 (CI: 44.148, 0.014)	NS
minor hypoglycaemic events – 52wk	Count	19522	1233		17312	1408			
minor hypoglycaemic events – 52wkc	Continuous	52		23.1	49		29.7		
Minor (confirmed) hypoglycaemia – 52wkc	Continuous	52		8.9	49		8.8		
Minor (confirmed) hypoglycaemia – 52wk	Count	19522	475		17312	417			
Minor (confirmed) hypoglycaemia – 52wk	Dichotomous	52			49			RR=1.010 (CI: 23.912, 0.043)	NS
Minor (unconfirmed) – 52wk	Dichotomous	52			49			RR=0.680 (CI: 33.099, 0.014)	NS
Minor (unconfirmed) – 52wk	Count	19522	758		17312	991			
Minor (unconfirmed) – 52wkc	Continuous	52		14.2	49		20.9		
Major/severe hypoglycaemic event – 52wk	Dichotomous	52			49			RR=0.440 (CI: 16.337, 0.012)	NS
Major/severe hypoglycaemic event – 52wk	Count	19522	5		17312	10			
Major/severe hypoglycaemic event – 52wkc	Continuous	52		0.1	49		0.2		
Symptomatic hypoglycaemia – 52wk	Dichotomous	52			49			RR=0.770 (CI: 47.212, 0.013)	NS

	Symptomatic hypoglycaemia – 52wk	Count	19477	1238		17310	1418			
	Symptomatic hypoglycaemia – 52wkc	Continuous	52		23.2	49		29.9		
	Nocturnal hypoglycaemia – 52wk	Dichotomous	52			49			RR=0.880 (CI: 18.018, 0.043)	NS
	Nocturnal hypoglycaemia – 52wk	Count	19522	211		17312	212			
	Nocturnal hypoglycaemia – 52wkc	Continuous	52		3.9	49		4.5		
	Adverse events: Any serious adverse event(s) – 52wk	Dichotomous	52	8	(15.4%)	49	13	(26.5%)		NR
	Lactic acidosis – 52wk	Dichotomous	52	0	(0.0%)	49	0	(0.0%)		
	Study drug exposure – 52wkd	Continuous	52		1771	49		5.2		NR
	Dropouts: Total dropouts – 52wk	Dichotomous	52	1	(1.9%)	49	3	(6.1%)		
	Dropout due to AEs – 52wk	Dichotomous	52	0	(0.0%)	49	2	(4.1%)		
	Insulin: Total daily dose (U) – 52wk	Mean change	52			49			MD=1.170 (CI: 0.900, 1.440)	0.233
	Total daily dose (U) – 52wk	Continuous	52		32.96 [rng 9–84]	49		28.25 [rng 6–108]		

[a] estimated from graph, assumed SE reported
[b] SE converted
[c] rate per patient years of exposure; no 95% CI reported
[d] mg/day

An analysis of covariance model was developed for the primary outcome, with patient as the random effect, treatment (metformin plus insulin

or repaglinide plus insulin) as the fixed effect, and baseline levels as the covariate. Hypoglycaemia was analysed by a Poisson regression model adjusted for overdispersion and exposure time. Categorical data were analysed either as odds ratios by logistic regression model, with treatment type as the fixed effect and baseline as the covariate, or as proportions by Wilcoxon rank sum test.

Table 24: Malone et al. (2004)

General

Phase:

☐ monotherapy
☐ dual therapy
☑ triple therapy
☐ insulin monotherapy
☐ insulin+oral

Parallel / crossover: Crossover

Country: USA

Authors' conclusions: In this study population, mix 75/25 plus metformin was associated with lower Hba1c than insulin glargine plus metformin, smaller rise in ppBG after breakfast and dinner, and higher proportion of patients achieving Hba1c <=7%, with a slight increase in overall (but not nocturnal) hypoglycaemia

Source of funding: Authors employed by Elli Lilly

Comments: Opan label, cross-over trial. Computer generated randomisation table.

Number and characteristics of patients	**Total number of patients:** 105 **Inclusion criteria:** patients aged 30-80 years with type 2 diabetes, with a BMI <=40 kg/m2. Patients had to demonstrate inadequate glycaemic control (Hba1c 1.3-2 times the upper limit of normal) within 30 days of the study while using >=1 OAD without insulin for at least 30 days before the start of the study **Exclusion criteria:** Not reported Pre-randomisation phase: There was a lead in period of 8 ± 2 weeks in which patients received NPH od at bedtime and metformin titrated to >=1500 but <=2550 mg/day in 2 or 3 daily doses.
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** all on oral hypoglycaemic drugs and/or insulin **Details of washout period:** All patients were taking at least one OAD at inclusion and these were discontinued (apart from metformin)
Lifestyle advice	-
Follow-up	**Total follow-up (wks):** 42 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 32 **Frequency of monitoring appointments:** Patients returned to the study center for monthly assessments
Arms	**(1) Insulin lispro mix 75/25 (tid) + metformin** N: 52 Treatment duration (wks): 16 Washout period (d): 0 Comments: patients stopped all OADs apart from metformin during the lead-in period (8-10 weeks). It was unclear whether there was a washout period before cross-over. Treatment(s): (a) Insulin lispro mix 75/25 (Subcutaneous) – flexible-dose (dose-adjusted) Frequency of dosing: twice a day Details of dosing regimen: Insulin lispro mix 75/25 was given before breakfast and dinner. Insulin doses were adjusted to achieve target FBG values 90-126 mg/dl and a 2h PPBG 144-180 mg/dl (b) Metformin (Oral) Minimum dose (mg/d): 1500 Maximum dose (mg/d): 2550 Frequency of dosing: variable **(2) Insulin glargine (od) + metformin** N: 53 Treatment duration (wks): 16 Washout period (d): 0 Comments: patients stopped all OADs apart from metformin during the lead-in period (8-10 weeks). It was unclear whether there was a washout period before cross-over. Treatment(s): (a) Insulin glargine (Subcutaneous) – flexible-dose (dose-adjusted) Frequency of dosing: once a day Details of dosing regimen: Insulin glargine was given at bedtime and targets were as insulin lispro mix group except there was no PPBG target due to the long action profile of glargine (b) Metformin (Oral) Minimum dose (mg/d): 1500 Maximum dose (mg/d): 2250 Frequency of dosing: variable
Outcomes	**General** Only Hba1c measures at week 16 (i.e. after the first treatment period and before crossover) were extracted in this evidence table. Outcomes not extracted include FBG, SMBG, hypoglycaemia, body weight as these were not reported for the first treatment period. 5 patients in each group discontinued from the study but were included as part of the efficacy analyses. 29 patients had potentially expired drugs in their possession at the time of the study 67/95 who completed the study had no expired drug in their posession and were included in efficacy analysis. All analyses were based on the ITT population, which included all randomised patients who received at least one dose of insulin. The LOCF method was used for missing values.

Baseline characteristics

		Insulin lispro mix 75/25 (tid) + metformin			Insulin glargine (od) + metformin				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Demographics: Age (years)	Continuous	52		54.5 (SD 11.4)	53		55.3 (SD 9.5)		

	Sex (n male)	Dichotomous	52	33	(63.5%)	53	33	(62.3%)		
	Duration of diabetes (yrs)	Continuous	52		8.1 (SD 5.8)	53		9.8 (SD 7.4)		
	Blood glucose: HbA1c (%) – 0wk	Continuous	52		8.7 (SD 1.3)	53		8.7 (SD 1.3)		
	Fasting plasma glucose (mmol/l)	Continuous	52		8.3370012 (SD 2.48)	53		8.6200818 (SD 2.78)		
	Body weight: BMI (kg/m2)	Continuous	52		30.1 (SD 5)	53		31.7 (SD 5.7)		
	Weight (kg)	Continuous	52		88.5 (SD 16.1)	53		94.4 (SD 19.8)		

Results

		Insulin lispro mix 75/25 (tid) + metformin			Insulin glargine (od) + metformin				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 16wka	Continuous	52		7.3 (SD 0.773)	53		7.93 (SD 1.58)		

[a] SD calculated from 95% CI estimated from graph

Analysis methods for a cross over design were used to evaluate both carry over effects and treatment effects. Statistical analyses were performed using the endpoint value defined as the last value observed for each patient during each period of the cross over study using Grizzle method (1965). The treatment, country and treatment by country interaction were factors included in the analysis

Table 25: Malone et al. (2005)

General

Phase:
☐ monotherapy
☐ dual therapy
☑ triple therapy
☐ insulin monotherapy
☐ insulin+oral

Parallel / crossover: Crossover

Country: Spain and France

Authors' conclusions: In patients with type 2 diabetes and inadequate glucose control while on insulin or insulin and oral agent combination therapy, treatment with a twice daily insulin lispro mixture plus metformin, which targets both post prandial and pre-meal BG, provided clinically significant improvements in Hba1c, significantly reduced post prandial BG after each meal and reduced nocturnal hypoglycaemia as compared with once-daily glargine plus metformin.

Source of funding: Authors employed by Eli Lilly

Comments: Multicentre, randomised, open label cross over trial.

Number and characteristics of patients

Total number of patients: 97

Inclusion criteria: patients aged 30-75 years with type 2 diabetes, with inadequate glycaemic control using NPH once or twice daily alone or in combination with an oral antidiabetic agent, or a once daily human insulin mixture with an oral agent for at least 30 days before study entry

Exclusion criteria: used a glitazone within 30 days prior to study entry

Pre-randomisation phase: There was a 6 week lead in period before randomisation-this was to stablise patients on a common insulin regimen.

Previous glucose-lowering therapy

Any participants previously taking glucose-lowering therapy? all on oral hypoglycaemic drugs and/or insulin

Details of washout period: All were taking insulin alone or in combination at study entry, during the lead in period all patients were required to use NPH once daily at bedtime and metformin two or three times daily. All other OADs were discontinued. Patients whose daily metformin dose was outside the acceptable therapeutic range (1500-2550 mg) were discontinued.

Lifestyle advice

Patients were given no special dietary instructions, but were expected to follow their usual diabetic diets

	during the trial
Follow-up	**Total follow-up (wks):** 32 **Length of titration period (wks):** 4 **Length of maintenance period (wks):** 12 **Frequency of monitoring appointments:** -
Arms	**(1) Insulin lispro mixture (bid) + metformin** N: 50 Treatment duration (wks): 16 Washout period (d): 0 Comments: OADs apart from metformin discontinued before study started. It was unclear whether there was a washout period before cross-over. Treatment(s): (a) Insulin lispro mix 75/25 (Subcutaneous) – flexible-dose (dose-adjusted) Frequency of dosing: twice a day Details of dosing regimen: The dose of insulin lispro mixture or glargine was adjusted by the investigators throughout the study in an attempt to achieve targets for fasting and pre-meal BG of 5-7 mmol/l. During treatment with insulin lispro mixture + metformin, an additonal BG target for 2h post prandial BG of 8-10 mmol/l was established. The recommended initial dose of insulin glargine was equal to or greater than the final dose of bedtime NPH during the lead-in period. (b) Metformin (Oral) Minimum dose (mg/d): 1500 Maximum dose (mg/d): 2550 Details of dosing regimen: 1500-2550 mg per day **(2) Insulin glargine (od) + metformin** N: 47 Treatment duration (wks): 16 Washout period (d): 0 Comments: OADs apart from metformin discontinued before study started. It was unclear whether there was a washout period before cross-over. Treatment(s): (a) Insulin glargine (Subcutaneous) – flexible-dose (dose-adjusted) Frequency of dosing: once a day Details of dosing regimen: See insulin lispro + metformin for dosing details. The recommended initial dose of insulin glargine was equal to or greater than the final dose of bedtime NPH during the lead-in period (b) Metformin (Oral) Minimum dose (mg/d): 1500 Maximum dose (mg/d): 2550
Outcomes	**General** Only Hba1c measures were extracted in this evidence table as this was the only measure reported for the first treatment period (before cross-over). Other measures not extracted include FBG, hypoglycaemia, body weight, SMBG and adverse events All analyses were based on the ITT population, which included all randomised patients who received insulin. The LOCF method was used for missing values. 84/97 completed the study (3/50 [6%] in lispro mixture group and 10/47 [21%] in glargine group)

Baseline characteristics

		Insulin lispro mixture (bid) + metformin			Insulin glargine (od) + metformin				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	50		59.18 (SD 8.58)	47		59.63 (SD 8.03)		
Sex (n male)	Dichotomous	50	25	(50.0%)	47	18	(38.3%)		
Duration of diabetes (yrs)	Continuous	50		13.52 (SD 8.18)	47		11.9 (SD 6.27)		
Blood glucose: HbA1c (%) – 0wk	Continuous	50		8.5 (SD 0.95)	47		8.48 (SD 0.8)		
Fasting plasma glucose (mmol/l)	Continuous	50		8.63 (SD 2.93)	47		8.21 (SD 2.09)		
Body weight: BMI (kg/m2)	Continuous	50		29.41 (SD 4.57)	47		29.64 (SD 5.16)		
Weight (kg)	Continuous	50		77.82 (SD 13.6)	47		77.21 (SD 15.9)		

	Previous blood glucose lowering drugs: Sulfonylurea	Dichotomous	50	14	(28.0%)	47	16	(34.0%)			

Results

		Insulin lispro mixture (bid) + metformin			Insulin glargine (od) + metformin				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 16wka	Continuous	50		8.05 (SD 0.919)	47		7.59 (SD 1.03)		

[a] SD calculated from estimated SEM from graph

Analysis methods for a cross over design were used to evaluate both carry over effects and treatment effects. Statistical analyses were performed using the endpoint value defined as the last value observed for each patient during each period of the cross over study using Grizzle method (1965). The treatment, country and treatment by country interaction were factors included in the analysis

Table 26: Meneghini et al. (2013)

General

Phase:
☐ monotherapy
☐ dual therapy
☑ triple therapy
☐ insulin monotherapy
☐ insulin+oral

Parallel / crossover: Parallel

Country: -

Authors' conclusions: -

Source of funding: -

Comments: -

Number and characteristics of patients

Total number of patients: 457

Inclusion criteria: -

Exclusion criteria: -

Previous glucose-lowering therapy

Any participants previously taking glucose-lowering therapy? all on oral hypoglycaemic drugs and/or insulin

Details of washout period: No wash out period

Lifestyle advice

-

Follow-up

Total follow-up (wks): -

Length of titration period (wks): -

Length of maintenance period (wks): -

Frequency of monitoring appointments: -

Arms

(1) Metformin + Insulin Detemir

N: 228

Treatment duration (wks): 26
Washout period (d): -
Comments: Participants (72.5%) who were on meformin + OAD at baseline discontinued the non-metformin OAD

Treatment(s): (a) Insulin detemir (Subcutaneous) – forced titration
Set dose (mg/d):10
Mean dose (mg/d): 57
Frequency of dosing: once a day
Details of dosing regimen: Mean (SD) determir dose at study end was 57 (30)U corresponding to a mean (SD) total insulin dose per kg per body weight of 0.70 (0.34)U/kg

(b) Metformin (Oral) – flexible-dose (dose-adjusted)
Minimum dose (mg/d): 1500

(2) Metformin + Insulin Glargine

N: 229
Treatment duration (wks): 26
Washout period (d): -
Comments: Participants (72.8%) who were on meformin + OAD at baseline discontinued the non-metformin OAD

Treatment(s): (a) Metformin (Oral)
(b) Insulin glargine (Subcutaneous) – forced titration
Set dose (mg/d):10
Frequency of dosing: once a day
Details of dosing regimen: Mean (SD) glargine dose at end of study was 51 (26) U, corresponding to mean (SD) total insulin dose per kg body weight of 0.61 (0.28)U/kg

Outcomes

Baseline characteristics

		Metformin + Insulin Detemir		
		N	**k**	**mean**
Demographics:				
Age (years)	Continuous	226		57.3 (SD 10.2)
Sex (n male)	Dichotomous	226	129a	(57.1%)
Duration of diabetes (yrs)	Continuous	226		8 (SD 5.6)
Blood glucose:				
HbA1c (%) – wk	Continuous	226		7.96 (SD 0.62)
HbA1c (%) – wk	Continuous	226		7.96 (SD 0.62)
Body weight:				
BMI (kg/m2)	Continuous	226		28.9 (SD 4)
Weight (kg) – wk	Continuous	226		82.8 (SD 17.2)
Weight (kg) – wk	Continuous	226		82.8 (SD 17.2)

[a] Estimated from reported percentages

		Metformin + Insulin Glargine		
		N	**k**	**mean**
Demographics:				
Age (years)	Continuous	227		57.3 (SD 10.3)
Sex (n male)	Dichotomous	227	127a	(55.9%)
Duration of diabetes (yrs)	Continuous	227		8.4 (SD 6.6)
Blood glucose:				
HbA1c (%) – wk	Continuous	227		7.86 (SD 0.58)
HbA1c (%) – wk	Continuous	227		7.86 (SD 0.58)
Body weight:				
BMI (kg/m2)	Continuous	227		29.1 (SD 3.9)
Weight (kg) – wk	Continuous	227		81.7 (SD 16.2)
Weight (kg) – wk	Continuous	227		81.7 (SD 16.2)

[a] Estimated from reported percentages

Results

		Metformin + Insulin Detemir		
		N	**k**	**mean**
Blood glucose:				
HbA1c (%) – 26wk	Continuous	226		7.48 (SD 0.91) a
HbA1c (%) – 26wk	Continuous	226		7.48 (SD 0.91) a
Body weight:				
Weight (kg) – 26wk	Mean change	226		-0.49 (SD 3.3) b
Weight (kg) – 26wk	Mean change	226		-0.49 (SD 3.3) b

Hypoglycaemic events: All hypoglycaemic events (no events) – 26wk	Count	37644	329	c
Dropouts: Total dropouts – 26wk	Dichotomous	228	38	(16.7%)
Dropout due to AEs – 26wk	Dichotomous	228	5	(2.2%)

[a] Data adjusted for baseline HbA1c, previous OAD and country
[b] Assumed data from full analysis set
[c] Patient days estimated from event rate and number of events

		Metformin + Insulin Glargine		
		N	k	mean
Blood glucose: HbA1c (%) – 26wk	Continuous	227		7.13 (SD 0.72) a
HbA1c (%) – 26wk	Continuous	227		7.13 (SD 0.72) a
Body weight: Weight (kg) – 26wk	Mean change	227		1 (SD 3.1) b
Weight (kg) – 26wk	Mean change	227		1 (SD 3.1) b
Hypoglycaemic events: All hypoglycaemic events (no events) – 26wk	Count	37824	457	c
Dropouts: Total dropouts – 26wk	Dichotomous	229	41	(17.9%)
Dropout due to AEs – 26wk	Dichotomous	229	3	(1.3%)

[a] Data adjusted for baseline HbA1c, previous OAD and country
[b] Assumed data from full analysis set
[c] Patient days estimated from event rate and number of events

Table 27: Milicevic et al. (2009)

General	**Phase:** ☐ monotherapy ☐ dual therapy ☑ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** Bulgaria, Croatia, Hungary, Israel, Romania, Slovakia and Turkey **Authors' conclusions:** Treatment with lispro mix 50/25 compared with glibenclamide + NPH in patients with inadequate control on combined OAMs yielded better postprandal and overall glycaemic control with a higher rate of hypoglycaemia **Source of funding:** Eli Lilly **Comments:** Randomised (block randomisation), open label trial. Randomisation lists were computer generated and permitted approximately equal numbers to each of the treatment arms.
Number and characteristics of patients	**Total number of patients:** 135 **Inclusion criteria:** Patients with type 2 diabetes who were treated with OAMs for at least 6 months before study entry and were on maximally tolerated doses of glibenclamide and metformin during at least the 6 week period preceding visit 1. Patients were aged between 40 and 80 years, with BMI between 25-32 kg/m2 **Exclusion criteria:** type 1 diabetes, if any other serious disease were present, had advanced forms of diabetic complications. Patients were not included if their treatment during the last month before the study included insulin or OAM other than glibenclamide and metformin or if BG values were in the optimal range. Pre-randomisation phase: Patients continued metformin and sulfonlyurea during the lead in period
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** all on oral hypoglycaemic drugs and/or insulin **Details of washout period:** All patients were taking metformin + sulfonylurea

Lifestyle advice	During visit 2, patients also receievd consultation on diet
Follow-up	**Total follow-up (wks):** 24 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 24 **Frequency of monitoring appointments:** Visits were scheduled at 2 and 4 weeks, followed by regular visits every 4 weeks
Arms	**(1) Lispro mix 50 (am) + lispro mix 25 (pm)** N: 68 Treatment duration (wks): 24 Washout period (d): 0 Comments: Both metformin + sulfonylurea was stopped in this arm Treatment(s): Insulin lispro mix 50 and mix 25 (Subcutaneous) – flexible-dose (dose-adjusted) Details of dosing regimen: Patients received lispro mix 50 immediately before breakfast and lispro mix 25 immediately before dinner. Insulin doses were adjusted at visit 2 and at every visit based on SMBG and target BG <6.7 mmol/l for fasting BG and <8 mmol/l for 2 hour postprandial BG. An initial dose of 0.3-0.5 units/kg body weight/day was recommended in the lispro mix group, followed by dose adjustments by the investigator to achieve the BG targets **(2) Glibenclamide + NPH (pm)** N: 67 Treatment duration (wks): 24 Washout period (d): 0 Comments: Metformin was stopped in this arm Treatment(s): (a) Sulfonylurea (Oral) Mean dose (mg/d): 15.2 Details of dosing regimen: Patents continued on maximally tolerated dose glibenclamide. The maximum daily dose of glibenclamide was defined as >=15 mg but not exceeding the maximum stated in the package in each country (b) NPH insulin (Subcutaneous) – flexible-dose (dose-adjusted) Frequency of dosing: once a day Details of dosing regimen: NPH was given at bedtime. An initial dose of 0.15 to 0.2 units/kg body weight/day was recommended in the glibenclamide/NPH group, followed by dose adjustments by the investigator to achieve the BG targets
Outcomes	**General** LOCF method was used, which included all data from all patients according to treatment received. 4/68 (5.9%) patients in the lispro mix group and 12/67 (17.9%) in the glibenclamide + NPH group discontinued the study Outcomes not extracted in this evidence table include SMBG levels including blood glucose profiles **Hypoglycaemic events** All hypoglycaemic events (no events) (defined as a SMBG measurement <3 mmol/l or any time hypoglycaemic symptoms were felt by the patient or observed by another person) Major/severe hypoglycaemic event (defined if assisstance by another person was required)

Baseline characteristics

		Lispro mix 50 (am) + lispro mix 25 (pm)			Glibenclamide + NPH (pm)				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	68		58.3 (SD 7.9)	67		56.4 (SD 8.3)		
Sex (n male)	Dichotomous	68	21	(30.9%)	67	22	(32.8%)		
Duration of diabetes (yrs)	Continuous	68		9.12 (SD 6.18)	67		9.16 (SD 6.64)		
Blood glucose: HbA1c (%) – 0wk	Continuous	68		9.7 (SD 1.7)	67		9.6 (SD 1.8)		
Body weight: BMI (kg/m2)	Continuous	68		28 (SD 2.3)	67		27.9 (SD 2.1)		
Weight (kg) – 0wk	Continuous	68		75.3 (SD 10)	67		76.5 (SD 9.8)		
Blood pressure: Systolic blood pressure (mmHg)	Continuous	68		139.2 (SD 17.4)	67		140 (SD 18.1)		

	Diastolic blood pressure (mmHg)	Continuous	68		83.3 (SD 9.4)	67		82.2 (SD 8.2)			

Results

		Lispro mix 50 (am) + lispro mix 25 (pm)			Glibenclamide + NPH (pm)				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 24wk	Continuous	68		8.42 (SD 1.4)	67		9.16 (SD 1.5)		0.01
HbA1c (%) – 24wk	Mean change	68		-1.3 (SD 2)	67		-0.5 (SD 1.6)		
Fasting plasma glucose (mmol/l) – 12wk	Mean change	68		0.87 (SD 4.15)	67		-1.37 (SD 3.52)		
Fasting plasma glucose (mmol/l) – 24wk	Continuous	68			67				0.417
Fasting plasma glucose (mmol/l) – 24wk	Mean change	68		-0.76 (SD 3.64)	67		-0.24 (SD 3.49)		
Body weight: Weight (kg) – 12wk	Mean change	68		0.65 (SD 2.46)	67		0.59 (SD 1.66)		
Weight (kg) – 24wk	Mean change	68		1.42 (SD 3.52)	67		1.2 (SD 2.5)		
Weight (kg) – 24wk	Continuous	68			67				NS
Hypoglycaemic events: All hypoglycaemic events (no events) – 12wk[a]	Continuous	68		0.48 (SD 0.99)	67		0.14 (SD 0.27)		
All hypoglycaemic events (no events) – 24wk	Dichotomous	68			67				0.037
All hypoglycaemic events (no events) – 24wk[a]	Continuous	68		0.37 (SD 0.7)	67		0.09 (SD 0.17)		
All hypoglycaemic events (no events) – 24wk[b]	Count	10080	124		10248	31			
Major/severe hypoglycaemic event – 24wk[c]	Dichotomous	68	2	(2.9%)	67	0	(0.0%)		NR
Dropouts: Total dropouts – 24wk	Dichotomous	68	16	(23.5%)	67	12	(17.9%)		
Dropout due to AEs – 24wk	Dichotomous	68	1	(1.5%)	67	5	(7.5%)		
Insulin: Total daily dose (U) – 24wk	Continuous	68		44.1 (SD 19.9)	67		21 (SD 9.4)		NR

[a] episodes per patient per 30 days; assumed SD reported
[b] person days estimated assuming dropout halfway through the study and no of events calculated using rates of all hypos reported
[c] assumed no of patients

A two way ANOVA model that included traetment effect, country and their interaction was used. Where treatment by country interaction was not significant, it was removed from the model

Table 28: Nauck et al. (2007)

General

Phase:
☐ monotherapy
☐ dual therapy
☑ triple therapy
☐ insulin monotherapy
☐ insulin+oral

Parallel / crossover: Parallel

	Country: 13 countries **Authors' conclusions:** Exenatide treatment resulted in HbA1c reduction similar to biphasic insulin aspart and provided better postprandial glycaemic control, making it a potential alternative for the treatment of type 2 diabetes. Treatment with biphasic insulin aspart was associated with weight gain and lower risk of adverse gastrointestinal events **Source of funding:** Authors employed with Eli Lilly **Comments:** Computer-generated randomisation table administered by the sponsor via an automated voice response system was used.
Number and characteristics of patients	**Total number of patients:** 505 **Inclusion criteria:** Eligible patients were between 30 and 75 years of age and had suboptimal glycaemic control despite receiving optimally effective metformin and sulfonylurea therapy for at least 3 months. Inclusion criteria included, at the time of screening, HbA1c levels =7.0 and =11.0%, a BMI =25 and =40 kg/m2, and a history of stable body weight (=10% variation for =3 months). **Exclusion criteria:** had had more than three episodes of severe hypoglycaemia within 6 months prior to screening; had used any prescription drug to promote weight loss within 3 months; or had been treated with insulin, thiazolidinediones, alpha-glucosidase inhibitors or meglitinides for longer than 2 weeks within 3 months.
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** all on oral hypoglycaemic drugs and/or insulin **Details of washout period:** All on metformin and sulfonylurea. Patients entering this study maintained optimally effective prestudy metformin and sulfonylurea dosages; if hypoglycaemia events occurred, investigators reduced the sulfonylurea dose by approximately 50% for patients on exenatide or adapted the insulin dose for patients on insulin.
Lifestyle advice	No details reported
Follow-up	**Total follow-up (wks):** 52 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 52 **Frequency of monitoring appointments:** HbA1c levels were measured at screening, randomisation (baseline, week 0), and at weeks 12, 16, 28, 40 and 52 (or early discontinuation)
Arms	**(1) Metformin + sulfonylurea + Exenatide** N: 253 Treatment duration (wks): 52 Washout period (d): 0 Treatment(s): (a) Metformin (Oral) Details of dosing regimen: no details of dosing of pre-existing metformin (b) Sulfonylurea (Oral) Details of dosing regimen: no details of dosing of pre-existing sulfonylurea (c) Exenatide (Subcutaneous) – fixed-dose Set dose (mg/d):10 Frequency of dosing: twice a day Details of dosing regimen: Patients assigned to the exenatide group used a multi-use pen to subcutaneously inject (within 15 min before morning and evening meals) a fixed dose of 5 µg twice daily for 4 weeks and 10 µg twice daily for the remainder of the study. If frequent nausea developed (daily episodes for >1 week duration), patients had the option to decrease their dose to 5 µg twice daily. **(2) Metformin + sulfonylurea + biphasic insulin aspart (30% aspart)** N: 248 Treatment duration (wks): 52 Washout period (d): 0 Treatment(s): (a) Metformin (Oral) (b) Sulfonylurea (Oral) (c) Biphasic insulin aspart (Subcutaneous) – flexible-dose (dose-adjusted) Mean dose (mg/d): 24.4 Frequency of dosing: twice a day Details of dosing regimen: Patients in the comparator group subcutaneously injected premixed insulin before the morning and evening meals. Investigators chose the starting insulin dose for patients following randomisation, and contacted patients at regular intervals to discuss glycaemic control. A forced titration schedule was not used in this trial. Investigators were instructed to adjust insulin doses to achieve an optimal balance between glycaemic control and risk of hypoglycaemia as dictated by best clinical practice. Multiple options were available to guide intensification of insulin therapy including: (1) ongoing analysis of the patient's diary and home glucose monitoring results; and (2) a titration guideline outlining minimum targets for fasting glucose (<7 mmol/l [126 mg/dl]) and 2-h postprandial glucose (<10 mmol/l [180 mg/dl].

Patients were were encouraged to optimise glucose control by titrating insulin doses as high as clinically possible.

The mean dose of premixed insulin increased from 15.7±9.5 U/day at week 2 to 24.4±15.6 U/day atweek 52

Outcomes

General

intention-to-treat (ITT) sample, defined as patients who received at least one dose of study medication and had at least one post-baseline measurement of HbA1c; and (2) a per-protocol sample, defined as patients who had at least 12 weeks of exposure to study medication and no violations of screening criteria or discontinuation criteria.

54 (21%) of patients in the exenatide group and 25 (10%) in insulin group withdrew from the study

Outcomes not extracted in this evidence table include beta cell function, insulin sensitivity, postprandial and self-monitored blood glucose levels

Hypoglycaemic events

The severity (mild, moderate or severe) and timing (nocturnal or daytime) of each hypoglycaemic event and whether it could be attributed to

therapy (yes or no) were assessed by the investigator

All hypoglycaemic events (no events) (A hypoglycaemic episode was defined as any time a patient experienced a sign or symptom of hypoglycaemia or noted a blood glucose level <3.4 mmol/l (60 mg/dl) during selfmonitoring, whether or not this level was associated with

signs, symptoms or treatment)

Baseline characteristics

		Metformin + sulfonylurea + Exenatide			Metformin + sulfonylurea + biphasic insulin aspart (30% aspart)			Δ	p
		N	k	mean	N	k	mean		
ITT									
Demographics:									
Age (years)	Continuous	253		59 (SD 9)	248		58 (SD 9)		
Sex (n male)	Dichotomous	253	134	(53.0%)	248	122a	(49.2%)		
Duration of diabetes (yrs)	Continuous	253		9.8 (SD 6.3)	248		10 (SD 6.2)		
Blood glucose:									
HbA1c (%) – 0wk	Continuous	253		8.6 (SD 1)	248		8.6 (SD 1.1)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	253		11 (SD 2.7)	248		11.3 (SD 2.8)		
Body weight:									
BMI (kg/m2)	Continuous	253		30.6 (SD 4)	248		30.2 (SD 4.2)		
Weight (kg) – 0wk	Continuous	253		85.5 (SD 15.7)	248		83.4 (SD 15.6)		
Blood pressure:									
Systolic blood pressure (mmHg) – 0wk	Continuous	253		138 (SD 16)	248		136 (SD 15)		
Diastolic blood pressure (mmHg) – 0wk	Continuous	253		81 (SD 10)	248		80 (SD 10)		
Lipids:									
Total cholesterol (mmol/l)	Continuous	253		5.1 (SD 1)	248		5 (SD 1)		
HDL cholesterol (mmol/l)	Continuous	253		1.2 (SD 0.3)	248		1.2 (SD 0.3)		
LDL cholesterol (mmol/l)	Continuous	253		3 (SD 0.9)	248		2.9 (SD 0.9)		

[a] approximated to nearest integer (percentages only presented in text)

Results

	Metformin + sulfonylurea + Exenatide	Metformin + sulfonylurea + biphasic insulin aspart (30% aspart)	Δ	p

		N	k	mean	N	k	mean		
Hypoglycaemic events: All hypoglycaemic events (no events) – 52wka	Count	82264	1059		85722	1315			
Major/severe hypoglycaemic event – 52wk	Count	82264	0		85722	0			
Nocturnal hypoglycaemia – 52wkb	Count	82264	136		85722	259			
Dropouts: Total dropouts – 52wk	Dichotomous	253	54	(21.3%)	248	25	(10.1%)		
ITT Blood glucose: HbA1c (%) – 16wkc	Continuous	253		7.35 (SD 0.159)	248		7.5 (SD 0.787)		
HbA1c (%) – 28wkc	Continuous	253		7.45 (SD 0.795)	248		7.6 (SD 0.787)		
HbA1c (%) – 52wkd	Mean change	253		-1.04 (SD 1.11)	248		-0.89 (SD 0.945)	MD=-0.150 (CI: -0.320, 0.020)	0.067
Fasting plasma glucose (mmol/l) – 52wke	Mean change	253		-1.8 (SD 3.18)	248		-1.7 (SD 3.15)	MD=-0.100 (CI: -0.600, 0.400)	0.689
Body weight: Weight (kg) – 16wkc	Mean change	253		-1.85 (SD 1.59)	248		1.2 (SD 1.57)		
Weight (kg) – 28wkc	Mean change	253		-2.2 (SD 1.59)	248		1.9 (SD 1.57)		
Weight (kg) – 52wkd	Mean change	253		-2.5 (SD 3.18)	248		2.9 (SD 3.15)	MD=-5.400 (CI: -5.900, -4.900)	<0.001
Hypoglycaemic events: All hypoglycaemic events (no events) – 52wkf	Continuous	253		4.7 (SD 11.1)	248		5.6 (SD 11)		
Major/severe hypoglycaemic event – 52wkg	Dichotomous	253	0	(0.0%)	248	0	(0.0%)		
Nocturnal hypoglycaemia – 52wkh	Continuous	253		0.6 (SD 3.18)	248		1.1 (SD 3.15)		
Nocturnal hypoglycaemia – 52wkg	Dichotomous	0	44	(17.4%)	0	62	(25.0%)		NSi
Nocturnal hypoglycaemia – 52wkg	Dichotomous	253	44	(17.4%)	248	62	(25.0%)		NSi
Adverse events: GI: nausea – 52wkg	Dichotomous	253	84	(33.2%)	248	1	(0.4%)		
Any serious adverse event(s) – 52wkg	Dichotomous	253	19	(7.5%)	248	11	(4.4%)		
Study drug-related adverse event – 52wkg	Dichotomous	253	179	(70.8%)	248	123	(49.6%)		
Arthralgia – 52wkg	Dichotomous	253	6	(2.4%)	248	4	(1.6%)		
Back pain – 52wkg	Dichotomous	253	11	(4.3%)	248	10	(4.0%)		

Bronchitis – 52wkg	Dichotomous	253	6	(2.4%)	248	6	(2.4%)		
cardiovascular AE – 52wkg	Dichotomous	253	10	(4.0%)	248	5	(2.0%)		
Death – 52wkg	Dichotomous	253	2	(0.8%)	248	1	(0.4%)		
Dyspepsia – 52wkg	Dichotomous	253	7	(2.8%)	248	1	(0.4%)		
GI: diarrhoea – 52wkg	Dichotomous	253	24	(9.5%)	248	5	(2.0%)		
GI: vomiting – 52wkg	Dichotomous	253	38	(15.0%)	248	8	(3.2%)		
Headache – 52wkg	Dichotomous	253	12	(4.7%)	248	13	(5.2%)		
Hypertension – 52wkg	Dichotomous	253	5	(2.0%)	248	7	(2.8%)		
Injection site – 52wkg	Dichotomous	253	4	(1.6%)	248	1	(0.4%)		
Nasopharyngitis – 52wkg	Dichotomous	253	28	(11.1%)	248	24	(9.7%)		
Pain (extremity) – 52wkg	Dichotomous	253	6	(2.4%)	248	8	(3.2%)		
Temperature/influenza – 52wkg	Dichotomous	253	18	(7.1%)	248	16	(6.5%)		
Dropouts:									
Dropout due to AEs – 52wk	Dichotomous	253	20	(7.9%)	248	0	(0.0%)		
Blood pressure:									
Systolic blood pressure (mmHg) – 52wk	Mean change	253		-5 (SD 15)	248		1 (SD 16)		
Diastolic blood pressure (mmHg) – 52wk	Mean change	253		-2 (SD 10)	248		1 (SD 10)		
PP									
Blood glucose:									
HbA1c (%) – 52wkd	Mean change	222		-1.04 (SD 1.04)	224		-0.89 (SD 0.894)		
Fasting plasma glucose (mmol/l) – 52wkd	Mean change	222		-1.8 (SD 2.99)	224		-1.7 (SD 2.99)		
Body weight:									
Weight (kg) – 52wkd	Mean change	222		-2.5 (SD 2.98)	224		2.9 (SD 2.99)		

[a] person days estimated assuming drop out half way through study and number of episodes calculated from reported rate (least squares means)
[b] person days estimated assuming drop out half way through study and number of episodes calculated from reported rate
[c] estimated from graph
[d] SD calculated from SEM
[e] serum glucose
[f] events per patient year (least squares means); SE reported
[g] No of patients
[h] events per patient year; SE reported
[i] adjusted for baseline Hba1c and country

Primary efficacy analyses were based on a mixed model repeated measures (MMRM) analysis of covariance with HbA1c as the dependent variable and treatment, baseline HbA1c, country, week of visit, and treatment-by-week interaction as fixed effects, and patient and error as random effects. All post-baseline measurements of the change in HbA1c were included in the analysis with no imputations of missing data. Fisher's exact tests were used for comparisons based on categorical variables (e.g. adverse events, incidence of hypoglycaemia). P-values for between group comparisons for adverse events, hypoglycaemia and blood pressure were not reported.

Table 29: Olsson & (2002)

General	**Phase:** ☐ monotherapy ☐ dual therapy ☑ triple therapy

	☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** Unclear **Authors' conclusions:** Both treatments improved glycaemic control to the same extent but the combinatioon of bedtime NPH and daytime sulfonlyurea gave a very small increase of body weight over a 6 month period. **Source of funding:** Unclear **Comments:** -
Number and characteristics of patients	**Total number of patients:** 16 **Inclusion criteria:** Patients with type 2 diabetes who were referred from primary care physicians owing to failure of OHAs (Hba1c 7.0 to 10.0%). Patients had been treated with oral agents for a minimum of 12 months **Exclusion criteria:** No details reported
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** all on oral hypoglycaemic drugs and/or insulin **Details of washout period:** all patients were with oral agents (sulfonylurea alone or with metformin). These were stopped in one arm and metformin was withheld throughout the study
Lifestyle advice	Patients had already participated in the regular diabetes programme with education on diet, exercise and SMBG
Follow-up	**Total follow-up (wks):** 24 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 24 **Frequency of monitoring appointments:** -
Arms	**(1) Prefixed combination (70% NPH 30% regular human insulin) of insulin BID** N: 8 Treatment duration (wks): 24 Washout period (d): 0 Comments: Previous treatments included sulfonlyurea alone or combined with metformin. Patient in twice daily insulin group did not take any oral agents. Metformin was withheld during the study Treatment(s): NPH insulin mix 70/30 (Subcutaneous) – flexible-dose (dose-adjusted) Frequency of dosing: twice a day Details of dosing regimen: Insulin was given before breakfast and dinner. Target BG levels were preprandial 4-7 mmol/l and postprandial <10 mmol/l **(2) Sulfonylurea + NPH (bedtime)** N: 8 Treatment duration (wks): 52 Washout period (d): 0 Comments: Previous treatments included sulfonlyurea alone or combined with metformin. Metformin was withheld during the study Treatment(s): (a) NPH insulin (Subcutaneous) – flexible-dose (dose-adjusted) Frequency of dosing: once a day Details of dosing regimen: NPH insulin was given at bedtime (b) Sulfonylurea (Oral)
Outcomes	**General** No details reported of ITT analysis or whether there were any discontinuations.

Baseline characteristics

		Prefixed combination (70% NPH 30% regular human insulin) of insulin BID			Sulfonylurea + NPH (bedtime)				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	8		63 (SD 8.49)	8		61 (SD 8.49)		
Blood glucose: HbA1c (%) – 0wk	Continuous	8		8.3 (SD 0.849)	8		8.3 (SD 0.849)		
Body weight: BMI (kg/m2) – 0wk	Continuous	8		24.3 (SD 2.83)	8		25.1 (SD 3.39)		
Weight (kg) – 0wk	Continuous	8		71.7 (SD 11.3)	8		70.8 (SD 13)		

Lipids: Total cholesterol (mmol/l) – 0wk	Mean change	8		6.6 (SD 1.53)	8		5.4 (SD 0.962)		
HDL cholesterol (mmol/l) – 0wk	Mean change	8		1.2 (SD 0.368)	8		1.1 (SD 0.283)		
Triglycerides (mmol/l) – 0wk	Mean change	8		2.6 (SD 1.64)	8		2.2 (SD 2.43)		
Insulin: Total daily dose (U) – 0wk	Continuous	8		45.8 (SD 11.9)	8		29.4 (SD 15.3)		
Total daily dose (U/kg) – 0wk	Continuous	8		0.61 (SD 0.198)	8		0.33 (SD 0.141)		

Results

		Prefixed combination (70% NPH 30% regular human insulin) of insulin BID			Sulfonylurea + NPH (bedtime)				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Blood glucose: HbA1c (%) – 24wk	Continuous	8		7 (SD 0.566)	8		6.8 (SD 1.41)		NS
Body weight: BMI (kg/m2) – 24wk	Continuous	8		26.2 (SD 3.11)	8		25.7 (SD 3.68)		NR
Weight (kg) – 12wk	Mean change	8		4.6 (SD 2.4)	8		1.8 (SD 2.83)		
Weight (kg) – 24wk	Continuous	8		77.6 (SD 12.4)	8		72.7 (SD 14.4)		
Weight (kg) – 24wk	Mean change	8		5.8 (SD 2.69)	8		1.9 (SD 2.83)		<0.02
Hypoglycaemic events: Major/severe hypoglycaemic event – 24wka	Count	1344	0		1344	0			
Major/severe hypoglycaemic event – 24wkb	Dichotomous	8	0	(0.0%)	8	0	(0.0%)		NR
Dropouts: Total dropouts – 24wk	Dichotomous	8	0	(0.0%)	8	0	(0.0%)		
Lipids: Total cholesterol (mmol/l) – 24wk	Mean change	8		6.6 (SD 1.98)	8		5.4 (SD 0.764)		NR
HDL cholesterol (mmol/l) – 24wk	Mean change	8		1.2 (SD 0.368)	8		1.3 (SD 0.566)		NR
Triglycerides (mmol/l) – 24wk	Mean change	8		2.3 (SD 1.98)	8		1.8 (SD 1.9)		NR
Insulin: Total daily dose (U) – 24wk	Continuous	8		45.8 (SD 11.9)	8		29.4 (SD 15.3)		NR
Total daily dose (U/kg) – 24wk	Continuous	8		0.61 (SD 0.198)	8		0.33 (SD 0.141)		NR

[a] person days estimated assuming dropout halfway through trial
[b] No patients

Differences between baseline and 24 weeks were tested with two tailed Student's t-test for paired data

Table 30: Pan et al. (2007)

General	**Phase:** ☐ monotherapy ☐ dual therapy ☑ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** Multi-national **Authors' conclusions:** The results confirm earlier reports that insulin glargine provides superior glycaemic control with less hypoglycaemia and demonstrates that these benefits are consistent between different ethnicities. **Source of funding:** Supported by a grant from sanofi-aventis **Comments:** Open label, Parallel group trial
Number and characteristics of patients	**Total number of patients:** 448 **Inclusion criteria:** Insulin naïve Asian patients aged between 40 and 80 years with type 2 diabetes who were poorly controlled on OHA therapy for >= 3 months prior to study entry (previous doses of sulfonylurea were equal to or greater than equivalent doses of 3mg glimepiride). Further inclusion criteria were BMI 20-35 kg/m2, Hba1c >=7.5 and <=10.5% and FBG >120 mg/dl. **Exclusion criteria:** Pregnancy, a history of ketoacidosis, and a liklihood of requiring treatmetn with drugs prohibited in the study protocol (e.g. beta blockers) Pre-randomisation phase: During the screening phase patients oral treatment was standardised to 3 mg glimepiride
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** all on oral hypoglycaemic drugs and/or insulin **Details of washout period:** During the screening phase patients oral treatment was standardised to 3 mg glimepiride
Lifestyle advice	No details reported
Follow-up	**Total follow-up (wks):** 24 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 24 **Frequency of monitoring appointments:** Patients visited the site 2,4,6,8,12,16,20 and 24 weeks after randomisation
Arms	**(1) Sulfonylurea + Insulin glargine** N: 220 Treatment duration (wks): 24 Washout period (d): 0 Treatment(s): (a) Sulfonylurea (Oral) – fixed-dose Set dose (mg/d):3 Frequency of dosing: once a day Details of dosing regimen: Sulfonlyurea was standardised to 3 mg during screening and was given once daily in the morning. The dose remained fixed throughout the study (b) Insulin glargine (Subcutaneous) – flexible-dose (dose-adjusted) Mean dose (mg/d): 9.6 Frequency of dosing: once a day Details of dosing regimen: Once daily insulin glargine was given at bedtime. Doses were titrated according to a target FBG <=120 mg/dl. The pre defined regimen started insulin doses at 0.15 U/Kg/day and titrated the dose, at the discretion of the investigator, upwards by 2U every 3 days until the target FBG was achieved. **(2) Sulfonylurea + NPH insulin** N: 223 Treatment duration (wks): 24 Washout period (d): 0 Treatment(s): (a) Sulfonylurea (Oral) – fixed-dose Set dose (mg/d):3 Details of dosing regimen: see insulin glargine arm for dosing details (b) NPH insulin (Subcutaneous) – flexible-dose (dose-adjusted) Mean dose (mg/d): 9.8 Frequency of dosing: once a day Details of dosing regimen: see insulin glargine arm for dosing details
Outcomes	**General** Analyses of efficacy were performed on the per-protocol set and the full analysis set and adverse events

were assessed in the safety analysis

5 patients withdrew from the study

Outcomes not extracted in this evidence table include SMBG and postprandial blood glucose.

Attrition rates have not been reported due to inconsistencies in numbers.

Hypoglycaemic events

Major/severe hypoglycaemic event (an event with symptoms consistent with hypoglycaemia, associated with a BG level <50 mg/dl (<2.8 mmol/l) or with prompt recovery after oral carbohydrate, IV glucose or glucagon administration and the requirement of third party assistance)

Nocturnal hypoglycaemia (hypoglycaemia that occurred while the patient was asleep, after the evening insulin and before getting up in the morning)

Baseline characteristics

		Sulfonylurea + Insulin glargine			Sulfonylurea + NPH insulin				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	220		55.6 (SD 8.4)	223		56.6 (SD 8.7)		
Sex (n male)	Dichotomous	220	89	(40.5%)	223	99	(44.4%)		
Duration of diabetes (yrs)	Continuous	220		10.3 (SD 6.3)	223		10 (SD 5.4)		
Blood glucose: HbA1c (%) – 0wk	Continuous	220		9.02 (SD 0.88)	223		9.05 (SD 0.84)		
Body weight: BMI (kg/m2) – 0wk	Continuous	220		24.8 (SD 3.1)	223		25.1 (SD 3.3)		
Insulin: Total daily dose (U) – 0wk	Continuous	220		9.6 (SD 1.5)	223		9.8 (SD 1.9)		

Results

		Sulfonylurea + Insulin glargine			Sulfonylurea + NPH insulin				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 24wk	Continuous	220		7.9 (SD 1.16)	223		8.13 (SD 1.19)	MD=0.220 (CI: 0.020, 0.420)	0.0319
HbA1c (%) – 24wka	Mean change	220		-1.1	223		-0.92		
Fasting plasma glucose (mmol/l) – 24wk	Continuous	220		6.494202 (SD 1.39)	223		6.605214 (SD 1.44)		NR
Fasting plasma glucose (mmol/l) – 24wka	Mean change	220		-5.883636	223		-5.772624		
Hba1c<7.5% – 24wkb	Dichotomous	220	84	(38.2%)	223	68	(30.5%)		NS
FBG <=120 mg/dl – 24wk	Dichotomous	220	137	(62.3%)	223	131	(58.7%)		NS
Body weight: BMI (kg/m2) – 24wkc	Continuous	220		1.4	223		1.29		
Hypoglycaemic events: All hypoglycaemic events (no events) – 24wk	Dichotomous	220			223				<0.004
All hypoglycaemic events (no events) – 24wkd	Count	36960	682		37464	1019			

	Major/severe hypoglycaemic event – 24wke	Count	35112	5		35616	28			
	Major/severe hypoglycaemic event – 24wk	Dichotomous	220			223				<0.03
	Symptomatic hypoglycaemia – 24wk	Dichotomous	220			223				<0.0003
	Symptomatic hypoglycaemia – 24wke	Count	35112	515		35616	908			
	Nocturnal hypoglycaemia – 24wk	Dichotomous	220			223				<0.001
	Nocturnal hypoglycaemia – 24wke	Count	35112	221		35616	620			
	Adverse events:									
	Any adverse event(s) – 24wkf	Dichotomous	220	120	(54.5%)	223	130	(58.3%)		
	Any serious adverse event(s) – 24wkf	Dichotomous	220	10	(4.5%)	223	12	(5.4%)		
	Insulin:									
	Total daily dose (U) – 24wk	Continuous	220		32.1 (SD 17.6)	223		21.8 (SD 18.9)		NR

[a] SD not reported
[b] approximated to nearest integer (percentages only presented in text)
[c] No height data reported; no details on dispersion
[d] No of events; patient days estimated assuming no attrition
[e] No of events
[f] No patients

ANCOVA was performed using change from baseline data to endpoint, with treatment and country as fixed effects and the corresponding baseline value as a covariate. Catergoric secondary variables were analysed for treatment differences by using Cochran-Mantel-Haenzel tests stratified by country. No p-values were reported for between group comparisons for adverse events.

Table 31: Park et al. (2014)

General	**Phase:** ☐ monotherapy ☐ dual therapy ☑ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** - **Authors' conclusions:** - **Source of funding:** - **Comments:** -
Number and characteristics of patients	**Total number of patients:** 99 **Inclusion criteria:** - **Exclusion criteria:** -
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** All treatment naive/ no OADs at screening **Details of washout period:** 4 week screening / titration phase
Lifestyle advice	-

Follow-up

Total follow-up (wks): -
Length of titration period (wks): -
Length of maintenance period (wks): -
Frequency of monitoring appointments: -

Arms

(1) Metformin + Insulin Glargine
N: 33
Treatment duration (wks): 28
Washout period (d): 0
Treatment(s): (a) Metformin (Oral) – fixed-dose
Set dose (mg/d):1500
(b) Insulin glargine (Subcutaneous) – forced titration
Set dose (mg/d):10
Frequency of dosing: once a day
Details of dosing regimen: Mean (SD) glargine dose increased from 12.2 (2.7) IU to 29.5 (13.3) IU

(2) Glimepiride + Insulin Glargine
N: 34
Treatment duration (wks): 28
Washout period (d): 0
Treatment(s): (a) Insulin glargine (Subcutaneous) – forced titration
Set dose (mg/d):10
Frequency of dosing: once a day
Details of dosing regimen: Mean insulin doses increased from 11.8 (2.0) IU to 27.2 (14.2) IU
(b) Sulfonylurea – fixed-dose
Set dose (mg/d):4

(3) Metformin + Glimepiride + Insulin Glargine
N: 32
Treatment duration (wks): 28
Washout period (d): 0
Treatment(s): (a) Insulin glargine (Subcutaneous) – forced titration
Set dose (mg/d):10
Frequency of dosing: once a day
Details of dosing regimen: Mean (SD) glargine doses increased from 12.5 (2.5) IU to 20.1 (10.3) IU
(b) Metformin (Oral) – fixed-dose
Set dose (mg/d):1500
(c) Sulfonylurea – fixed-dose
Set dose (mg/d):4

Outcomes

Baseline characteristics

		Metformin + Insulin Glargine		
		N	**k**	**mean**
Demographics:				
Age (years)	Continuous	33		55.8 (SD 10.5)
Sex (n male)	Dichotomous	33	20	(60.6%)
Duration of diabetes (yrs)	Continuous	33		11.3 (SD 6.4)
Blood glucose:				
HbA1c (%) – wk	Continuous	33		8.5 (SD 0.9) a
HbA1c (%) – wk	Continuous	33		8.5 (SD 0.9) a
Body weight:				
BMI (kg/m2)	Continuous	33		25.1 (SD 3.6) b
Weight (kg) – 0wk	Continuous	33		70.84224 (SD 10.16064) c
Waist circumference (cms)	Continuous	33		89.4 (SD 10.4)

[a] Data taken from text (mean of 8.4 is reported in table)
[b] No height data provided
[c] No height data provided; estimated from BMI assuming mean height of 1.68m

	Glimepiride + Insulin Glargine

		N	k	mean
Demographics:				
Age (years)	Continuous	34		57.3 (SD 9.2)
Sex (n male)	Dichotomous	34	20	(58.8%)
Duration of diabetes (yrs)	Continuous	34		13 (SD 8)
Blood glucose:				
HbA1c (%) – wk	Continuous	34		8.4 (SD 1)
HbA1c (%) – wk	Continuous	34		8.4 (SD 1)
Body weight:				
BMI (kg/m2)	Continuous	34		25.6 (SD 2.7) a
Weight (kg) – 0wk	Continuous	34		72.25344 (SD 7.62048) b
Waist circumference (cms)	Continuous	34		89.7 (SD 6.4)

[a] No height data provided
[b] No height data provided; estimated from BMI assuming mean height of 1.68m

		Metformin + Glimepiride + Insulin Glargine		
		N	k	mean
Demographics:				
Age (years)	Continuous	32		56.8 (SD 10.9)
Sex (n male)	Dichotomous	32	23	(71.9%)
Duration of diabetes (yrs)	Continuous	32		11.7 (SD 5)
Blood glucose:				
HbA1c (%) – wk	Continuous	32		8.7 (SD 0.9)
HbA1c (%) – wk	Continuous	32		8.7 (SD 0.9)
Body weight:				
BMI (kg/m2)	Continuous	32		25.2 (SD 2.7) a
Weight (kg) – 0wk	Continuous	32		71.12448 (SD 7.62048) b
Waist circumference (cms)	Continuous	32		90.7 (SD 6.9)

[a] No height data provided
[b] No height data provided; estimated from BMI assuming mean height of 1.68m

Results

		Metformin + Insulin Glargine		
		N	k	mean
Blood glucose:				
HbA1c (%) – 28wk	Continuous	33		7.7 (SD 0.8)
HbA1c (%) – 28wk	Continuous	33		7.7 (SD 0.8)
Hypoglycaemic events:				
All hypoglycaemic events (no events) – 28wk	Count	5698	64	a
Dropouts:				
Total dropouts – 28wk	Dichotomous	33	7	(21.2%)
Dropout due to AEs – 28wk	Dichotomous	33	0	(0.0%)

[a] patient days calculated from event rate and number of events

		Glimepiride + Insulin Glargine		
		N	k	mean
Blood glucose:				
HbA1c (%) – 28wk	Continuous	34		7.7 (SD 1.3)
HbA1c (%) – 28wk	Continuous	34		7.7 (SD 1.3)
Body weight:				
Weight (kg) – 28wk	Mean change	34		1.26 (SD 2.6)
Hypoglycaemic events:				
All hypoglycaemic events (no events) – 28wk	Count	5978	95	a

	Dropouts: Total dropouts – 28wk		Dichotomous	34	7 (20.6%)
	Dropout due to AEs – 28wk		Dichotomous	34	0 (0.0%)

[a] patient days calculated from event rate and number of events

		Metformin + Glimepiride + Insulin Glargine		
		N	**k**	**mean**
Blood glucose: HbA1c (%) – 28wk	Continuous	32		7.3 (SD 0.6)
HbA1c (%) – 28wk	Continuous	32		7.3 (SD 0.6)
Body weight: Weight (kg) – 28wk	Mean change	32		1.38 (SD 2.97)
Hypoglycaemic events: All hypoglycaemic events (no events) – 28wk	Count	5940	83	a
Dropouts: Total dropouts – 28wk	Dichotomous	32	8	(25.0%)
Dropout due to AEs – 28wk	Dichotomous	32	0	(0.0%)

[a] patient days calculated from event rate and number of events

Table 32: Raz et al. (2005)

General	**Phase:** ☐ monotherapy ☐ dual therapy ☑ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** 8 countries (Canada, Croatia, Poland, Israel, Hong Kong, Thailand, Australia, South Africa) **Authors' conclusions:** BIAsp 30 plus pioglitazone provided an efficacious and well-tolerated treatment alternative to glibenclamide + pioglitazone or BIAsp 30 alone in this population of patients who previously were not well controlled on glibenclamide **Source of funding:** Novo Nordisk **Comments:** Multinational, multicentre, open label trial
Number and characteristics of patients	**Total number of patients:** 283 **Inclusion criteria:** Patients with type 2 diabetes, aged >=18 years with a BMI <=40 kg/m2, who were treated with sulfonylurea therapy (monotherapy or combination therapy) for >= 3 months before screening and had insufficient glycaemic control (Hba1c 7.4 to 14.7%). It was unclear whether patients were on maximum or stable dose of SU at baseline **Exclusion criteria:** patients with significant disease likely to affect trial or health outcomes were excluded
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** all on oral hypoglycaemic drugs and/or insulin **Details of washout period:** All patients were taking sulfonylurea (either alone or in combination) but patients discontinued their current (SU) therapy (monotherapy or combination) when administration of trial products started.
Lifestyle advice	-
Follow-up	**Total follow-up (wks):** 18 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 18 **Frequency of monitoring appointments:** -
Arms	**(1) BIAsp 30 monotherapy**

N: 97

Treatment duration (wks): 18
Washout period (d): 0
Comments: Patients discontinued current therapy before starting the intervention therapy

Treatment(s): Biphasic insulin aspart (Subcutaneous) – flexible-dose (dose-adjusted)

Details of dosing regimen: For patients taking BIAsp 30, insulin was injected immediately before breakfast and before dinner. It was intiiated at a dose of 0.3 IU/kg per day. In both groups, BIAsp 30 was titrated individually by patients using SMBG to achieve a target fasting BG level 5 to 8 mmol/l.

(2) BIAsp 30 + pioglitazone

N: 93

Treatment duration (wks): 18
Washout period (d): 0
Comments: Patients discontinued current therapy before starting the intervention therapy

Treatment(s): (a) Biphasic insulin aspart (Subcutaneous) – flexible-dose (dose-adjusted)

Details of dosing regimen: Insulin was intiiated at a dose of 0.2 IU/kg per day. A lower dose of BIAsp 30 was initiated in patients combining insulin with pioglitazone to limit the number of hypoglycaemic events

(b) Pioglitazone (Oral) – fixed-dose

Set dose (mg/d):30
Frequency of dosing: once a day
Details of dosing regimen: The recommended starting dose for pioglitazone is 15-30 mg once daily. Patients took 30 mg OD either with or immediately after breakfast. The dose remained unchanged throughout the trial

Outcomes

General

Data from 2/3 arms were extracted into this evidence table. The arm examining glibenclamide + pioglitazone therapy was not included as part of the decision space for second intensification, therefore this data was not extracted.

Efficacy and safety endpoints were evaluated using ITT population (all patients exposed to the trial drug). 5 patients who had been receiving repaglinide at baseline instaed of sulfonylurea were randomised and are included as part of the ITT population

Outcomes not extracted in this evidence table include SMBG profiles

8/97 (8.2%) patients in the BIAsp 30 group and 7/93 (7.5%) in the BIAsp + pioglitazone group discontinued the study

Hypoglycaemic events

Minor (confirmed) hypoglycaemia (a minor episode was considered to have occurred when a BG <50 mg/dl and the patient handled th event without assistance from others)

Major/severe hypoglycaemic event (defined as an event where a patient is unable to self-traet, when BG levels fall below 50 mg/dl, or when symptoms remitted after administrat)

symptomatic (unconfirmed) hypoglycaemia (symptomatic episodes occurred when hypoglycaemic symptoms were present but not confirmed with a BG measurement and assistance from others was not required)

Baseline characteristics

		BIAsp 30 monotherapy			BIAsp 30 + pioglitazone				
		N	k	mean	N	k	mean	Δ	p
Demographics:									
Age (years)	Continuous	97		55.2 (SD 9.1)	93		56.7 (SD 10.5)		
Sex (n male)	Dichotomous	97	63	(64.9%)	93	49	(52.7%)		
Duration of diabetes (yrs)	Continuous	97		10 (SD 5.8)	93		9.2 (SD 5.3)		
Blood glucose:									
HbA1c (%) – 0wk	Continuous	97		9.5 (SD 1.3)	93		9.6 (SD 1.3)		
Body weight:									
BMI (kg/m2)	Continuous	97		29.5 (SD 4.9)	93		29.4 (SD 4.6)		
Weight (kg) – 0wka	Continuous	97		83.2608 (SD 13.8)	93		82.97856 (SD 13)		
Previous blood glucose lowering drugs:									
Metforminb	Dichotomous	97	78	(80.4%)	93	78	(83.9%)		
Meglitinideb	Dichotomous	97	1	(1.0%)	93	3	(3.2%)		
Sulfonylurea	Dichotomous	97	13	(13.4%)	93	13	(14.0%)		
Insulin:									
Total daily dose (U/kg) – 0wk	Continuous	97		0.3	93		0.2		

[a] estimated from BMI assuming mean height of 1.68m
[b] additional drugs taken with sulfonylurea

Results

		BIAsp 30 monotherapy			BIAsp 30 + pioglitazone				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 18wk	Continuous	97		9 (SD 1.3)	93		8.4 (SD 1.2)		NR
Fasting plasma glucose (mmol/l) – 18wka	Continuous	97		-0.888096	93		-1.720686		NR
Body weight: Weight (kg) – 18wka	Continuous	97		2.2	93		4		NR
Hypoglycaemic events: All hypoglycaemic events (no events) – 18wkb	Count	11718	221		11277	134			
All hypoglycaemic events (no events) – 18wkc	Continuous	97		0.132	93		0.083		
Minor (confirmed) hypoglycaemia – 18wkd	Count	11560.61	47		10964	15			
Minor (confirmed) hypoglycaemia – 18wke	Dichotomous	97	15	(15.5%)	93	11	(11.8%)		NR
Minor (confirmed) hypoglycaemia – 18wkf	Dichotomous	97	47	(48.5%)	93	15	(16.1%)		NR
Minor (confirmed) hypoglycaemia – 18wk	Dichotomous	97	47f	(48.5%)	93	11e	(11.8%)		NR
Minor (confirmed) hypoglycaemia – 18wk	Dichotomous	97	15e	(15.5%)	93	15f	(16.1%)		NR
Major/severe hypoglycaemic event – 18wk	Dichotomous	97	0	(0.0%)	93	0	(0.0%)		NR
Major/severe hypoglycaemic event – 18wkd	Count	11560.61	0		10964	0			
symptomatic (unconfirmed) hypoglycaemia – 18wkd	Count	11560.61	171		10964	115			
symptomatic (unconfirmed) hypoglycaemia – 18wk	Dichotomous	97	171f	(176.3%)	93	32e	(34.4%)		NR
symptomatic (unconfirmed) hypoglycaemia – 18wk	Dichotomous	97	39e	(40.2%)	93	115f	(123.7%)		NR
symptomatic (unconfirmed) hypoglycaemia – 18wke	Dichotomous	97	39	(40.2%)	93	32	(34.4%)		NR
symptomatic (unconfirmed) hypoglycaemia – 18wkf	Dichotomous	97	171	(176.3%)	93	115	(123.7%)		NR
Adverse events: Any serious adverse event(s) – 18wk	Dichotomous	97	2	(2.1%)	93	0	(0.0%)		NR
Edema peripheral – 18wk	Dichotomous	97	0	(0.0%)	93	6g	(6.5%)		NR
Dropouts: Total dropouts – 18wk	Dichotomous	97	8	(8.2%)	93	7	(7.5%)		
Dropout due to AEs – 18wk	Dichotomous	97	2	(2.1%)	93	1	(1.1%)		NR
Drop out due to unsatisfactory effect – 18wk	Dichotomous	97	4	(4.1%)	93	2	(2.2%)		NR

Lipids: Total cholesterol (mmol/l) – 18wk	Continuous	97		5.27544	93		5.48232		
HDL cholesterol (mmol/l) – 18wk	Continuous	97		0.07758 (SD 0.0259)	93		0.10344 (SD 0.0259)		<=0.001
Triglycerides (mmol/l) – 18wk	Continuous	97		1.78382 (SD 0.994)	93		1.68221 (SD 0.994)		NR
Insulin: Total daily dose (U/kg) – 18wk	Mean change	97			93				0.002
Total daily dose (U/kg) – 18wk	Continuous	97		0.7	93		0.5		

[a] SD not reported
[b] person days calculated using rate reported for all hypos; assumed all events are sum of minor and symptomatic
[c] episodes per patient week; 95% CI not reported
[d] person days calculated using rate reported for all hypos
[e] No of patients
[f] No episodes
[g] approximated to nearest integer (percentages only presented in text)

An ANOVA including treatment and country as fixed effects and with covariate adjustment for baseilne was applied. Hypoglycaemic episodes were analysed by log-linear Poisson regression model, including traetment and country as factors and duration of exposure as an offset. Increase in insulin dose was compared between treatment groups with the Wilcoxon-Mann Whitney test. P-values for comparisons between the insulin groups and the glibenclamide + pioglitazone (data not extracted) are njot reported here.

Table 33: Riddle & (1998)

General

Phase:
☐ monotherapy
☐ dual therapy
☑ triple therapy
☐ insulin monotherapy
☐ insulin+oral

Parallel / crossover: Parallel

Country: USA

Authors' conclusions: Injection of 70/30 insulin before supper safely restored glycemic control of type 2 diabetes not controlled by glimepiride alone. Control was restored more rapidly and with less injected insulin when glimepiride was continued

Source of funding: supported financially by Hoechst Marion Roussel Pharmaceuticals

Comments: Double-blind trial

Number and characteristics of patients

Total number of patients: 145

Inclusion criteria: patients with type 2 diabetes who had successfully used a sulfonylurea for at least 6 months but were not subsequently well controlled with full

dosage. They were between 45 and 70 years old and weighed between 130 and 170% of desirable weight at entry.

Exclusion criteria: pregnancy or nursing; duration of diabetes >15 years; history of ketoacidosis, autoimmune disease, or major systemic illness other than diabetes; allergy or intolerance to sulfonylureas; use of glucocorticoid agents, phenytoin, nicotinic acid, sympathomimetics, phenothiazines,

or isoniazid; serum creatinine or serum alanine aminotransferase >1.5 times the upper limit of normal; and fasting serum C-peptide <0.4 pmol/ml.

Pre-randomisation phase: Eligible subjects discontinued their previous hypoglycemic therapy and were given glimepiride alone at doses titrated up to 8 mg twice daily for 8 weeks. The initial dosage was 8 mg before breakfast. FPG was tested at weekly intervals, and if the value was >150 mg/dl (8.3 mmol/1), the dosage was increased incrementally to 12 mg once daily, 16 mg once daily, and finally to 8 mg before breakfast and before supper after 3

weeks of treatment. If the FPG was <150 mg/dl on two consecutive visits, the patient was dropped from the study. Subjects were also ineligible to continue if, after 2 weeks of treatment with 8 mg glimepiride twice daily, their FPG was <180 mg/dl (10 mmol/1) or >300 mg/dl (16.7 mmol/1). Those continuing treatment took 8 mg twice daily to the end of the 8-week open-label period.

Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** all on oral hypoglycaemic drugs and/or insulin **Details of washout period:** Patients were all taking sulfonylurea at study entry but previous hypoglycaemic therapy was discontinued before starting the open label period
Lifestyle advice	-
Follow-up	**Total follow-up (wks):** 32 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 24 **Frequency of monitoring appointments:** Subjects visited the clinic weekly during the open-label phase, at baseline and 2 and 4 weeks into the randomised treatment phase, then every 4 weeks thereafter to the end of the 24-week treatment period.
Arms	**(1) Glimepiride + insulin (70% NPH 30% regular insulin)** N: 72 Treatment duration (wks): 24 Washout period (d): 0 Comments: Patients were all taking sulfonylurea at study entry but previous hypoglycaemic therapy was discontinued before starting the open label period Treatment(s): (a) Sulfonylurea (Oral) – fixed-dose Set dose (mg/d):16 Details of dosing regimen: continued with glimepiride 8 mg twice daily, before breakfast and supper (b) NPH insulin mix 70/30 (Subcutaneous) – flexible-dose (dose-adjusted) Details of dosing regimen: All subjects started 70/30 (70% NPH insulin/30% regular insulin) human insulin injected 30 min before supper. The initial dosage was 10 U/day for the first 2 weeks. After that, the dosage was titrated upward according to FBG measurements taken by SMBG. Insulin dosage was increased by 10 U weekly until FBG was <=140 mg/dl (7.8 mmol/1) for 2 consecutive days, then 5 U weekly until FBG was <=120 mg/dl (6.7 mmol/1) for 2 consecutive days. Once the FBG was consistently 100 mg/dl (5.5 mmol/1) to 120 mg/dl, a constant insulin dosage was maintained. Small decreases of insulin were permitted to curtail symptoms suggesting hypoglycemia **(2) Insulin (70% NPH 30% regular insulin)** N: 73 Treatment duration (wks): 24 Washout period (d): 0 Comments: Patients were all taking sulfonylurea at study entry but previous hypoglycaemic therapy was discontinued before starting the open label period Treatment(s): NPH insulin mix 70/30 (Subcutaneous) – flexible-dose (dose-adjusted) Details of dosing regimen: See glimepiride + insulin group fpr details
Outcomes	**General** 11/73 (15%) patients in the insulin group and 2/72 (3%) in the glimepiride + insulin group discontinued the study. Details of ITT analysis not reported (all patients with baseline and postbaseline data were included in the analysis) Outcomes not extracted in this evidence table include serum insulin and c-peptide

Baseline characteristics

		Glimepiride + insulin (70% NPH 30% regular insulin)			Insulin (70% NPH 30% regular insulin)				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	72		58 (SD 8)	73		58 (SD 8)		
Sex (n male)	Dichotomous	72	45	(62.5%)	73	40	(54.8%)		
Duration of diabetes (yrs)	Continuous	72		7 (SD 4)	73		7 (SD 4)		
Blood glucose: HbA1c (%) – 0wk	Continuous	72		9.7	73		9.9		
Body weight: BMI (kg/m2)	Continuous	72		32.2 (SD 4.4)	73		33.7 (SD 5.4)		
Weight (kg) – 0wka	Continuous	72		90.88128 (SD 12.4)	73		95.11488 (SD 15.2)		

Full analysis set (FAS) or efficacy analysis pop										
Blood glucose:										
HbA1c (%) – 0wk	Continuous	70		9.7 (SD 1.3)	62		9.8 (SD 1.3)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	70		13.9 (SD 2.5)	62		14.5 (SD 2.3)		
Body weight:										
Weight (kg) – 0wk	Continuous	70		93.9 (SD 15.9)	62		99.2 (SD 20.8)		
Blood pressure:										
Systolic blood pressure (mmHg) – 0wk	Continuous	70		132 (SD 16)	62		137 (SD 17)		
Diastolic blood pressure (mmHg) – 0wk	Continuous	70		80 (SD 8)	62		81 (SD 9)		
Lipids:										
Total cholesterol (mmol/l) – 0wk	Continuous	70		5.89608 (SD 1.24)	62		5.6892 (SD 1.14)		
HDL cholesterol (mmol/l) – 0wk	Continuous	70		1.21542 (SD 0.233)	62		1.1637 (SD 0.284)		
Triglycerides (mmol/l) – 0wk	Continuous	70		3.1612 (SD 3.33)	62		3.11604 (SD 2.05)		
LDL cholesterol (mmol/l) – 0wk	Continuous	70		3.41352 (SD 0.931)	62		3.20664 (SD 0.957)		

[a] estimated from BMI assuming mean height of 1.68m

Results

		Glimepiride + insulin (70% NPH 30% regular insulin)			**Insulin (70% NPH 30% regular insulin)**				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Blood glucose:									
HbA1c (%) – 24wk	Mean change	72		-2.2 (SD 1)	73		-2.1 (SD 1)		
HbA1c (%) – 24wk	Continuous	72			73				NS
Fasting plasma glucose (mmol/l) – 24wk	Continuous	72			73				NR
Body weight:									
Weight (kg) – 24wk	Continuous	72			73				NS
Hypoglycaemic events:									
Major/severe hypoglycaemic event – 24wka	Dichotomous	72	0	(0.0%)	73	0	(0.0%)		NR
symptomatic (unconfirmed) hypoglycaemia – 24wk	Dichotomous	72	37b	(51.4%)	73	27a	(37.0%)		<0.05
moderate hypoglycaemia – 24wka	Dichotomous	72	8	(11.1%)	73	11	(15.1%)		NS
Adverse events:									
Any adverse event(s) – 24wkb	Dichotomous	72	66	(91.7%)	73	66	(90.4%)		NR
Any serious adverse event(s) – 24wka	Dichotomous	72	5	(6.9%)	73	3	(4.1%)		NR
Death – 24wk	Dichotomous	72	0	(0.0%)	73	0	(0.0%)		NR
Dropouts:									
Total dropouts – 24wk	Dichotomous	72	2	(2.8%)	73	11	(15.1%)		
Dropout due to AEs – 24wk	Dichotomous	72	0	(0.0%)	73	3	(4.1%)		
Dropout due to hypoglycaemia – 24wk	Dichotomous	72	0	(0.0%)	73	0	(0.0%)		NR
Blood pressure:									
Systolic blood pressure (mmHg) – 24wk	Continuous	72			73				NS
Diastolic blood pressure (mmHg) – 24wk	Continuous	72			73				NS

	Lipids: Total cholesterol (mmol/l) – 24wk	Continuous	72			73				NS
	HDL cholesterol (mmol/l) – 24wk	Continuous	72			73				<0.05
	Triglycerides (mmol/l) – 24wk	Continuous	72			73				NS
	LDL cholesterol (mmol/l) – 24wk	Continuous	72			73				NS
	Insulin: Total daily dose (U) – 24wk	Continuous	72		49	73		78		<0.001
	Full analysis set (FAS) or efficacy analysis pop Blood glucose: HbA1c (%) – 24wk	Continuous	70		7.6 (SD 0.8)	62		7.7 (SD 1)		
	Fasting plasma glucose (mmol/l) – 16wkc	Continuous	70		145 (SD 25.1)	62		150 (SD 23.6)		
	Fasting plasma glucose (mmol/l) – 24wk	Continuous	70		7.6 (SD 1.8)	62		7.6 (SD 2.2)		
	Body weight: Weight (kg) – 24wk	Continuous	70		98.2 (SD 16.5)	62		103.2 (SD 20.3)		
	Blood pressure: Systolic blood pressure (mmHg) – 24wk	Continuous	70		134 (SD 16)	62		135 (SD 17)		
	Diastolic blood pressure (mmHg) – 24wk	Continuous	70		80 (SD 9)	62		80 (SD 8)		
	Lipids: Total cholesterol (mmol/l) – 24wk	Continuous	70		5.61162 (SD 1.11)	62		5.50818 (SD 0.905)		
	HDL cholesterol (mmol/l) – 24wk	Continuous	70		1.24128 (SD 0.259)	62		1.293 (SD 0.31)		
	Triglycerides (mmol/l) – 24wk	Continuous	70		2.32574 (SD 1.98)	62		2.05478 (SD 1.05)		
	LDL cholesterol (mmol/l) – 24wk	Continuous	70		3.3618 (SD 0.802)	62		3.25836 (SD 0.828)		

[a] No of patients
[b] No of patients; approximated to nearest integer (percentages only presented in text)
[c] estimated from graph

An analysis of variance model was used to evaluate change of HbAlc from baseline to end point and change of FPG from baseline to week 2. The Mantel-Haenszel test and Wilcoxons signed-rank test were used to examine between-treatment difference and change from baseline, respectively.

Table 34: Riddle et al. (1992)

General

Phase:
☐ monotherapy
☐ dual therapy
☑ triple therapy
☐ insulin monotherapy
☐ insulin+oral

Parallel / crossover: Parallel

Country: Unclear but assumed USA

Authors' conclusions: The data support combined therapy of NPH mixed insulin with sulfonylurea as one option for treating obese people with type 2 diabetes who are no longer responsive to oral therapy alone

Source of funding: Supported in part by a research grant from Hoechst-Roussel Pharmaceuticals

Comments: Randomised, double masked, placebo controlled design. Patients were randomised by assigment of study number to a treatment code determined by the manufacturer of the study drug.

Number and characteristics of patients	**Total number of patients:** 21 **Inclusion criteria:** Ambulatory patients were studied. All patients had type 2 diabetes (gradual onset after the age of 40 years) for at least one year duration and were obese with BMI ranging from 29.1 to 43.1 kg/m2 (mean 36 kg/m2). All patients previously used a sulfonylurea but reported no longer having adequate glycaemic control **Exclusion criteria:** No patients had used corticosteroids, estrogens, thyroid hormone, adrenergic blockers or diuretics in the month prior to study entry Pre-randomisation phase: Prior sulfonylurea treatment was discontinued and all patients took 20 mg glyburide daily (10 mg before breakfast and 10 mg before supper) for 3 weeks. All patients had FPG averaging >7.8 mmol/l during this baseline period.
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** all on oral hypoglycaemic drugs and/or insulin **Details of washout period:** All patients were taking sulfonylurea but this was discontinued and standarised before randomisation
Lifestyle advice	-
Follow-up	**Total follow-up (wks):** 16 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 16 **Frequency of monitoring appointments:** -
Arms	**(1) Insulin (NPH 70% regular 30%)** N: 10 Treatment duration (wks): 16 Washout period (d): 0 Comments: All patients standardised sulfonylurea therapy before starting the study Treatment(s): NPH insulin mix 70/30 (Subcutaneous) – flexible-dose (dose-adjusted) Frequency of dosing: once a day Details of dosing regimen: All patients took insulin daily before supper. The insulin used was Novolin 70/30 (human 70% NPH 30%). The dose of insulin was adjusted weekly using SMBG values. This started with 30 units daily, increased by 20 units for fasting SMBG >10 mmol/l, 10 units for SMBG 6.7 to 7.8 mmol/l and 5 units for SMBG 5.6 to 6.7 mmol/l. No increases were made when hypoglycaemic symptoms were reported or when SMBG averaged <=5.6 mmol/l **(2) Insulin (NPH 70%, regular 30%) + glyburide** N: 11 Treatment duration (wks): 16 Washout period (d): 0 Comments: All patients standardised sulfonylurea therapy before starting the study Treatment(s): (a) NPH insulin mix 70/30 (Subcutaneous) – flexible-dose (dose-adjusted) Frequency of dosing: once a day Details of dosing regimen: See insulin monotherapy group for dosing details (b) Sulfonylurea (Oral) – fixed-dose Set dose (mg/d):20 Frequency of dosing: twice a day Details of dosing regimen: 10 mg glyburide was given twice daily
Outcomes	**General** Drop outs and ITT analysis not reported (all assumed to be included in analysis). Outcomes not extracted in this evidence table include c-peptide, free fatty acid and free insulin. **Hypoglycaemic events** All hypoglycaemic events (no events) (No definitions reported) Major/severe hypoglycaemic event (Hypoglycaemic causing impaired consciousness or the need for parenteral glucose or glucagon)

Baseline characteristics

		Insulin (NPH 70% regular 30%)			Insulin (NPH 70%, regular 30%) + glyburide				
		N	k	mean	N	k	mean	Δ	p
Demographics:									
Age (years)	Continuous	10		52 (SD 22.1)	11		55 (SD 6.63)		
Duration of diabetes (yrs)	Continuous	10		4 (SD 3.16)	11		6 (SD 3.32)		

Blood glucose: HbA1c (%) – 0wka	Continuous	10		10.5	11		11.4			
Fasting plasma glucose (mmol/l)	Continuous	10		12.5 (SD 3.48)	11		12.5 (SD 2.98)			
Body weight: BMI (kg/m2)	Continuous	10		36.1 (SD 4.74)	11		35.8 (SD 2.98)			
Weight (kg) – 0wkb	Continuous	10		101.88864 (SD 13.4)	11		101.04192 (SD 8.42)			
Lipids: Total cholesterol (mmol/l) – 0wk	Mean change	10		5.4 (SD 1.26)	11		6.2 (SD 1.66)			
HDL cholesterol (mmol/l) – 0wk	Mean change	10		1.2 (SD 0.632)	11		1.1 (SD 0.332)			
Triglycerides (mmol/l) – 0wk	Mean change	10		3.1 (SD 1.9)	11		2.8 (SD 1.33)			
LDL cholesterol (mmol/l) – 0wk	Mean change	10		3.1 (SD 0.632)	11		3.7 (SD 1.33)			

[a] estimated from follow-up and change *** to check ***
[b] estimated from BMI assuming mean height of 1.68m

Results

		Insulin (NPH 70% regular 30%)			Insulin (NPH 70%, regular 30%) + glyburide			Δ	p
		N	k	mean	N	k	mean		
Blood glucose: HbA1c (%) – 16wk	Continuous	10		9.7 (SD 0.632)	11		10.1 (SD 0.663) a		
HbA1c (%) – 16wk	Mean change	10		-0.8 (SD 0.632) a	11		-1.3 (SD 0.332)		<0.05
Body weight: Weight (kg) – 16wka	Mean change	10		3.3 (SD 3.79)	11		4.9 (SD 3.32)		NS
Hypoglycaemic events: All hypoglycaemic events (no events) – 16wkb	Count	1120	69		1232	97			
All hypoglycaemic events (no events) – 16wkc	Continuous	10		6.9 (SD 6.64)	11		8.8 (SD 6.63)		
All hypoglycaemic events (no events) – 16wk	Dichotomous	10			11				NS
Major/severe hypoglycaemic event – 16wkd	Count	1120	0		1232	0			
Major/severe hypoglycaemic event – 16wk	Dichotomous	10	0	(0.0%)	11	0	(0.0%)		NR
Dropouts: Total dropouts – 16wk	Dichotomous	10	0	(0.0%)	11	0	(0.0%)		
Lipids: Total cholesterol (mmol/l) – 16wk	Mean change	10		5.3 (SD 0.632)	11		6 (SD 1.33)		NS
HDL cholesterol (mmol/l) – 16wk	Mean change	10		1.2 (SD 0.316)	11		1.3 (SD 0.332)		NS
Triglycerides (mmol/l) – 16wk	Mean change	10		2.5 (SD 1.26)	11		2 (SD 0.995)		NS
LDL cholesterol (mmol/l) – 16wk	Mean change	10		3.3 (SD 0.949)	11		3.8 (SD 0.995)		NS
Insulin: Total daily dose (U) – 16wk	Continuous	10		101 (SD 41.1)	11		50 (SD 16.6)		NR

[a] SD calculated from SEM
[b] person days estmiated assuming dropout halfway through the trial and no of events calculated using mean no hypos
[c] No of events
[d] person days estmiated assuming dropout halfway through the trial

Statistical comparisons were made using unpaired or paired t-tests as appropriate.

Table 35: Robbins et al. (2007)

General	**Phase:** ☐ monotherapy ☐ dual therapy ☑ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** Australia, Greece, India, The Netherlands, Poland, Puerto Rico and USA **Authors' conclusions:** In these patients with type 2 diabetes, meal time lispro mix (50/50) + metformin was associated with lower overall Hba1c and preprandial BG and PPBG levels with similar nocturnal hypoglycaemia and less glycaemic variability compared with insulin glargine + metformin **Source of funding:** - **Comments:** Open label, parallel group trial. Stratified randomisation through a central interactive telephone system
Number and characteristics of patients	**Total number of patients:** 315 **Inclusion criteria:** Male and female patients with type 2 diabetes aged 35-75 years, with an Hba1c 6.5 to 11.0% and current use of metformin and/or a sulfonylurea with a stable dose of 0 to 2 daily insulin injections over the previous 3 months were eligible for inclusion. **Exclusion criteria:** patients receiving continuous SC insulin infusion, >=3 daily insulin injections, or a total daily insulin dose >2.0 U/kg, or who had a change in the type or dose of lipid altering medications or thiazolidinedione up to 3 months before the study, fasting triclycerides >4.5 mmol/l, serum creatinine >134 µmol/L (men) or >109 µmol/L (women) and/or clinical signs of liver disease. Women of child bearing age were required to have a negative pregnancy test result before lead in and to use an effective method of contraception throughout the study Pre-randomisation phase: There was a 6 ± 2 week lead in period was used to allow patients who were insulin naïve time to adjust to injecting insulin and to adjust their insulin doses, and to allow those who were metformin-naïve time to increase their doses to the maximally tolerated daily dosage of 1000 to 2000 mg in 2 divided doses.
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** all on oral hypoglycaemic drugs and/or insulin **Details of washout period:** Patients had current use of metformin and/or a sulfonylurea with a stable dose of 0 to 2 daily insulin injections over the previous 3 months were eligible for inclusion. Other OAMs were discontinued
Lifestyle advice	Patients received verbal and written instructions about appropriate diet and exercise
Follow-up	**Total follow-up (wks):** 32 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 24 **Frequency of monitoring appointments:** -
Arms	**(1) Metformin + insulin lispro mix (50/50)** N: 158 Treatment duration (wks): 24 Washout period (d): 0 Treatment(s): (a) Metformin (Oral) – forced titration Frequency of dosing: twice a day Details of dosing regimen: There was a 6 ± 2 week lead in period was used to allow patients who were insulin naïve time to adjust to injecting insulin and to adjust their insulin doses, and to allow those who were metformin-naïve time to increase their doses to the maximally tolerated daily dosage of 1000 to 2000 mg in 2 divided doses. (b) Insulin lispro mix 50/50 (Subcutaneous) – flexible-dose (dose-adjusted) Frequency of dosing: three times a day Details of dosing regimen: Investigators were asked to adjust doses of both insulins as needed throughout the study, using a dose-titration algorithm as a guidance to achieve target BG levels (FBG <6.7 mmol/l) LM 50/50 was also titrated to a target 2 hour PPBG concentration <8 mmol/l. Insulin was started with 80% of total daily LM 75/25 dose with one third injected at each meal in patients receiving LM 50/50 and the entire dose injected at bedtime in patients receiving glargine. Ideally dose optimisation occurred within 8 weeks after randomisation. Patients receiving LM 50/50 + metformin were unable to reach the FBG target could be switched to pre-supper LM 75/25 to increase the basal insulin component. LM 50/50 in insulin pens TID before meals plus metformin BID

(2) Metformin + insulin glargine

N: 159

Treatment duration (wks): 24

Washout period (d): 0

Treatment(s): (a) Metformin (Oral)

Frequency of dosing: twice a day

Details of dosing regimen: As LM 50/50 group

(b) Insulin glargine (Subcutaneous) – flexible-dose (dose-adjusted)

Frequency of dosing: once a day

Details of dosing regimen: QD at bedtime. See LM 50/50 for details of dosing.

Outcomes

General

Analyses were performed on data from randomised patients wgo received >=1 dose of the study drug (ITT). LOCF was used for patients who discontinued before week 24.

15 (9.5%) patients in the LM 50/50 group and 22 (13.8%) in the glargine group discontinued the study

Outcomes not extracted in this evidence table include self monitored BG and PPBG

Hypoglycaemic events

All hypoglycaemic events (no events) (All episodes when a patient experienced, or another person observed, signs and symptoms of hypoglycaemia or when BG measured <3.5 mmol/L)

Major/severe hypoglycaemic event (episodes requiring the assistance of another person and with BG <2.9 mmol/L or prompt recovery from symptoms after ingsting oral carbohydrate, IV glucose or glucagon)

Nocturnal hypoglycaemia (episodes occurring after bedtime and before awakening)

Baseline characteristics

		Metformin + insulin lispro mix (50/50)			Metformin + insulin glargine				
		N	k	mean	N	k	mean	Δ	p
ITT									
Demographics:									
Age (years)	Continuous	157		57.4 (SD 9.2)	158		58.1 (SD 8.9)		
Sex (n male)	Dichotomous	157	79	(50.3%)	158	78	(49.4%)		
Duration of diabetes (yrs)	Continuous	157		11.3 (SD 5.8)	158		12.5 (SD 6.8)		
Blood glucose:									
HbA1c (%) – 0wk	Continuous	157		7.8 (SD 0.9)	158		7.8 (SD 1)		
Body weight:									
BMI (kg/m2)	Continuous	157		32.1 (SD 6.3)	158		32 (SD 6)		
Weight (kg) – 0wk	Continuous	157		89.1 (SD 20.4)	158		88.1 (SD 19)		
Lipids:									
Total cholesterol (mmol/l)	Continuous	157		4.9 (SD 1)	158		4.8 (SD 1)		
Triglycerides (mmol/l)	Continuous	157		1.6 (SD 0.9)	158		1.6 (SD 0.8)		
Previous blood glucose lowering drugs:									
Metformin	Dichotomous	157	99	(63.1%)	158	85	(53.8%)		
Sulfonylurea	Dichotomous	157	10	(6.4%)	158	16	(10.1%)		
Metformin + Sulfonylurea	Dichotomous	157	45	(28.7%)	158	54	(34.2%)		
Other	Dichotomous	157	3	(1.9%)	158	3	(1.9%)		
Insulin therapya	Continuous	157		0.6 (SD 0.3)	158		0.6 (SD 0.3)		

[a] total daily dose (U/kg) after lead-in

Results

		Metformin + insulin lispro mix (50/50)			Metformin + insulin glargine				
		N	k	mean	N	k	mean	Δ	p
Blood glucose:									
HbA1c (%) – 24wk	Mean change	157			158				<0.001
HbA1c < 7% or <=7% – 24wk	Dichotomous	157			158				0.005
HbA1c <= 6.5% – 24wk	Dichotomous	157			158				0.001

Fasting plasma glucose (mmol/l) – 24wk	Continuous	157			158				<0.001
Body weight:									
Weight (kg) – 24wk	Continuous	157			158				<0.001
Hypoglycaemic events:									
All hypoglycaemic events (no events) – 24wka	Count	25116	586		24696	247			
All hypoglycaemic events (no events) – 24wk	Dichotomous	157			158				0.07
Nocturnal hypoglycaemia – 24wkb	Count	25284	180		24864	266			
Nocturnal hypoglycaemia – 24wk	Dichotomous	157			158				NS
Dropouts:									
Total dropouts – 24wk	Dichotomous	157	15	(9.6%)	158	22	(13.9%)		
Insulin:									
Total daily dose (U) – 24wk	Continuous	157			158				<0.001
Total daily dose (U/kg) – 24wk	Continuous	157			158				<0.001
ITT									
Blood glucose:									
HbA1c (%) – 12wkc	Continuous	157			158				
HbA1c (%) – 24wk	Continuous	157		7.1 (SD 0.9)	158		7.5 (SD 0.9)		
HbA1c < 7% or <=7% – 24wk	Dichotomous	157	85	(54.1%)	158	58	(36.7%)		
HbA1c <= 6.5% – 24wk	Dichotomous	157	46	(29.3%)	158	21	(13.3%)		
Fasting plasma glucose (mmol/l) – 24wk	Continuous	157		8.1 (SD 1.8)	158		6.5 (SD 1.6)		
Body weight:									
Weight (kg) – 24wk	Continuous	157		90 (SD 20.5)	158		87.6 (SD 19.3)		
Weight (kg) – 24wk	Mean change	157		1.2 (SD 3.2)	158		-0.5 (SD 2.8)		
Hypoglycaemic events:									
All hypoglycaemic events (no events) – 24wkd	Continuous	157		0.8 (SD 1.4)	158		0.5 (SD 1)		
Major/severe hypoglycaemic event – 24wke	Dichotomous	157	3	(1.9%)	158	2	(1.3%)		
Nocturnal hypoglycaemia – 24wkd	Continuous	157		0.2 (SD 0.7)	158		0.3 (SD 0.6)		
Adverse events:									
Any adverse event(s) – 24wkf	Dichotomous	157	111	(70.7%)	158	95	(60.1%)		
Any serious adverse event(s) – 24wkf	Dichotomous	157	11	(7.0%)	158	5	(3.2%)		
Arthralgia – 24wkf	Dichotomous	157	8	(5.1%)	158	0	(0.0%)		
Back pain – 24wkf	Dichotomous	157	9	(5.7%)	158	0	(0.0%)		
GI: diarrhoea – 24wkf	Dichotomous	157	10	(6.4%)	158	9	(5.7%)		
Headache – 24wkf	Dichotomous	157	10	(6.4%)	158	10	(6.3%)		
Infection (upper airway or other common) – 24wkf	Dichotomous	157	14	(8.9%)	158	11	(7.0%)		
Nasopharyngitis – 24wkf	Dichotomous	157	14	(8.9%)	158	11	(7.0%)		
Pain (extremity) – 24wkf	Dichotomous	157	9	(5.7%)	158	0	(0.0%)		
Dropouts:									
Dropout due to AEs – 24wk	Dichotomous	157	5	(3.2%)	158	1	(0.6%)		
Insulin:									
Total daily dose (U) – 24wk	Continuous	157		65.3 (SD 37.2)	158		54.9 (SD 36.7)		
Total daily dose (U/kg) – 24wk	Continuous	157		0.7 (SD 0.3)	158		0.6 (SD 0.3)		

[a] person days estimated assuming dropout half way through trial and no of events calculated using reported rates (episodes per patient per 30 days)

	[b] person days estimated assuming dropout half way through trial and no of events calculated using reported rates [c] error bars in graph not symmetrical [d] no episodes per patient per 30 days [e] No patients [f] No of patients
	Categorical data were analysed using chi-squared. Hypoglycaemia incidence and Hba1c targets were analysed using Fishers exact test. Mean data were analysed using type III ANCOVA with treatment and country as fixed effects and baseline value as covariate. An LOCF analysis was performed, with adjustments for missing values for variables measured at least twice. P-values for adverse events were not reported.

Table 36: Russell-Jones et al. (2009)

General	**Phase:** ☐ monotherapy ☐ dual therapy ☑ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** 17 countries **Authors' conclusions:** In conclusion, this 26 week trial demonstrated that the once-daily human GLP-1 analogue liraglutide added to combination therapy with metformin and glimepiride in patients with type 2 diabetes resulted in statistically significant superior glycaemic control compared with insulin glargine, but the difference was within the predefined non-inferiority margin of 0.4 percentage points **Source of funding:** Novo Nordisk **Comments:** Open label trial. Randomisation (using a telephone or web-based randomisation system). Investigators, participants and study monitors were blinded to the treatment status of the liraglutide and placebo groups at all times.
Number and characteristics of patients	**Total number of patients:** 581 **Inclusion criteria:** 18–80 years old, with type 2 diabetes treated with oral glucose-lowering drugs (OGLAs) (94–95% combination therapy) for at least 3 months before screening. Criteria included HbA1c level of 7.5–10% if on OGLA monotherapy or 7–10% if on OGLA combination therapy, and BMI=45kg/m2 **Exclusion criteria:** used insulin within 3 months prior to the trial (except for short-term treatment for intercurrent illness); had impaired hepatic or renal function, clinically significant cardiovascular disease, proliferative retinopathy or maculopathy, hypertension (=180/100 mmHg) or cancer; were pregnant; experienced recurrent hypoglycaemia or hypoglycaemia unawareness, or used any drugs except for OGLAs that could affect blood glucose levels Pre-randomisation phase: Patients were randomised if they met the inclusion criteria, had received glimepiride (4 mg) and metformin (2 g) treatment for at least 3 weeks and had a fasting plasma glucose (FPG) between 7.5 and 12.8 mmol/l after the 6 week run-in.
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** all on oral hypoglycaemic drugs and/or insulin **Details of washout period:** patients who were not adequately controlled on metformin + sulfonlyurea were included and this combination was standardised during the 6 week run-in period
Lifestyle advice	No details reported
Follow-up	**Total follow-up (wks):** 32 **Length of titration period (wks):** 6 **Length of maintenance period (wks):** 26 **Frequency of monitoring appointments:** 9 visits in total
Arms	**(1) Metformin + sulfonylurea + liraglutide** N: 230 Treatment duration (wks): 26 Washout period (d): 0 Treatment(s): (a) Metformin (Oral) Details of dosing regimen: During the run-in period there was forced metformin and glimepiride dose escalation over 3 weeks followed by a 3 week maintenance period. Participants already on 2 g metformin and sulfonylurea therapy could proceed directly to the maintenance regimen at the discretion of the

investigator. During the dose-escalation period, doses of metformin and glimepiride were increased by up to 2 g/day and 4 mg/day, respectively.

(b) Sulfonylurea (Oral)

Mean dose (mg/d): 3.4

Details of dosing regimen: see metformin for details

(c) Liraglutide (Subcutaneous) – fixed-dose

Set dose (mg/d):1.8

Frequency of dosing: once a day

Details of dosing regimen: After randomisation, patients in the liraglutide group underwent a 2 week dose escalation, starting at 0.6 mg once daily with weekly increments of 0.6 mg, reaching a final daily dose of 1.8 mg by the end of the second week; daily placebo injections were matched for volume. After the 2 week dose-escalation period the liraglutide dose was fixed for 24 weeks. Trial medication was administered by subcutaneous injection in the abdomen, thigh or upper arm using a pre-filled pen device

(2) Metformin + sulfonylurea +insulin glargine

N: 232

Treatment duration (wks): 26

Washout period (d): 0

Treatment(s): (a) Metformin (Oral)

Details of dosing regimen: During the run-in period there was forced metformin and glimepiride dose escalation over 3 weeks followed by a 3 week maintenance period. Participants already on 2 g metformin and sulfonylurea therapy could proceed directly to the maintenance regimen at the discretion of the

investigator. During the dose-escalation period, doses of metformin and glimepiride were increased by up to 2 g/day and 4 mg/day, respectively.

(b) Sulfonylurea (Oral)

Mean dose (mg/d): 3.6

Details of dosing regimen: see metformin for details

(c) Insulin glargine (Subcutaneous)

Mean dose (mg/d): 24

Details of dosing regimen: Insulin was titrated by patients following instruction by the investigator according to a specific and widely adopted dosing algorithm for insulin glargine based on fasting concentration of blood glucose (adapted from A Trial comparing Lantus Algorithms to achieve Normal blood glucose Targets in patients with Uncontrolled blood Sugar [AT-LANTUS]).The starting dose of insulin glargine was numerically equivalent to the highest FPG value in mmol/l over the previous 7 days. During the first 8 weeks of treatment, the dose was titrated twice weekly by the participant, based on self-measured FPG, aiming for a target value of FPG=5.5 mmol/l. After 8 weeks of treatment, the frequency of monitoring and titration was at the investigator's discretion, but at minimum the insulin glargine dose was adjusted at the 12 and 18 week visits. The investigator reviewed the doses and these could be changed at his/her discretion.

Outcomes

General

The data were analysed for the intent-to-treat population, defined as patients who were exposed to at least one dose of trial product(s) after randomisation. For the primary endpoint, HbA1c, the statistical analysis was also performed without the last observation carried forward on the perprotocol population.

10% of patients in the liraglutide group, 16% in the placebo group and 6% in the insulin group withdrew from the study.

Outcomes not extracted in this evidence table include beta cell function, postprandial blood glucose

Hypoglycaemic events

hypoglycaemic episodes based on symptoms and PG (<3.1 mmol/l).

Major/severe hypoglycaemic event (Episodes requiring third-party medical assistance were classified as major)

Baseline characteristics

		Metformin + sulfonylurea + liraglutide			Metformin + sulfonylurea +insulin glargine			Δ	p
		N	k	mean	N	k	mean		
Demographics:									
Age (years)	Continuous	230		57.6 (SD 9.5)	232		57.5 (SD 10.5)		
Sex (n male)	Dichotomous	230	131	(57.0%)	232	139a	(59.9%)		
Duration of diabetes (yrs)	Continuous	230		9.2 (SD 5.8)	232		9.7 (SD 6.4)		
Blood glucose:									
HbA1c (%) – 0wk	Continuous	230		8.3 (SD 0.9)	232		8.2 (SD 0.9)		

	Fasting plasma glucose (mmol/l) – 0wk	Continuous	230		9.1 (SD 2.1)	232		9.1 (SD 2)		
	Body weight: BMI (kg/m2)	Continuous	230		30.4 (SD 5.3)	232		30.3 (SD 5.3)		
	Weight (kg) – 0wk	Continuous	230		85.5 (SD 19.4)	232		85 (SD 17.9)		
	Blood pressure: Systolic blood pressure (mmHg) – 0wk	Continuous	230		135 (SD 15)	232		133 (SD 14.7)		
	Diastolic blood pressure (mmHg) – 0wk	Continuous	230		80.8 (SD 9.1)	232		80.5 (SD 8)		

[a] approximated to nearest integer (percentages only presented in text)

Results

		Metformin + sulfonylurea + liraglutide			Metformin + sulfonylurea +insulin glargine				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 26wk	Continuous	230			232			MD=-0.240 (CI: -0.390, -0.090)	0.0015
Body weight: Weight (kg) – 26wk	Continuous	230			232			MD=-3.430 (CI: -4.000, -2.860)	<0.0001
Hypoglycaemic events: minor hypoglycaemic events – 26wka	Count	39767	131		19110	68			
minor hypoglycaemic events – 26wkb	Continuous	230	1.2		232	1.3			
minor hypoglycaemic events – 26wkc	Dichotomous	230	63	(27.4%)	232	67	(28.9%)		
Major/severe hypoglycaemic event – 26wka	Count	39767	7		19110	0			
Major/severe hypoglycaemic event – 26wkb	Continuous	230	0.06		232	0			
Symptomatic hypoglycaemia – 26wkd	Count	39767	109		41041	202			
Symptomatic hypoglycaemia – 26wkb	Continuous	230	1		232	1.8			
Adverse events: GI: nausea – 26wke	Dichotomous	230	32	(13.9%)	232	3	(1.3%)		
GI: nausea – 26wkf	Count	39767	41		41041	3			
Any serious adverse event(s) – 26wkg	Dichotomous	230	9	(3.9%)	232	16	(6.9%)		
Arthralgia – 26wke	Dichotomous	230	4	(1.7%)	232	6	(2.6%)		
Back pain – 26wke	Dichotomous	230	7	(3.0%)	232	8	(3.4%)		
Dizziness – 26wke	Dichotomous	230	3	(1.3%)	232	1	(0.4%)		
Dyspepsia – 26wke	Dichotomous	230	15	(6.5%)	232	4	(1.7%)		
Gastrointestinal disorders (any) – 26wke	Dichotomous	230	87	(37.8%)	232	18	(7.8%)		
GI: diarrhoea – 26wke	Dichotomous	230	23	(10.0%)	232	3	(1.3%)		
GI: vomiting – 26wke	Dichotomous	230	15	(6.5%)	232	1	(0.4%)		
GI: abdominal pain – 26wke	Dichotomous	230	10	(4.3%)	232	2	(0.9%)		
GI: gastritis – 26wke	Dichotomous	230	3	(1.3%)	232	1	(0.4%)		

GI: gatroenteritis – 26wke	Dichotomous	230	3	(1.3%)	232	3	(1.3%)		
GI: discomfort – 26wke	Dichotomous	230	3	(1.3%)	232	1	(0.4%)		
GI: abdominal distension – 26wke	Dichotomous	230	3	(1.3%)	232	1	(0.4%)		
GI: constipation – 26wke	Dichotomous	230	5	(2.2%)	232	2	(0.9%)		
Headache – 26wke	Dichotomous	230	22	(9.6%)	232	13	(5.6%)		
liver function/liver enzymes – 26wk	Dichotomous	230	3e		232	h			
Musculoskeletal and connective tissue disorders – 26wke	Dichotomous	230	22	(9.6%)	232	34	(14.7%)		
Nasopharyngitis – 26wke	Dichotomous	230	21	(9.1%)	232	26	(11.2%)		
Pancreatitis – 26wke	Dichotomous	230	0	(0.0%)	232	0	(0.0%)		
Dropouts:									
Total dropouts – 26wk	Dichotomous	230	23	(10.0%)	232	13	(5.6%)		
Dropout due to AEs – 26wk	Dichotomous	230	11	(4.8%)	232	5	(2.2%)		
Drop out due to unsatisfactory effect – 26wk	Dichotomous	230	2	(0.9%)	232	1	(0.4%)		
Blood pressure:									
Systolic blood pressure (mmHg) – 26wki	Mean change	230		-4	232		0.54	MD=-4.510 (CI: -6.820, -2.200)	0.0001
Diastolic blood pressure (mmHg) – 26wkh	Continuous	230			232				NS
Diabetic complications:									
Retinopathy – 26wk	Dichotomous	230	2	(0.9%)	232	4	(1.7%)		
ITT									
Blood glucose:									
HbA1c (%) – 12wkj	Continuous	230		6.75 (SD 1.82)	232		7.1 (SD 1.5)		
HbA1c (%) – 26wkk	Mean change	230		-1.33 (SD 1.36)	232		-1.09 (SD 1.37)		
Fasting plasma glucose (mmol/l) – 12wkl	Continuous	230		7.35 (SD 1.52)	232		7.1 (SD 3.05)		
Fasting plasma glucose (mmol/l) – 26wkl	Continuous	230		7.6 (SD 3.03)	232		7.3 (SD 2.74)		
Body weight:									
Weight (kg) – 12wkm	Continuous	230		83.6 (SD 2.4)	232		86.2 (SD 2.1)		
Weight (kg) – 26wkk	Mean change	230		-1.8 (SD 5)	232		1.6 (SD 5.03)		

[a] person years estimated assuming dropout halfway through the study and no of events calculated using reported rates
[b] events per patient per year
[c] FBG<3.1 mmol/l during treatment period; No of patients
[d] person days estimated assuming dropout halfway through the study and no of events calculated using reported rates
[e] No of patients
[f] Number of events; person days estimated assuming dropout halfway through the study
[g] approximated to nearest integer (percentages only presented in text)
[h] NR
[i] SD not reported
[j] SD calculated from SE estimated from graph
[k] SD calculated from reported SEM
[l] estimated from graph
[m] estimated from graph (assumed SD as not otherwise noted)

	Each endpoint was analysed using an analysis of covariance (ANCOVA) model with treatment, pre-treatment and country as fixed effects and baseline as the covariate. Missing baseline values were not imputed; that is, participants without a baseline value were excluded from the primary analysis. Post-baseline missing values were replaced using last observation carried . The proportion of participants achieving HbA1c targets was compared using a logistic regression model with treatment as fixed effect and baseline HbA1c as a covariate. Hypoglycaemic episodes were analysed using a generalised linear model including treatment and country as fixed effects. Other safety data were compared by descriptive statistics.

Table 37: Shanmugasundar et al. (2012)

General	**Phase:** ☐ monotherapy ☐ dual therapy ☑ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** India **Authors' conclusions:** The thrice daily biphasic human insulin regimen is non-inferior to the basal bolus insulin analogue regimen in terms of efficacy and safety in patients with poorly controlled type 2 diabetes. Howevere, these data require further substantiation in large long term prospective studies **Source of funding:** Unclear funding **Comments:** Open label, randomised trial
Number and characteristics of patients	**Total number of patients:** 54 **Inclusion criteria:** patients with type 2 diabetes who were inadequately controlled while receiving biphasic human insulin (BHI 30/70) bid, metformin 2g/day and pioglitazone 30 mg/day were recruited, with Hba1c >7%, single time insulin dose >25 units and having post-lunch and/or pre dinner hyperglycaemia **Exclusion criteria:** Patients with deranged liver function tests, serum creatinine >1.5 mg/dl, decompensated heart failure/unstable angina/MI within 6 months, untreated proliferative retinopathy, pregnancy, any other acute co-morbid illness, drug or alcohol dependence
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** all on oral hypoglycaemic drugs and/or insulin **Details of washout period:** All patients were on biphasic insulin + metformin + pioglitazone at study entry
Lifestyle advice	Lifestyle modifications were reinforced
Follow-up	**Total follow-up (wks):** 12 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 12 **Frequency of monitoring appointments:** -
Arms	**(1) BHI (biphasic human insulin) + metformin + pioglitazone** N: 27 Treatment duration (wks): 12 Washout period (d): 0 Comments: all on biphasic insulin + metformin + pioglitazone at study entry Treatment(s): (a) Metformin (Oral) Set dose (mg/d):2000 Details of dosing regimen: continued metformin + pioglitazone (b) Pioglitazone (Oral) Set dose (mg/d):30 Details of dosing regimen: continued metformin + pioglitazone (c) Biphasic human insulin (Subcutaneous) – flexible-dose (dose-adjusted) Details of dosing regimen: Mixtard 30/70 was administered 30 mins before each meal. The total daily dose was distributed in 40/20/40 ratio (breakfast/lunch/dinner). Doses were adjusted throughout the treatment period targeting ranges FBG 80-110 mg/dl, 2h PPG <140 mg/dl **(2) BB (basal bolus insulin-mealtime aspart + bedtime detemir) + metformin + pioglitazone** N: 27 Treatment duration (wks): 12 Washout period (d): 0 Comments: all on biphasic insulin + metformin + pioglitazone at study entry

Treatment(s): (a) Metformin (Oral)
Set dose (mg/d):2000
Details of dosing regimen: continued metformin + pioglitazone
(b) Pioglitazone (Oral)
Mean dose (mg/d): 30
Details of dosing regimen: continued metformin + pioglitazone
(c) Insulin (long acting + short acting) (Subcutaneous) – flexible-dose (dose-adjusted)
Details of dosing regimen: In the basal bolus regimen, aspart was injected immediately before breakfast, lunch and dinner, while determir was administered at bedtime. The total daily dose was split between aspart (60%) and determir (40%). Doses were adjusted throughout the treatment period targeting ranges FBG 80-110 mg/dl, 2h PPG <140 mg/dl

Outcomes

General
Outcomes not reported in this evidence table include costs
2/27 patients in each group discontinued the study and not included in analysis.
Study completers were analysed
Hypoglycaemic events
Nocturnal hypoglycaemia (occurred between 10pm and 6am)

Baseline characteristics

		BHI (biphasic human insulin) + metformin + pioglitazone			BB (basal bolus insulin-mealtime aspart + bedtime detemir) + metformin + pioglitazone			Δ	p
		N	k	mean	N	k	mean		
Study completers/observed cases									
Demographics: Age (years)	Continuous	25		53.9 (SD 8.1)	25		53.8 (SD 9.5)		
Sex (n male)	Dichotomous	25	10	(40.0%)	25	15	(60.0%)		
Duration of diabetes (yrs)	Continuous	25		14.1 (SD 5.1)	25		13.2 (SD 6.4)		
Blood glucose: HbA1c (%) – 0wk	Continuous	25		9 (SD 0.9)	25		9.4 (SD 1.3)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	25		9.2528502 (SD 3.54)	25		10.3574196 (SD 4.48)		
Body weight: BMI (kg/m2) – 0wk	Continuous	25		29.2 (SD 4.8)	25		31.25 (SD 4.7)		
Weight (kg) – 0wka	Continuous	25		82.41408 (SD 13.5)	25		88.2 (SD 13.3)		
Waist circumference (cms)	Continuous	25		101.1 (SD 9.13)	25		107.2 (SD 10.5)		
Insulin: Total daily dose (U)	Continuous	25		58.9 (SD 7.01)	25		60.2 (SD 6.75)		
Total daily dose (U/kg) – 0wk	Continuous	25		0.8 (SD 0.15)	25		0.72 (SD 0.1)		

[a] estimated from BMI assuming mean height of 1.68m

Results

		BHI (biphasic human insulin) + metformin + pioglitazone			BB (basal bolus insulin-mealtime aspart + bedtime detemir) + metformin + pioglitazone			Δ	p
		N	k	mean	N	k	mean		
Blood glucose: HbA1c (%) – 12wk	Continuous	27			27				NS
Fasting plasma glucose (mmol/l) – 12wk	Continuous	27			27				NR
Body weight: BMI (kg/m2) – 12wk	Mean change	27			27				NR

Weight (kg) – 12wk	Mean change	27			27				NS
Hypoglycaemic events:									
minor hypoglycaemic events – 12wk	Dichotomous	27			27				NS
Major/severe hypoglycaemic event – 12wk	Dichotomous	27			27				NS
Symptomatic hypoglycaemia – 12wk	Dichotomous	27			27				0.03a
Nocturnal hypoglycaemia – 12wk	Dichotomous	27			27				NS
Insulin:									
Total daily dose (U/kg) – 12wk	Mean change	27			27				<0.001
Study completers/observed cases									
Blood glucose:									
HbA1c (%) – 12wkb	Mean change	25		-1.1 (SD 0.5)	25		-1.2 (SD 0.6)		
HbA1c (%) – 12wkb	Continuous	25		7.9 (SD 0.8)	25		8.2 (SD 1)		
HbA1c < 7% or <=7% – 12wk	Dichotomous	25	4	(16.0%)	25	4	(16.0%)		
Fasting plasma glucose (mmol/l) – 12wk	Continuous	25		5.7004662 (SD 1.04)	25		6.2000202 (SD 0.76)		
Body weight:									
BMI (kg/m2) – 12wk	Mean change	25		0.58 (SD 0.61)	25		0.62 (SD 0.6)		
Weight (kg) – 12wk	Continuous	25		76 (SD 11.6)	25		86.9 (SD 14.4)		
Weight (kg) – 12wk	Mean change	25		1.45 (SD 0.33)	25		1.38 (SD 0.34)		
Hypoglycaemic events:									
minor hypoglycaemic events – 12wk	Count	2100	53		2100	37			
minor hypoglycaemic events – 12wkc	Continuous	25		9.2	25		6.4		
minor hypoglycaemic events – 12wkd	Dichotomous	25	20	(80.0%)	25	15	(60.0%)		
Major/severe hypoglycaemic event – 12wk	Count	2100	2		2100	3			
Major/severe hypoglycaemic event – 12wkc	Continuous	25		0.35	25		0.52		
Major/severe hypoglycaemic event – 12wkd	Dichotomous	25	2	(8.0%)	25	3	(12.0%)		
Symptomatic hypoglycaemia – 12wk	Count	2100	30		2100	16			
Nocturnal hypoglycaemia – 12wk	Count	2100	15		2100	13			
Nocturnal hypoglycaemia – 12wkc	Continuous	25		2.6	25		2.3		

	Nocturnal hypoglycaemia – 12wkd	Dichotomous	25	12	(48.0%)	25	8	(32.0%)		
	Insulin:									
	Total daily dose (U/kg) – 12wk	Continuous	25		0.94 (SD 0.21)	25		1.18 (SD 0.36)		
	Total daily dose (U/kg) – 12wk	Mean change	25		-0.15 (SD 0.21)	25		-0.46 (SD 0.32)		

[a] post hoc analysis
[b] assumed SD reported
[c] episodes per patient year; no 95% CI reported
[d] No patients

For normally distributed continuous data, students t-test for two groups was used. For time related comparison paired t-test or wilcoxon signed rank test were applied. Categorical variables were compared using chi square or fishers exact test.

Table 38: Stehouwer et al. (2003)

General	**Phase:** ☐ monotherapy ☐ dual therapy ☑ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** Unclear but assumed The Netherlands **Authors' conclusions:** The glimepiride + NPH insulin treatment resulted in a higher Hba1c level as compared to the other regimens. In the clinical setting of this multicentre study, good glycaemic control was only achieved in a minority of the patients, irrespective of the applied regimen **Source of funding:** Aventis **Comments:** Open label trial. A central office carried out randomisation
Number and characteristics of patients	**Total number of patients:** 261 **Inclusion criteria:** obese patients with type 2 diabetes with secondary failure to oral blood glucose lowering agents (metformin + sulfonylurea). Hba1c >7% with diet and oral hypoglycaemic drugs (at least 3 tablets of sulfonylurea and 1 g metformin), aged 40-70 years and BMI 25-40 kg/m2. **Exclusion criteria:** Details not reported Pre-randomisation phase: There was a 12 week run-in phase in which patients received a combination of glimepiride and metformin (500 mg bid). The glimepiride was titrated to 6 mg targeting a FBG below 7.4 mmol/l. patients with Hba1c >6.5% at the end of the run-in phase were randomly assigned
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** all on oral hypoglycaemic drugs and/or insulin **Details of washout period:** All patients were taking metformin + sulfonylurea at study entry. Metformin was stopped in all arms.
Lifestyle advice	Patients were seen by a diabetologist and diabetes nurse educator every 3 months. The dietary advice was focused on healthy nutrition. Seevre energy restriction was discouraged.
Follow-up	**Total follow-up (wks):** 51 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 39 **Frequency of monitoring appointments:** -
Arms	**(1) Glimepiride + NPH (bedtime)** N: 86 Treatment duration (wks): 36 Washout period (d): 0 Comments: patients were taking metformin + glimepiride at study entry (metformin was stopped in all arms). No additional medication that might inflence glycaemia was prescribed in the therapy groups. Treatment(s): (a) Sulfonylurea (Oral) – flexible-dose (dose-adjusted) Details of dosing regimen: The dose of glimepiride achieved during the run-in phase was assumed to be maintained through the treatment phase.

(b) NPH insulin (Subcutaneous) – flexible-dose (dose-adjusted)
Frequency of dosing: once a day
Details of dosing regimen: Glycaemic targets were 4-7.4 mmol/l for FBG and 4-10 mmol/l for postprandial levels. The therapeutic aim was a Hba1c <=6.5%. The insulin dose was adjusted twice a week in steps of 2 to 4 IU until targets were achieved.

(2) NPH insulin (bid)

N: 88

Treatment duration (wks): 39
Washout period (d): 0
Comments: patients were taking metformin + glimepiride at study entry (metformin was stopped in all arms). No additional medication that might inflence glycaemia was prescribed in the therapy groups.

Treatment(s): NPH insulin (Subcutaneous) – flexible-dose (dose-adjusted)
Frequency of dosing: twice a day

Outcomes

General

No details of drop outs reported

No details of ITT analysis

All outcomes were extracted in this evidence table

Hypoglycaemic events

minor hypoglycaemic events (Symptoms of mild hypoglycaemic events include sweating, trembling, excessive hunger, fatigue and/or measured BG <3.5 mmol/L.)

Major/severe hypoglycaemic event (Events requiring the assistance of another person)

Baseline characteristics

		Glimepiride + NPH (bedtime)			NPH insulin (bid)			Δ	p
		N	k	mean	N	k	mean		
Demographics: Age (years)	Continuous	86		57.6 (SD 8.4)	88		58.4 (SD 7.3)		
Sex (n male)	Dichotomous	86	45	(52.3%)	88	43	(48.9%)		
Duration of diabetes (yrs)	Continuous	86		8.1 (SD 4.9)	88		7.9 (SD 5.2)		
Blood glucose: HbA1c (%) – 0wk	Continuous	86		9.4 (SD 1.4)	88		9.4 (SD 1.4)		
Body weight: BMI (kg/m2) – 0wk	Continuous	86		29.8 (SD 3.7)	88		29.2 (SD 3.2)		
Weight (kg) – 0wk	Continuous	86		86 (SD 13.9)	88		82.1 (SD 11.6)		

Results

		Glimepiride + NPH (bedtime)			NPH insulin (bid)			Δ	p
		N	k	mean	N	k	mean		
Blood glucose: HbA1c (%) – 36wk	Continuous	86		8.9 (SD 1.2)	88		8.3 (SD 1)		<0.001
HbA1c <= 6.5% – 36wk	Dichotomous	86	1	(1.2%)	88	3	(3.4%)		
Body weight: BMI (kg/m2) – 36wk	Continuous	86			88				NS
Weight (kg) – 36wk	Continuous	86		89.8 (SD 14.5)	88		87.5 (SD 13.1)		NS
Hypoglycaemic events: minor hypoglycaemic events – 36wka	Count	21672	253		22176	355			
minor hypoglycaemic events – 36wkb	Dichotomous	86	53	(61.6%)	88	63	(71.6%)		NS
minor hypoglycaemic events – 36wkc	Continuous	86		0.35	88		0.48		
Major/severe hypoglycaemic event – 36wkd	Count	23478	0		24024	0			

	Major/severe hypoglycaemic event – 36wk	Dichotomous	86	0	(0.0%)	88	0	(0.0%)		NS
	Dropouts:									
	Total dropouts – 36wk	Dichotomous	86	0	(0.0%)	88	0	(0.0%)		
	Insulin:									
	Total daily dose (U) – 36wk	Continuous	86		44 (SD 3.9)	88		46.8 (SD 2.9)		NS

[a] person days estimated assuming dropout halfway through the study and no events calculated using reported rates
[b] No of patients
[c] events per patient month; 95% CI not reported
[d] person days estimated assuming dropout halfway through the study

Differences between groups for Hba1c over time were analysed using repeated measures ANOVA. Using multivariate analyses for baseline values, the changes were adjusted for gender and age. Differences in the number of patients with hypoglycaemic events between groups were analysed using chi sqaured and incidences were compared using ANOVA.

Table 39: Ushakova et al. (2007)

General

Phase:
☐ monotherapy
☐ dual therapy
☑ triple therapy
☐ insulin monotherapy
☐ insulin+oral

Parallel / crossover: Parallel

Country: Russian Federation

Authors' conclusions: In these patients with type 2 diabetes that was poorly controlled by OADs, BIAsp30 TID and BIAsp 30 BID plus metformin were associated with significantly greater reductions in Hba1c and postprandial BG compared with OADs alone. The insulin regimens were associated with significantly more weight gain than OADs alone. There were no differences in rates of hypoglycaemia between the insulin regimens

Source of funding: Novo Nordisk

Comments: Randomised, open label, parallel-group trial. Randomisation was carried out using sealed codes, prepared by blocks.

Number and characteristics of patients

Total number of patients: 308

Inclusion criteria: The study population consisted of insulin naïve men and women with type 2 diabetes who had been receiving treatment with >=1 OAD for at least 6 months. They were aged 40-70 years and had a BMI <= 35.0 kg/m2 and a Hba1c >=8.0%

Exclusion criteria: patients with significant medical problems or using medication known to interfere with glucose metabolism were excluded, as were pregnant or breastfeeding women.

Previous glucose-lowering therapy

Any participants previously taking glucose-lowering therapy? all on oral hypoglycaemic drugs and/or insulin

Details of washout period: All patients were taking >=1 OAD (some were on monotherapy and some were on dual therapy), these current treatments were discontinued in the insulin arms

Lifestyle advice

-

Follow-up

Total follow-up (wks): 16

Length of titration period (wks): 8

Length of maintenance period (wks): 8

Frequency of monitoring appointments: -

Arms

(1) BIAsp 30 BID then TID

N: 104

Treatment duration (wks): 16
Washout period (d): 0
Comments: Current OAD treatments were discontinued in both insulin arms

Treatment(s): Biphasic insulin aspart (Subcutaneous) – flexible-dose (dose-adjusted)
Frequency of dosing: three times a day
Details of dosing regimen: Treatment began the day after randomisation. During the first 2

weeks of the titration period, BIAsp 30 was receievd BID, started at a total daily dose of 0.3 to 0.5 U/kg body weight, with half given at breakfast and half at the evening meal. After 2 weeks, the investigator divided the total daily insulin dose into 3 injections given before each meal. After week 8, no further titration of insulin or OADs were allowed for the remaining 8 weeks except as required for daily glucose control. The target for all three treatment groups was achievement of premeal/bedtime BG 4.4 to 7.0 mmol/l and postprandial BG 4.4 to 9.0 mmol/l

(2) BIAsp 30 BID + metformin

N: 100

Treatment duration (wks): 16
Washout period (d): 0
Comments: Current OAD treatments were discontinued in both insulin arms

Treatment(s): (a) Biphasic insulin aspart (Subcutaneous) – flexible-dose (dose-adjusted)

Frequency of dosing: twice a day
Details of dosing regimen: Treatment began the day after randomisation. During the first 2 weeks of the titration period, BIAsp 30 was receievd BID, started at a total daily dose of 0.3 to 0.5 U/kg body weight, with half given at breakfast and half at the evening meal. After 2 weeks, patients continued treatment with the addition of metformin.

(b) Metformin (Oral) – flexible-dose (dose-adjusted)

Maximum dose (mg/d): 2000
Details of dosing regimen: Metformin was added to insulin as 500 mg once or twice daily, or 850 mg once daily. The metformin dose was adjusted and titrated based on SMBG and individual tolerance. Metformin could be given up to three times daily, but the final total daily dose not to exceed 2000 mg

Outcomes

General

Data from 2/3 arms have been extracted into this evidence table. Data from the OAD arm has not been extracted as this mixed treatment was not part of the decision space for second intensification. Outcomes not exatracted into this evidence table include SMBG profiles, treatment satisfaction and quality of life.

Efficacy measures were evaluated using data from all randomised patients who provided postbaseline efficacy data (ITT analysis). The safety population included all randomised patients who received at least 1 or a partial dose of the study drug. LOCF method was used to impute missing data.

4/104 (3.8%) patients in BIAsp TID group and 5/100 (5%) in the BIAsp + metformin group discontinued the study

Hypoglycaemic events

Minor (confirmed) hypoglycaemia (defined as a confirmed BG reading <3.1 mmol/l, with or without symptoms, that was handled by the patient)

Major/severe hypoglycaemic event (defined as one that required the help of another person in association with a BG reading <3.1 mmol/l or symptoms that reveresed after ingestion of food or administration of glucagon/IV glucose)

symptomatic (unconfirmed) hypoglycaemia (defined as symptoms considered related to hypoglycaemia but not confirmed by BG measurement)

Baseline characteristics

		BIAsp 30 BID then TID			BIAsp 30 BID + metformin				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	104		58 (SD 6.41)	100		58.4 (SD 6.44)		
Sex (n male)	Dichotomous	104	17	(16.3%)	100	27	(27.0%)		
Duration of diabetes (yrs)	Continuous	104		9.9 (SD 6.2)	100		8.4 (SD 5.65)		
Blood glucose: HbA1c (%) – 0wk	Continuous	104		10.4 (SD 1.44)	100		10.4 (SD 1.69)		
Body weight: BMI (kg/m2)	Continuous	104		29.8 (SD 3.5)	100		29.2 (SD 3.77)		
Weight (kg) – 0wk	Continuous	104		79.3 (SD 11.8)	100		78.4 (SD 13)		
Previous blood glucose lowering drugs: Metformin	Dichotomous	104	0	(0.0%)	100	0	(0.0%)		
Meglitinide	Dichotomous	104	4	(3.8%)	100	2	(2.0%)		
Sulfonylurea	Dichotomous	104	58	(55.8%)	100	53	(53.0%)		
Metformin + Sulfonylurea	Dichotomous	104	42	(40.4%)	100	42	(42.0%)		

Results

		BIAsp 30 BID then TID			BIAsp 30 BID + metformin				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 16wk	Continuous	104			100			MD=0.200 (CI: -0.108, 0.508)	NR
HbA1c < 7% or <=7% – 16wk	Dichotomous	104			100				NS
Body weight: Weight (kg) – 16wk	Continuous	104			100				NR
Hypoglycaemic events: All hypoglycaemic events (no events) – 16wk	Dichotomous	104			100				NR
All hypoglycaemic events (no events) – 16wk	Count	11424	23	a	10920	21	b		
Minor (confirmed) hypoglycaemia – 16wkc	Count	11424	4		10920	9			
Minor (confirmed) hypoglycaemia – 16wk	Dichotomous	104			100				NR
Major/severe hypoglycaemic event – 16wk	Dichotomous	104			100				NR
Major/severe hypoglycaemic event – 16wkc	Count	11424	0		10920	0			
symptomatic (unconfirmed) hypoglycaemia – 16wk	Dichotomous	104			100				NR
Adverse events: Any adverse event(s) – 16wk	Dichotomous	104			100				NR
Any serious adverse event(s) – 16wk	Dichotomous	104			100				NR
Gastrointestinal disorders (any) – 16wk	Dichotomous	104			100				NR
Infection (upper airway or other common) – 16wk	Dichotomous	104			100				NR
Nervous system disorders – 16wk	Dichotomous	104			100				NR
Dropouts: Total dropouts – 16wk	Dichotomous	104	4	(3.8%)	100	5	(5.0%)		
Dropout due to AEs – 16wk	Dichotomous	104			100				NR
Drop out due to unsatisfactory effect – 16wk	Dichotomous	104			100				NR
Insulin: Total daily dose (U) – 16wk	Continuous	104			100				NR
ITT Blood glucose: HbA1c (%) – 16wk	Mean change	100		-2.9 (SD 1.5)	100		-3 (SD 1.6)		
HbA1c < 7% or <=7% – 16wk	Dichotomous	100	42	(42.0%)	100	45	(45.0%)		
Body weight: Weight (kg) – 16wkd	Mean change	100		1.71	100		1.5		
Dropouts: Dropout due to AEs – 16wk	Dichotomous	100	1	(1.0%)	100	1	(1.0%)		
Drop out due to unsatisfactory effect – 16wk	Dichotomous	100	0	(0.0%)	100	1	(1.0%)		

	Insulin: Total daily dose (U) – 16wk	Continuous	100		55.5 (SD 16.2)	100		44.8 (SD 12.6)		
	Safety population Hypoglycaemic events: All hypoglycaemic events (no events) – 16wke	Continuous	102		0.73	100		0.69		
	Minor (confirmed) hypoglycaemia – 16wkf	Dichotomous	102	4	(3.9%)	100	9	(9.0%)		
	Major/severe hypoglycaemic event – 16wkf	Dichotomous	102	0	(0.0%)	100	0	(0.0%)		
	symptomatic (unconfirmed) hypoglycaemia – 16wkg	Dichotomous	102	28	(27.5%)	100	28	(28.0%)		
	Adverse events: Any adverse event(s) – 16wkg	Dichotomous	102	35	(34.3%)	100	25	(25.0%)		
	Any serious adverse event(s) – 16wkg	Dichotomous	102	0	(0.0%)	100	0	(0.0%)		
	Gastrointestinal disorders (any) – 16wkg	Dichotomous	102	4	(3.9%)	100	4	(4.0%)		
	Infection (upper airway or other common) – 16wkg	Dichotomous	102	12	(11.8%)	100	12	(12.0%)		
	Nervous system disorders – 16wkg	Dichotomous	102	7	(6.9%)	100	6	(6.0%)		

[a] patient days estimated using 104 randomised patients and assuming dropout halfway through the study
[b] patient days estimated assuming dropout halfway through the study
[c] person days estimated by reviewer (assuming drop out halfway through study)
[d] SD not reported
[e] episodes per patient year; 95% CI not reported
[f] No of episodes
[g] No patients

	Efficacy endpoints were analysed using ANCOVA with adjustment for baseline Hba1c and centre

Table 40: Yki-Jarvinen et al. (2006)

General	**Phase:** ☐ monotherapy ☐ dual therapy ☑ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** Finland and UK **Authors' conclusions:** Good glycaemic control can be achieved with both insulin glargin + metformin and NPH insulin + metformin. Use of glargine + metformin reduces symptomatic hypoglycaemia during the first 12 weeks and dinnertime hyperglycaemia compared with NPH + metformin **Source of funding:** Supported by grants from the Academy of Finland and Aventis **Comments:** Mulicentre, open, randomised trial. Randomisation using minimisation of differences
Number and characteristics of patients	**Total number of patients:** 110 **Inclusion criteria:** Male or female patients aged 35-75 years with type 2 diabetes who have been treated with a stable dose (any dose) of sulfonylurea and metformin (.=1.5g) or with metformin alone for at least 3 months prior to screening. Further criteria included BMI 20-40 kg/m2, Hba1c >=8%, a mean FBG >=7 mmol/l and fasting c peptide >=0.33 mmol/l **Exclusion criteria:** use of other oral antihyperglycaemic agents, prior use of insulin, positive GAD antibodies or history of ketoacidosis, abnormal safety laboratory tests including liver enzymes, current or past history of alcohol or drug abuse, night shift work, pregnancy, treatment with any investigational drug in the 2 months before study entry, use of drugs likely to interfere with glucose control, clinically relevant major systemic disease and mental health conditions that prevent participants from understanding the nature of the study Pre-randomisation phase: there was a 4 week run-in period

Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** all on oral hypoglycaemic drugs and/or insulin **Details of washout period:** Patients were included if they were on metformin + sulfonylurea or metformin alone. At baseline the sulfonylurea was discontinued.
Lifestyle advice	No other (except for education relating to SMBG) education or lifestyle advice was recommended to be given
Follow-up	**Total follow-up (wks):** 40 **Length of titration period (wks):** 0 **Length of maintenance period (wks):** 36 **Frequency of monitoring appointments:** -
Arms	**(1) Insulin glargine + metformin** N: 61 Treatment duration (wks): 36 Washout period (d): 0 Comments: Sulfonylurea was discontinued and metformin was continued Treatment(s): (a) Insulin glargine (Subcutaneous) – flexible-dose (dose-adjusted) Mean dose (mg/d): 68 Details of dosing regimen: Insulin therapy was started if FBG still >7 mmol/l. Patients were taught to inject either glargine or NPH using the Optipen pro 1 . The initial bedtime insulin dose was 10IU for all patients who were using metformin alone and 20IU if the patient had used both sulfonylurea and metformin previously. The goal was to achieve FBG 4-5.5 mmol/l in both groups. Patients were taught to increase their insulin dose by 2IU if FBG>5.5 mmol/l and by 4IU if FBG>10 mmol/l on three consecutive mornings. (b) Metformin (Oral) Mean dose (mg/d): 2280 **(2) Insulin NPH + metformin** N: 49 Treatment duration (wks): 36 Washout period (d): 0 Comments: Sulfonylurea was discontinued and metformin was continued Treatment(s): (a) NPH insulin (Subcutaneous) – flexible-dose (dose-adjusted) Mean dose (mg/d): 70 Details of dosing regimen: See glargine + metformin for dosing details (b) Metformin (Oral) Mean dose (mg/d): 2190
Outcomes	**General** Outcomes not extracted in this evidence table include c-peptides and SMBG 1 (1.6%) patient in the glargine group and 1 (2%) in the NPH group discontinued the study **Hypoglycaemic events** Major/severe hypoglycaemic event (defined as an event with symptoms consistent with hypoglycaemia during which the participant required assisstance from another person and was associated with BG<3.1 mmol/l or prompt recovery after oral carbohydrate, IV glucose or glucagon) confirmed hypoglycaemia (defined as BG <=4 mmol/l)

Baseline characteristics

		Insulin glargine + metformin			Insulin NPH + metformin				
		N	k	mean	N	k	mean	Δ	p
Demographics:									
Age (years)	Continuous	61		56 (SD 7.81)	49		57 (SD 7)		
Sex (n male) a	Dichotomous	61	38	(62.3%)	49	32	(65.3%)		
Duration of diabetes (yrs)	Continuous	61		9 (SD 7.81)	49		9 (SD 7)		
Blood glucose:									
HbA1c (%) – 0wkb	Continuous	61		9.13 (SD 0.781)	49		9.26 (SD 0.7)		
Fasting plasma glucose (mmol/l)	Continuous	61		13 (SD 2.34)	49		12.9 (SD 2.1)		
Body weight:									
BMI (kg/m2)	Continuous	61		31.3 (SD 5.47)	49		32 (SD 5.6)		
Weight (kg) – 0wk	Continuous	61		92 (SD 18.7)	49		94.4 (SD 18.2)		

Adverse events: liver enzymes: abnormal ALT – 0wk	Continuous	61		44 (SD 27.3)	49		40 (SD 24.5)		
Lipids: HDL cholesterol (mmol/l) – 0wk	Continuous	61		1.18 (SD 0.312)	49		1.18 (SD 0.28)		
Triglycerides (mmol/l) – 0wk	Continuous	61		2.3 (SD 1.56)	49		2.5 (SD 1.4)		
LDL cholesterol (mmol/l) – 0wk	Continuous	61		2.8 (SD 0.781)	49		2.9 (SD 0.7)		
Previous blood glucose lowering drugs: Sulfonylureaa	Dichotomous	61	48	(78.7%)	49	42	(85.7%)		

[a] approximated to nearest integer (percentages only presented in text)

[b] ***from text not table data***

Results

		Insulin glargine + metformin			Insulin NPH + metformin				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Blood glucose: HbA1c (%) – 12wka	Continuous	61		8 (SD 0.391)	49		8.05 (SD 0.35)		
HbA1c (%) – 24wka	Continuous	61		7.3 (SD 0.391)	49		7.3 (SD 0.35)		
HbA1c (%) – 36wkb	Continuous	61		7.14 (SD 0.937)	49		7.16 (SD 0.98)		NS
Body weight: Weight (kg) – 12wka	Mean change	61		1.1 (SD 1.56)	49		1.4 (SD 1.4)		
Weight (kg) – 24wka	Mean change	61		2 (SD 2.34)	49		2.6 (SD 2.8)		
Weight (kg) – 36wk	Mean change	61		2.6 (SD 4.69)	49		3.5 (SD 4.9)		NS
Hypoglycaemic events: All hypoglycaemic events (no events) – 36wk	Dichotomous	61			49				NR
All hypoglycaemic events (no events) – 36wk	Count	15246	226		12222	268			
All hypoglycaemic events (no events) – 36wkc	Continuous	61		5.4	49		8		
Major/severe hypoglycaemic event – 36wk	Count	15246	0		12222	0			
Major/severe hypoglycaemic event – 36wk	Dichotomous	61	0	(0.0%)	49	0	(0.0%)		NR
symptomatic (confirmed) – 36wk	Dichotomous	61			49				NS
symptomatic (confirmed) – 36wk	Count	15246	209		12222	259			
symptomatic (confirmed) – 36wkc	Continuous	61		5	49		7.7		
Symptomatic hypoglycaemia – 36wkd	Dichotomous	61			49				0.12
Adverse events: Any adverse event(s) – 36wke	Dichotomous	61	33	(54.1%)	49	24	(49.0%)		
Any serious adverse event(s) – 36wke	Dichotomous	61	1	(1.6%)	49	4	(8.2%)		
liver enzymes: abnormal ALT – 12wka	Continuous	61		36 (SD 19.5)	49		31 (SD 10.5)		
liver enzymes: abnormal ALT – 24wka	Continuous	61		36 (SD 27.3)	49		29 (SD 10.5)		
liver enzymes: abnormal ALT – 36wka	Continuous	61		34 (SD 19.5)	49		30 (SD 24.5)		
Dropouts: Total dropouts – 36wk	Dichotomous	61	1	(1.6%)	49	1	(2.0%)		

	Dropout due to AEs – 36wk	Dichotomous	61	1	(1.6%)	49	1	(2.0%)		
	Lipids: HDL cholesterol (mmol/l) – 36wk	Mean change	61		1.24 (SD 0.312)	49		1.25 (SD 0.28)		
	Triglycerides (mmol/l) – 12wka	Continuous	61		1.58 (SD 0.625)	49		1.58 (SD 0.56)		
	Triglycerides (mmol/l) – 24wka	Continuous	61		1.7 (SD 0.625)	49		1.8 (SD 0.7)		
	Triglycerides (mmol/l) – 36wk	Mean change	61		1.6 (SD 0.781)	49		1.8 (SD 0.7)		
	LDL cholesterol (mmol/l) – 36wk	Mean change	61		2.8 (SD 0.781)	49		2.9 (SD 0.7)		
	Insulin: Total daily dose (U) – 36wk	Continuous	61		68 (SD 39.1)	49		70 (SD 42)		NS
	[a] estimated from graph [b] SD calculated from assumed SE [c] mean episodes per patient year [d] NR [e] No of patients									
	Two way ANOVA was used to (repeated measures for changes over time) for analysis between groups. P-values for between group comparisons for lipid, liver enzymes and adverse events were not reported.									

Table 41: Yki-JaŶˆrvinen et al. (1999)

General	**Phase:** ☐ monotherapy ☐ dual therapy ☑ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** four trial centers (unclear but assumed to be Finland) **Authors' conclusions:** Combination therapy with bedtime insulin plus metformin prevents weight gain. This regimen also seems superior to other bedtime insulin regimens with respect to improvement in glycemic control and frequency of hypoglycemia **Source of funding:** Academy of Finland. Funding authorities had no role in analysis **Comments:** Randomisation was carried out using minimisation of differences. Partially blinded trial.
Number and characteristics of patients	**Total number of patients:** 96 **Inclusion criteria:** patients with type 2 diabetes whose disease was inadequately controlled with sulfonylurea therapy alone. Patients were aged 40 to 70 years, body mass index less than 35 kg/m2, fasting blood glucose level greater than 8 mmol/L [>144 mg/dL], duration of diabetes more than 3 years, previous oral therapy with either glipizide (>15 mg/d) or glyburide (>10 mg/d), and fasting serum C-peptide level more than 0.33 nmol/L **Exclusion criteria:** congestive heart failure, myocardial infarction, or stroke in the past 6 months; epilepsy or other severe disease; liver disease, serum creatinine concentration greater than 120 mmol/L [1.36 mg/dL], or macroalbuminuria; proliferative retinopathy or severe maculopathy; previous insulin therapy for more than 2 weeks; excessive alcohol consumption (>20 g/d); and night work Pre-randomisation phase: There was a 6 week run-in period (The purpose of the run-in period was to ensure that the patients were able to accurately perform home glucose monitoring and that patients who still responded to conventional therapy would not be unnecessarily treated with insulin.)
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** all on oral hypoglycaemic drugs and/or insulin **Details of washout period:** All patients were taking sulfonylurea alone at study entry
Lifestyle advice	A similar educational program was used in all participating centers.The patients were not instructed to change their diet (except for treatment of hypoglycemia) or exercise habits because of insulin therapy.
Follow-up	**Total follow-up (wks):** 58 **Length of titration period (wks):** 0

	Length of maintenance period (wks): 52 **Frequency of monitoring appointments:** Follow-up visits took place at 3 and 6 weeks and every 3 months for 1 year
Arms	**(1) intermediate acting neutral human isophane insulin + glyburide** N: 22 Treatment duration (wks): 52 Washout period (d): 0 Treatment(s): (a) Sulfonylurea (Oral) – fixed-dose Set dose (mg/d):10.5 Frequency of dosing: twice a day Compliance: Compliance, monitored through pill counting, was more than 95% for patients who completed the study. Details of dosing regimen: glyburide 10.5 mg was given as one 3.5-mg tablet before breakfast and two 3.5-mg tablets before dinner. Doses of oral agents remained the same. (b) NPH insulin (Subcutaneous) – flexible-dose (dose-adjusted) Frequency of dosing: once a day Details of dosing regimen: All patients in each group injected intermediate acting neutral human isophane insulin, 100 IU/mL at 9 p.m. Insulin therapy was started if the fasting glucose level still exceeded 8 mmol/L (144 mg/dL). The initial bedtime insulin dosage (measured in IU/d) was equal to the fasting blood glucose level (measured in mmol/L). increase the dose by 4 IU/d if the fasting glucose level exceeds 8 mmol/L on three consecutive measurements and by 2 IU/d if the fasting glucose level exceeds 6 mmol/L (108 mg/dL) on three measurements. The goal was to decrease the fasting glucose level to less than 6 mmol/L, which was predicted to decrease the hemoglobin A1c value to less than 7.5% **(2) intermediate acting neutral human isophane insulin + metformin** N: 19 Treatment duration (wks): 52 Washout period (d): 0 Treatment(s): (a) Metformin (Oral) – fixed-dose Set dose (mg/d):2000 Frequency of dosing: twice a day Details of dosing regimen: metformin 2 g was given as two 500-mg tablets before breakfast and two 500-mg tablets before dinner, and three tablets (one before breakfast and two before dinner) (b) NPH insulin (Subcutaneous) – flexible-dose (dose-adjusted) Frequency of dosing: once a day Details of dosing regimen: See insulin + glyburide for details **(3) intermediate acting neutral human isophane insulin + glyburide + metformin** N: 23 Treatment duration (wks): 52 Washout period (d): 0 Treatment(s): (a) Sulfonylurea (Oral) – fixed-dose Set dose (mg/d):10.5 Frequency of dosing: twice a day (b) Metformin (Oral) – fixed-dose Set dose (mg/d):2000 Frequency of dosing: twice a day (c) NPH insulin (Subcutaneous) – flexible-dose (dose-adjusted) Frequency of dosing: once a day Details of dosing regimen: See insulin + glyburide for details **(4) intermediate acting neutral human isophane insulin** N: 24 Treatment duration (wks): 52 Washout period (d): 0 Treatment(s): NPH insulin (Subcutaneous) – flexible-dose (dose-adjusted) Frequency of dosing: twice a day Details of dosing regimen: A second injection of neutral human isophane insulin before breakfast was added
Outcomes	**General** No details of ITT analysis reported (analysis carried out in those who completed study) Outcomes not extracted in this evidence table include SMBG 88/96 patients completed the study (8 discontinued-5 in insulin + metformin, 1 in insulin + metformin +

glyburide, 2 in insulin + glyburide)

Baseline characteristics

		intermediate acting neutral human isophane insulin + glyburide			intermediate acting neutral human isophane insulin + metformin			Δ	p
		N	k	mean	N	k	mean		
Demographics: Age (years)	Continuous	22		61 (SD 9.38)	19		57 (SD 8.72)		
Sex (n male)	Dichotomous	22	13	(59.1%)	19	11	(57.9%)		
Blood glucose: HbA1c (%) – 0wk	Continuous	22		9.8 (SD 1.41)	19		9.8 (SD 1.74)		
Fasting plasma glucose (mmol/l)	Continuous	22		11.7 (SD 2.35)	19		12.3 (SD 2.18)		
Body weight: BMI (kg/m2)	Continuous	22		29.7 (SD 4.69)	19		28.9 (SD 4.79)		
Weight (kg) – 0wka	Continuous	22		83.82528 (SD 13.2)	19		81.56736 (SD 13.5)		
Waist/hip ratio – 0wk	Continuous	22		0.93 (SD 0.0938)	19		0.93 (SD 0.0872)		
Lipids: Total cholesterol (mmol/l)	Mean change	22		5.7 (SD 0.938)	19		5.9 (SD 1.31)		
HDL cholesterol (mmol/l)	Mean change	22		1.1 (SD 0.469)	19		1.2 (SD 0.436)		
Triglycerides (mmol/l) – 0wk	Mean change	22		2.7 (SD 2.35)	19		2.4 (SD 1.74)		

[a] estimated from BMI assuming mean height of 1.68m

		intermediate acting neutral human isophane insulin + glyburide			intermediate acting neutral human isophane insulin + glyburide + metformin			Δ	p
		N	k	mean	N	k	mean		
Demographics: Age (years)	Continuous	22		61 (SD 9.38)	23		55 (SD 9.59)		
Sex (n male)	Dichotomous	22	13	(59.1%)	23	14	(60.9%)		
Blood glucose: HbA1c (%) – 0wk	Continuous	22		9.8 (SD 1.41)	23		9.9 (SD 1.44)		
Fasting plasma glucose (mmol/l)	Continuous	22		11.7 (SD 2.35)	23		11.5 (SD 2.88)		
Body weight: BMI (kg/m2)	Continuous	22		29.7 (SD 4.69)	23		29.5 (SD 4.32)		
Weight (kg) – 0wka	Continuous	22		83.82528 (SD 13.2)	23		83.2608 (SD 12.2)		
Waist/hip ratio – 0wk	Continuous	22		0.93 (SD 0.0938)	23		0.95 (SD 0.0959)		
Lipids: Total cholesterol (mmol/l)	Mean change	22		5.7 (SD 0.938)	23		5.8 (SD 0.959)		
HDL cholesterol (mmol/l)	Mean change	22		1.1 (SD 0.469)	23		1.1 (SD 0.48)		
Triglycerides (mmol/l) – 0wk	Mean change	22		2.7 (SD 2.35)	23		2.3 (SD 0.959)		

[a] estimated from BMI assuming mean height of 1.68m

	intermediate acting neutral human isophane insulin + glyburide	intermediate acting neutral human isophane insulin	Δ	p

		N	k	mean	N	k	mean		
Demographics: Age (years)	Continuous	22		61 (SD 9.38)	24		58 (SD 9.8)		
Sex (n male)	Dichotomous	22	13	(59.1%)	24	16	(66.7%)		
Blood glucose: HbA1c (%) – 0wk	Continuous	22		9.8 (SD 1.41)	24		10.1 (SD 1.96)		
Fasting plasma glucose (mmol/l)	Continuous	22		11.7 (SD 2.35)	24		12.1 (SD 2.45)		
Body weight: BMI (kg/m2)	Continuous	22		29.7 (SD 4.69)	24		28.5 (SD 5.39)		
Weight (kg) – 0wka	Continuous	22		83.82528 (SD 13.2)	24		80.4384 (SD 15.2)		
Waist/hip ratio – 0wk	Continuous	22		0.93 (SD 0.0938)	24		0.94 (SD 0.098)		
Lipids: Total cholesterol (mmol/l)	Mean change	22		5.7 (SD 0.938)	24		5.8 (SD 1.47)		
HDL cholesterol (mmol/l)	Mean change	22		1.1 (SD 0.469)	24		1.2 (SD 0.49)		
Triglycerides (mmol/l) – 0wk	Mean change	22		2.7 (SD 2.35)	24		2.6 (SD 2.45)		

[a] estimated from BMI assuming mean height of 1.68m

		intermediate acting neutral human isophane insulin + metformin			intermediate acting neutral human isophane insulin + glyburide + metformin			Δ	p
		N	k	mean	N	k	mean		
Demographics: Age (years)	Continuous	19		57 (SD 8.72)	23		55 (SD 9.59)		
Sex (n male)	Dichotomous	19	11	(57.9%)	23	14	(60.9%)		
Blood glucose: HbA1c (%) – 0wk	Continuous	19		9.8 (SD 1.74)	23		9.9 (SD 1.44)		
Fasting plasma glucose (mmol/l)	Continuous	19		12.3 (SD 2.18)	23		11.5 (SD 2.88)		
Body weight: BMI (kg/m2)	Continuous	19		28.9 (SD 4.79)	23		29.5 (SD 4.32)		
Weight (kg) – 0wka	Continuous	19		81.56736 (SD 13.5)	23		83.2608 (SD 12.2)		
Waist/hip ratio – 0wk	Continuous	19		0.93 (SD 0.0872)	23		0.95 (SD 0.0959)		
Lipids: Total cholesterol (mmol/l)	Mean change	19		5.9 (SD 1.31)	23		5.8 (SD 0.959)		
HDL cholesterol (mmol/l)	Mean change	19		1.2 (SD 0.436)	23		1.1 (SD 0.48)		
Triglycerides (mmol/l) – 0wk	Mean change	19		2.4 (SD 1.74)	23		2.3 (SD 0.959)		

[a] estimated from BMI assuming mean height of 1.68m

		intermediate acting neutral human isophane insulin + metformin			intermediate acting neutral human isophane insulin			Δ	p
		N	k	mean	N	k	mean		
Demographics: Age (years)	Continuous	19		57 (SD 8.72)	24		58 (SD 9.8)		
Sex (n male)	Dichotomous	19	11	(57.9%)	24	16	(66.7%)		

Blood glucose: HbA1c (%) – 0wk	Continuous	19		9.8 (SD 1.74)	24		10.1 (SD 1.96)		
Fasting plasma glucose (mmol/l)	Continuous	19		12.3 (SD 2.18)	24		12.1 (SD 2.45)		
Body weight: BMI (kg/m2)	Continuous	19		28.9 (SD 4.79)	24		28.5 (SD 5.39)		
Weight (kg) – 0wka	Continuous	19		81.56736 (SD 13.5)	24		80.4384 (SD 15.2)		
Waist/hip ratio – 0wk	Continuous	19		0.93 (SD 0.0872)	24		0.94 (SD 0.098)		
Lipids: Total cholesterol (mmol/l)	Mean change	19		5.9 (SD 1.31)	24		5.8 (SD 1.47)		
HDL cholesterol (mmol/l)	Mean change	19		1.2 (SD 0.436)	24		1.2 (SD 0.49)		
Triglycerides (mmol/l) – 0wk	Mean change	19		2.4 (SD 1.74)	24		2.6 (SD 2.45)		

[a] estimated from BMI assuming mean height of 1.68m

		intermediate acting neutral human isophane insulin + glyburide + metformin			intermediate acting neutral human isophane insulin				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	23		55 (SD 9.59)	24		58 (SD 9.8)		
Sex (n male)	Dichotomous	23	14	(60.9%)	24	16	(66.7%)		
Blood glucose: HbA1c (%) – 0wk	Continuous	23		9.9 (SD 1.44)	24		10.1 (SD 1.96)		
Fasting plasma glucose (mmol/l)	Continuous	23		11.5 (SD 2.88)	24		12.1 (SD 2.45)		
Body weight: BMI (kg/m2)	Continuous	23		29.5 (SD 4.32)	24		28.5 (SD 5.39)		
Weight (kg) – 0wka	Continuous	23		83.2608 (SD 12.2)	24		80.4384 (SD 15.2)		
Waist/hip ratio – 0wk	Continuous	23		0.95 (SD 0.0959)	24		0.94 (SD 0.098)		
Lipids: Total cholesterol (mmol/l)	Mean change	23		5.8 (SD 0.959)	24		5.8 (SD 1.47)		
HDL cholesterol (mmol/l)	Mean change	23		1.1 (SD 0.48)	24		1.2 (SD 0.49)		
Triglycerides (mmol/l) – 0wk	Mean change	23		2.3 (SD 0.959)	24		2.6 (SD 2.45)		

[a] estimated from BMI assuming mean height of 1.68m

Results

		intermediate acting neutral human isophane insulin + glyburide			intermediate acting neutral human isophane insulin + metformin				
		N	k	mean	N	k	mean	Δ	p
Hypoglycaemic events: Major/severe hypoglycaemic event – 52wka	Count	8372	0		7826	0			
Symptomatic hypoglycaemia – 52wkb	Count	8372	68		7826	25			
Dropouts: Total dropouts – 52wk	Dichotomous	24	2c	(8.3%)	24	5	(20.8%)		

Dropout due to AEs – 52wk	Dichotomous	24	1	(4.2%)	24	4	(16.7%)		
Study completers/observed cases									
Blood glucose:									
HbA1c (%) – 52wk	Continuous	22			19				<0.05
HbA1c (%) – 52wk	Mean change	22		-1.8d	19		-2.5 (SD 1.74)		
Body weight:									
Weight (kg) – 52wk	Continuous	22			19				<0.01
Weight (kg) – 52wk	Mean change	22		3.9 (SD 3.28)	19		0.9 (SD 5.23)		
Waist/hip ratio – 52wk	Continuous	22			19				<0.05
Waist/hip ratio – 52wk	Mean change	20		0.012 (SD 0.0281)	14		-0.002 (SD 0.0305)		
Hypoglycaemic events:									
Major/severe hypoglycaemic event – 52wke	Dichotomous	22	0	(0.0%)	19	0	(0.0%)		NR
Major/severe hypoglycaemic event – 52wke	Dichotomous	20	0	(0.0%)	14	0	(0.0%)		NR
Symptomatic hypoglycaemia – 52wk	Dichotomous	22			19				NR
Symptomatic hypoglycaemia – 52wkf	Continuous	22		3.4 (SD 4.69)	19		1.8 (SD 1.74)		
confirmed hypoglycaemia – 52wke	Dichotomous	22	20	(0.6%)	19	14	(0.4%)		<0.01
confirmed hypoglycaemia – 52wke	Dichotomous	3184	20	(0.6%)	3350	14	(0.4%)		<0.01
Lipids:									
Triglycerides (mmol/l) – 52wk	Mean change	20		-0.8 (SD 1.41)	14		-0.7 (SD 1.31)		NS
Triglycerides (mmol/l) – 52wk	Mean change	22		-0.8 (SD 1.41)	19		-0.7 (SD 1.31)		NS
Insulin:									
Total daily dose (U) – 52wk	Continuous	22		24 (SD 14.1)	19		36 (SD 39.2)		<0.01
Total daily dose (U) – 52wk	Continuous	20		24 (SD 14.1)	14		36 (SD 39.2)		<0.01

[a] person days estimated assuming dropout halfway through the study
[b] person days estimated assuming dropout halfway through the study and no of events calculated using reported mean symptomatic events
[c] 5
[d] estimated from graph; no SE reported
[e] no of episodes
[f] mean no episodes per patient

		intermediate acting neutral human isophane insulin + glyburide			**intermediate acting neutral human isophane insulin + glyburide + metformin**				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Hypoglycaemic events:									
Major/severe hypoglycaemic event – 52wka	Count	8372	0		8554	0			

Symptomatic hypoglycaemia – 52wkb	Count	8372	68		8554	73			
Dropouts:									
Total dropouts – 52wk	Dichotomous	24	2c	(8.3%)	24	1	(4.2%)		
Dropout due to AEs – 52wk	Dichotomous	24	1	(4.2%)	24	1	(4.2%)		
Study completers/observed cases									
Blood glucose:									
HbA1c (%) – 52wk	Continuous	22			23				NS
HbA1c (%) – 52wkd	Mean change	22		-1.8	23		-2.1		
Body weight:									
Weight (kg) – 52wk	Continuous	22			23				NS
Weight (kg) – 52wk	Mean change	22		3.9 (SD 3.28)	23		3.6 (SD 3.84)		
Waist/hip ratio – 52wk	Continuous	22			23				NR
Waist/hip ratio – 52wk	Mean change	20		0.012 (SD 0.0281)	22		0.008 (SD 0.0192)		
Hypoglycaemic events:									
Major/severe hypoglycaemic event – 52wke	Dichotomous	22	0	(0.0%)	23	0	(0.0%)		NR
Major/severe hypoglycaemic event – 52wke	Dichotomous	20	0	(0.0%)	22	0	(0.0%)		NR
Symptomatic hypoglycaemia – 52wk	Dichotomous	22			23				NR
Symptomatic hypoglycaemia – 52wkf	Continuous	22		3.4 (SD 4.69)	23		3.3 (SD 7.67)		
confirmed hypoglycaemia – 52wke	Dichotomous	22	20	(0.6%)	23	22	(0.6%)		NS
confirmed hypoglycaemia – 52wke	Dichotomous	3184	20	(0.6%)	3954	22	(0.6%)		NS
Lipids:									
Triglycerides (mmol/l) – 52wk	Mean change	20		-0.8 (SD 1.41)	22		-0.4 (SD 0.959)		NS
Triglycerides (mmol/l) – 52wk	Mean change	22		-0.8 (SD 1.41)	23		-0.4 (SD 0.959)		NS
Insulin:									
Total daily dose (U) – 52wk	Continuous	22		24 (SD 14.1)	23		20 (SD 14.4)		NR
Total daily dose (U) – 52wk	Continuous	20		24 (SD 14.1)	22		20 (SD 14.4)		NR

[a] person days estimated assuming dropout halfway through the study
[b] person days estimated assuming dropout halfway through the study and no of events calculated using reported mean symptomatic events
[c] 5
[d] estimated from graph; no SE reported
[e] no of episodes
[f] mean no episodes per patient

	intermediate acting neutral human isophane insulin + glyburide			intermediate acting neutral human isophane insulin				
	N	k	mean	N	k	mean	Δ	p

Hypoglycaemic events:									
Major/severe hypoglycaemic event – 52wka	Count	8372	0		8736	0			
Symptomatic hypoglycaemia – 52wkb	Count	8372	68		8736	94			
Dropouts:									
Total dropouts – 52wk	Dichotomous	24	2c	(8.3%)	24	0	(0.0%)		
Dropout due to AEs – 52wk	Dichotomous	24	1	(4.2%)	24	0	(0.0%)		
Study completers/observed cases									
Blood glucose:									
HbA1c (%) – 52wk	Continuous	22			24				NS
HbA1c (%) – 52wkd	Mean change	22		-1.8	24		-1.9		
Body weight:									
Weight (kg) – 52wk	Continuous	22			24				NS
Weight (kg) – 52wk	Mean change	22		3.9 (SD 3.28)	24		4.6 (SD 4.9)		
Waist/hip ratio – 52wk	Continuous	22			24				NR
Waist/hip ratio – 52wk	Mean change	20		0.012 (SD 0.0281)	24		0.016 (SD 0.0343)		
Hypoglycaemic events:									
Major/severe hypoglycaemic event – 52wke	Dichotomous	22	0	(0.0%)	24	0	(0.0%)		NR
Major/severe hypoglycaemic event – 52wke	Dichotomous	20	0	(0.0%)	24	0	(0.0%)		NR
Symptomatic hypoglycaemia – 52wk	Dichotomous	22			24				NR
Symptomatic hypoglycaemia – 52wkf	Continuous	22		3.4 (SD 4.69)	24		3.9 (SD 7.84)		
confirmed hypoglycaemia – 52wke	Dichotomous	22	20	(0.6%)	24	24	(0.6%)		<0.01
confirmed hypoglycaemia – 52wke	Dichotomous	3184	20	(0.6%)	3936	24	(0.6%)		<0.01
Lipids:									
Triglycerides (mmol/l) – 52wk	Mean change	20		-0.8 (SD 1.41)	24		-0.9 (SD 1.47)		NS
Triglycerides (mmol/l) – 52wk	Mean change	22		-0.8 (SD 1.41)	24		-0.9 (SD 1.47)		NS
Insulin:									
Total daily dose (U) – 52wk	Continuous	22		24 (SD 14.1)	24		24 (SD 14.7)		NR
Total daily dose (U) – 52wk	Continuous	20		24 (SD 14.1)	24		24 (SD 14.7)		NR

[a] person days estimated assuming dropout halfway through the study
[b] person days estimated assuming dropout halfway through the study and no of events calculated using reported mean symptomatic events
[c] 5
[d] estimated from graph; no SE reported
[e] no of episodes
[f] mean no episodes per patient

		intermediate acting neutral human isophane insulin + metformin			intermediate acting neutral human isophane insulin + glyburide + metformin			Δ	p
		N	k	mean	N	k	mean		
Hypoglycaemic events: Major/severe hypoglycaemic event – 52wka	Count	7826	0		8554	0			
Symptomatic hypoglycaemia – 52wkb	Count	7826	25		8554	73			
Dropouts: Total dropouts – 52wk	Dichotomous	24	5	(20.8%)	24	1	(4.2%)		
Dropout due to AEs – 52wk	Dichotomous	24	4	(16.7%)	24	1	(4.2%)		
Study completers/observed cases									
Blood glucose: HbA1c (%) – 52wk	Continuous	19			23				NS
HbA1c (%) – 52wk	Mean change	19		-2.5 (SD 1.74)	23		-2.1c		
Body weight: Weight (kg) – 52wk	Continuous	19			23				<0.01
Weight (kg) – 52wk	Mean change	19		0.9 (SD 5.23)	23		3.6 (SD 3.84)		
Waist/hip ratio – 52wk	Continuous	19			23				<0.05
Waist/hip ratio – 52wk	Mean change	14		-0.002 (SD 0.0305)	22		0.008 (SD 0.0192)		
Hypoglycaemic events: Major/severe hypoglycaemic event – 52wkd	Dichotomous	19	0	(0.0%)	23	0	(0.0%)		NR
Major/severe hypoglycaemic event – 52wkd	Dichotomous	14	0	(0.0%)	22	0	(0.0%)		NR
Symptomatic hypoglycaemia – 52wk	Dichotomous	19			23				NR
Symptomatic hypoglycaemia – 52wke	Continuous	19		1.8 (SD 1.74)	23		3.3 (SD 7.67)		
confirmed hypoglycaemia – 52wkd	Dichotomous	19	14	(0.4%)	23	22	(0.6%)		<0.05
confirmed hypoglycaemia – 52wkd	Dichotomous	3350	14	(0.4%)	3954	22	(0.6%)		<0.05
Lipids: Triglycerides (mmol/l) – 52wk	Mean change	14		-0.7 (SD 1.31)	22		-0.4 (SD 0.959)		NS
Triglycerides (mmol/l) – 52wk	Mean change	19		-0.7 (SD 1.31)	23		-0.4 (SD 0.959)		NS
Insulin: Total daily dose (U) – 52wk	Continuous	19		36 (SD 39.2)	23		20 (SD 14.4)		<0.01
Total daily dose (U) – 52wk	Continuous	14		36 (SD 39.2)	22		20 (SD 14.4)		<0.01

[a] person days estimated assuming dropout halfway through the study

[b] person days estimated assuming dropout halfway through the study and no of events calculated using reported mean symptomatic events
[c] estimated from graph; no SE reported
[d] no of episodes
[e] mean no episodes per patient

		intermediate acting neutral human isophane insulin + metformin			intermediate acting neutral human isophane insulin				
		N	k	mean	N	k	mean	Δ	p
Hypoglycaemic events: Major/severe hypoglycaemic event – 52wka	Count	7826	0		8736	0			
Symptomatic hypoglycaemia – 52wkb	Count	7826	25		8736	94			
Dropouts: Total dropouts – 52wk	Dichotomous	24	5	(20.8%)	24	0	(0.0%)		
Dropout due to AEs – 52wk	Dichotomous	24	4	(16.7%)	24	0	(0.0%)		
Study completers/observed cases Blood glucose: HbA1c (%) – 52wk	Continuous	19			24				<0.05
HbA1c (%) – 52wk	Mean change	19		-2.5 (SD 1.74)	24		-1.9c		
Body weight: Weight (kg) – 52wk	Continuous	19			24				<0.01
Weight (kg) – 52wk	Mean change	19		0.9 (SD 5.23)	24		4.6 (SD 4.9)		
Waist/hip ratio – 52wk	Continuous	19			24				<0.05
Waist/hip ratio – 52wk	Mean change	14		-0.002 (SD 0.0305)	24		0.016 (SD 0.0343)		
Hypoglycaemic events: Major/severe hypoglycaemic event – 52wkd	Dichotomous	19	0	(0.0%)	24	0	(0.0%)		NR
Major/severe hypoglycaemic event – 52wkd	Dichotomous	14	0	(0.0%)	24	0	(0.0%)		NR
Symptomatic hypoglycaemia – 52wk	Dichotomous	19			24				<0.05
Symptomatic hypoglycaemia – 52wke	Continuous	19		1.8 (SD 1.74)	24		3.9 (SD 7.84)		
confirmed hypoglycaemia – 52wkd	Dichotomous	19	14	(0.4%)	24	24	(0.6%)		NS
confirmed hypoglycaemia – 52wkd	Dichotomous	3350	14	(0.4%)	3936	24	(0.6%)		NS
Lipids: Triglycerides (mmol/l) – 52wk	Mean change	14		-0.7 (SD 1.31)	24		-0.9 (SD 1.47)		NS
Triglycerides (mmol/l) – 52wk	Mean change	19		-0.7 (SD 1.31)	24		-0.9 (SD 1.47)		NS
Insulin: Total daily dose (U) – 52wk	Continuous	19		36 (SD 39.2)	24		24 (SD 14.7)		<0.01
Total daily dose (U) – 52wk	Continuous	14		36 (SD 39.2)	24		24 (SD 14.7)		<0.01

[a] person days estimated assuming dropout halfway through the study
[b] person days estimated assuming dropout halfway through the study and no of events calculated using reported mean symptomatic events
[c] estimated from graph; no SE reported
[d] no of episodes
[e] mean no episodes per patient

		intermediate acting neutral human isophane insulin + glyburide + metformin			intermediate acting neutral human isophane insulin				
		N	k	mean	N	k	mean	Δ	p
Hypoglycaemic events: Major/severe hypoglycaemic event – 52wka	Count	8554	0		8736	0			
Symptomatic hypoglycaemia – 52wkb	Count	8554	73		8736	94			
Dropouts: Total dropouts – 52wk	Dichotomous	24	1	(4.2%)	24	0	(0.0%)		
Dropout due to AEs – 52wk	Dichotomous	24	1	(4.2%)	24	0	(0.0%)		
Study completers/observed cases Blood glucose: HbA1c (%) – 52wk	Continuous	23			24				NS
HbA1c (%) – 52wkc	Mean change	23		-2.1	24		-1.9		
Body weight: Weight (kg) – 52wk	Continuous	23			24				NS
Weight (kg) – 52wk	Mean change	23		3.6 (SD 3.84)	24		4.6 (SD 4.9)		
Waist/hip ratio – 52wk	Continuous	23			24				NR
Waist/hip ratio – 52wk	Mean change	22		0.008 (SD 0.0192)	24		0.016 (SD 0.0343)		
Hypoglycaemic events: Major/severe hypoglycaemic event – 52wkd	Dichotomous	23	0	(0.0%)	24	0	(0.0%)		NR
Major/severe hypoglycaemic event – 52wkd	Dichotomous	22	0	(0.0%)	24	0	(0.0%)		NR
Symptomatic hypoglycaemia – 52wk	Dichotomous	23			24				NR
Symptomatic hypoglycaemia – 52wke	Continuous	23		3.3 (SD 7.67)	24		3.9 (SD 7.84)		
confirmed hypoglycaemia – 52wkd	Dichotomous	23	22	(0.6%)	24	24	(0.6%)		<0.05
confirmed hypoglycaemia – 52wkd	Dichotomous	3954	22	(0.6%)	3936	24	(0.6%)		<0.05
Lipids: Triglycerides (mmol/l) – 52wk	Mean change	22		-0.4 (SD 0.959)	24		-0.9 (SD 1.47)		NS
Triglycerides (mmol/l) – 52wk	Mean change	23		-0.4 (SD 0.959)	24		-0.9 (SD 1.47)		NS

Insulin: Total daily dose (U) – 52wk	Continuous	23		20 (SD 14.4)	24		24 (SD 14.7)		NR
Total daily dose (U) – 52wk	Continuous	22		20 (SD 14.4)	24		24 (SD 14.7)		NR

[a] person days estimated assuming dropout halfway through the study
[b] person days estimated assuming dropout halfway through the study and no of events calculated using reported mean symptomatic events
[c] estimated from graph; no SE reported
[d] no of episodes
[e] mean no episodes per patient

Comparison of normally distributed variables between the groups (in patients who completed the trial) during the 12-month treatment period was

performed by using analysis of variance for repeated measures. For comparison of means when the variance was not normally distributed

(symptomatic hypoglycemic episodes), the Kruskal–Wallis test was used. Frequencies of hypoglycemia among the groups were compared by using the chi-square test.

Table 42: Zinman et al. (2011)

General	**Phase:** ☐ monotherapy ☐ dual therapy ☑ triple therapy ☐ insulin monotherapy ☐ insulin+oral **Parallel / crossover:** Parallel **Country:** 28 clinics in four countries (Canada, India, South Africa, and the USA) **Authors' conclusions:** Insulin degludec provides comparable glycaemic control to insulin glargine without additional adverse events and might reduce dosing frequency due to its ultra-long action profile **Source of funding:** sponsored by Novo Nordisk **Comments:** 16-week, randomised, open-label, parallel group trial. Block randomisation was computer-generated and done by use of an interactive voice and web-based system. Participants were stratified according to previous oral antidiabetic drug treatment. Investigators were masked to data until database release from the statistician
Number and characteristics of patients	**Total number of patients:** 245 **Inclusion criteria:** Men and women diagnosed with type 2 diabetes for at least 3 months and who were aged 18–75 years with an HbA1C of 7·0–11·0% and a bodymass index of 23–42 kg/m² were eligible for enrolment. Before trial entry, participants had to be insulin-naïve and have been treated with one or two oral antidiabetic drugs (metformin, a-glucosidase inhibitors, sulphonylurea, or meglitindes) for more than 2 months at stable half-maximum to maximum allowed doses. **Exclusion criteria:** treated with thiazolidinediones, dipeptidyl peptidase-4 inhibitors, or other interventions that could interfere with glucose metabolism within 3 months of the start of the trial. Patients were excluded if they had contraindications to metformin, substantial medical issues, a history of recurrent hypoglycaemia, or unawareness of hypoglycaemia. Women who were breastfeeding or pregnant were also excluded Pre-randomisation phase: Before randomisation, eligible participants discontinued their pretrial oral antidiabetic drug treatment and underwent a 2-week forced metformin-titration period (dose increased to 2000 mg per day; 1000 mg at breakfast and evening meal), which was followed up by a 1-week metformin maintenance period. Patients were eligible for randomisation if the maximum metformin dose (2000 mg) or maximum-tolerated dose (1500 mg) per day remained unchanged in the maintenance period, and if the median before-breakfast selfmonitored blood glucose value (measured on 3 consecutive days immediately before randomisation) was 7·5 mmol/L or more.
Previous glucose-lowering therapy	**Any participants previously taking glucose-lowering therapy?** all on oral hypoglycaemic drugs and/or insulin **Details of washout period:** eligible participants discontinued their pretrial oral antidiabetic drug treatment and underwent a 2-week forced metformin-titration period
Lifestyle advice	-

Follow-up	**Total follow-up (wks):** 16 **Length of titration period (wks):** 3 **Length of maintenance period (wks):** 16 **Frequency of monitoring appointments:** -
Arms	**(1) Metformin + insulin degludec (3 times weekly)** N: 62 Treatment duration (wks): 16 Washout period (d): 0 Treatment(s): (a) Metformin (Oral) – forced titration Frequency of dosing: twice a day Details of dosing regimen: Before randomisation, eligible participants discontinued their pretrial oral antidiabetic drug treatment and underwent a 2-week forced metformin-titration period (dose increased to 2000 mg per day; 1000 mg at breakfast and evening meal), which was followed up by a 1-week metformin maintenance period. Patients were eligible for randomisation if the maximum metformin dose (2000 mg) or maximum-tolerated dose (1500 mg) per day remained unchanged in the maintenance period, and if the median before-breakfast selfmonitored blood glucose value (measured on 3 consecutive days immediately before randomisation) was 7·5 mmol/L or more. (b) Insulin degludec (Subcutaneous) – flexible-dose (dose-adjusted) Frequency of dosing: three times weekly Details of dosing regimen: insulin degludec was given three times a week (900 nmol/mL formulation, dosed in the evening on Monday, Wednesday, and Friday). For the three doses a week group, the starting dose was double that of the once a day group B dose (ie, 20 U or 180 nmol). On the basis of concentrations of selfmonitored blood glucose before breakfast (lowest value from 3 consecutive days), insulin doses were individually titrated once a week throughout the trial (by clinic or telephone contacts), aiming at a fasting glucose concentration of 4·0–6·0 mmol/L. **(2) Metformin + insulin degludec (once daily group A)** N: 60 Treatment duration (wks): 16 Washout period (d): 0 Treatment(s): (a) Metformin (Oral) – forced titration (b) Insulin degludec (Subcutaneous) – flexible-dose (dose-adjusted) Frequency of dosing: once a day Details of dosing regimen: insulin degludec group A (600 nmol/mL formulation) once a day. The starting dose for all participants who were randomly allocated to once a day treatments was 10 U per injection (60 nmol for insulin degludec group A, 60 nmol for the insulin glargine group, and 90 nmol for insulin degludec group B). On the basis of concentrations of self monitored blood glucose before breakfast (lowest value from 3 consecutive days), insulin doses were individually titrated once a week throughout the trial (by clinic or telephone contacts), aiming at a fasting glucose concentration of 4·0–6·0 mmol/L. **(3) Metformin + insulin degludec (once daily group B)** N: 61 Treatment duration (wks): 16 Washout period (d): 0 Treatment(s): (a) Metformin (Oral) – forced titration (b) Insulin degludec (Subcutaneous) – flexible-dose (dose-adjusted) Frequency of dosing: once a day Details of dosing regimen: insulin degludec group B (900 nmol/mL formulation) once a day. See group A for details of titration **(4) Metformin + insulin glargine (once daily)** N: 62 Treatment duration (wks): 16 Washout period (d): 0 Treatment(s): (a) Metformin (Oral) – forced titration (b) Insulin glargine (Subcutaneous) – flexible-dose (dose-adjusted) Frequency of dosing: once a day Details of dosing regimen: insulin glargine (600 nmol/mL formulation) once a day. See group A for details of titration
Outcomes	**General** All randomly allocated participants were included in the statistical assessment of HbA1C, fasting plasma glucose, bodyweight, and hypoglycaemic episodes, which was done on an intention-to-treat basis. Missing values for HbA1C, fasting plasma glucose, and body weight were imputed with the method of last observation carried forward

4 patients in arm one, 9 patients in arm 2, 9 patients in arm 3 and 6 patients in arm 4 discontinued the study

Outcomes not extracted in this evidence table include postprandial BG levels

Hypoglycaemic events

Major/severe hypoglycaemic event (Hypoglycaemia was classifi ed as severe if assistance from another person was required)

confirmed hypoglycaemia (confi rmed if a plasma glucose measurement of less than 3·1 mmol/L was reported irrespective of symptoms or classification as severe)

Nocturnal (confirmed) (nocturnal if time of onset was between 2300 h and 0559 h (inclusive).)

Baseline characteristics

		Metformin + insulin degludec (3 times weekly)			Metformin + insulin degludec (once daily group A)			Δ	p
		N	k	mean	N	k	mean		
Demographics:									
Age (years)	Continuous	62		54.4 (SD 8.8)	60		55.3 (SD 8.7)		
Sex (n male)	Dichotomous	62	28	(45.2%)	60	33	(55.0%)		
Duration of diabetes (yrs)	Continuous	62		6.6 (SD 5.4)	60		7.3 (SD 5.2)		
Blood glucose:									
HbA1c (%) – 0wk	Continuous	62		8.8 (SD 1.1)	60		8.6 (SD 1.2)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	62		10.7 (SD 3.5)	60		9.9 (SD 3.2)		
Body weight:									
BMI (kg/m2)	Continuous	62		29.7 (SD 5.3)	60		29.5 (SD 5.1)		
Weight (kg) – 0wk	Continuous	62		78.8 (SD 20.8)	60		78.6 (SD 17)		
Waist circumference (cms)	Continuous	62		101.1 (SD 14.8)	60		100.6 (SD 11.3)		
Previous blood glucose lowering drugs:									
Metformin + Sulfonylurea	Dichotomous	62	36	(58.1%)	60	35	(58.3%)		
Insulin:									
Insulin dose per week (U/kg) – 0wk	Continuous	62		1.2 (SD 0.3)	60		0.9 (SD 0.2)		

		Metformin + insulin degludec (3 times weekly)			Metformin + insulin degludec (once daily group B)			Δ	p
		N	k	mean	N	k	mean		
Demographics:									
Age (years)	Continuous	62		54.4 (SD 8.8)	61		53.9 (SD 8.5)		
Sex (n male)	Dichotomous	62	28	(45.2%)	61	39	(63.9%)		
Duration of diabetes (yrs)	Continuous	62		6.6 (SD 5.4)	61		7.2 (SD 4.4)		
Blood glucose:									
HbA1c (%) – 0wk	Continuous	62		8.8 (SD 1.1)	61		8.8 (SD 1.1)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	62		10.7 (SD 3.5)	61		10.6 (SD 3.6)		
Body weight:									
BMI (kg/m2)	Continuous	62		29.7 (SD 5.3)	61		29.5 (SD 4.8)		
Weight (kg) – 0wk	Continuous	62		78.8 (SD 20.8)	61		81.2 (SD 21)		
Waist circumference (cms)	Continuous	62		101.1 (SD 14.8)	61		103.1 (SD 13.3)		
Previous blood glucose lowering drugs:									
Metformin + Sulfonylurea	Dichotomous	62	36	(58.1%)	61	35	(57.4%)		

Insulin: Insulin dose per week (U/kg) – 0wk	Continuous	62		1.2 (SD 0.3)	61		1.4 (SD 0.4)		

		Metformin + insulin degludec (3 times weekly)			Metformin + insulin glargine (once daily)				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	62		54.4 (SD 8.8)	62		53.1 (SD 10.2)		
Sex (n male)	Dichotomous	62	28	(45.2%)	62	37	(59.7%)		
Duration of diabetes (yrs)	Continuous	62		6.6 (SD 5.4)	62		6.7 (SD 5)		
Blood glucose: HbA1c (%) – 0wk	Continuous	62		8.8 (SD 1.1)	62		8.7 (SD 1.1)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	62		10.7 (SD 3.5)	62		9.8 (SD 3.1)		
Body weight: BMI (kg/m2)	Continuous	62		29.7 (SD 5.3)	62		29.4 (SD 5.3)		
Weight (kg) – 0wk	Continuous	62		78.8 (SD 20.8)	62		79.3 (SD 18.6)		
Waist circumference (cms)	Continuous	62		101.1 (SD 14.8)	62		101.3 (SD 13.1)		
Previous blood glucose lowering drugs: Metformin + Sulfonylurea	Dichotomous	62	36	(58.1%)	62	35	(56.5%)		
Insulin: Insulin dose per week (U/kg) – 0wk	Continuous	62		1.2 (SD 0.3)	62		0.9 (SD 0.2)		

		Metformin + insulin degludec (once daily group A)			Metformin + insulin degludec (once daily group B)				
		N	k	mean	N	k	mean	Δ	p
Demographics: Age (years)	Continuous	60		55.3 (SD 8.7)	61		53.9 (SD 8.5)		
Sex (n male)	Dichotomous	60	33	(55.0%)	61	39	(63.9%)		
Duration of diabetes (yrs)	Continuous	60		7.3 (SD 5.2)	61		7.2 (SD 4.4)		
Blood glucose: HbA1c (%) – 0wk	Continuous	60		8.6 (SD 1.2)	61		8.8 (SD 1.1)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	60		9.9 (SD 3.2)	61		10.6 (SD 3.6)		
Body weight: BMI (kg/m2)	Continuous	60		29.5 (SD 5.1)	61		29.5 (SD 4.8)		
Weight (kg) – 0wk	Continuous	60		78.6 (SD 17)	61		81.2 (SD 21)		
Waist circumference (cms)	Continuous	60		100.6 (SD 11.3)	61		103.1 (SD 13.3)		
Previous blood glucose lowering drugs: Metformin + Sulfonylurea	Dichotomous	60	35	(58.3%)	61	35	(57.4%)		
Insulin: Insulin dose per week (U/kg) – 0wk	Continuous	60		0.9 (SD 0.2)	61		1.4 (SD 0.4)		

		Metformin + insulin degludec (once daily group A)			Metformin + insulin glargine (once daily)			Δ	p
		N	k	mean	N	k	mean		
Demographics:									
Age (years)	Continuous	60		55.3 (SD 8.7)	62		53.1 (SD 10.2)		
Sex (n male)	Dichotomous	60	33	(55.0%)	62	37	(59.7%)		
Duration of diabetes (yrs)	Continuous	60		7.3 (SD 5.2)	62		6.7 (SD 5)		
Blood glucose:									
HbA1c (%) – 0wk	Continuous	60		8.6 (SD 1.2)	62		8.7 (SD 1.1)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	60		9.9 (SD 3.2)	62		9.8 (SD 3.1)		
Body weight:									
BMI (kg/m2)	Continuous	60		29.5 (SD 5.1)	62		29.4 (SD 5.3)		
Weight (kg) – 0wk	Continuous	60		78.6 (SD 17)	62		79.3 (SD 18.6)		
Waist circumference (cms)	Continuous	60		100.6 (SD 11.3)	62		101.3 (SD 13.1)		
Previous blood glucose lowering drugs:									
Metformin + Sulfonylurea	Dichotomous	60	35	(58.3%)	62	35	(56.5%)		
Insulin:									
Insulin dose per week (U/kg) – 0wk	Continuous	60		0.9 (SD 0.2)	62		0.9 (SD 0.2)		

		Metformin + insulin degludec (once daily group B)			Metformin + insulin glargine (once daily)			Δ	p
		N	k	mean	N	k	mean		
Demographics:									
Age (years)	Continuous	61		53.9 (SD 8.5)	62		53.1 (SD 10.2)		
Sex (n male)	Dichotomous	61	39	(63.9%)	62	37	(59.7%)		
Duration of diabetes (yrs)	Continuous	61		7.2 (SD 4.4)	62		6.7 (SD 5)		
Blood glucose:									
HbA1c (%) – 0wk	Continuous	61		8.8 (SD 1.1)	62		8.7 (SD 1.1)		
Fasting plasma glucose (mmol/l) – 0wk	Continuous	61		10.6 (SD 3.6)	62		9.8 (SD 3.1)		
Body weight:									
BMI (kg/m2)	Continuous	61		29.5 (SD 4.8)	62		29.4 (SD 5.3)		
Weight (kg) – 0wk	Continuous	61		81.2 (SD 21)	62		79.3 (SD 18.6)		
Waist circumference (cms)	Continuous	61		103.1 (SD 13.3)	62		101.3 (SD 13.1)		
Previous blood glucose lowering drugs:									
Metformin + Sulfonylurea	Dichotomous	61	35	(57.4%)	62	35	(56.5%)		
Insulin:									
Insulin dose per week (U/kg) – 0wk	Continuous	61		1.4 (SD 0.4)	62		0.9 (SD 0.2)		

Results

		Metformin + insulin degludec (3 times weekly)			Metformin + insulin degludec (once daily group A)				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 16wk	Continuous	62		7.3 (SD 1.1)	60		7.4 (SD 1)	MD=0.080 (CI: -0.230, 0.390)	
HbA1c (%) – 16wk	Mean change	62		-1.5 (SD 1.1)	60		-1.3 (SD 1.1)		
Fasting plasma glucose (mmol/l) – 16wk	Mean change	62		-4.2 (SD 3.5)	60		-3.6 (SD 3.3)		
Fasting plasma glucose (mmol/l) – 16wk	Continuous	62		6.5 (SD 2.4)	60		6.3 (SD 2.1)	MD=-0.130 (CI: -1.010, 0.750)	
Body weight: Weight (kg) – 16wk	Mean change	62		0.1 (SD 2.6)	60		0 (SD 1.9)		
Weight (kg) – 16wk	Continuous	62		78.9 (SD 20.9)	60		78.6 (SD 17.1)	MD=-0.050 (CI: -0.860, 0.760)	
Hypoglycaemic events: Major/severe hypoglycaemic event – 16wka	Dichotomous	62	1	(1.6%)	60	0	(0.0%)		NR
Major/severe hypoglycaemic event – 16wk	Count	6720	1		6216	0			
Major/severe hypoglycaemic event – 16wkb	Continuous	62		0.1	60		0		
symptomatic (confirmed) – 16wka	Dichotomous	62	13	(21.0%)	60	3	(5.0%)		NR
symptomatic (confirmed) – 16wkb	Continuous	62		0.7	60		0.2		
symptomatic (confirmed) – 16wk	Count	6720	13		6216	3			
confirmed hypoglycaemia – 16wkb	Continuous	62		2.3	60		0.6		
confirmed hypoglycaemia – 16wka	Dichotomous	62	41	(66.1%)	60	10	(16.7%)	RaR=0.380 (CI: 23.299, 0.006)	
confirmed hypoglycaemia – 16wk	Count	6720	41		6216	10			
Nocturnal (confirmed) – 16wk	Count	6720	4		6216	2			
Nocturnal (confirmed) – 16wkb	Continuous	62		0.2	60		0.1		
Nocturnal (confirmed) – 16wka	Dichotomous	62	4	(6.5%)	60	2	(3.3%)		NR
Dropouts: Total dropouts – 16wk	Dichotomous	62	4	(6.5%)	60	9	(15.0%)		
Dropout due to AEs – 16wk	Dichotomous	62	0	(0.0%)	60	0	(0.0%)		
Insulin: Insulin dose per week (U/kg) – 16wk	Mean change	62		2.2 (SD 1.7)	60		2.2 (SD 1.5)		

Insulin dose per week (U/kg) – 16wk	Continuous	62		3.4 (SD 1.7)	60		3.1 (SD 1.5)		NR

[a] No of episodes
[b] events per patient year of exposure; 95% CI not reported

		Metformin + insulin degludec (3 times weekly)			Metformin + insulin degludec (once daily group B)				
		N	k	mean	N	k	mean	Δ	p
Blood glucose: HbA1c (%) – 16wk	Continuous	62		7.3 (SD 1.1)	61		7.5 (SD 1.1)	MD=0.190 (CI: -0.120, 0.500)	
HbA1c (%) – 16wk	Mean change	62		-1.5 (SD 1.1)	61		-1.3 (SD 1.1)		
Fasting plasma glucose (mmol/l) – 16wk	Mean change	62		-4.2 (SD 3.5)	61		-4.2 (SD 4.3)		
Fasting plasma glucose (mmol/l) – 16wk	Continuous	62		6.5 (SD 2.4)	61		6.4 (SD 3.2)	MD=-0.230 (CI: -1.120, 0.660)	
Body weight: Weight (kg) – 16wk	Mean change	62		0.1 (SD 2.6)	61		0.7 (SD 2.5)		
Weight (kg) – 16wk	Continuous	62		78.9 (SD 20.9)	61		82.2 (SD 21.7)	MD=0.600 (CI: -0.230, 1.430)	
Hypoglycaemic events: Major/severe hypoglycaemic event – 16wk	Count	6720	1		6328	0			
Major/severe hypoglycaemic event – 16wka	Continuous	62		0.1	61		0		
Major/severe hypoglycaemic event – 16wkb	Dichotomous	62	1	(1.6%)	61	0	(0.0%)		NR
symptomatic (confirmed) – 16wkb	Dichotomous	62	13	(21.0%)	61	7	(11.5%)		NR
symptomatic (confirmed) – 16wka	Continuous	62		0.7	61		0.4		
symptomatic (confirmed) – 16wk	Count	6720	13		6328	7			
confirmed hypoglycaemia – 16wkb	Dichotomous	62	41	(66.1%)	61	15	(0.2%)	RaR=0.460 (CI: 20.850, 0.010)	
confirmed hypoglycaemia – 16wka	Continuous	62		2.3	61		0.9		
confirmed hypoglycaemia – 16wkb	Dichotomous	62	41	(66.1%)	6328	15	(0.2%)	RaR=0.460 (CI: 20.850, 0.010)	
confirmed hypoglycaemia – 16wk	Count	6720	41		6328	15			
Nocturnal (confirmed) – 16wk	Count	6720	4		6328	2			
Nocturnal (confirmed) – 16wka	Continuous	62		0.2	61		0.1		
Nocturnal (confirmed) – 16wkb	Dichotomous	62	4	(6.5%)	61	1	(1.6%)		NR

Dropouts: Total dropouts – 16wk	Dichotomous	62	4	(6.5%)	61	9	(14.8%)		
Dropout due to AEs – 16wk	Dichotomous	62	0	(0.0%)	61	1	(1.6%)		
Insulin: Insulin dose per week (U/kg) – 16wk	Mean change	62		2.2 (SD 1.7)	61		3 (SD 2)		
Insulin dose per week (U/kg) – 16wk	Continuous	62		3.4 (SD 1.7)	61		4.5 (SD 1.9)		NR

[a] events per patient year of exposure; 95% CI not reported
[b] No of episodes

		Metformin + insulin degludec (3 times weekly)			Metformin + insulin glargine (once daily)				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Blood glucose: HbA1c (%) – 16wk	Continuous	62		7.3 (SD 1.1)	62		7.2 (SD 0.9)	MD=0.080 (CI: -0.230, 0.390)	
HbA1c (%) – 16wk	Mean change	62		-1.5 (SD 1.1)	62		-1.5 (SD 1.1)		
Fasting plasma glucose (mmol/l) – 16wk	Mean change	62		-4.2 (SD 3.5)	62		-3.4 (SD 2.9)		
Fasting plasma glucose (mmol/l) – 16wk	Continuous	62		6.5 (SD 2.4)	62		6.4 (SD 2.6)	MD=0.040 (CI: -0.840, 0.920)	
Body weight: Weight (kg) – 16wk	Mean change	62		0.1 (SD 2.6)	62		-0.3 (SD 2.4)		
Weight (kg) – 16wk	Continuous	62		78.9 (SD 20.9)	62		79.1 (SD 18.7)	MD=0.410 (CI: -0.410, 1.230)	
Hypoglycaemic events: Major/severe hypoglycaemic event – 16wka	Dichotomous	62	1	(1.6%)	62	0	(0.0%)		NR
Major/severe hypoglycaemic event – 16wk	Count	6720	1		6608	0			
Major/severe hypoglycaemic event – 16wkb	Continuous	62		0.1	62		0		
symptomatic (confirmed) – 16wka	Dichotomous	62	13	(21.0%)	62	12	(19.4%)		NR
symptomatic (confirmed) – 16wkb	Continuous	62		0.7	62		0.7		
symptomatic (confirmed) – 16wk	Count	6720	13		6608	12			
confirmed hypoglycaemia – 16wkb	Continuous	62		2.3	62		1.1		
confirmed hypoglycaemia – 16wka	Dichotomous	62	41	(66.1%)	62	20	(32.3%)	RaR=1.170 (CI: 8.561, 0.160)	
confirmed hypoglycaemia – 16wk	Count	6720	41		6608	20			
Nocturnal (confirmed) – 16wk	Count	6720	4		6608	0			
Nocturnal (confirmed) – 16wkb	Continuous	62		0.2	62		0		
Nocturnal (confirmed) – 16wka	Dichotomous	62	4	(6.5%)	62	0	(0.0%)		NR

Dropouts: Total dropouts – 16wk	Dichotomous	62	4	(6.5%)	62	6	(9.7%)		
Dropout due to AEs – 16wk	Dichotomous	62	0	(0.0%)	62	1	(1.6%)		
Insulin: Insulin dose per week (U/kg) – 16wk	Mean change	62		2.2 (SD 1.7)	62		2.4 (SD 1.6)		
Insulin dose per week (U/kg) – 16wk	Continuous	62		3.4 (SD 1.7)	62		3.3 (SD 1.6)		NR

[a] No of episodes
[b] events per patient year of exposure; 95% CI not reported

		Metformin + insulin degludec (once daily group A)			Metformin + insulin degludec (once daily group B)				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Blood glucose: HbA1c (%) – 16wk	Continuous	60		7.4 (SD 1)	61		7.5 (SD 1.1)	MD=0.110 (CI: -0.210, 0.430)	
HbA1c (%) – 16wk	Mean change	60		-1.3 (SD 1.1)	61		-1.3 (SD 1.1)		
Fasting plasma glucose (mmol/l) – 16wk	Mean change	60		-3.6 (SD 3.3)	61		-4.2 (SD 4.3)		
Fasting plasma glucose (mmol/l) – 16wk	Continuous	60		6.3 (SD 2.1)	61		6.4 (SD 3.2)	MD=-0.110 (CI: -1.010, 0.790)	
Body weight: Weight (kg) – 16wk	Mean change	60		0 (SD 1.9)	61		0.7 (SD 2.5)		
Weight (kg) – 16wk	Continuous	60		78.6 (SD 17.1)	61		82.2 (SD 21.7)	MD=0.640 (CI: -0.200, 1.480)	
Hypoglycaemic events: Major/severe hypoglycaemic event – 16wk	Count	6216	0		6328	0			
Major/severe hypoglycaemic event – 16wka	Continuous	60		0	61		0		
Major/severe hypoglycaemic event – 16wkb	Dichotomous	60	0	(0.0%)	61	0	(0.0%)		NR
symptomatic (confirmed) – 16wkb	Dichotomous	60	3	(5.0%)	61	7	(11.5%)		NR
symptomatic (confirmed) – 16wka	Continuous	60		0.2	61		0.4		
symptomatic (confirmed) – 16wk	Count	6216	3		6328	7			
confirmed hypoglycaemia – 16wkb	Dichotomous	60	10	(16.7%)	61	15	(0.2%)	RaR=1.220 (CI: 6.731, 0.221)	
confirmed hypoglycaemia – 16wka	Continuous	60		0.6	61		0.9		
confirmed hypoglycaemia – 16wkb	Dichotomous	60	10	(16.7%)	6328	15	(0.2%)	RaR=1.220 (CI: 6.731, 0.221)	
confirmed hypoglycaemia – 16wk	Count	6216	10		6328	15			

Nocturnal (confirmed) – 16wk	Count	6216	2		6328	2			
Nocturnal (confirmed) – 16wka	Continuous	60		0.1	61		0.1		
Nocturnal (confirmed) – 16wkb	Dichotomous	60	2	(3.3%)	61	1	(1.6%)		NR
Dropouts:									
Total dropouts – 16wk	Dichotomous	60	9	(15.0%)	61	9	(14.8%)		
Dropout due to AEs – 16wk	Dichotomous	60	0	(0.0%)	61	1	(1.6%)		
Insulin:									
Insulin dose per week (U/kg) – 16wk	Mean change	60		2.2 (SD 1.5)	61		3 (SD 2)		
Insulin dose per week (U/kg) – 16wk	Continuous	60		3.1 (SD 1.5)	61		4.5 (SD 1.9)		NR

[a] events per patient year of exposure; 95% CI not reported
[b] No of episodes

		Metformin + insulin degludec (once daily group A)			Metformin + insulin glargine (once daily)				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Blood glucose:									
HbA1c (%) – 16wk	Continuous	60		7.4 (SD 1)	62		7.2 (SD 0.9)	MD=0.170 (CI: -0.150, 0.490)	
HbA1c (%) – 16wk	Mean change	60		-1.3 (SD 1.1)	62		-1.5 (SD 1.1)		
Fasting plasma glucose (mmol/l) – 16wk	Mean change	60		-3.6 (SD 3.3)	62		-3.4 (SD 2.9)		
Fasting plasma glucose (mmol/l) – 16wk	Continuous	60		6.3 (SD 2.1)	62		6.4 (SD 2.6)	MD=-0.090 (CI: -0.970, 0.790)	
Body weight:									
Weight (kg) – 16wk	Mean change	60		0 (SD 1.9)	62		-0.3 (SD 2.4)		
Weight (kg) – 16wk	Continuous	60		78.6 (SD 17.1)	62		79.1 (SD 18.7)	MD=0.360 (CI: -0.460, 1.180)	
Hypoglycaemic events:									
Major/severe hypoglycaemic event – 16wka	Dichotomous	60	0	(0.0%)	62	0	(0.0%)		NR
Major/severe hypoglycaemic event – 16wk	Count	6216	0		6608	0			
Major/severe hypoglycaemic event – 16wkb	Continuous	60		0	62		0		
symptomatic (confirmed) – 16wka	Dichotomous	60	3	(5.0%)	62	12	(19.4%)		NR
symptomatic (confirmed) – 16wkb	Continuous	60		0.2	62		0.7		
symptomatic (confirmed) – 16wk	Count	6216	3		6608	12			
confirmed hypoglycaemia – 16wkb	Continuous	60		0.6	62		1.1		
confirmed hypoglycaemia – 16wka	Dichotomous	60	10	(16.7%)	62	20	(32.3%)	RaR=0.440 (CI: 18.618, 0.010)	

confirmed hypoglycaemia – 16wk	Count	6216	10		6608	20			
Nocturnal (confirmed) – 16wk	Count	6216	2		6608	0			
Nocturnal (confirmed) – 16wkb	Continuous	60		0.1	62		0		
Nocturnal (confirmed) – 16wka	Dichotomous	60	2	(3.3%)	62	0	(0.0%)		NR
Dropouts:									
Total dropouts – 16wk	Dichotomous	60	9	(15.0%)	62	6	(9.7%)		
Dropout due to AEs – 16wk	Dichotomous	60	0	(0.0%)	62	1	(1.6%)		
Insulin:									
Insulin dose per week (U/kg) – 16wk	Mean change	60		2.2 (SD 1.5)	62		2.4 (SD 1.6)		
Insulin dose per week (U/kg) – 16wk	Continuous	60		3.1 (SD 1.5)	62		3.3 (SD 1.6)		NR

[a] No of episodes
[b] events per patient year of exposure; 95% CI not reported

		Metformin + insulin degludec (once daily group B)			Metformin + insulin glargine (once daily)				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Blood glucose: HbA1c (%) – 16wk	Continuous	61		7.5 (SD 1.1)	62		7.2 (SD 0.9)	MD=0.280 (CI: -0.040, 0.600)	
HbA1c (%) – 16wk	Mean change	61		-1.3 (SD 1.1)	62		-1.5 (SD 1.1)		
Fasting plasma glucose (mmol/l) – 16wk	Mean change	61		-4.2 (SD 4.3)	62		-3.4 (SD 2.9)		
Fasting plasma glucose (mmol/l) – 16wk	Continuous	61		6.4 (SD 3.2)	62		6.4 (SD 2.6)	MD=-0.200 (CI: -1.080, 0.680)	
Body weight: Weight (kg) – 16wk	Mean change	61		0.7 (SD 2.5)	62		-0.3 (SD 2.4)		
Weight (kg) – 16wk	Continuous	61		82.2 (SD 21.7)	62		79.1 (SD 18.7)	MD=1.000 (CI: 0.170, 1.830)	<0.05
Hypoglycaemic events: Major/severe hypoglycaemic event – 16wk	Count	6328	0		6608	0			
Major/severe hypoglycaemic event – 16wka	Continuous	61		0	62		0		
Major/severe hypoglycaemic event – 16wkb	Dichotomous	61	0	(0.0%)	62	0	(0.0%)		NR
symptomatic (confirmed) – 16wkb	Dichotomous	61	7	(11.5%)	62	12	(19.4%)		NR
symptomatic (confirmed) – 16wka	Continuous	61		0.4	62		0.7		
symptomatic (confirmed) – 16wk	Count	6328	7		6608	12			
confirmed hypoglycaemia – 16wkb	Dichotomous	61	15	(0.2%)	62	20	(32.3%)	RaR=0.540 (CI: 15.805, 0.018)	

confirmed hypoglycaemia – 16wka	Continuous	61		0.9	62		1.1		
confirmed hypoglycaemia – 16wkb	Dichotomous	6328	15	(0.2%)	62	20	(32.3%)	RaR=0.540 (CI: 15.805, 0.018)	
confirmed hypoglycaemia – 16wk	Count	6328	15		6608	20			
Nocturnal (confirmed) – 16wk	Count	6328	2		6608	0			
Nocturnal (confirmed) – 16wka	Continuous	61		0.1	62		0		
Nocturnal (confirmed) – 16wkb	Dichotomous	61	1	(1.6%)	62	0	(0.0%)		NR
Dropouts:									
Total dropouts – 16wk	Dichotomous	61	9	(14.8%)	62	6	(9.7%)		
Dropout due to AEs – 16wk	Dichotomous	61	1	(1.6%)	62	1	(1.6%)		
Insulin:									
Insulin dose per week (U/kg) – 16wk	Mean change	61		3 (SD 2)	62		2.4 (SD 1.6)		
Insulin dose per week (U/kg) – 16wk	Continuous	61		4.5 (SD 1.9)	62		3.3 (SD 1.6)		NR

[a] events per patient year of exposure; 95% CI not reported
[b] No of episodes

Treatment differences in HbA1C, fasting plasma glucose, and bodyweight after 16 weeks of treatment were estimated by analysis of variance (ANOVA), which was adjusted by country, sex, age, and HbA1C (and fasting plasma glucose or bodyweight for these estimates) at randomisation and

by oral antidiabetic drug treatment at screening. Estimates of rate ratio of hypoglycaemic episodes during the exposure to trial insulin were made by a

negative binomial regression model, in which the number of episodes per patient-year of exposure (events per patient-year) was adjusted by country, sex, age, and HbA1C at randomisation and by oral antidiabetic drug treatment at screening.16 The proportion of participants having at least one confirmed hypoglycaemic episode was estimated with a logistic-regression model (which was not prespecifi ed in the protocol), expressing the difference between treatments in terms of odds ratios and adjusted for the characteristics as previously mentioned.

E.2 Review question 2: What are the serious adverse effects of long-term use of pharmacological interventions to control blood glucose in people with type 2 diabetes?

RCTs

Gallwitz (2012)

Study characteristics

Country: 16 countries (Bulgaria, Denmark, France, Germany, Hong Kong, Hungary, India, Ireland, Italy, Netherlands, Norway, Poland, South Africa, Sweden, UK, USA)

Funding: Boehringer Ingelheim

Study design: Randomised controlled trial

Number of participants: 1552

Duration of follow up: 2 years

Method of identifying participants: People aged 18 to 90 with type two diabetes, receiving metformin at a stable dose of 1500mg/day or more alone or with one other oral antidiabetic drug , with HbA1c 6.0 to 10 % , and BMI less than 40kg/m2 or less. Patients were excluded for the following reasons: diagnosis of MI, stroke, TIA 6 months before screening, impaired hepatic function at screening, treatment with rosiglitazone, pioglitazone, GLP-1 analogue or agonist, insulin or an antiobesity drug in the 3 months before screening.

Participants receiving metformin monotherapy had a 2 week open label placebo run in period.

Participants receiving metformin plus additional oral antidiabetics entered a 6 week washout period followed by a 2 week open label placebo run in period.

Participants with HbA1c between 6.5 and 10% at the end of the placebo run in were randomly assigned in a double bind fashion to the treatment arms. Patients were randomly assigned by computer generated random sequence via a voice or web response system to linagliptin (5mg) or glimepiride (1 to 4 mg) orally once daily.

Patient characteristics

	Linagliptin n= 766	**Glimepiride n= 775**
Sex	male= 60%	male=61%
Age	mean= 59.8 years	mean= 59.8 years
BMI	mean= 30.2	mean= 30.3
Duration of diabetes	1 year or less= 7% >1 year, less than 5 years= 41% >5 years= 52%	1 year or less= 8% >1 year, less than 5 years= 39% >5 years= 54%
Pharmacological therapy	Mono= 70% Dual= 30%	Mono= 71% Dual= 29%

		Triple= <1%	Triple= <1%
	Duration of use	-	-
	Baseline HBa1c	7.7	7.7
	Fasting blood glucose	-	-
Summary of baseline characteristics	Demographic and clinical characteristics were well balanced between groups. Cardiovascular risk factors were well balanced between groups. Most participants received other treatments in additional to the study drugs e.g. antihypertensive drugs, lipid lowering drugs, aspirin, and the prescription patterns were similar between groups.		
Results	**Outcome**	**RR (95% CI)**	
	All cause mortality (all judged to be unrelated to study drug)	No significant difference between groups (4 in each group)	
	Major cardiovascular events	0.46 (0.23 to 0.91)	
	CV death	*1.00 (0.14 to 7.07)*	
	MI	*0.60 (0.22 to 1.64)*	
	Stroke	*0.27 (0.08 to 0.97)*	
	Admission due to unstable angina	*1.00 (0.20 to 4.93)*	
Authors conclusions	Linagliptin was associated with fewer major cardiovascular events than glimepiride.		
Quality			

Holman (1999) – UKPDS

Study characteristics	**Country**: UK **Funding**: Bayer UK is thanked for their support **Study design**: RCT **Number of participants**: subgroup of 1946 patients enrolled in the UKPDS **Duration of follow up**: 3 years **Method of identifying participants**: Patients attending UKPDS clinics between May and September 1994 who agreed to take part in this study investigating the addition of Acarbose to the UKPDS randomised therapy. Patients were seen in UKPDS clinics at four monthly intervals. Randomisation was performed centrally, and the study was conducted in a double blind fashion. Patients were randomised to acarbose or placebo. Patients took 50mg for the first week, 100mg for the 2nd week and 150 mg thereafter (if tolerated and in the

absence of side effects). At 4 months, patients were asked to increase their dose in a similar fashion until they reached 300mg per day.

Patient characteristics

	Acarbose n= 973	**Placebo n=973**
Sex	-	-
Age	60	60
BMI		
Duration of diabetes	7.9 years	8.0 years
Pharmacological therapy	Diet alone = 14% Sulfonylurea alone= 26% Metformin alone= 6% Insulin alone= 20% Sulfonylurea + metformin= 16% Sulfonylurea + insulin= 4% Multiple insulin= 14%	
Duration of use	-	-
Baseline HBa1c	8.7	8.7
Fasting blood glucose	7.9	8.0

Summary of baseline characteristics

Data not reported. Nod discussed by authors in text. Groups appear equally matched

Results

	Relative Risk (95% confidence interval
	Acarbose in comparison to placebo
Any diabetes related end point	1.00 (0.81 to 1.23)

Authors conclusions

No significant differences were seen in frequency of major clinical events.

Quality	

UKPDS (1998)

Study characteristics	**Study design**: Randomised controlled trial **Country**: UK **Funding**: UK Medical Research Council, British Diabetic Association, UK Department of Health, US National Eye Institute, US National Institute of Diabetes Digestive and Kidney Disease, British Heart Foundation, Wellcome Trust, Charles Wolfson Charitable Trust, Cloth Workers Foundation, Health Promotion Research Trust, Alan and Babette Sainsbury Trust, Oxford University Medical Research Fund Committee, Novo-Nordisk, Bayer, Bristol-Myers Squibb, Hoechst, Lilly, Lipha, Farmitalia Carlo Erba. Boehringer Mannheim, Becton Dickinson, Owen Mumford, Securicor, Kodak, Cortecs Diagnostics, Galxo Wellcome, Smith Kline Beecham, Pfizer, Zeneca, Pharmacia and Upjohn, Roche **Number of participants**: 4209 **Duration of follow up**: 10 years **Method of identifying participants**: Between 1977 and 1991 general practitioners in the catchment area of the 23 participating hospitals were asked to refer all patients with newly diagnosed diabetes aged 25 to 65 years. Patients generally attended a study clinic within 2 weeks of referral. Patients with FPG greater than 6mmol/L on two mornings 1 to 3 weeks apart were eligible for the study. Exclusion criteria were: ketonuria >3mmol/L, serum creatinine greater than 175 umol/L, MI in previous year, current angina or heart failure, more than one vascular event, retinopathy requiring laser treatment, malignant hypertension, uncorrected endocrine disorder, occupation that precluded insulin (HGV driver), severe concurrent illness that would limit life or require systemic treatment, inadequate understanding, unwillingness to participate in study. Patients had a 3 month dietary run in where they attended monthly clinics and were seen by a physician and dietician. After the run in period, mean FPG was calculated from measurements on 3 days over 2 weeks. Patients were included if their mean FPG was between 6 and 15 mmol/L. Patients were stratified according to their weight and were randomly allocated to conventional therapy (diet) or intensive therapy (sulphonylurea or insulin). Overweight patients also had the possibility of receiving metformin. Of the overweight participants, 342 received metformin. Randomisation was achieved by centrally produced computer generated therapy allocations in sealed opaque envelopes that were opened in sequence. The trial was open once patients were randomised. The Hypertension in Diabetes Study, and the Acarbose study (Holman 1999) took a samples from this population
Patient characteristics	

	All centres **(Any intensive vs conventional)** **n=3867**	**15 centres** **(comparing chlorpropamide, glibenclamide, insulin vs conventional)** **n= 3041**	**All centres** **(comparing all intensive vs conventional +/- metformin in obese patients)** **n= 1704**

Sex	Male=61%	Male=62%	Male= 46%
Age	53.3	54	53
BMI	27.5	27.2	31.4
Duration of diabetes	newly diagnosed	newly diagnosed	newly diagnosed
Pharmacological therapy	Conventional= 1138 Intensive= 2729	Conventional= 896 Insulin= 911 Chlorpromide= 619 Glibenclamide= 615	Conventional= 411 Metformin= 342 Insulin= 409 Chlorpromide= 265 Glibenclamide= 277
Duration of use	-	-	
Baseline HBa1c	7.08	6.2	
Fasting blood glucose	8.0	8.0	

Summary of baseline characteristics

No tests for differences between groups are reported. Not described by authors in the text.

Results

All patients with newly diagnosed type two diabetes were randomised to conventional therapy (diet, n= 1138) or intensive treatment (chlorpropamide or glibenclamide n=1573, insulin n=1157, or metformin for overweight patients only n=342)

	Relative risk (95% CI) All patients (overweight and not overweight)			
Outcome	**Any intensive vs conventional**	**Chlorpropamide vs conventional**	**Glibenclamide vs conventional**	**Insulin vs conventional**
Any diabetes related end point	**0.88 (0.79 to 0.99)**	0.93 (0.79 to 1.99)	**0.82 (0.69 to 0.97)**	0.87 (0.75 to 1.01)
Diabetes related deaths	0.90 (0.73 to 1.11)	0.92 (0.68 to 1.23)	0.92 (0.69 to 1.24)	0.90 (0.69 to 1.18)
All cause mortality	0.94 (0.80 to 1.10)	1.02 (0.82 to 1.27)	0.91 (0.73 to 1.15)	0.93 (0.76 to 1.14)
Any MI	0.84 (0.71 to 1.00)	0.87 (0.68 to 1.12)	0.78 (0.60 to 1.01)	0.87 (0.70 to 1.09)
Fatal MI	0.94 (0.68 to 1.30)	0.99 (0.64 to 1.56)	0.82 (0.51 to 1.33)	0.95 (0.63 to 1.43)
Non Fatal MI	0.79 (0.58 to 1.09)	0.87(0.56 to 1.36)	0.74 (0.46 to 1.19)	0.81 (0.54 to 1.22)

Any Stroke	1.11 (0.81 to 1.51)	1.01 (0.65 to 1.58)	1.38 (0.92 to 2.08)	0.86 (0.57 to 1.13)
Fatal stroke	1.17 (0.54 to 2.54)	1.06 (0.34 to 3.30)	1.90 (0.71 to 5.09)	1.13 (0.41 to 3.12)
Non fatal stroke	1.07 (0.68 to 1.69)	0.99 (0.52 to 1.91)	1.30 (0.71 to 2.38)	0.76 (0.41 to 1.43)
Amputation or death from PVD	0.65 (0.36 to 1.18)	0.47 (0.17 to 1.28)	0.48 (0.17 to 1.31)	1.08 (0.54 to 2.17)
Microvascular	**0.75 (0.60 to 0.93)**	0.86 (0.63 to 1.17)	**0.66 (0.47 to 0.93)**	**0.70 (0.52 to 0.93)**
Sudden death	0.54 (0.24 to 1.21)	0.57 (0.16 to 1.97)	0.67 (0.21 to 2.16)	0.58 (0.19 to 1.70)
Heart failure	0.91 (0.54 to 1.52)	0.92 (0.44 to 1.93)	1.20 (0.61 to 2.39)	0.78 (0.39 to 1.55)
Angina	1.02 (0.71 to 1.46)	1.46 (0.91 to 2.36)	0.84 (0.48 to 1.47)	1.20 (0.76 to 1.89)
Diabetes end point= sudden death, death from hyper- or hypo- glycaemia, MI, angina, heart failure, stroke, renal failure, amputation of at least 1 digit, vitreous haemorrhage, retinal photocoagulation, blindness in one eye, cataract extraction				

Patients randomised to sulfonylurea (overweight and non-overweight who were treated with maximum doses of sulfonylurea and had FPG of 6.1 to 15 mmol/l without signs of hyperglycaemia were randomised to early addition of metformin (n=269)or continued sulfonylurea (n=268)

	Relative risk (95% CI) **All patients (overweight and not overweight) who were originally randomised to sulfonylurea**
Outcome	**Sulfonylurea alone vs sulfonylurea plus metformin**
Any diabetes related end point	RR=1.04 (0.77 to 1.42)
Diabetes related death	RR=1.96 (1.02 to 3.75)
All cause mortality	RR=1.60 (1.02 to 2.52)
MI	RR=1.09 (0.67 to 1.78)
Stroke	RR=1.21 (0.58 to 2.55)
Peripheral vascular disease	RR=2.12 (0.19 to 23.3)
Microvascular disease	RR=0.84 (0.43 to 1.66)
Diabetes end point= sudden death, death from hyper- or hypo- glycaemia, MI, angina, heart failure, stroke, renal failure, amputation of at least 1 digit, vitreous haemorrhage, retinal photogoagulation, blindness in one eye, cataract extraction **Diabetes related death**= death from MI, stroke, PVD, renal disease, hyper- or hypo- glycaemia	

Subgroup analysis of overweight patients who were randomised to conventional treatment (n=411), metformin (n=342), sulfonylurea (n=542; 265 chlorpropamide, 277 glibencalmide) or insulin (n=409)

	Relative Risk (95% CI) Overweight only	
Outcome	**metformin vs conventional**	**Any intensive vs conventional**
Any diabetes related end point	0.68 (0.53 to 0.87)	0.93 (0.77 to 1.12)
Diabetes related deaths	0.58 (0.37 to 0.91)	0.80 (0.58 to 1.11)
All cause mortality	0.64 (0.45 to 0.91)	0.92 (0.71 to 1.18)
Any MI	0.61 (0.41 to 0.89)	0.79 (0.60 to 1.05)
Any Stroke	0.59 (0.29 to 1.18)	1.14 (0.70 to 1.84)
PVD	0.74 (0.26 to 2.09)	0.56 (0.24 to 1.33)
Microvascular	0.71 (0.43 to 1.19)	0.84 (0.57 to 1.24)
Diabetes end point= sudden death, death from hyper- or hypo- glycaemia, MI, angina, heart failure, stroke, renal failure, amputation of at least 1 digit, vitreous haemorrhage, retinal photogoagulation, blindness in one eye, cataract extraction **Diabetes related death**= death from MI, stroke, PVD, renal disease, hyper- or hypo- glycaemia		

Authors conclusions

OVERALL: Intensive blood glucose control in T2D by either sulphonylureas or insulin substantially decreases the risk of microvascular complications, but not macrovascular disease. None of the individual drugs had an adverse effect on cardiovascular outcomes.

OVERWEIGHT PATIENTS ONLY: Intensive glucose control with metformin appears to decrease the risk of diabetes related end points in overweight diabetic patients.

Quality

COHORT

DIGAMI/ Aas (2009)

Study characteristics

Country: Unclear- possibly Norway, Sweden & Demark

Funding: Research grants from the Norwegian Foundation for Health and Rehabilitation and The Norwegian Diabetes Association, The Swedish Heart-Lung foundation, AFA insurance, The King Gustav V and Queen Victoria foundation, the Swedish Medical Research council, The Swedish Diabetes Association. Unconditional grants from Aventis Sweden and Novo Nordisk Denmark

Study design: Prospective cohort of a subgroup of randomised controlled trial participants.

Number of participants: 865

Duration of follow up: up to 3 years

Method of identifying participants: Participants had been recruited into the DIGAMI 2 randomised controlled trial, which randomised patients with T2D and suspected MI to insulin regimens (24h insulin glucose infusion followed by a multidose regimen of subcutaneous insulin aiming for strict glycaemic control, or 24 hour glucose infusion followed by conventional management) or local conventional management strategies (authors do not describe what this could entail).

For the purpose of this subgroup analysis, the patients were regrouped according to the glucose lowering treatment they actually received during the first year of follow up. Patients who died, withdrew, changed glucose lowering treatment, or who lacked detailed treatment information were excluded from this subgroup analysis. The primary objective was to investigate whether insulin induced weight gain was accompanied by an increase in non fatal reinfarction, stroke, and/or increased CV mortality.

Patient characteristics

	No OHA/insulin during 1st year of follow up	**OHA during 1st year of follow up**	**Insulin during 1st year of follow up**	**Continued insulin during 1st year of follow up**
Sex	male= 74%	male= 71%	male= 69%	male= 68%
Age	67.4	66.4	65	67
BMI	-	-	-	-
Duration of diabetes	1.1	5.8	6.2	13.3
Pharmacological therapy	n=99	n=250	n=245	n=271
Duration of use	-	-	-	-
Baseline HBa1c	7.0	7.2	7.3	7.4
Fasting blood glucose	-	-	-	-

Summary of baseline characteristics

Patients without pharmacological therapy had shorter duration of diabetes, lower blood glucose and a lower BMI than patients in the other groups.

Patients who previously were treated with insulin and continued with insulin had longer duration of diabetes and higher CVD score, used lipid lowering drugs more frequently, and had lower levels of cholesterol. There was also a higher percentage of patients using CV drugs than in the other groups.

Results

Outcome	**Comparator**	**Hazard ratio and 95% confidence interval**
CV death	Patients who continued insulin compared to all other groups	HR= 2.38, CI= 1.34 to 4.22
Reinfarction	New users of insulin compared to all other groups	HR= 2.49, CI= 1.23 to 5.03

Authors conclusions	Initiation of insulin treatment after MI was associated with a significant increase in weight and incidence of reinfarction. The increased weight did not explain the increased rate of reinfarction.
Quality	

Bruno (1999 & 2003)

Study characteristics	**Country**: Italy **Funding**: This work was partially supported by AIRC (Associazione Italiana per la Ricera sul Cancro) and MURST (Ministero della Universita e della Ricerca Scientifica e Technologica Italy. **Study design**: prospective cohort **Number of participants**: 1967 **Duration of follow up**: 7 years **Method of identifying participants**: Patients were identified in 1988 in a prevalence survey of diabetic patients drawn from diabetic clinics, GPs, hospital discharges, prescriptions, sale records of agent strips and syringes. Diagnosis of diabetes was verified with the collaboration of general practitioners using criteria defined by the National Diabetes Data Group. Patients were visited during their periodic appointments either at the diabetes clinic or at the GP office. In 1995 a mortality follow up study was conducted. Mortality information was obtained from the demographical files of towns of patients residence or death
Patient characteristics	

	Baseline characteristics
Sex	-
Age	Males= mean 64 (SD 10.6) Females= mean 68.4 (SD 10.7)
BMI	-
Duration of diabetes	Mean=8.5 (SD= 7) years
Pharmacological therapy	Diet= 10.3% Oral drugs alone= 76.2% Insulin alone= 10.0% Oral + insulin= 3.5%
Duration of use	-
Baseline HBa1c	-
Fasting blood glucose	8.5 (2.6 mmol/l

Summary of baseline characteristics

There were no differences between the sexes for mortality rates, but higher mortality was associated with increasing age. There were more deaths from ischaemic and cerebrovascular diseases but no increase in mortality from either malignant neoplasms or other causes of death.

Results

7 year outcomes	Adjusted Relative Risk and 95% confidence intervals			
	Diet	**Sulphonylureas**	**Sulphonylureas + biguanides**	**Insulin**
Any cause mortality	Ref	1.14 (0.82 to 1.58)	1.13 (0.79 to 1.62)	1.71 (1.18 to 2.48)
Cardiovascular mortality	Ref	1.02 (0.64 to 1.63)	1.04 (0.62 to 1.75)	1.35 (0.79 to 2.32)
Ischaemic heart mortality	Ref	1.63 (0.64 to 1.14)	2.49 (0.96 to 6.50)	2.95 (1.07 to 8.10)
Cerebrovascular mortality	Ref	1.09 (0.52 to 2.32)	0.91 (0.39 to 2.12)	1.00 (0.41 to 2.45)
Relative risk of all cause mortality were estimated by means of multivariate poisson regression. Sex, 5 year age group, calendar period (10 years groups), duration of diabetes (10 year groups), and referring physician, antidiabetic treatment, hypertension, fasting plasma glucose (tertiles), BMI, and smoking status were included in the model.				

10 year outcomes	Adjusted relative risk and 95% confidence intervals		
	Diet	Oral drugs	Insulin
Chronic renal failure	Ref	1.40 (0.55 to 3.59)	2.26 (0.82 to 6.19
Cox multiple regression analysis was performed, and adjusted for age, sex and attained time of follow up			

Authors conclusions

Antidiabetic treatment was an important predictor of ischaemic heart disease with and almost 3 times higher risk of death in people treated with insulin, and 2.5 times higher in people treated with a combination of oral hypoglycaemic drugs. No effect of antidiabetic treatment on cerebrovascular disease was found.

Diabetic medication was not a significant predictor of end stage renal disease.

Quality

Fisman (2001)

Study characteristics

Country: Israel
Funding: Not stated
Study design: Prospective cohort
Number of participants: 2275
Duration of follow up: Mean= 7.7 years (range= 6.2 to 9 years)
Method of identifying participants: The initial population comprised 12402 patients screened for participation but not included in another trial (Bezafibrate infarction prevention study). This cohort included 2275 diabetics and 9047 non diabetics which acted as a reference group.

Patient characteristics

	Diet	Glyburide	Metformin	Combined
Sex	Male= 76%	Male= 76%	Male= 66%	Male=66%
Age	Mean= 60.3	Mean= 59.8	Mean= 59.5	Mean= 60.7
BMI	Mean= 27	Mean= 27	Mean= 29	Mean= 27
Duration of diabetes	-	-	-	-
Pharmacological therapy	n=990	n=953	n=79	n=253
Duration of use	-	-	-	-
Baseline HBa1c	-	-	-	-
Fasting blood glucose	-	-	-	-

Summary of baseline characteristics

No significant differences between the groups were found, except for weight (higher in metformin group) BMI (higher in metformin group), gender (majority were men), glucose (higher in combined group), triglycerides (higher in combined group).

Results

Outcome	HR (95% CI)	Adjustment
All cause mortality (Combined compared to diet)	1.53 (1.20 to 1.96)	age, gender, glucose, total cholesterol, triglycerides, previous MI, functional class, hypertension, peripheral vascular disease, previous cerebrovascular accident, angina, smoking BMI, beta blockers, antiplatelet drugs
All cause mortality (Glyburide compared to diet)	1.21 (1.02 to 1.44)	Adjusted for significant variables only (gender, weight, BMI, glucose, triglycerides)
All cause mortality (Metformin compared to diet)	1.19 (0.76 to 1.84)	

	All cause mortality (Combined compared to diet)	1.53 (1.20 to 1.95)	
Authors conclusions	Monotherapy with either glyburide or metformin in diabetic patients with CAD yielded a similar outcome and was associated with a modest increase in mortality. Time related mortality was markedly increased when a combined glyburide/metformin treatment was used.		
Quality			

Henricsson (1997)

Study characteristics	**Country**: Sweden **Funding**: Supported by the Gorthon, Zoega and Segerfalk Foundations, Helsingborg, Foreningen Synskadades Vanner I Kristiansands Ian, HSF, Jarnhardts Foundation, Research funds at Malmo University Hospital and Kronprinsessan Margaretas Arbetsnamnd for Synskadade. **Study design**: Prospective cohort **Number of participants**: 1378 **Duration of follow up**: 3.1 years **Method of identifying participants**: Cohort of patients identified from a retinopathy screening programme which is offered to all diabetic patients aged 30 and older. Examination is performed at diagnosis of diabetes and every 2 years thereafter. (70% of the known diabetic population are estimated to participate in the screening programme. Patients who were aged 40+ at diagnosis of diabetes, who participated in screening and who were examined between 1990 and 1995 were included. 2414 patient met this criteria, but only 1036 patients were examined only once and were excluded from the study, leaving 1378 for inclusion.

Patient characteristics

	Oral treatment or diet alone	**Changed to insulin during treatment**	**Insulin**
Sex	Male= 513 Female= 356	Male= 99 Female= 75	Male= 168 Female= 166
Age (at diagnosis)	Mean= 56.9 (SD= 8.8)	Mean= 54.6 (SD=7.6)	Mean= 52.3 (SD= 9.2)
BMI	-	-	-
Duration of diabetes	Mean= 5.3 (SD= 5.2)	Mean= 8.6 (SD= 6.3)	Mean= 11.5 (SD= 7.7)
Pharmacological therapy	N=871	N=174	N=333
Duration of use	-	-	-
Baseline HBa1c	-	-	-
Fasting blood glucose	-	-	-

Summary of baseline characteristics	Insulin treated patients had more advanced retinopathy, macular oedema and macular treatment at baseline that the other groups
Results	Cox multivariate analysis was adjusted for differences in age, sex, and duration of diabetes. Insulin treatment per se was not an independent risk factor for retinopathy progression Relative risk of retinopathy progression to 3 or more levels was RR= 0.98 (0.98 to 1.19) for insulin in comparison to non-insulin users.
Authors conclusions	Change of treatment form oral drugs to insulin was associated with a 100% increased risk of retinopathy progression and a 3 fold increased risk of blindness/visual impairment.
Quality	

	RR (95% CI)	**Adjustments**
Risk of progression of retinopathy 3 or more levels in those who changed from orals to insulin compared to those who remained on orals	RR= 2.0 (1.7 to 2.3)	adjusted for age, sex and duration of diabetes
Risk of progression of retinopathy 3 or more levels in those who changed from orals to insulin compared to those who remained on orals	RR=1.6 (1.3 to 1.9)	adjusted for age, sex and duration of diabetes , HbA1c during study
Risk of progression of retinopathy 3 or more levels in patients on insulin with HbA1c above the median compared to patients on insulin with HbA1c below the median	RR=1.5 (1.1 to 2.1)	adjusted for age, sex, duration of diabetes
Risk of progression of retinopathy 3 or more levels in patients with any retinopathy at baseline compared to those with no retinopathy at baseline	RR=1.6 (1.1 to 2.0)	adjusted for age, sex, duration of diabetes
Risk of blindness and visual impairment due to retinopathy in those who changed from orals to insulin	RR=2.7 (1.8 to 4.0)	unclear if adjusted or not

ZODIAC/Landman (2010)

Study characteristics

Country: The Netherlands
Funding: not stated
Study design: Prospective cohort
Number of participants: 1353
Duration of follow up: 10 years
Method of identifying participants: Part of the ZODIAC study which involved hospital based diabetes specialist nurses assisting GPs in their care of type 2 diabetic patients. Patients with very short life expectancy or insufficient cognitive abilities were excluded. Baseline data were collected in 1998 and 1999. Laboratory and physical assessment data were collected annually. In 2009 life status and cause of death were retrieved from records maintained by hospitals and general practitioners.

Patient characteristics

	Baseline characteristics
Sex	Female= 57.6%
Age	Mean= 67.8
BMI	28.9
Duration of diabetes	Mean= 6.0 years
Pharmacological therapy	insulin= 16.5% Sulfonylurea= 55% Diet only= 13%
Duration of use	-
Baseline HBa1c	7.5
Fasting blood glucose	-

Summary of baseline characteristics

No significant difference sin baseline characteristics except for BMI, HbA1c and eGFR – all were significantly higher among metformin users than non metformin users). Sulfonylurea and insulin use were significantly lower in metformin users than non metformin users.

Results

Outcome	**HR (95%CI)**	**Adjustments**
Cancer mortality (metformin compared to no metformin)	0.43 (0.23 to 0.80)	Adjusted by model 1 (all 13 variables measured at baseline- age, sex, diabetes duration, smoking, BMI, systolic blood pressure, HbA1c, eGFR, cholesterol to HDL ratio, Albumin to creatinine ration, macrovascular complications, insulin use, sulfonylurea use, diet only))
Cancer mortality (metformin compared to no metformin)	0.46 (0.26 to 0.83)	Adjusted by model 2 (Factors directly related to cancer mortality- age, sex, BMI, insulin use, sulfonylurea use)
Cancer mortality	0.69 (0.36 to 1.34)	presume unadjusted but this is not clear in the paper

	(sulfonylurea- unclear what this was compared to)		
	Cancer mortality (insulin – unclear what this was compared to)	0.70 (0.36 to 1.34)	presume unadjusted but this is not clear in the paper
	Total mortality (metformin compared to no metformin)	0.94 (0.73 to 1.22)	adjusted for all covariates
	Cardiovascular mortality (metformin compared to no metformin)	2.27 (1.36 to 3.78)	adjusted for all covariates
	All other causes of death (metformin compared to no metformin)	0.97 (0.72 to 1.30)	adjusted for all covariates
	The HR for metformin as a continuous variable for cancer mortality was 0.58 (0.36 to 0.93). The hazard for cancer mortality decreased by 42% for every 1g increase in metformin		
Authors conclusions	Patients with type two diabetes are at increased risk for cancer mortality. The use of metformin was associated with a lower cancer mortality than the non use of metformin, suggesting a protective effect of metformin on cancer.		
Quality			

E.3 Review question 3: What are the optimal target values for HbA1c, fasting blood glucose and post prandial blood glucose in people with type 2 diabetes?

Evidence Table 1: (Zoungas et al ADVANCE, 2012, Diabetologia)

<table>
<tr><td>Bibliographic reference (Ref ID)</td><td>Zoungas et al 2012 – Association of HbA_{1c} levels with vascular complications and death in patients with type 2 diabetes: evidence of glycaemic thresholds</td></tr>
<tr><td>Study type & aim</td><td>This post hoc analysis aimed to quantify macrovascular, microvascular and mortality risks associated with HbA_{1c} level in a contemporary cohort with established T2D</td></tr>
<tr><td>Number and Characteristics of patients</td><td>Total number of patients:
11,140 participants randomised; 5571 to intensive glucose control; 5569 to standard glucose control
11,086 included in the observational analysis after the exclusion of 54 participants where HbA_{1c} at baseline were not available</td></tr>
<tr><td>Monitoring information and definitions</td><td>Glycaemic exposure: glycaemic levels were assessed as the mean HbA_{1c} of measurements taken at baseline, 6mths and every 12mths for each individual.</td></tr>
<tr><td>Intervention</td><td></td></tr>
<tr><td>Comparator</td><td></td></tr>
<tr><td>Length of follow up</td><td>ADVANCE study, average duration of treatment and follow-up; 4.5yrs</td></tr>
<tr><td>Outcomes measures and effect sizes</td><td>The average HbA_{1c} was the mean as obtained by weighting each measurement for the individual by the time intervals between measurements during follow-up and prior to the first event.
Mean age: 66±6 years
Baseline:
Mean HbA1c at baseline was 7.5% (SD 1.6%)

Risks of major vascular outcomes and mortality:
The mean HbA_{1c} of participants was 7.1% (SD 1.1%), range 4.6% to 14.8%

Unadjusted and adjusted hazard ratio (95%CI) of adverse outcomes associated with per 1% higher mean HbA_{1c} above and below specified knots</td></tr>
</table>

		Overall				Intensive glucose control	Standard glucose control	
		Unadjusted	P value	Adjusted*	P value	Adjusted*	Adjusted*	P value

Bibliographic reference (Ref ID)	**Zoungas et al 2012 – Association of HbA_{1c} levels with vascular complications and death in patients with type 2 diabetes: evidence of glycaemic thresholds**

Endpoints	HbA_{1c} knots#							(intensive vs standard)
Macrovascular events#	Below 7.0	1.07 (0.92, 1.26)	0.4117	1.02 (0.86, 1.21)	0.8310	1.13 (0.89, 1.43)	0.82 (0.65, 1.04)	0.7362
	Above 7.0	1.43 (1.35, 1.51)	<0.0001	1.38 (1.30, 1.47)	<0.0001	1.58 (1.43, 1.75)	1.31 (1.21, 1.42)	0.0974
Microvascular events#	Below 6.5	1.06 (0.79, 1.42)	0.7012	1.02 (0.76, 1.39)	0.8744	1.06 (0.69, 1.63)	0.82 (0.54, 1.25)	0.9016
	Above 6.5	1.58 (1.51, 1.65)	<0.0001	1.40 (1.33, 1.47)	<0.0001	1.72 (1.59, 1.87)	1.26 (1.18, 1.35)	<0.0001
All-cause death#	Below 7.0	1.04 (0.88, 1.23)	0.6246	1.01 (0.85, 1.21)	0.9158	1.12 (0.87, 1.44)	0.81 (0.64, 1.04)	0.9008
	Above 7.0	1.42 (1.34, 1.51)	<0.0001	1.38 (1.29, 1.48)	<0.0001	1.67 (1.50, 1.86)	1.29 (1.18, 1.41)	0.0080

*adjusted for age, sex, randomised BP, glucose treatment (not in treatment subgroup analysis), mean OACR, mean eGFR, mean SBP, mean triacylglycerol, mean LDL-C, mean HDL-C, mean BMI, and the additional baseline covariates of currently treated hypertension, history of macrovascular disease, history of microvascular disease, smoking, drinking, ECG abnormality, duration of diabetes

(# using estimates and bootstraps for the quadratic nadirs the authors concluded that the threshold was in 6.5% and 7.0% for macrovascular events and death, and 6.0% to 6.5% for microvascular events. The most appropriate risk thresholds for HbA1c were 7.0% and 6.5%)

Funding	
Authors' conclusion	In those with type 2 diabetes, HbA_{1c} levels were associated with lower risks of macrovascular events and death down to a threshold of 7.0% and microvascular events down to a threshold of 6.5%. There was no evidence of lower risks below these levels but neither was there clear evidence of harm
Comments	

Evidence Table 2: (Adler et al 1999, American Heart Journal)

Bibliographic reference (Ref ID)	**Adler et al 1999 – Hyperglycaemia and hyperinsulinemia at diagnosis of diabetes and their association with subsequent cardiovascular disease in the United Kingdom Prospective Diabetes Study (UKPDS 47)**
Study type & aim	To address the association between relative hyperglycaemia and hyperinsuminaemia, at diagnosis of type 2 diabetes, as they relate to subsequent ischaemic heart disease and stroke
Number and Characteristics of patients	**Total number of patients:** UKPDS 5102 patients (25-65yrs, newly diagnosed T2D) Current analysis 5,063 white, south Asian and Afro-Caribbean participants
Monitoring information and definitions	Measurements taken at diagnosis and after 3-4mths of diet therapy Associations between HbA1c and fasting plasma glucose at diagnosis and after run-in period Multivariate model of HbA1c after dietary run-in
Intervention	
Comparator	
Length of follow up	Median follow-up 10.0 to 10.3yrs
Outcomes measures and effect sizes	**Outcomes:** During follow-up 694/5063 (14%) had fatal/non-fatal MI, 315/5063 (6%) developed angina, 254/5063 (5%) had fatal/non-fatal stroke

Fasting plasma glucose	**Fatal/non-fatal MI (HR 95% CI)**	**Newly diagnosed angina (HR 95% CI)**	**Fatal/non-fatal stroke (HR 95% CI)**
At diagnosis mmol/L	**N=694 (5045 in analysis)**	**N=315 (5036 in analysis)**	**N=253 (5040 in analysis)**
≤9.7	1.0	1.0	1.0
>9.7 to ≤13.4	1.1 (0.9, 1.4)	1.3 (1.0, 1.7)	1.3 (0.9, 1.7)
>13.4	1.3 (1.1, 1.6)	1.2 (0.9, 1.5)	1.3 (1.0, 1.8)
After dietary run-in	**N=694 (5059 in analysis)**	**N=315 (5050 in analysis)**	**N=254 (5054 in analysis)**

Bibliographic reference (Ref ID)	Adler et al 1999 – Hyperglycaemia and hyperinsulinemia at diagnosis of diabetes and their association with subsequent cardiovascular disease in the United Kingdom Prospective Diabetes Study (UKPDS 47)

≤7.2	1.0	1.0	1.0
>7.2 to ≤9.8	1.2 (1.0, 1.4)	1.1 (0.8, 1.5)	1.1 (0.8, 1.5)
>9.8	1.5 (1.2, 1.8)	1.3 (1.0, 1.7)	1.4 (1.0, 1.9)

HbA1c	**Fatal/non-fatal MI (HR 95% CI)**	**Newly diagnosed angina (HR 95% CI)**	**Fatal/non-fatal stroke (HR 95% CI)**
At diagnosis	**N=611 (4582 in analysis)**	**N=288 (4574 in analysis)**	**N=211 (4578 in analysis)**
≤8.0	1.0	1.0	1.0
>8.0 to ≤10.2	1.2 (1.0, 1.5)	1.4 (1.1, 1.9)	1.1 (0.8, 1.6)
>10.2	1.4 (1.1, 1.7)	1.2 (0.8, 1.6)	1.0 (0.7, 1.4)
After dietary run-in	**N=569 (4315 in analysis)**	**N=278 (4307 in analysis)**	**N=207 (4103 in analysis)**
≤6.3	1.0	1.0	1.0
>6.3 to ≤7.6	1.2 (1.0, 1.5)	1.5 (1.1, 2.0)	1.1 (0.8, 1.5)
>7.6	1.5 (1.2, 1.9)	1.7 (1.3, 2.3)	1.1 (0.8, 1.6)

Multivariate analysis (controlled for age at diagnosis, sex, ethnicity, smoking at diagnosis, fitness, social class, total cholesterol, triglyceride, HDL cholesterol, BMI, DBP, history of MI)

HbA1c	**Fatal/non-fatal MI (HR 95% CI)**	**Newly diagnosed angina (HR 95% CI)**	**Fatal/non-fatal stroke (HR 95% CI)**
After dietary run-in	**N=492 (3845 in analysis)**	**N=251 (3836 in analysis)**	**N=170 (3670 in analysis)**
≤6.3	1.0	1.0	1.0
>6.3 to ≤7.6	1.2 (0.9, 1.5)	1.5 (1.1, 2.0)	1.2 (0.8, 1.7)
>7.6	1.5 (1.2, 1.8)	1.6 (1.1, 2.1)	1.1 (0.7, 1.6)

Bibliographic reference (Ref ID)	Adler et al 1999 – Hyperglycaemia and hyperinsulinemia at diagnosis of diabetes and their association with subsequent cardiovascular disease in the United Kingdom Prospective Diabetes Study (UKPDS 47)
Funding	
Authors' conclusion	Hyperglycaemia at diagnosis and after dietary run-in period was associated with an increased risk of ischaemic heart disease, no effect with stroke was observed
Comments	Multivariate models developed for both end points (hyperinsulinemia data not included in this evidence table)

Evidence Table 3: (Adler et al 2002, Diabetes Care)

Bibliographic reference (Ref ID)	Adler et al 2002 – UKPDS 59: Hyperglycaemia and other potentially modifiable risk factors for peripheral vascular disease in Type 2 Diabetes
Study type & aim	Using UKPDS data to identify risk factors measured shortly after diagnosis of T2D for the development of PVD at 6yrs after diabetes UK
Number and Characteristics of patients	**Total number of patients:** 4,987/5,063 white, south Asian and Afro-Caribbean participants had data for PVD measurement at diagnosis 3,834 who did not have PVD re-examined at 6yrs (those not followed were older (52.6 vs 51.9yrs), higher SBP (138vs 2134mmHg), white (86 vs 81%), more likely to smoke (35 vs 30%)) 2,398/3,834 had data on all of the risk factors for the model (did not differ on age, sex, ethnicity compared to those where complete data were not available)
Monitoring information and definitions	**PVD:** Diagnostic criteria; any two of – ankle-arm index <0.8, absence of both dorsal pedis and posterior tibial pulses in at least one leg, intermittent claudication Incident PVD defined as PVD at 6yrs in those without PVD at diagnosis Potential risk factors chosen from risk factors for PVD in the general population (included age, sex, ethnic group, HbA1c, fasting plasma insulin, height, BMI, SBP, DBP)
Intervention	
Comparator	
Length of follow up	Assessed at diagnosis and every 3yrs up to 18yrs after diagnosis of diabetes Mean follow-up 8.9yrs
Outcomes measures and	At diagnosis 58/4,987, 1.2%, (95%CI 0.9, 1.5) had PVD, at 18yrs this was 12.5% (95%CI 3.8, 21.2)

Bibliographic reference (Ref ID)	Adler et al 2002 – UKPDS 59: Hyperglycaemia and other potentially modifiable risk factors for peripheral vascular disease in Type 2 Diabetes
effect sizes	**Characteristics measured at baseline in those with/without PVD at 6yrs after diagnosis, univariate associations between potential risk factors and incident PVD:**

Potential risk factor	PVD at 6yrs but not at diagnosis (SD)		P value
	Yes	No	
	61	2,337	
Age (yrs)	57.6	60.0	<0.001
Sex (%, male/female)	57	60	0.67
Race (% white/south Asian/Afro-Caribbean)	84/11/5	82/11/7	0.79, 0.48
Height (cm)	166.6 (9)	167.8 (10)	0.35
BMI	26.7 (4.2)	27.6 (5.06)	0.17
SBP	145 (22)	134 (19)	<0.001
DBP	83 (10)	82 (10)	0.39
HbA1c (%)	7.9 (1.8)	7.2 (1.8)	<0.001
Fasting plasma insulin (mU/L)	13.0 (7.0-23.6)	11.9 (6.7-21.2)	0.22
Total cholesterol (mmol/L)	5.5 (1.0)	5.3 (1.1)	0.12
LDL cholesterol (mmol/L)	3.7 (1.0)	3.5 (1.1)	0.013
HDL cholesterol (mmol/L)	1.0 (0.2)	1.1 (0.2)	0.011
Triglyceride (mmol/L)	1.7 (1.0-2.8)	1.5 (0.9-2.5)	0.057
Haemoglobin	14.9 (1.4)	15.0 (1.4)	0.58
White blood cell count (1000cells/mm^3)	7.2 (1.8)	6.9 (1.9)	0.24
ESR (upper quartile)	40%	25%	0.008
Albuminuria	16.2%	6.6%	0.003
Biothesiometer reading (volts)	15.7 (9.4-26.3)	12.2 (7.4-20.2)	<0.001
Retinopathy	49%	35%	0.021
Former cardiovascular disease	13%	4%	<0.001
Erectile dysfunction	9%	6%	0.57
Alcohol	72%	76%	0.49
Aspirin use (current)	18%	19%	0.83
Exercise (% sedentary/moderate/active/fit)	28/33/36/3	21/34/41/4	0.58

<table>
<tr><td>Bibliographic reference (Ref ID)</td><td>Adler et al 2002 – UKPDS 59: Hyperglycaemia and other potentially modifiable risk factors for peripheral vascular disease in Type 2 Diabetes</td></tr>
<tr><td></td><td>
<table>
<tr><td>Smoking (% current/former/never)</td><td>53/26/21</td><td>29/36/35</td><td><0.001</td></tr>
</table>

Factors entered into SBP, HbA1c, retinopathy, history of cardiovascular disease, smoking, increased total and LDL cholesterol, triglyceride, albuminuria, vibration perception threshold, ESR, decreased HDL)

Outcomes of the multivariate model of incident PVD at 6yrs, based on 61 (of 2,398) participants:
<table>
<tr><th></th><th>Comparison</th><th>Odds ratio</th><th>95%CI</th></tr>
<tr><td>Age</td><td>Each year older at diagnosis of diabetes</td><td>1.10</td><td>1.05, 1.15</td></tr>
<tr><td>HbA1c</td><td>Each 1% increase</td><td>1.28</td><td>1.12, 1.46</td></tr>
<tr><td>SBP</td><td>Each 10mmHg increase</td><td>1.25</td><td>1.10, 1.43</td></tr>
<tr><td>HDL</td><td>Each 0.1mmol/L decrease</td><td>1.22</td><td>1.07, 1.39</td></tr>
<tr><td>Former smoking</td><td>Never smoked</td><td>0.80</td><td>0.37, 1.72</td></tr>
<tr><td>Current smoking</td><td>Never smoked</td><td>2.90</td><td>1.46, 5.73</td></tr>
<tr><td>Cardiovascular disease</td><td>None</td><td>3.00</td><td>1.30, 6.70</td></tr>
<tr><td>Retinopathy</td><td>Presence of retinopathy</td><td>1.64</td><td>0.97, 2.78</td></tr>
<tr><td>Peripheral sensory neuropathy</td><td>Doubling of voltage threshold</td><td>1.31</td><td>0.89, 1.93</td></tr>
</table>
Increased age, increased HbA1c, increased SBP, lower HDL cholesterol, previous cardiovascular disease and smoking were independent risk factors for PVD at 6yrs
</td></tr>
<tr><td>Funding</td><td>Grant from the Wellcome Trust</td></tr>
<tr><td>Authors' conclusion</td><td>Hyperglycaemia (as well as smoking dyslipidaemia and BP) are potentially modifiable risk factors for the development of PVD</td></tr>
<tr><td>Comments</td><td>Logistic regression used to evaluate the association between potential risk factors and PVD and for interactions with HbA1c</td></tr>
</table>

Evidence Table 4: (Drechsler et al 2009, Circulation)

Bibliographic reference (Ref ID)	**Drechsler et al 2009 – Glycaemic control and cardiovascular events in diabetic hemodialysis patients**
Study type & aim	To investigate the association of HbA1c with the risk of sudden cardiac death, MI, stroke, combined cardiovascular events (CVE),

<table>
<tr><td>Bibliographic reference (Ref ID)</td><td>Drechsler et al 2009 – Glycaemic control and cardiovascular events in diabetic hemodialysis patients</td></tr>
<tr><td></td><td>death resulting from heart failure, all-cause mortality

(4D study – prospective RCT, double-blind placebo trial)
Germany</td></tr>
<tr><td>Number and Characteristics of patients</td><td>Total number of patients:
1255 patients with T2D on maintenance haemodialysis; data from the German Diabetes Dialysis Study (4D study)

Included:
18 to 80yrs, haemodialysis for <2yrs , recruited between March 1998-October 2002
Mean age 65.7yrs (SD 8.3yrs), 54% male
Mean baseline HbA1c 6.7% (SD 1.3%), no significant difference between atorvastatin and placebo groups</td></tr>
<tr><td>Monitoring information and definitions</td><td>Primary end point:
Composite (CVE) of death resulting from cardiac causes, fatal or non-fatal stroke, non-fatal MI, whichever occurred first (composite of combined cardiovascular events; CVE)
For the analysis in this paper, sudden cardiac death, MI (fatal and non-fatal), stroke (fatal and non-fatal), CVE, death from congestive heart failure, all-cause mortality were all chosen to be separate outcome measures and were based on the primary judgement of the end point committee during the 4D study</td></tr>
<tr><td>Intervention</td><td>Atorvastatin 20mg (n=619)</td></tr>
<tr><td>Comparator</td><td>Placebo (n=636)</td></tr>
<tr><td>Length of follow up</td><td>Median 4yr follow-up</td></tr>
<tr><td>Outcomes measures and effect sizes</td><td>Study population divided by HbA1c at baseline; normal (≤6%), elevated (>6% to ≤8%), high (>8%)

During follow-up 469 reached the primary end point of CVE, 617 died (160 sudden cardiac death), 41 died of CHF, 200 had an MI (fatal or non-fatal), 103 had a stroke (fatal or non-fatal)

Baseline HbA1c, risk of sudden death:
Absolute rates of sudden cardiac death; HbA1c ≤6%, 3.0/100 person-years; HbA1c 6 to 8%, 5.0/100 person-years; HbA1c >8%, 6.3/100 person-years
<table>
<tr><td rowspan="2">Model</td><td colspan="5">HbA1c</td></tr>
<tr><td>≤6% (n=404)</td><td>>6% to ≤8% (n=664)</td><td>P value</td><td>>8% (n=187)</td><td>P value</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference (Ref ID)	Drechsler et al 2009 – Glycaemic control and cardiovascular events in diabetic hemodialysis patients

	HR	HR (95% CI)		HR (95% CI)	
Crude	1	1.69 (1.14, 2.49)	0.008	2.14 (1.33, 3.44)	0.002
Adjusted*	1	1.82 (1.20, 2.77)	0.005	2.25 (1.32, 3.81)	0.003
Adjusted plus CAD and CHF	1	1.85 (1.22, 2.81)	0.004	2.26 (1.33, 3.85)	0.003

HbA1c as a continuous variable:

Absolute rates of sudden death, MI, stroke, primary end point, all-cause mortality, HF death and mortality except for sudden death (95% CI per unit increase in HbA1c):

	Sudden death	MI (fatal/non-fatal)	Stroke (fatal/non-fatal)	Primary end point	All-cause mortality	Heart failure death	Mortality except for sudden death
Events	160	200	103	469	617	41	457
Time, person-yrs	3555	3368	3465	3287	3555	3555	3555
Incidence rate/100 person-yrs	4.5	5.9	3.0	14.3	17.4	1.2	12.9
HbA1c crude HR (95%CI)	1.18 (1.05, 1.32)	0.98 (0.87, 1.09)	1.13 (0.98, 1.31)	1.08 (1.01, 1.16)	1.08 (1.02, 1.15)	1.14 (0.91, 1.43)	1.05 (0.98, 1.13)
HbA1c adjusted* HR (95%CI)	1.21 (1.06, 1.38)	0.94 (0.83, 1.07)	1.11 (0.93, 1.32)	1.09 (1.01, 1.18)	1.09 (1.02, 1.17)	1.30 (1.00, 1.68)	1.04 (0.96, 1.13)

When investigated as a continuous variable the HR to sudden cardiac death increased by 18% per unit (1% increase in HbA1c) (Additional analysis using HbA1c quartiles (≤5.8%, >5.8 to ≤6.6%, >6.6 to ≤7.4%, >7.4%) showed similar results)

Baseline HbA1c and risk of MI, stroke, primary end point, death resulting from heart failure:

Model and HbA1c	Sudden death		MI (fatal and non-fatal)		Stroke (fatal and non-fatal)		Primary end point	
	HR (95%CI)	P value	HR (95%CI)	P value	HR (95%CI)	P value	HR (95%CI)	P value
Crude								
≤6	1		1		1		1	
>6 to ≤8	1.69	0.008	1.04	0.814	1.58	0.058	1.29	0.019

Bibliographic reference (Ref ID)	Drechsler et al 2009 – Glycaemic control and cardiovascular events in diabetic hemodialysis patients

	(1.14, 2.49)		(0.77, 1.41)		(0.98, 2.54)		(1.04, 1.59)	
>8	2.14 (1.33, 3.44)	0.002	0.80 (0.50, 1.28)	0.358	1.74 (0.96, 3.18)	0.070	1.32 (0.99, 1.75)	0.056
Adjusted								
≤6	1		1		1		1	
>6 to ≤8	1.85 (1.22, 2.81)	0.004	0.94 (0.68, 1.30)	0.707	1.56 (0.93, 2.62)	0.093	1.31 (1.05, 1.65)	0.018
>8	2.26 (1.33, 3.85)	0.003	0.77 (0.47, 1.26)	0.299	1.67 (0.84, 3.30)	0.142	1.37 (1.00, 1.87)	0.050

Model and HbA1c	All-cause mortality		Heart failure death		Mortality except for sudden death	
	HR 95%CI)	P value	HR (95%CI)	P value	HR (95%CI)	P value
Crude						
≤6	1		1		1	
>6 to ≤8	1.29 (1.07, 1.55)	0.006	1.34 (0.65, 2.75)	0.427	1.19 (0.97, 1.47)	0.098
>8	1.31 (1.02, 1.68)	0.033	1.44 (0.56, 3.71)	0.452	1.10 (0.82, 1.47)	0.543
Adjusted						
≤6	1		1		1	
>6 to ≤8	1.34 (1.10, 1.63)	0.004	1.53 (0.70, 3.33)	0.288	1.19 (0.96, 1.50)	0.117
>8	1.34 (1.02, 1.76)	0.039	2.12 (0.75, 5.98)	0.155	1.10 (0.80, 1.52)	0.546

The primary end point showed an adjusted higher 37% risk than ≤6%, this was explained mainly by the impact of HbA1c on sudden cardiac death as no association was found for CVE except sudden death

Funding	Research Fellowship from the European Renal Association – European Dialysis and Transplant Association and the Deutsche

Bibliographic reference (Ref ID)	Drechsler et al 2009 – Glycaemic control and cardiovascular events in diabetic hemodialysis patients
	Forschungsgeneinschaft
Authors' conclusion	Poor glycaemic control was strongly associated with sudden cardiac death in those with T2D having haemodialysis, which accounted for increased cardiovascular events and mortality. MI was not affected. Whether interventions achieving tight glycaemic control decrease sudden death requires further evaluation
Comments	Absolute (incidence) rates calculated as the number of events occurring per 100 person-years of follow-up *Cox regression analysis adjusted for the confounders; age, sex, atorvastatin, SBP, duration of T2D, time of dialysis, smoking status, BMI, LDL cholesterol, triglycerides, albumin, haemoglobin, calcium, phosphate, C-reactive protein) To test robustness of results divided into quartiles of HbA1c at baseline and repeated analysis on the effect of glycaemic control. All analyses repeated in the placebo group only to eliminate any potential influence of atorvastatin

Evidence Table 5: (Eeg-Olofsson et al 2010, Journal of Internal Medicine)

Bibliographic reference (Ref ID)	Eeg-Olofsson et al 2010 – New aspects of HbA1c as a risk factor for cardiovascular diseases in type 2 diabetes: an observational study from the Swedish National Diabetes Register (NDR)
Study type & aim	To determine the association between glycaemic control and CHD, stroke, CVD, and total mortality in patients with T2D treated in everyday clinical practice (using data from the Swedish National Diabetes Register) Cohort study Sweden
Number and Characteristics of patients	**Total number of patients:** 18,334 patients with T2D **Included:** Reporting to the NDR is not mandatory, but all hospital diabetes outpatient clinics and primary healthcare are encouraged to do so Age 30-79yrs, 18% had a history of CVD Baseline HbA1c 5.0 to 10.9% Divided into two subgroups; - according to median diabetes duration (≤7yrs, n=10,016; >7yrs, n=8,318) - history of CVD (history, n=3276; no history, n=15,058) - those with HbA1c between 6.0 to 8.9%, n=14,211 (6.0 to 6.9%, n=4841; 7.0 to 7.9%, n=5660; 8.0 to 8.9%, n=3710) - those treated with OHAs or insulin at baseline, n=14,509 (OHAs alone, n=6687; insulin alone or in combination with OHAs, n=7822)

Bibliographic reference (Ref ID)	**Eeg-Olofsson et al 2010 – New aspects of HbA1c as a risk factor for cardiovascular diseases in type 2 diabetes: an observational study from the Swedish National Diabetes Register (NDR)**

Baseline characteristics by HbA1c group:

	All patients in the study	Baseline HabA1c 6.0-6.9%	Baseline HabA1c 7.0-7.9%	Baseline HabA1c 8.0-8.9%	P value
Numbers	18,334	4841	5660	3710	
HbA1c baseline, %	7.6 (1.2)	6.5 (0.3)	7.5 (0.3)	8.5 (0.3)	<0.001
Age, yrs	64 (10)	64 (10)	64 (10)	63 (9)	<0.01
Duration, yrs	8 (7)	6 (7)	9 (7)	10 (7)	<0.001
BMI	28.8 (5)	28.6 (5)	28.7 (5)	29.0 (5)	<0.001
SBP	148 (19)	148 (19)	148 (19)	148 (19)	NS
Male	56.7	58.8	56.7	56.0	<0.05
Smokers	14.2	13.4	13.8	14.7	NS
Antihypertensives	53.8	53.8	54.2	53.9	NS
Lipid-lowering drugs	15.6	14.8	16.5	16.8	<0.05
Albuminuria	23.2	19.7	23.4	26.6	<0.001
History of CVD - CHD - Stroke	 13.6 5.9				
History of CHF	6.4	5.5	6.3	7.2	<0.01
Diet alone	20.9	35.9	13.7	7.6	<0.001
OHA alone	36.5	37.9	43.3	34.5	<0.001
OHA and insulin	12.9	6.2	13.0	19.2	<0.001
Insulin alone	29.7	20.0	30.0	38.8	<0.001

Monitoring information and definitions	Patients followed from baseline until a cardiovascular event, death or 31st December 2003 **End points:** Fatal or non-fatal CHD, fatal or non-fatal stroke, fatal or non-fatal CVD, total mortality
Intervention	

Bibliographic reference (Ref ID)	**Eeg-Olofsson et al 2010 – New aspects of HbA1c as a risk factor for cardiovascular diseases in type 2 diabetes: an observational study from the Swedish National Diabetes Register (NDR)**
Comparator	
Length of follow up	Data reported based on annual clinical visits Followed from 1997/1998 until 2003
Outcomes measures and effect sizes	Baseline; longer mean diabetes duration and higher frequency of albuminuria with increasing HbA1c; those treated with insulin higher mean HbA1c, longer disease duration, higher frequency of albuminuria, history of CVD and CHF compared with those taking OHAs **Events, HbA1c in all patients:** HR (95%CI) per 1% unit increase in baseline HbA1c and updated mean HbA1c Event rates and hazard ratios were adjusted for sex, age, diabetes duration, BMI, smoking status, SBP, antihypertensive or lipid lowering drug treatment, albuminuria >20µgmin^{-1} and hypoglycaemic treatment 6-yr mean rates (%) of outcomes:

Outcome	Groups	No. of events	Event rate Mean (SD)	Baseline HbA1c HR (95%CI)	P value	Mean HbA1c HR (95%CI)	P value
Fatal/non-fatal CHD	All patients	2623	16.6 (10.1)	1.11 (1.07, 1.15)	<0.001	1.13 (1.09, 1.17)	<0.001
	Duration ≤7yrs	1111	12.9 (8.2)	1.09 (1.03, 1.15)	0.003	1.09 (1.03, 1.15)	0.005
	Duration >7yrs	1512	21.3 (10.4)	1.11 (1.06, 1.16)	<0.001	1.15 (1.10, 1.21)	<0.001
	Previous CHD	854	30.1 (10.0)	1.08 (1.02, 1.15)	0.01	1.10 (1.03, 1.17)	0.005
	No previous CHD	1769	13.8 (8.5)	1.12 (1.07, 1.16)	<0.001	1.15 (1.10, 1.20)	<0.001
Fatal/non-fatal stroke	All patients	1574	10.4 (7.1)	1.08 (1.03, 1.13)	0.002	1.09 (1.04, 1.14)	<0.001
	Duration ≤7yrs	657	8.1 (6.3)	1.06 (0.98, 1.14)	0.1	1.05 (0.97, 1.13)	0.2
	Duration >7yrs	917	13.1 (10.1)	1.07 (1.01, 1.14)	0.03	1.10 (1.03, 1.17)	0.003
	Previous CHD	519	19.6 (8.4)	1.11 (1.03, 1.20)	0.01	1.13 (1.04, 1.23)	0.004
	No previous CHD	1055	8.4 (6.0)	1.06 (1.00, 1.12)	0.04	1.07 (1.01, 1.13)	0.03
Fatal/non-fatal CVD	All patients	3823	23.9 (13.8)	1.10 (1.07, 1.13)	<0.001	1.11 (1.08, 1.15)	<0.001
	Duration ≤7yrs	1625	18.9 (11.9)	1.08 (1.03, 1.13)	0.001	1.07 (1.02, 1.12)	0.009
	Duration >7yrs	2198	30.0 (13.7)	1.10 (1.06, 1.14)	<0.001	1.13 (1.09, 1.18)	<0.001
	Previous CHD	1235	42.3 (13.1)	1.10 (1.05, 1.16)	<0.001	1.11 (1.05, 1.17)	<0.001

Bibliographic reference (Ref ID)	Eeg-Olofsson et al 2010 – New aspects of HbA1c as a risk factor for cardiovascular diseases in type 2 diabetes: an observational study from the Swedish National Diabetes Register (NDR)

	No previous CHD	2588	19.8 (11.9)	1.09 (1.06, 1.13)	<0.001	1.11 (1.07, 1.16)	<0.001
Fatal CVD	All patients	1456	9.4 (9.2)	1.10 (1.05, 1.16)	<0.001	1.12 (1.07, 1.18)	<0.001
	Duration ≤7yrs	529	6.1 (6.8)	1.14 (1.05, 1.24)	0.001	1.12 (1.03, 1.22)	0.008
	Duration >7yrs	927	13.4 (10.7)	1.07 (1.01, 1.14)	0.02	1.11 (1.05, 1.19)	<0.001
	Previous CHD	656	23.6 (13.6)	1.09 (1.01, 1.17)	0.02	1.13 (1.05, 1.21)	0.002
	No previous CHD	800	6.3 (6.6)	1.11 (1.04, 1.19)	0.001	1.11 (1.04, 1.19)	0.002
Total mortality	All patients	1902	12.1 (11.8)	1.09 (1.05, 1.14)	<0.001	1.10 (1.05, 1.15)	<0.001
	Duration ≤7yrs	715	8.3 (9.0)	1.13 (1.05, 1.21)	<0.001	1.08 (1.00, 1.16)	0.04
	Duration >7yrs	1187	16.7 (12.4)	1.07 (1.01, 1.13)	0.01	1.11 (1.05, 1.17)	<0.001
	Previous CHD	787	27.7 (15.7)	1.08 (1.01, 1.15)	0.02	1.11 (1.03, 1.18)	0.004
	No previous CHD	1115	8.7 (9.2)	1.10 (1.04, 1.16)	<0.001	1.09 (1.03, 1.16)	0.003

Baseline HbA1c;
Divided into subgroups; 6.0 to 6.9%, 7.0 to 7.9%, 8.0 to 8.9%

6-yr rates of CHD, CVD and total mortality in three patient subgroups of baseline HbA1c, with HR for these outcomes

Outcome	HbA1c interval (mean)	Patients/No. of events	Kaplan-Meier 6-yr rate (%)#	Cox model Mean (SD)	Ratio	Cox regression HR (95%CI)	P value
Fatal/non-fatal CHD	6.0-6.9% (6.5)	4841/559	13.6	13.9 (9.2)	1.0	1.0	
	7.0-7.9% (7.5)	5660/845	17.0	17.3 (11.1)*	1.24	1.25 (1.11, 1.39)	<0.001
	8.0-8.9% (8.5)	3710/625	19.7	19.9 (13.2)*	1.43	1.36 (1.20, 1.55)	<0.001
Fatal/non-fatal CVD	6.0-6.9% (6.5)	4841/856	20.5	20.9 (12.7)	1.0	1.0	
	7.0-7.9% (7.5)	5660/1226	24.4	24.6 (14.3)*	1.18	1.18 (1.08, 1.29)	<0.001
	8.0-8.9% (8.5)	3710/894	27.7	27.8 (16.4)*	1.33	1.31 (1.18, 1.45)	<0.001
Fatal CVD	6.0-6.9% (6.5)	4841/323	7.6	7.8 (9.2)	1.0	1.0	
	7.0-7.9% (7.5)	5660/444	8.9	9.1 (10.6)*	1.17	1.11 (0.96, 1.29)	NS
	8.0-8.9% (8.5)	3710/344	11.2	11.2 (13.3)*	1.44	1.27 (1.07, 1.50)	0.005
Total mortality	6.0-6.9% (6.5)	4841/436	10.2	10.3 (11.4)	1.0	1.0	

Bibliographic reference (Ref ID)	Eeg-Olofsson et al 2010 – New aspects of HbA1c as a risk factor for cardiovascular diseases in type 2 diabetes: an observational study from the Swedish National Diabetes Register (NDR)

	7.0-7.9% (7.5)	5660/583	11.7	11.7 (12.7)*	1.14	1.08 (0.95, 1.23)	NS
	8.0-8.9% (8.5)	3710/439	14.3	14.2 (15.6)*	1.38	1.19 (1.03, 1.38)	0.02

#6-yr failure rates at survival analysis estimated in each group of different HbA1c

*significance levels for difference between two mean rates, after logarithmic transformation of the rates, with the group of HbA1c 6-6.9% as reference

Funding	The Swedish Association of Local Authorities funds the NDR
Authors' conclusion	This study showed progressively increasing risks of CHD, CVD, and total mortality with higher HbA1c, and no risk increase at low HbA1c levels even with longer duration of diabetes, previous CVD or treatment with insulin or OHAs. Those achieving HbA1c <7% showed benefits of risk reduction
Comments	Cox regression analyses were used to estimate adjusted HR, 95% CI, for the outcomes CHD, stroke, CVD, total mortality per 1% unit increase in baseline HbA1c or updated mean HbA1c with adjustments for covariates The updated mean HbA1c treated as a time-dependent variable to evaluate glycaemic exposure during follow-up, allowing the use of a recent value of updated mean HbA1c at each specific time point in the modelling process

Evidence Table 6: (Landman et al 2010, British Journal of General Practice)

Bibliographic reference (Ref ID)	Landman et al 2010 – The relationship between glycaemic control and mortality in patients with type 2 diabetes in general practice (ZODIAC-11)
Study type & aim	To investigate the relationship between the glycaemic control (indicated by HbA1c) and mortality in patients with T2D Cohort The Netherlands
Number and Characteristics of patients	**Total number of patients:** 1145 with T2D **Included:** Patients with T2D in 32 primary care practices in the Zwolle Outpatient Diabetes project Integrating Available Care (ZODIAC) – GPs were assisted in their care of those with T2D by hospital-based nurses specialising in diabetes, patients consult these nurses annually **Excluded:** Those being treated by specialists in internal medicine Those considered to have short life expectancy or insufficient cognitive abilities

Bibliographic reference (Ref ID)	Landman et al 2010 – The relationship between glycaemic control and mortality in patients with type 2 diabetes in general practice (ZODIAC-11)

Those with insufficient baseline data

Baseline characteristics: (means ±SD)

	Total (n=1145)	Deceased patients (n=335)	Patients that survived (n=810)
Age	68.7 (±11.5)	76.5 (±8.7)	65.5 (±11.0)*
Female, %	54.3	58.8	57.5
Duration of diabetes, yrs	7.7 (±7.5)	9.2 (±8.5)	7.1 (±7.0)*
Smoking - Never - Former - Current	 50.4 30.6 18.1	 51.9 31.6 14.9	 49.8 30.1 19.4
BMI	28.9 (±4.8)	28.3 (±5.0)	29.2 (±4.7)#
SBP	155.1 (±25)	154.0 (±27)	154.3 (±24)
HbA1c	7.5 (±1.3)	7.6 (±1.3)	7.5 (±1.2)˜
Creatinine clearance, ml/min	63.2 (±20.0)	51.5 (±16.7)	68.1 (±19.2)*
Total cholesterol/HDL ration	5.3 (±1.60)	5.2 (±1.7)	5.2 (±1.5)
LDL cholesterol, mmol/L	3.4 (±1.0)	3.3 (±1.0)	3.4 (±1.0)
Statin use, %	11.2	10.2	12.1
Insulin use, %	15.4	21.2	12.3*
Microalbuminuria, %	41.8	55.3	36.6*
Macroalbuminuria, %	5.5	7.9	4.5˜
Macrovascular complications, %	61.4	77.9	54.5*

*p<0.001, #p<0.01, ˜p<0.05

335 (31%) died during median follow-up of 5.8yrs, of the 315 known causes of death, n=161 (51%) were due to cardiovascular disease, n=70 (21%) malignancies, n=34 (10%) respiratory disease

Monitoring information and definitions	Enrolled in the Zwolle Outpatient Diabetes project Integrating Available Care (ZODIAC) in 1998, survival status recorded in September 2004. Data collected annually

<table>
<tr><th>Bibliographic reference (Ref ID)</th><th>Landman et al 2010 – The relationship between glycaemic control and mortality in patients with type 2 diabetes in general practice (ZODIAC-11)</th></tr>
<tr><td></td><td>As part of ZODIAC patients in 32 primary care practices consulted diabetes specialist nurses annually</td></tr>
<tr><td>Intervention</td><td></td></tr>
<tr><td>Comparator</td><td></td></tr>
<tr><td>Length of follow up</td><td>Data reported based on annual clinical visits
Followed from 1997/1998 until 2003</td></tr>
<tr><td>Outcomes measures and effect sizes</td><td>(Included in the models as possible cofounders; age, sex, smoking, duration of diabetes, creatinine, BMI, SBP, total/HDL cholesterol ratio, macrovascular complications, use of statins, insulin use and albuminuria)

Outcomes:
Standardised mortality ratio (95%CI) for total mortality 1.86 (1.66, 2.06); for cardiovascular mortality 2.21 (1.42, 3.42)
All-cause mortality, mean HbA1c (continuous, per 1% reduction), HR 1.21 (95%CI, 1.07, 1.36)

Categorical HbA1c: (6.5-7% used as a reference)
<table>
<tr><th>HbA1c</th><th>HR (95%CI), all-cause mortality</th><th>HR (95%CI), cardiovascular mortality</th></tr>
<tr><td><6.5% (n=228)</td><td>1.11 (0.71, 1.74)</td><td>0.94 (0.47, 1.91)</td></tr>
<tr><td>6.5-7% (n=245)</td><td>1</td><td>1</td></tr>
<tr><td>7-8% (n=318)</td><td>1.40 (0.99, 1.97)</td><td>1.40 (0.84, 2.31)</td></tr>
<tr><td>8-9% (n=208)</td><td>1.43 (0.97, 2.10)</td><td>1.71 (0.99, 2.96)</td></tr>
<tr><td>≥9% (n=144)</td><td>2.26 (1.39, 3.67)</td><td>3.13 (1.62, 6.05)</td></tr>
</table></td></tr>
<tr><td>Funding</td><td>Not reported</td></tr>
<tr><td>Authors' conclusion</td><td>HbA1c level was associated with mortality and this effect seems largely attributable to those with really poor glycaemic control. The absence of differences in mortality in the groups with lower HbA1c supports the position that there is no basis for continually deceasing target HbA1c</td></tr>
<tr><td>Comments</td><td>Updated mean of annually measured HbA1c calculated for each individual from baseline to the end of follow-up (in accordance with the technique used in UKPDS 35)

Cox proportional hazard model was used to assess the association between updated mean HbA1c levels and mortality (all-cause and cardiovascular)</td></tr>
</table>

Evidence Table 7: (Molyneaux et al 1998, Diabetes Research and Clinical Practice)

Bibliographic reference (Ref ID)	Molyneaux et al 1998, Better glycaemic control and risk reduction of diabetic complications in type 2 diabetes: comparison with DCCT
Study type & aim	To evaluate of improvements in glycaemic control in T2D will result in risk reduction in diabetic complications (comparison with T1D study) Cohort Australia
Number and Characteristics of patients	**Total number of patients:** 963 NIDDM patients attending the complications assessment service with no initial retinopathy (subgroup of 399 with normal urine albumin concentration) **Included:** NIDDM patients attending the complications assessment service on >1 occasion (patients referred by primary care physicians for assessment of diabetic complications) No retinopathy at initial visit Baseline characteristics; - Median age 57.5yrs (IQ range 50.0-64.6) - Median duration of diabetes 3.8yrs (IQ range 0.8-8.8) - 27% on diet, 63% oral agent, 10% insulin treatment - Median HbA1c 7.8% (IQ 6.7-9.5)
Monitoring information and definitions	Retinopathy was defined as the development of any diabetic retinopathy on fundal examination (conducted by one physician and verified against an ophthalmologist, agreement was measured and considered excellent) Subgroup analysed for development of microalbuminuria (defined as urinary albumin concentration >30mg/L) Relationship with glucose exposure over time and new retinopathy or microalbuminuria was assessed using the mean of serial HbA1c
Intervention	
Comparator	
Length of follow up	Median of 3.5visits (range 2-6) over median follow-up of 28mths (IQ range 16.4-45.1)
Outcomes measures and	**Outcomes:**

Bibliographic reference (Ref ID)	Molyneaux et al 1998, Better glycaemic control and risk reduction of diabetic complications in type 2 diabetes: comparison with DCCT
effect sizes	Retinopathy Microalbuminuria **Annual incidence:** Annual incidence of retinopathy 5.7% (95%CI; 4.0, 7.2) Annual incidence of microalbuminuria 8.3% (95%CI; 5.7, 10.9) Relative risk reductions for retinopathy and microalbuminuria associated with a 10% lower mean HbA1c: - Retinopathy; 24% risk reduction, (95%CI; 16, 23), p<0.0001 - Microalbuminuria; 9%, risk reduction (95%CI; -2, 19) Absolute risk (risk per 100 patient years) of developing diabetic retinopathy or microalbuminuria and mean HbA1c results showed a smooth curve with increasing HbA1c and absolute risk for both retinopathy and microalbuminuria
Funding	Not reported
Authors' conclusion	The development of diabetic retinopathy in those with T2D is related to the magnitude of hyperglycaemia
Comments	60% of patients had a follow-up complication assessment within the 4yr study period – comparison with those who did not return (63% vs 55%) revealed NS difference in clinical and complication status (except a higher proportion of oral hypoglycaemic agent treatment) Risk gradients for retinopathy and microalbuminuria estimated from a Poisson regression model using the natural log of mean serial HbA1c

Evidence Table 8: (van Hateren et al 2011, International Journal of Clinical Practice)

Bibliographic reference (Ref ID)	van Hateren et al 2011 – Glycaemic control and risk of mortality in elderly type 2 diabetic patients (ZODIAC-20)
Study type & aim	To explore the relationship between HbA1c and (cardiovascular) mortality and the role of diabetes duration, in elderly patients (>75yrs) Cohort Netherlands

Bibliographic reference (Ref ID)	**van Hateren et al 2011 – Glycaemic control and risk of mortality in elderly type 2 diabetic patients (ZODIAC-20)**

Number and Characteristics of patients

Total number of patients:
1145 with T2D, selected those >75yrs, n=374

Included:
Patients with T2D in 32 primary care practices

Excluded:
Those being treated by specialists in internal medicine
Those considered to have short life expectancy or insufficient cognitive abilities
Those with insufficient baseline data

Baseline characteristics: (means ±SD)

	Overall, n=374	Diabetes duration			P value
		Tertile 1 (<5yrs), n=111	Tertile 2 (5-11yrs), n=139	Tertile 3 (≥11yrs), n=124	
Age	80 (78-83)	80 (78-83)	80 (78-83)	80 (78-83)	0.887
Male sex	130 (34.8)	34 (30.6)	57 (41.0)	39 (31.5)	0.148
BMI	27.8 (4.4)	28.6 (4.4)	28.0 (4.3)	26.9 (4.2)	0.012
Duration of T2D, yrs	8 (4-13)	2 (1-3)	7 (6-9)	16 (13-20)	-
SBP	155.7 (24.7)	153.1 (24.3)	156.8 (24.9)	156.7 (24.9)	0.416
Current smoking	33 (8.8)	4 (3.7)	11 (8.0)	18 (14.8)	0.011
HbA1c, %	7.4 (1.2)	7.3 (1.3)	7.5 (1.1)	7.4 (1.2)	0.292
Albuminuria present	206 (55.1)	53 (47.7)	84 (60.4)	69 (55.6)	0.133
Cholesterol-HDL ratio	4.9 (1.6)	5.2 (1.7)	4.8 (1.6)	4.7 (1.5)	0.099
Serum creatinine, µmol/L	98 (86-115)	98 (82-111)	99 (87-123)	98 (87-111)	0.165
Macrovascular complications present	162 (43.3)	45 (40.5)	62 (44.6)	55 (44.4)	0.780
Treatment					
- Diet	40 (10.7)	19 (17.1)	13 (9.4)	8 (6.5)	0.025
- Oral agents	265 (70.9)	85 (76.6)	102 (73.4)	78 (62.9)	0.050
- Insulin	79 (21.1)	7 (63)	32 (23.0)	40 (32.3)	<0.001

Bibliographic reference (Ref ID)	**van Hateren et al 2011 – Glycaemic control and risk of mortality in elderly type 2 diabetic patients (ZODIAC-20)**

Receiving antihypertensive	231 (61.8)	71 (65.1)	82 (59.4)	78 (63.9)	0.610
Receiving lipid lowering treatment	17 (4.5)	5 (4.6)	8 (5.8)	4 (3.3)	0.627

Monitoring information and definitions

Enrolled in the Zwolle Outpatient Diabetes project Integrating Available Care (ZODIAC) in 1998, survival status recorded in September 2004. Data collected annually

As part of ZODIAC patients in 32 primary care practices consulted diabetes specialist nurses annually

Intervention

Comparator

Length of follow up

Early 2009, data retrieved from records maintained by hospital and GPs
10yr follow-up

Outcomes measures and effect sizes

Clinical end points:
All-cause mortality, cardiovascular disease mortality

Overall group:
Increase of 1% in HbA1c showed an increase in CVD mortality risk by 26% (95%CI; 6, 49%). The unadjusted HR and HR adjusted for age and gender were not relevantly different – relationship with all-cause mortality was NS in both models

Stratified according to diabetes duration:
Updated mean HbA1c as a continuous variable was positively related to all-cause mortality and CVD, HR (95% CI)

	Model	Diabetes duration		
		Tertile 1 (<5yrs), n=111	Tertile 2 (5-11yrs), n=139	Tertile 3 (≥11yrs), n=124
All-cause mortality	Unadjusted	1.24 (1.01, 1.52)	1.01 (0.83, 1.24)	0.90 (0.82, 1.20)
	Adjusted*	1.27 (1.03, 1.55)	1.04 (0.85, 1.26)	1.03 (0.84, 1.26)
	Adjusted[#]	1.51 (1.17, 1.95)	1.04 (0.84, 1.28)	1.05 (0.85, 1.30)
CVD mortality	Unadjusted	1.35 (1.00, 1.81)	1.17 (0.87, 1.57)	1.19 (0.91, 1.55)
	Adjusted*	1.37 (1.02, 1.84)	1.19 (0.99, 1.15)	1.28 (0.98, 1.68)
	Adjusted[#]	1.72 (1.19, 2.48)	1.18 (0.87, 1.60)	1.16 (0.86, 1.58)

* Adjusted for age and gender
[#] Adjusted for age, gender, smoking, BMI, duration of diabetes, creatinine level, macrovascular complications, albuminuria, SBP, total

Bibliographic reference (Ref ID)	van Hateren et al 2011 – Glycaemic control and risk of mortality in elderly type 2 diabetic patients (ZODIAC-20)
	cholesterol-HDL ratio, use of insulin Population attributable risk %: PAR% of HbA1c ≥7% for all-cause mortality 23% (95%CI, 2, 36%); for CVD mortality 39% (95%CI 17, 48%) For those with a duration of diabetes ≥5yrs results were NS
Funding	Not reported
Authors' conclusion	Poor glycaemic control is related to all-cause and CVD mortality in those >75yrs with T2D of short duration (<5yrs)
Comments	Updated mean of annually measured HbA1c calculated for each individual from baseline to the end of follow-up (in accordance with the technique used in UKPDS 35) Cox proportional hazard model used to investigate the relationship between the updated mean HbA1c as a time-dependent covariate, and mortality with and without adjustment for selected confounders

Evidence Table 9: (Morisaki et al 1994, American Geriatrics Society)

Bibliographic reference (Ref ID)	Morisaki et al 1994 – Diabetic control and progression of retinopathy in elderly patients: five-year follow-up study
Study type & aim	Followed elderly diabetic patients for 5yrs and analysed progression of retinopathy as a function of diabetic control Cohort Japan
Number and Characteristics of patients	**Total number of patients:** 114, NIDDM **Included:** Outpatient clinic patients, no more than mild retinopathy, >60yrs at the start of follow-up Baseline characteristics: Incidence (%) or mean ±SD

Bibliographic reference (Ref ID)	**Morisaki et al 1994 – Diabetic control and progression of retinopathy in elderly patients: five-year follow-up study**
	Sex (male: female), % 26:74 Age, yrs 68±6 Duration of diabetes 5.7±5.3 BMI 24±3 Incidence, % of - Hypertension 81 - Hyperlipidaemia 55 - Smoking 6 - Retinopathy 13 - Nephropathy 11 - CHD 23 - Cerebrovascular disease 10 - Arteriosclerosis 4
Monitoring information and definitions	Severity of lesions; grade 0, no lesion; grade 1, non-proliferative retinopathy (microaneurysms only or plus haemorrhages and/or hard exudates); grade 2, pre-proliferative retinopathy (non-proliferative retinopathy plus ≥1 soft exudates, intraretinal microvasuclar abnormalities and venous bleeding); grade 3, proliferative retinopathy (new vessels) Parameters (HbA1c, BP, lipids) measured at least 30 times during the follow-up period
Intervention	
Comparator	
Length of follow up	5-yr follow-up
Outcomes measures and effect sizes	**Outcomes:** Retinopathy **Mean (SD) levels of parameters during follow-up:** Means calculated based on all the data during follow-up HbA1c 7.53±1.43 SBP 145±13 DBP 78±8 Total cholesterol (mg/dL) 200±37

Bibliographic reference (Ref ID)	Morisaki et al 1994 – Diabetic control and progression of retinopathy in elderly patients: five-year follow-up study

Triglyceride (mg/dL) 134±74
HDL-cholesterol (mg/dL) 46.5±13.3

Progression of retinopathy:
All cases (n=114), 23.6% showed progression of retinopathy from grade 0 or grade 1 to a higher grade
Cases without retinopathy initially (n=99), 22.2% showed progression from grade 0 to a higher grade
Cases with retinopathy initially (n=15), 33.3% showed progression from grade 1 to grade 2 or 3

Comparison of those with and without retinopathy:

	No progression	Progression	P value
Age	68±6	66±5	NS
Duration of diabetes, yrs	10±5	13±5	<0.02
BMI	24±3	24±3	NS
HbA1c	7.1±1.2	8.8±1.1	<0.0001
SBP	144±12	149±14	NS
DBP	78±8	78±8	NS
Total cholesterol (mg/dL)	202±40	191±37	NS
Triglyceride (mg/dL)	133±81	145±82	NS
HDL-cholesterol (mg/dL)	47±13	47±16	NS

Multivariate analysis logistic regression of association between parameters and progression of retinopathy:

	t value	P value
Sex	1.559	NS
Age	-1.194	NS
Duration of diabetes	1.632	NS
BMI	1.310	NS
Smoking	1.476	NS
HbA1c	3.409	<0.001
SBP	0.454	NS
Total cholesterol	-1.620	NS

Bibliographic reference (Ref ID)	**Morisaki et al 1994 – Diabetic control and progression of retinopathy in elderly patients: five-year follow-up study**
	Triglyceride 0.786 NS HDL-cholesterol 1.186 NS
Funding	Grant for 'studies on abnormal metabolism in the elderly', from the fund for Longevity Science Projects of the Ministry of Health and Welfare of Japan
Authors' conclusion	Control of diabetes is the most important factor associated with the prevention of progression of retinopathy in elderly patients
Comments	Ophthalmologists with no knowledge of current treatment or glycaemic control evaluated photographs of fundi of the right eye at the beginning and end of the 5-yr follow-up Patients with hypertensions and hyperlipidaemia were treated for those conditions by their own doctors without any set rules The significance of difference between two groups was determined by Student's *t*-test. Multivariate logistic regression analysis

Evidence Table 10: (Nakagami et al 1997, Diabetes Care)

Bibliographic reference (Ref ID)	**Nakagami et al 1997 – Glycaemic control and prevention of retinopathy in Japanese NIDDM patients**
Study type & aim	To examine the importance of glycaemic control in the development of retinopathy, followed early diagnosed NIDDM patients for 10yrs Cohort Japan
Number and Characteristics of patients	**Total number of patients:** 137, NIDDM **Included:** Those with NIDDM admitted to the Diabetes Centre of Tokyo Women's Medical College, first visit between 1st January 1983 and 31st December 1985 Age at initial diagnosis between 30 and 65yrs Duration of diabetes <3yrs No retinopathy at first visit **Baseline characteristics:** 61 male, 76 female

<table>
<tr><td>Bibliographic reference (Ref ID)</td><td>Nakagami et al 1997 – Glycaemic control and prevention of retinopathy in Japanese NIDDM patients</td></tr>
<tr><td></td><td>Mean age 49.9±9.3yrs</td></tr>
<tr><td>Monitoring information and definitions</td><td>Optic fundi examined by an ophthalmologist at least annually
Simple retinopathy levels 21-53, proliferative retinopathy levels 60-80 of modified Airlie House System</td></tr>
<tr><td>Intervention</td><td></td></tr>
<tr><td>Comparator</td><td></td></tr>
<tr><td>Length of follow up</td><td>10-yr follow-up</td></tr>
<tr><td>Outcomes measures and effect sizes</td><td>Outcomes:
Retinopathy

Mean (SD) levels during follow-up:
Means calculated based on all the data obtained each month during follow-up
HbA1c 9.6±3.0%
SBP 131.0±21.3
DBP 81.0±12.2
Mean BMI 23.5±7.2

Prevalence of retinopathy:
<table>
<tr><th>Mean HbA1c</th><th>Prevalence</th></tr>
<tr><td><6%</td><td>0% (0/11)</td></tr>
<tr><td>6-6.9%</td><td>17.2% (5/29)</td></tr>
<tr><td>7-7.9%</td><td>14.3% (5/35)</td></tr>
<tr><td>8-8.9%</td><td>41.9% (13/31)</td></tr>
<tr><td>>9%</td><td>54.8% (17/31)</td></tr>
</table>
The prevalence of retinopathy increased with the increase in mean HbA1c over 10yrs (trend p<0.005)

Multiple logistic regression analysis of association between parameters and retinopathy in the 10th year of follow-up:
<table>
<tr><th></th><th>χ^2</th><th>P value</th></tr>
<tr><td>Sex</td><td>3.1548</td><td>0.0757</td></tr>
</table></td></tr>
</table>

Bibliographic reference (Ref ID)	Nakagami et al 1997 – Glycaemic control and prevention of retinopathy in Japanese NIDDM patients
	Age at onset: 2.1648; 0.1059 HbA1c at registration: 2.0271; 0.1545 Mean HbA1c for 10yrs: 5.9225; 0.0149 Mean SBP: 0.2569; 0.6122 Change in BMI: 1.8838; 0.1699
Funding	Not reported
Authors' conclusion	Results support the concept that an early diagnosis and better control lessen the risk for the development of retinopathy in Japanese NIDDM patients
Comments	Grade of retinopathy judged from the results of ophthalmological examinations

Evidence Table 11: (Schulze et al 2004, Diabetologia)

Bibliographic reference (Ref ID)	Schulze et al 2004 – Joint role of non-HDL cholesterol and glycated haemoglobin in predicting future coronary heart disease events among women with type 2 diabetes
Study type & aim	To determine whether non-HDL cholesterol predicts CHD events among diabetic women independently of currently established risk factors and the status of glycaemic control Cohort USA
Number and Characteristics of patients	**Total number of patients:** 921, from 32,826 study participants from the Nurses' Health Study **Included:** Participants from the study with confirmed T2D (from validated supplementary questionnaire) and who did not report a diagnosis of MI, CABG, PTCA or stroke as reported in a on any of the biennial questionnaires before blood collection, and for whom complete biomarker data was available **Baseline characteristics of those with and without CHD:** (mean ± SD)

	With incident CHD	Without CHD events	P value
Age	60.6±5.6	58.0±6.7	<0.001
Weight	77.8±21.2	78.3±22.8	0.841

Bibliographic reference (Ref ID)	Schulze et al 2004 – Joint role of non-HDL cholesterol and glycated haemoglobin in predicting future coronary heart disease events among women with type 2 diabetes

BMI	29.7±5.9	30.1±6.4	0.951
Physical activity (METs/wk)	19.3±90.4	32.1±134.7	0.152
Currently smoking, %	17.2	12.9	0.195
Aspirin use, %	36.9	33.8	0.502
Postmenopausal hormone use, %	31.2	26.4	0.272
Insulin use, %	29.5	17.7	0.002
Oral hypoglycaemic drugs, %	32.8	18.3	<0.001
Cholesterol-lowering drugs, %	7.4	3.4	0.034
Parental history of CHD, %	30.3	21.7	0.033
History of hypertension, %	72.1	58.0	0.003
History of angina, %	20.5	9.8	<0.001
Diabetes prevalent at blood collection, %	86.9	71.3	<0.001
Alcohol intake (g/day)	2.5±6.1	2.9±7.9	0.439
Total cholesterol (mmol/L)	6.15±1.10	5.82±1.12	0.001
LDL cholesterol (mmol/L)	3.79±0.94	3.58±0.97	0.011
HDL cholesterol (mmol/L)	1.29±0.41	1.34±0.38	0.090
Non-HDL cholesterol (mmol/L)	4.85±1.11	4.47±1.13	<0.001
Ratio of total cholesterol:HDL cholesterol	5.22±2.10	4.64±1.48	0.001
Fasting triglycerides (mmol/L)	2.56±1.62	2.15±1.60	0.009
ApoB100 (g/L)	1.09±0.24	1.02±0.25	0.001
Lipoprotein (µmol/L)	0.74±0.90	0.63±0.89	0.142
HbA1c	7.6±1.9	6.8±1.7	<0.001

Monitoring information and definitions	CHD endpoints consisted of fatal CHD, non-fatal MI and CABG/PTCA (did not include angina) Participants who were diagnosed with CHD, stroke or died during follow-up were censored at the date of diagnosis or death. All others followed through June 2000
Intervention	
Comparator	

<table>
<tr><td>Bibliographic reference (Ref ID)</td><td>Schulze et al 2004 – Joint role of non-HDL cholesterol and glycated haemoglobin in predicting future coronary heart disease events among women with type 2 diabetes</td></tr>
<tr><td>Length of follow up</td><td>Nurses' Health Study of 121,700 nurses at study initiation in 1976, average 7.2yrs follow-up
Blood samples from 1989/1990</td></tr>
<tr><td>Outcomes measures and effect sizes</td><td>Outcomes:
CHD
(used biomarker quartiles to assess relative risk of CHD, only reporting HbA1c here)

Relative risk (95%CI) of CHD by quartile: (these were also reported for lipids not in this evidence table)
<table>
<tr><th rowspan="2">HbA1c</th><th colspan="4">Quartiles of HbA1c</th><th rowspan="2">P for trend</th></tr>
<tr><th>1 (low)</th><th>2</th><th>3</th><th>4 (high)</th></tr>
<tr><td>Median, %</td><td>5.21</td><td>5.80</td><td>6.90</td><td>8.97</td><td>-</td></tr>
<tr><td>Age-adjusted RR</td><td>1.00</td><td>2.56 (1.24, 5.31)</td><td>3.11 (1.53, 6.31)</td><td>4.66 (2.36, 9.20)</td><td><0.001</td></tr>
<tr><td>Multivariate-adjusted* RR</td><td>1.00</td><td>2.49 (1.19, 5.23)</td><td>3.19 (1.56, 6.53)</td><td>4.92 (2.46, 9.85)</td><td><0.001</td></tr>
</table>
*adjusted for age, physical activity, alcohol intake, parental history of CHD, history of high BP, aspirin use, smoking, postmenopausal hormone use, BMI
The multivariate adjusted RR for an increase of 1 unit was 1.24 (95%CI; 1.13, 1.35)

The joint effect of blood lipids and HbA1c by cross-clarifying participants according to lipids and HbA1c, appeared to show an association with an increased CHD risk at any lipid level</td></tr>
<tr><td>Funding</td><td>Research grants from the National Institutes of Health</td></tr>
<tr><td>Authors' conclusion</td><td>Study suggests that non-HDL cholesterol and HbA1c are potent predictors of CHD risk in diabetic women</td></tr>
<tr><td>Comments</td><td>Cox proportional hazard analysis stratified on 5-yr age categories and over each 2-yr follow-up interval to estimate the relative risks for each biomarker quartile compared with the lowest quartile</td></tr>
</table>

Evidence Table 12: (Torffvit and Agardh, 2001, Journal of Diabetes and its Complications)

Bibliographic reference (Ref ID)	**Torffvit and Agardh 2001 – The impact of metabolic and blood pressure control on incidence and progression of nephropathy. A 10-year study of 385 type 2 diabetic patients**
Study type & aim	To investigate which medical risk indicators predict or modulate the 10-yr outcomes on development and progression of nephropathy in those with type 2 diabetes

Bibliographic reference (Ref ID)	Torffvit and Agardh 2001 – The impact of metabolic and blood pressure control on incidence and progression of nephropathy. A 10-year study of 385 type 2 diabetic patients
	Cohort Sweden
Number and Characteristics of patients	**Total number of patients:** 385 **Included:** All T2D patients attending hospital-based outpatient clinic during a 2-yr period Only those not requiring insulin treatment within 2yrs of diagnosis ≥30yrs **Excluded:** Ketonuria at diabetes diagnosis or later admitted for ketoacidosis 18 lost to follow-up **Baseline characteristics:** Median age 54 (30-83)yrs Age at diagnosis 44 (30-83)yrs BMI 27 (16-44)kg/m^2
Monitoring information and definitions	Development of nephropathy defined according to the highest level of the ration between albumin and creatinine clearance (ACCR) achieved during the study; normoalbuminuria <$0.01x10^{-3}$, microalbuminuria 0.01-$0.1x10^{-3}$, macroalbuminuria >$0.1x10^{-3}$ Endpoint renal failure – present if a serum creatinine level >200µmol/L during the study and/or needed dialysis and/or had a renal transplantation Fractional albumin clearance, ratio between albumin and creatinine clearance, ACCR
Intervention	
Comparator	
Length of follow up	9-yr median follow-up (range 0-13yrs) Examined 2-4 times/yr
Outcomes measures and effect sizes	(This study reported on HbA1c and BP combination effects, not included in this ET) **Outcomes:** Of the 385 participants, 252 had normoalbuminuria at baseline, of these 95 (38%) developed microalbuminuria and 26 (10%)

Bibliographic reference (Ref ID)	Torffvit and Agardh 2001 – The impact of metabolic and blood pressure control on incidence and progression of nephropathy. A 10-year study of 385 type 2 diabetic patients

developed macroalbuminuria

Analysis grouped; n=162 with normoalbuminuria and no antihypertensive treatment at baseline; n=223 with antihypertensive treatment and/or micro- macro-albuminuria at baseline (antihypertensive treatment may decrease albuminuria, not possible to evaluate whether the antihypertensive treated patients had albuminuria before starting treatment or not)

Incidence of nephropathy:

Patients with normoalbuminuria and no antihypertensive treatment (n=162), mean ±SD

	Persistent normoalbuminuria (n=90)	Micro- and macro-albuminuria (n=72)
Baseline:		
Age, yrs	51±10	50±11
Diabetes duration, yrs	8±6	7±7
HbA1c, %	7.8±1.6	8.2±1.7
SBP	137±16	136±16
DBP	81±7	81±7
S-creatinine, µmol/L	79 (51-109)	81 (56-162)
ACCR ($x10^{-3}$)	0.001 (0.001-0.004)	0.001 (0.001-0.008), p<0.05
Mean level during study:		
HbA1c, %	7.8±1.5	8.5±1.6, p<0.05
SBP	139±13	143±15
DBP	80±6	82±6
Maximal S-creatinine, µmol/L	93 (58-161)	97 (64-307)
Maximal ACCR ($x10^{-3}$)	0.001 (0-0.01)	0.01 (0.01-6), p<0.001

Progression of nephropathy:

Patients with antihypertensive treatment and/or micro- and macro-albunimuria at baseline (n=223), mean ±SD

Bibliographic reference (Ref ID)	**Torffvit and Agardh 2001 – The impact of metabolic and blood pressure control on incidence and progression of nephropathy. A 10-year study of 385 type 2 diabetic patients**

	<2 x ACCR (n=112)	≥2 x ACCR (n=111)	<2 x S-CREA (n=196)	≥2 x S-CREA (n=27)
Male/female	33/79	42/69	65/131	10/17
Age, yrs	59±10	55±8, p<0.01	57±9	60±9
Age at diabetes onset, yrs	50±10	46±10, p<0.001	48±10	49±11
BMI	28±5	28±5	28±5	28±5
No insulin (n=57)	44	13, p<0.001	55	2, p<0.05
Insulin from baseline (n=110)	50	60	94	16
Started on insulin (n=56)	18	38	47	9
HbA1c, %	7.8±1.3	8.5±1.2, p<0.001	8.1±1.2	8.4±1.7
SBP	154±15	155±15	153±14	161±17, p<0.05
DBP	86±7	86±6	86±6	87±6
Maximum S-creatinine, µmol/L	105 (60-488)	109 (59-979)	102 (59-488)	430 (142-979), p<0.001

Doubling ACCR, had higher HbA1c

Doubling serum creatinine, no difference in HbA1c

(Mortality:

28% (n=109) died (MI n=42; uraemia n=7, stroke n=7, sudden death n=5, heart failure n=13, cancer n=15, other causes n=20)

Kaplan-Meier estimates of survival curves for all causes of mortality for the three levels of albuminuria at baseline; normoalbuminuria vs. microalbuminuria (p<0.01); normo- or microalbuminuria vs. overt nephropathy (p<0.001))

Funding	Grants from the Almer Foundation, Lisa and Johan Gronbergs Foundation, Malmoe Diabetes Association, the Swedish Medical Research Council, the Novo Nordisk Foundation, Novo Nordisk Pharma, Sweden, Skane County Council Foundation for Research and Development, the Swedish Diabetes Federation, the University of Lund, Ake Wibergs Foundation
Authors' conclusion	Poor metabolic control is associated with development and high blood pressure with progression of nephropathy in those with type 2 diabetes
Comments	Mean levels of all clinical parameters were calculated for each calendar year to evaluate the change over time and a mean of all registrations during the study for risk factor analysis Cox regression analysis with forward stepwise selection based on log likelihood investigated the association between a renal event within other variables

Evidence Table 13: (Hsu et al 2012, Diabetologia)

<table>
<tr><th>Bibliographic reference (Ref ID)</th><th>Hsu et al 2012 – HbA1c variability is associated with microalbuminuria development in type 2 diabetes: a 7-year prospective cohort study</th></tr>
<tr><td>Study type & aim</td><td>To explore the relationship between HbA1c, variability and microalbuminuria development in patients with T2D
Cohort
Taiwan</td></tr>
<tr><td>Number and Characteristics of patients</td><td>Total number of patients:
821 with T2D

Included:
T2D patients enrolled for the Diabetes Management through an Integrated Delivery System (DMIDS) project

Excluded:
<3 eligible urine albumin to creatinine ratio (ACR) tests
Microalbuminuria at baseline (ACR ≥3.4mg/mmol in two consecutive urine tests)</td></tr>
<tr><td>Monitoring information and definitions</td><td>Incidence of mciroalbuminuria estimated by the number of observed new microalbuminuria cases per 1000 person-yrs</td></tr>
<tr><td>Intervention</td><td></td></tr>
<tr><td>Comparator</td><td></td></tr>
<tr><td>Length of follow up</td><td>Recruited 2003 to 2005, followed through to the end of 2010</td></tr>
<tr><td>Outcomes measures and effect sizes</td><td>Outcomes:

Progression to microalbuminuria;
Progressors more likely to have lower education, longer diabetes duration, poorer metabolic profiles, higher baseline urine ACR, poorer BP control, poorer glucose control
Those with microalbuminuria had higher HbA1c variability
<table>
<tr><th></th><th>All (n=821)</th><th>Non-progressors</th><th>Progressors</th><th>P value</th></tr>
</table>
</td></tr>
</table>

Bibliographic reference (Ref ID)	Hsu et al 2012 – HbA1c variability is associated with microalbuminuria development in type 2 diabetes: a 7-year prospective cohort study				
			(n=520)	(n=301)	
	Male, %	46.1	44.0	49.8	0.108
	Education ≤6yrs, %	54.9	51.5	60.7	0.012
	Age at diabetes onset, yrs	51.2±8.3	51.2±8.6	51.1±9.1	0.305
	Diabetes duration at recruitment, yrs	2.9±2.7	2.7±2.2	3.3±3.3	<0.001
	Follow-up, yrs	6.2±0.7	6.2±0.6	6.2±0.7	0.542
	Smoking;				0.299
	Non-smoker, %	73.1	74.8	70.1	
	Ex-smoker, %	7.1	6.9	7.3	
	Current smoker, %	19.8	18.3	22.6	
	Baseline drug treatment;				
	Glucose-lowering drugs, %				
	Sulfonylurea	88.7	84.2	96.6	0.305
	Biguanide	80.6	76.1	88.3	0.265
	Other oral glucose-lowering drugs	18.2	15.9	22.2	0.367
	Insulin	2.4	1.7	3.6	0.131
	Antihypertensive drugs, %				
	ACE inhibitor	32.7	28.4	40.1	0.325
	ARB	9.0	7.8	10.9	0.281
	CCB	33.8	32.3	36.5	0.737
	β blocker	32.1	30.0	35.8	0.386
	diuretics	19.0	17.5	21.5	0.619
	Baseline biomarkers;				
	Hypertension, %	56.1	52.3	63.4	0.002
	SBP	129.3±14.3	128.1±11.3	130±18.1	<0.001
	DBP	77.2±10.6	77.2±6.3	77.3±13.1	<0.001
	HDL-cholesterol	1.51±3.33	1.37±1.86	1.60±3.99	0.333
	Triglycerides	2.76±14.3	2.19±7.05	3.12±17.4	0.362
	Urine ACR	1.47±2.14	1.15±1.75	2.02±2.60	<0.001
	HbA1c characteristics;				
	Baseline HbA1c, %	8.2±1.8	8.0±1.7	8.4±2.0	0.002

Bibliographic reference (Ref ID)	Hsu et al 2012 – HbA1c variability is associated with microalbuminuria development in type 2 diabetes: a 7-year prospective cohort study

During follow-up;				
Number of HbA1c measurements	9.0±2.7	9.1±2.8	8.9±2.7	0.543
Mean serial HbA1c	7.9±1.2	7.7±1.1	8.2±1.3	<0.001
SD of serial HbA1c				
Crude SD	1.12±0.53	1.04±0.48	1.23±0.59	<0.001
CV of SD	0.13±0.06	0.13±0.05	0.14±0.06	0.035
Adjusted SD	1.03±0.51	0.97±0.47	1.14±0.54	0.004

Baseline characteristics according to quartiles of intrapersonal adjusted SD of serial HbA1c measurements:

Those with higher HbA1c variability – earlier diabetes onset, use more glucose-lowering drugs, poorer glycaemic control at baseline

	Q1	Q2	Q3	Q4	P value
No. of patients	204	206	202	209	
Range of adjusted HbA1c SD	0.09-0.66	0.67-0.95	0.96-1.29	1.30-3.48	
Age at diabetes onset, yrs	53.1±8.7	51.2±8.9	50.7±8.6	49.7±8.7	0.001
Diabetes duration at recruitment, yrs	3.0±2.7	3.0±3.4	2.7±2.1	3.0±2.5	0.555
Follow-up duration, yrs	6.2±0.6	6.2±0.6	6.3±0.7	6.2±0.7	0.357
Baseline glucose-lowering drugs, %					
Sulfonylurea	84.8	81.5	92.0	96.6	0.017
Biguanide	72.0	77.1	86.6	86.6	0.013
Other oral glucose-lowering drugs	12.2	17.9	19.8	22.9	0.434
Insulin	0.9	2.4	2.4	3.8	0.370
Baseline biomarkers					
Hypertension, %	53.9	53.4	57.7	60.3	0.433
SBP	129.5±11.1	129.5±11.5	129.0±14.6	12.9±18.7	0.983
DBP	77.5±6.2	78.7±6.9	77.6±11.6	77.7±15.0	0.623
HDL-cholesterol	1.26±0.34	1.24±0.31	1.24±0.30	1.25±0.40	0.785
Triglycerides	1.66±0.96	1.73±1.41	2.02±1.82	1.85±2.08	0.116
Urine ACR, mg/mmol	1.28±1.72	1.44±1.40	1.54±2.08	1.63±2.16	0.014
Baseline HbA1c, %	7.3±1.2	7.6±1.4	8.3±1.5	9.4±2.2	<0.001
≤7%, %	38.2	35.0	21.3	17.2	<0.001

Bibliographic reference (Ref ID)	Hsu et al 2012 – HbA1c variability is associated with microalbuminuria development in type 2 diabetes: a 7-year prospective cohort study

7-9%, % >9%	56.9 4.9	45.2 19.8	39.6 39.1	25.4 57.4	
During follow-up Number of HbA1c measurements Mean of serially measured HbA1, %	 8.0±3.1 7.3±1.3	 9.4±2.5 7.6±1.4	 9.3±2.6 8.4±1.5	 9.4±2.5 9.4±2.3	 <0.001 <0.001

Risk factors in T2D patients contribute to progression to microalbuminuria during 7-yr follow-up:

Both mean and adjusted SD of HbA1c were significantly related to microalbuminuria development in univariate analysis and separate multivariate regressions. Comparison between quartiles of HbA1c

Other covariates; lower education, diabetes duration, high BP, subsequent use of ACE inhibitors or angiotensin receptor blockers had marginal effects on the development of microalbuminuria after controlling for other covariates

Risk factor	Univariate HR (95%CI)	Multivariate HR (95%CI) – model 1	Multivariate HR (95%CI) – model 2	Multivariate HR (95%CI) – model 3
Sex (female/male)	1.22 (0.98, 1.54)	1.25 (0.94, 1.67)	1.23 (0.92, 1.64)	1.24 (0.93, 1.65)
Education (≤6/>6yrs)	1.33 (1.05, 1.68) p<0.05	1.45 (1.10, 1.90) p<0.05	1.43 (1.08, 1.88) p<0.05	1.41 (1.07, 1.86) p<0.05
Diabetes onset age (per 1yr increment)	1.00 (0.99, 1.01)	0.99 (0.97, 1.00)	0.99 (0.97, 1.00)	0.99 (0.98, 1.00)
Diabetes duration (per 1yr increment)	1.07 (1.03, 1.10) p<0.05	1.03 (0.99, 1.07)	1.03 (1.00, 1.08) p<0.05	1.04 (1.00, 1.07)
ACE inhibitor and/or ARB use (Y/N)	1.27 (1.02, 1.59)	1.26 (1.00, 1.58)	1.26 (1.00, 1.58)	1.26 (1.00, 1.58)
Baseline biomarkers; BP (≥130/80 vs <130/80) HDL-cholesterol (low vs high) Triacyglycerols (≥1.69 vs <1.69)	 1.45 (1.14, 1.83), p<0.05 0.81 (0.65, 1.02) 0.93 (0.74, 1.17)	 1.30 (1.03, 1.65), p<0.05 0.89 (0.69, 1.15) 0.92 (0.73, 1.18)	 1.25 (0.98, 1.59) 0.87 (0.68, 1.12) 0.95 (0.75, 1.21)	 1.25 (0.98, 1.59) 0.88 (0.68, 1.13) 0.95 (0.75, 1.21)
HbA1c during follow-up; Mean serial HbA1c (per 1% increment) Adjusted SD of HbA1c; 1.13 (0.83, 1.56)	 1.13 (0.83, 1.56), p<0.05	 1.10 (1.00, 1.20), p<0.05		1.04 (0.94, 1.14)

Bibliographic reference (Ref ID)	Hsu et al 2012 – HbA1c variability is associated with microalbuminuria development in type 2 diabetes: a 7-year prospective cohort study

Quartile2/Quartile 1	1.35 (1.04, 1.77), p<0.05		1.06 (0.74, 1.50)	1.03 (0.72, 1.48)
Quartile3/Quartile 1	1.73 (1.26, 2.38), p<0.01		1.13 (0.80, 1.60)	1.09 (0.75, 1.57)
Quartile4/Quartile 1			1.57 (1.13, 2.17), p<0.01	1.48 (1.03, 2.12) <0.05
P for trend	<0.001		0.001	0.043

Incidence (events per 1000 person-yrs observed) and risk of microalbuminuria in individuals in different quartiles of adjusted HbA1c SD and in different levels of mean HbA1c, stratified by HbA1c, follow-up time and baseline HbA1c:

Variable	Adjusted SD Q1	Adjusted SD Q2	Adjusted SD Q3	Adjusted SD Q4	P for trend (Q1 to Q4)[#]	HR per 1% HbA1c increment	P for interactions (adjusted SD x mean of HbA1c)[~]
HbA1c follow-up time – Overall (up to 7yrs);							
Cases/person-yrs	66/1125	67/1143	70/1150	102/1109			
Incidence	58.4	58.6	60.8	91.9	0.001		
HR (95%CI)	1	1.06 (0.74, 1.50)	1.13 (0.80, 1.60)	1.57 (1.13, 2.17)		1.10 (1.00, 1.20)*	0.951
2 years;							
Cases/person-yrs	62/1112	65/1137	69/1145	101/1103			
Incidence	55.7	57.2	60.2	91.5	0.019		
HR (95%CI)	1	1.19 (0.77, 1.84)	1.32 (0.86, 2.03)	1.42 (0.93, 2.17)		1.03 (0.92, 1.15)*	0.920
Baseline HbA1c – ≤8%;							
Cases/person-yrs	33/650	33/653	37/656	48/449			
Incidence	50.7 (35.5, 70.4)	50.5 (35.3, 70.1)	56.4 (40.3, 76.9)	106.9 (79.7, 140.6)	0.026		
HR (95%CI)	1	1.00 (0.60,	1.05 (0.65,	1.41 (0.91,		1.13 (0.91,	0.371

Bibliographic reference (Ref ID)	Hsu et al 2012 – HbA1c variability is associated with microalbuminuria development in type 2 diabetes: a 7-year prospective cohort study

		1.65)	1.71)	2.22)		1.39)*	
>8%;							
Cases/person-yrs	33/475	34/490	33/494	48/449			
Incidence	69.4 (48.6, 96.4)	69.3 (44.8, 95.8)	66.8 (46.7, 92.7)	106.9 (79.7, 140.6)	0.047		
HR (95%CI)	1	1.01 (0.61, 1.67)	1.29 (0.82, 2.03)	1.64 (1.04, 2.59)		1.18 (1.04, 1.34)*	0.365

[#]models controlled for sex, age of diabetes onset, education, diabetes duration, smoking status, BP, waist circumference, HDL-cholesterol, triacylglycerols, ACE inhibitor/ARB use and adjusted SD of HbA1c

* models controlled for sex, age of diabetes onset, education, diabetes duration, smoking status, BP, waist circumference, HDL-cholesterol, triacylglycerols, ACE inhibitor/ARB use and mean of HbA1c

[~] models controlled for sex, age of diabetes onset, education, diabetes duration, smoking status, BP, waist circumference, HDL-cholesterol, triacylglycerols, ACE inhibitor/ARB use and mean of HbA1c, adjusted HbA1c and (mean x adjusted SD) of HbA1c

Funding	National Health Research Institutes
Authors' conclusion	In addition to mean HbA1c values, HbA1c variability, even measured as early as 2yrs, is independently associated with the development of microalbuminuria in patients with T2D
Comments	Kaplan-Meier analyses and univariate Cox proportional hazard models were used to explore the association between quartiles of adjusted HbA1c SD and microalbuminuria development. The predictability of 2-yr HbA1c SD for development of microalbuminuria conveys a clinical message that sustaining glycaemic control at the early stage is crucial for the management of T2D Multivariate Cox proportional hazard modelling was used to determine the independent effects of HbA1c variability on microalbuminuria development Only data relevant to mean HbA1c (and not HbA1c variability) was used.

Evidence Table 14: (Stratton et al 2000, BMJ)

Bibliographic reference (Ref ID)	Stratton et al 2000 – Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study
Study type & aim	To evaluate the relation between exposure to glycaemia over time and the development of microvascular and macrovascular complications Cohort UK

<table>
<tr><td>Bibliographic reference (Ref ID)</td><td>Stratton et al 2000 – Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study</td></tr>
<tr><td>Number and Characteristics of patients</td><td>Total number of patients:
3642

Included:
From 5102 UKPDS patients, 4585 with HbA1c measured 3mths after diagnosis of diabetes, of these 3642 with complete data for potential cofounders included in the analyses of relative risk

Baseline characteristics:
<table>
<tr><td></td><td>Proportional hazards model of observational data (n=3642), mean (SD)</td></tr>
<tr><td>Age, yrs</td><td>53 (8)</td></tr>
<tr><td>Proportion male, %</td><td>60</td></tr>
<tr><td>Ethnicity (% while/Asian Indian/Afro-Caribbean/other)</td><td>82/10/8/0</td></tr>
<tr><td>BMI</td><td>27.7 (5.3)</td></tr>
<tr><td>Fasting plasma glucose, mmol/L</td><td>7.9 (6.6-10)</td></tr>
<tr><td>HbA1c</td><td>7.1 (1.8)</td></tr>
<tr><td>SBP</td><td>135 (19)</td></tr>
<tr><td>LDL-cholesterol, mmol/L</td><td>3.5 (1.0)</td></tr>
<tr><td>HDL-cholesterol, mmol/L</td><td>1.06 (0.24)</td></tr>
<tr><td>Triglyceride, mmol (median, interquartile range)</td><td>1.5 (0.9-2.5)</td></tr>
<tr><td>Albuminuria, % (>50ml/L in single morning sample)</td><td>13.3</td></tr>
</table></td></tr>
<tr><td>Monitoring information and definitions</td><td>Aggregate end points:
- Complications related to diabetes (MI, sudden death, angina, stroke, renal failure, lower extremity amputation or death from PVD, death from hyperglycaemia or hypoglycaemia, heart failure, vitreous haemorrhage, retinal photocoagulation, and cataract extraction)
- Death related to diabetes (MI, sudden death, stroke, lower extremity amputation or fatal PVD, renal disease, hyperglycaemia or hypoglycaemia
- All-cause mortality
- MI (fatal MI, non-fatal MI, and sudden death)
- Stroke (fatal and non-fatal stroke)</td></tr>
</table>

<table>
<tr><td>Bibliographic reference (Ref ID)</td><td>Stratton et al 2000 – Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study</td></tr>
<tr><td></td><td>- Lower extremity amputation or death from PVD
- Microvascular complications (retinopathy requiring phototcoagulation, vitreous haemorrhage, and fatal or non-fatal renal failure)

Single end points:
- Heart failure (non-fatal, without a precipitating MI)
- Cataract extraction</td></tr>
<tr><td>Intervention</td><td></td></tr>
<tr><td>Comparator</td><td></td></tr>
<tr><td>Length of follow up</td><td>Exposure to glycaemia measured firstly at baseline HbA1c, and over time as an updated mean of annual measurements of HbA1c – calculated for each individual from baseline to each year of follow-up

HbA1c categories (median): <6% (5.6%), 6 - <7% (6.5%), 7 - <8% (7.5%), 8 - <9% (8.5%), 9 - <10% (9.5%), ≥10% (10.6%) over the range of updated mean HbA1c of 4.6-11.2% (1st to 99th centile)

Follow-up calculated from the end of the initial period of dietary treatment of the UKPDS study to the first occurrences of that complication or loss to follow-up, death from another cause, or to the end of the study on 30th September 1997. Therefore follow-up time is equivalent to duration of diabetes. Median follow-up for all-cause mortality was 10.4yrs</td></tr>
<tr><td>Outcomes measures and effect sizes</td><td>Outcomes:
The incidence rates for any end point related to diabetes, adjusted for age, sex, ethnic group, and duration of diabetes, increased with each higher category of updated mean HbA1c

Incidence of complications in patients with T2D by category of mean HbA1c (rates per 1000 person years follow-up adjusted in regression model to white men aged 50-45yrs at diagnosis followed for 7.5 to <12.5yrs):
<table>
<tr><th>Aggregate end point</th><th><6%</th><th>6% to <7%</th><th>7% to <8%</th><th>8% to <9%</th><th>9% to <10%</th><th>≥10%</th></tr>
<tr><td>Complications related to diabetes:</td><td colspan="6"></td></tr>
<tr><td>Events/person yrs</td><td>229/9195</td><td>391/11432</td><td>369/8464</td><td>268/5605</td><td>159/2542</td><td>88/1334</td></tr>
<tr><td>Unadjusted rate</td><td>24.9</td><td>34.2</td><td>43.6</td><td>47.8</td><td>62.5</td><td>65.9</td></tr>
<tr><td>Adjusted rate</td><td>35.9
(29.9, 43.1)</td><td>48.7
(41.3, 57.3)</td><td>65.5
(55.5, 77.2)</td><td>74.5
(62.6, 88.8)</td><td>103.2
(84.2, 126.5)</td><td>124.9
(97.3, 160.3)</td></tr>
</table></td></tr>
</table>

Bibliographic reference (Ref ID)	Stratton et al 2000 – Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study					
	Deaths related to diabetes:					
	Events/person yrs	56/10113	101/13143	116/10054	84/6595	47/3137	19/1537
	Unadjusted rate	5.5	7.7	11.5	12.7	15.0	12.4
	Adjusted rate	8.9 (6.3, 12.7)	12.0 (8.9, 16.3)	19.9 (14.8, 26.7)	23.5 (17.2, 32.0)	29.5 (20.4, 42.6)	33.0 (19.8, 55.1)
	All-cause mortality:						
	Events/person yrs	112/10113	207/13143	188/10054	123/6595	64/3137	26/1537
	Unadjusted rate	11.1	15.8	18.7	18.7	20.4	16.9
	Adjusted rate	17.0 (13.1, 22.0)	23.3 (18.5, 29.2)	30.0 (23.8, 37.7)	31.8 (24.7, 40.8)	37.0 (27.3, 40.8)	40.7 (26.5, 64.5)
	Fatal or non-fatal MI:						
	Events/person yrs	100/9870	163/12590	159/9579	101/6331	60/3016	23/1490
	Unadjusted rate	10.1	13.0	16.6	16.0	19.9	15.4
	Adjusted rate	16.0 (12.1, 21.2)	20.8 (16.2, 26.7)	29.2 (22.8, 39.4)	30.0 (22.8, 39.4)	39.6 (28.8, 54.5)	38.6 (24.4, 61.0)
	Fatal or non-fatal stroke:						
	Events/person yrs	32/9916	67/12869	59/9822	32/6424	13/3062	9/1509
	Unadjusted rate	3.2	5.2	6.0	5.0	4.2	6.0
	Adjusted rate	4.3 (2.6, 7.0)	6.6 (4.4, 10.1)	8.3 (5.4, 12.7)	7.4 (4.5, 11.9)	6.7 (3.5, 12.7)	12.0 (5.7, 25.3)
	Amputation or death from PVD:						
	Events/person yrs	3/10018	7/12993	7/9897	9/6492	15/3061	7/1502
	Unadjusted rate	0.3	0.5	0.7	1.4	4.9	4.7
	Adjusted rate	1.2 (0.4, 3.2)	1.2 (0.5, 3.1)	35.9 (29.9, 43.1)	4.0 (1.1, 5.8)	10.9 (5.0, 23.7)	12.2 (4.6, 32.4)
	Fatal or non-fatal microvascular						

Bibliographic reference (Ref ID)	Stratton et al 2000 – Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study

disease:						
Events/person yrs	38/9814	77/12707	86/9438	91/6185	73/2855	47/1432
Unadjusted rate	3.9	6.1	9.1	14.7	25.6	32.8
Adjusted rate	6.1 (4.1, 9.0)	9.3 (6.7, 12.9)	14.2 (10.3, 19.5)	22.8 (16.7, 31.3)	40.4 (28.9, 56.5)	57.8 (39.3, 85.1)
Single endpoints						
Heart failure:						
Events/person yrs	17/9967	34/12928	36/9782	20/6432	10/3062	10/1514
Unadjusted rate	1.7	2.6	3.7	3.1	3.3	6.6
Adjusted rate	2.3 (1.2, 4.5)	3.4 (1.9, 5.8)	5.0 (2.9, 8.6)	4.4 (2.4, 8.2)	5.0 (2.3, 10.6)	11.9 (5.5, 25.8)
Cataract extraction:						
Events/person yrs	35/9841	59/12763	49/9692	45/6355	19/3009	19/1495
Unadjusted rate	3.6	4.6	5.1	7.1	6.3	12.7
Adjusted rate	4.1 (2.5, 6.5)	4.5 (3.0, 6.9)	4.9 (3.1, 7.6)	6.9 (4.4, 10.8)	6.6 (3.8, 11.6)	14.4 (8.1, 25.7)

Relation between glycaemic exposure and complications of diabetes as estimated by decrease in risk for 1% reduction in HbA1c, measured at baseline and as updated mean (controlled for age at diagnosis, sex, ethnic group, smoking, albuminuria, SBP, HDL and LDL cholesterol, triglycerides):

	No. of events	Baseline HbA1c		Updated mean HbA1c	
		Decrease in risk, %/(1%) reduction (95%CI)	P value	Decrease in risk, %/(1%) reduction (95%CI)	P value
Aggregate end points					
Any end point related to diabetes	1255	11 (8, 13)	<0.0001	21 (17, 24)	<0.0001
Deaths related to diabetes	346	9 (3, 14)	0.0018	21 (15, 27)	<0.0001

Bibliographic reference (Ref ID)	Stratton et al 2000 – Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study

All-cause mortality	597	6 (2, 10)	0.0081	14 (9, 19)	<0.0001
MI	496	5 (0, 9)	0.067	14 (8, 21)	<0.0001
Stroke	162	-4 (-14, 6)	0.44	12 (1, 21)	0.035
Lower extremity amputation or fatal PVD	41	28 (18, 37)	<0.0001	43 (31, 53)	<0.0001
Microvascular disease	323	23 (20, 27)	<0.0001	37 (33, 41)	<0.0001
Single end points					
Heart failure	104	0 (-12, 11)	0.99	16 (3, 26)	0.016
Cataract extraction	195	9 (2, 16)	0.013	19 (11, 26)	<0.0001

There was no indication of a threshold for any complication below which risk no longer decreased nor a level above which risk no longer increased

Decrease in risk, HR for each 1% reduction in updated mean HbA1c, using the categorical HbA1c with the reference category of <6%: (data adjusted for age at diagnosis, sex, ethnic group, smoking, presence of albuminuria, SBP, HDL and LDL-cholesterol, triglycerides)

- Any end point related to diabetes; 21% decrease per 1% reduction in HbA1c, p<0.0001
- Death related to diabetes; 21% decrease per 1% reduction in HbA1c, p<0.0001
- All-cause mortality; 14% decrease per 1% reduction in HbA1c, p<0.0001
- Fatal and non-fatal MI; 14% decrease per 1% reduction in HbA1c, p<0.0001
- Fatal and non-fatal stroke;12% decrease per 1% reduction in HbA1c, p=0.035
- Microvascular end points; 37% decrease per 1% reduction in HbA1c, p<0.0001
- Cataract extraction; 19% decrease per 1% reduction in HbA1c, p<0.0001
- Amputation or death from PVD; 43% decrease per 1% reduction in HbA1c, p<0.001
- Heart failure; 16% decrease per 1% reduction in HbA1c, p=0.021

These estimated hazard ratios are associated with the different categories of mean updated HbA1c, related to the lowest category. Mortality related to diabetes and all-cause mortality were both strongly associated with glycemia (p<0.0001)

Funding	The major grants were from the UK Medical Research Council, the British Diabetic Association, the UK Department of Health. The National Eye Institute, the National Institute of Digestive, Diabetes and Kidney Disease in the National Institute of Health, US, the British Heart Foundation, Novo Nordisk, Bayer, Bristol-Myers Squibb, Hoechst, Lilly, Lipha, and Farmitalia Carlo Erba
Authors' conclusion	In those with T2D the risk of diabetic complications was strongly associated with previous hyperglycaemia. Any reduction in HbA1c is likely to reduce the risk of complications, with the lowest risk being in those with HbA1c in the normal range (<6%)

Bibliographic reference (Ref ID)	Stratton et al 2000 – Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study
Comments	Unadjusted incidence rates calculated by dividing the number of people with a given complication by the person years of follow-up for the given complication within each category of updated mean HbA1c and reported as events per 1000yrs of follow-up To assess potential association between updated mean HbA1c and complications proportional hazards regression (Cox) models used Hazard ratio used to estimate relative risk

Evidence Table 15: (Hunt et al 2013, Annals of Epidemiology)

Bibliographic reference (Ref ID)	Hunt et al 2013 – Impact of diabetes control on mortality by race in a national cohort of veterans
Study type & aim	To investigate the association between HbA1c, medication compliance/use and mortality stratified according to ethnicity in veterans with type 2 diabetes Cohort USA
Number and Characteristics of patients	**Total number of patients:** 892,223 **Included:** Veterans with type 2 diabetes Cohort was identified using Veterans Health Administration (VHA) National Patient Care and Pharmacy Benefits Management (PBM) databases.
Monitoring information and definitions	Details not provided
Intervention	
Comparator	
Length of follow up	Mean±SD follow up: 4.4±1.27 years (2002 to December 2006)
Outcomes measures and effect sizes	**Outcomes:** All cause mortality

Bibliographic reference (Ref ID)	Hunt et al 2013 – Impact of diabetes control on mortality by race in a national cohort of veterans

Demographics of study cohort stratified by ethnicity:

	All (n=892,223)	Non-Hispanic White (n=548,808)	Non-Hispanic Black (n=108,356)	Hispanic (n=123,670)
Age, years (mean±SD)	66.2±11.15	67.9±10.25	62.4±11.96	67.4±11.26
Sex: male (%)	97.65	97.92	97.13	97.59
Marital status: married (%)	64.37	68.93	47.51	60.05
Baseline HbA1c (%) in 2002 (mean±SD)*	7.4±1.34	7.3±1.22	7.8±1.63	7.6±1.41
Baseline medication use in 2002 (%)	77.44	91.73	81.95	28.58
Adherent medication use in 2002 (%)	47.42	58.19	43.57	16.95
Comorbidities				
Cancer (%)	7.58	7.89	8.99	8.02
Cerebrovascular disease (%)	11.47	11.95	13.07	12.95
Congestive heart failure (%)	11.54	12.36	11.53	13.09
Cardiovascular disease (%)	3.51	3.85	2.94	4.02
Peripheral vascular disease (%)	10.97	12.51	10.52	9.80
Substance abuse (%)	3.58	2.59	8.48	4.05
Depression (%)	10.99	11.84	11.00	8.85
Psychoses (%)	4.03	3.63	6.84	4.54
Vital status: deceased (%)	20.83	25.09	18.75	7.20
Follow-up in years (mean±SD)	4.4±1.27	4.3±1.32	4.4±1.24	4.5±1.22

*post-entry mean HbA1c of all observations recorded within a year was used

Adjusted HR and 95% CI from Cox proportional hazard models for mortality stratified by race:

HbA1c	Non-Hispanic White	Non-Hispanic Black	Hispanic
<7.0%	0.99 (0.97, 1.00)	1.07 (1.02, 1.12)	1.02 (0.95, 1.09)
7.0-8.0%	1.00	1.00	1.00
8.0-9.0%	1.10 (1.08, 1.13)	1.00 (0.94, 1.06)	1.09 (1.00, 1.19)
>9.0%	1.17 (1.14, 1.20)	1.09 (1.03, 1.15)	1.15 (1.06, 1.25)

Bibliographic reference (Ref ID)	**Hunt et al 2013 – Impact of diabetes control on mortality by race in a national cohort of veterans**
	*adjusted for age, sex, marital status, location of residence, geographic region, medication status, number of comorbidities
Funding	Grants from VHA Health Services Research and Development program
Authors' conclusion	There is evidence for ethnic differences in the association between glycaemic control and mortality, which varied with medication use/adherence.
Comments	Cohort comprise mainly men (97.65%) who were veterans and the duration of diabetes has not been provided

Evidence Table 16: (Salinero-Fort et al 2013, PLoS ONE)

Bibliographic reference (Ref ID)	**Salinero-Fort et al 2013 – Four-year incidence of diabetic retinopathy in a Spanish cohort: the MADIABETES study**
Study type & aim	To identify the risk factors associated with incident diabetic retinopathy in people with type 2 diabetes Prospective cohort Spain (multi-centre)
Number and Characteristics of patients	**Total number of patients:** 2405 in final sample (3443 in original cohort, 403 did not have an eye examination, 292 had diabetic retinopathy and 343 were lost to follow up. Drop out = 343/2748 [12.5%]) **Included:** Adults (>30 years) with type 2 diabetes enrolled in the Madrid Diabetes Study from 2007 and followed up every year from 2008 to 2011. **Excluded:** Type 1 diabetes and housebound people
Monitoring information and definitions	Patients were followed up every year
Intervention	
Comparator	

Bibliographic reference (Ref ID)	**Salinero-Fort et al 2013 – Four-year incidence of diabetic retinopathy in a Spanish cohort: the MADIABETES study**
Length of follow up	4 years (2008 to 2011)
Outcomes measures and effect sizes	**Outcomes:** Diabetic retinopathy (mild, moderate or severe non-proliferative diabetic retinopathy, proliferative diabetic retinopathy, diabetic macular oedema i.e. retinal thickening and hard exudate in posterior pole)

Baseline characteristics of follow up patients:

	All patients (n=2405)	Diabetic retinopathy (n=194)	No diabetic retinopathy (n=2211)
Age, years (mean±SD)	67.5±10.6	66.6±11.2	67.6±10.5
Sex: female (%)	49.4	51.5	49.2
Body mass index, kg/m^2 (mean±SD)	29.3±5.3	29.4±5.4	29.3±5.3
Diabetes duration, years (mean+SD)	7.6±7.2	9.4±8.8	7.4±7.0
Non-smoker (%)	73.4	74.2	73.4
Medication use			
Oral antidiabetic drugs (%)	75.3	78.8	75.0
Insulin (%)	17.1	29.5	16.0
Comorbidities			
Hypertension (%)	70.3	72.7	70.1
Stroke (%)	7.1	7.2	7.1
Myocardial infarction (%)	7.9	9.8	7.7
Blood glucose measures			
HbA1c, % (mean±SD)	7.0±1.2	7.4±1.4	7.0±1.2
Proportion (%) of patients with HbA1c <7%	55.5	45.9	56.3
FBG, mg/dL (mean±SD)	142.8±40.3	149.6±55.0	142.2±38.8
Systolic blood pressure, mmHg (mean±SD)	133.4±13.3	134.0±12.1	133.3±13.4
Diastolic blood pressure, mmHg (mean±SD)	76.8±7.9	76.1±7.7	76.9±8.0
Total cholesterol, mg/dL (mean±SD)	192.5±35.6	194.3±39.3	192.3±35.2
LDL-C, mg/dL (mean±SD)	115.3±29.7	117.9±32.1	115.1±29.5
HDL-C, mg/dL (mean±SD)	49.1±12.7	48.4±12.2	49.1±12.8
Triglycerides, mg/dL (mean±SD)	145.4±86.9	142.4±83.1	145.6±87.3

Bibliographic reference (Ref ID)	Salinero-Fort et al 2013 – Four-year incidence of diabetic retinopathy in a Spanish cohort: the MADIABETES study

Microalbuminuria (%)	22.3	24.2	22.1

Adjusted HR and 95% CI from Cox proportional hazard models for diabetic retinopathy:

HbA1c	Adjusted HR (95% CI)
<7%	1.00
7 to 8%	1.39 (1.01, 1.92)
>8%	1.90 (1.30, 2.77)

*adjusted for sex, duration of diabetes, microalbuminuria, LDL-C, blood pressure and use of aspirin

Funding	Grant from Spanish Ministry of Science and Innovation via the Instituto de Salud Carlos III
Authors' conclusion	Higher baseline HbA1c, higher HDL-C, longer duration of diabetes and aspirin use were significant risk factors for diabetic retinopathy
Comments	Study conducted in Spain Dropout 12.5% Excluded housebound people

Evidence Table 17: (Zhao et al 2013, Diabetes Care)

Bibliographic reference (Ref ID)	Zhao et al 2013 – HbA1c and lower-extremity amputation risk in low-income patients with diabetes
Study type & aim	To determine the association between HbA1c levels and risk of lower-extremity amputation in people with type 2 diabetes from low income background Prospective cohort Louisiana, USA (multi-centre)
Number and Characteristics of patients	**Total number of patients:** 35368 (19808 African Americans, 15560 Whites) **Included:** Patients (30-94 years) of seven public hospitals first diagnosed with type 2 diabetes were identified using the Louisiana State University Hospital-based Longitudinal Study database (1st January 1999 to 31st December 2009) and taken as the baseline

<table>
<tr><td>Bibliographic reference (Ref ID)</td><td>Zhao et al 2013 – HbA1c and lower-extremity amputation risk in low-income patients with diabetes</td></tr>
<tr><td></td><td>No history of lower-extremity amputation
Complete data for all risk factor variables</td></tr>
<tr><td>Monitoring information and definitions</td><td>Details not provided</td></tr>
<tr><td>Intervention</td><td></td></tr>
<tr><td>Comparator</td><td></td></tr>
<tr><td>Length of follow up</td><td>Mean follow up: 6.83 years
Cohort established via database (1st January 1999 to 31st December 2009) and patients were followed up until 31st May 2012</td></tr>
<tr><td>Outcomes measures and effect sizes</td><td>Outcomes:
Lower-extremity amputation

Baseline characteristics of follow up patients:
<table>
<tr><td></td><td>African Americans (n=19808)</td><td>Whites (n=15560)</td></tr>
<tr><td>Age, years (mean±SD)</td><td>51.1±10.2</td><td>53.7±10.4</td></tr>
<tr><td>Sex: male, N (%)</td><td>7019 (35.4)</td><td>6344 (40.8)</td></tr>
<tr><td>Body mass index, kg/m^2 (mean±SD)</td><td>33.8±8.5</td><td>34.7±8.7</td></tr>
<tr><td>Current smoker, N (%)</td><td>6437 (32.5)</td><td>5825 (37.4)</td></tr>
<tr><td>Income, USD/family (mean+SD)</td><td>8886±10833</td><td>11033±12048</td></tr>
<tr><td>Type of insurance, N (%)
Free (low income ≤200% of federal poverty level or uninsured)
Self-pay (uninsured but income not low enough to qualify for free care)
Medicaid
Medicare
Commercial</td><td>
15500 (78.3)
1151 (5.9)
1197 (6.0)
1625 (8.2)
330 (1.6)</td><td>
11840 (76.1)
586 (3.8)
628 (4.0)
2049 (13.2)
457 (2.9)</td></tr>
<tr><td>Medication use, N (%)
Glucose-lowering medication
Lipid-lowering medication
Antihypertensive medication</td><td>
13093 (66.1)
10903 (55.0)
14923 (75.3)</td><td>
9487 (61.0)
9037 (58.1)
10813 (69.5)</td></tr>
</table></td></tr>
</table>

Bibliographic reference (Ref ID)	Zhao et al 2013 – HbA1c and lower-extremity amputation risk in low-income patients with diabetes

Comorbidities, *N* (%)		
Peripheral arterial disease at baseline	554 (2.8)	751 (4.8)
Peripheral arterial disease during follow up	2518 (12.7)	2685 (17.3)
Ulcer at baseline	232 (1.2)	230 (1.5)
Ulcer during follow up	1370 (6.9)	1219 (7.8)
Foot deformity at baseline	105 (0.5)	52 (0.3)
Foot deformity during follow up	984 (5.0)	387 (2.5)
Blood glucose measures		
HbA1c at baseline, % (mean)	8.0	7.3
HbA1c during follow up, % (mean)	7.7	7.2
Systolic blood pressure, mmHg (mean±SD)	133.4±13.3	134.0±12.1
Diastolic blood pressure, mmHg (mean±SD)	76.8±7.9	76.1±7.7
LDL-C, mg/dL (mean±SD)	114±40	110±40
Glomerular filtration rate (mL/min/1.73m^2), *N* (%)		
≥90	10651 (53.8)	5576 (35.9)
60-89	6962 (35.2)	7307 (47.0)
30-59	1481 (9.3)	2415 (15.5)
15-29	217 (1.1)	178 (1.1)
<15	112 (0.6)	56 (0.4)

Adjusted HR and 95% CI from Cox proportional hazard models for lower-extremity amputation for African Americans:

HbA1c	At baseline				During follow up			
	Sample size	Cases	Person years	Adjusted HR (95% CI)	Sample size	Cases	Person years	Adjusted HR (95% CI)
<6.0%	5121	27	32733	1.00	4212	22	25216	1.00
6 to 6.9%	4938	51	35317	1.73 (1.07, 2.80)	5094	46	35125	1.51 (0.87, 2.63)
7 to 7.9%	2613	38	20075	1.65 (0.99, 2.77)	3570	62	27580	1.95 (1.13, 3.38)
8 to 8.9%	1713	32	13736	1.96 (1.14, 3.36)	2419	56	19319	2.27 (1.29, 3.98)
9 to 9.9%	1327	45	10347	3.02 (1.81, 5.04)	1748	50	14188	2.96 (1.66, 5.27)
≥10%	4096	143	29693	3.30 (2.10, 5.20)	2765	100	20473	3.14 (1.81, 5.45)

Bibliographic reference (Ref ID)	Zhao et al 2013 – HbA1c and lower-extremity amputation risk in low-income patients with diabetes

Each 1% increase	NA	NA	NA	1.12 (1.08, 1.17)	NA	NA	NA	1.07 (1.02, 1.12)

*adjusted for age, sex, type of insurance, income, smoking, peripheral arterial disease, ulcer, and foot deformity at baseline and during follow up; for baseline (in the baseline analyses) and updated mean (in the follow-up analyses) of BMI, LDL-C, systolic blood pressure and glomerular filtration rate; and use of antihypertensive drugs, glucose lowering drugs and cholesterol lowering agents

Adjusted HR and 95% CI from Cox proportional hazard models for lower-extremity amputation for Whites:

HbA1c	At baseline				During follow up			
	Sample size	Cases	Person years	Adjusted HR (95% CI)	Sample size	Cases	Person years	Adjusted HR (95% CI)
<6.0%	5536	27	32427	1.00	4483	18	24270	1.00
6 to 6.9%	3770	29	24760	1.16 (0.66, 2.02)	4345	33	28248	1.40 (0.74, 2.65)
7 to 7.9%	2044	42	14432	2.28 (1.35, 3.85)	2824	53	20227	2.70 (1.46, 5.01)
8 to 8.9%	1317	32	9138	2.38 (1.36, 4.18)	1735	45	12190	3.12 (1.67, 5.84)
9 to 9.9%	987	32	6663	2.99 (1.71, 5.22)	1082	42	7674	3.70 (1.93, 7.10)
≥10%	1906	80	12168	3.25 (1.98, 5.33)	1091	51	6978	3.96 (2.08, 7.53)
Each 1% increase	NA	NA	NA	1.15 (1.09, 1.21)	NA	NA	NA	1.13 (1.06, 1.21)

*adjusted for age, sex, type of insurance, income, smoking, peripheral arterial disease, ulcer, and foot deformity at baseline and during follow up; for baseline (in the baseline analyses) and updated mean (in the follow-up analyses) of BMI, LDL-C, systolic blood pressure and glomerular filtration rate; and use of antihypertensive drugs, glucose lowering drugs and cholesterol lowering agents

Subgroup analyses: Adjusted HR and 95% CI from Cox proportional hazard models for lower-extremity amputation for total population at baseline:

HbA1c	Sex		Age (years)			BMI (kg/m^2)			
	Male (n=13362)	Female (n=22005)	<50	50-59	60-94	<25	25-29.9	30-39.9	≥40
<6.0%	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
6 to 6.9%	1.48 (0.95, 2.26)	1.63 (0.80, 3.32)	1.80 (0.95, 3.43)	1.13 (0.66, 1.94)	2.02 (0.94, 4.35)	0.89 (0.43, 1.85)	2.89 (1.34, 6.26)	1.79 (0.98, 3.28)	0.99 (0.36, 2.75)
7 to	1.85 (1.20,	2.37 (1.17,	2.41 (1.27,	1.50 (0.86,	3.19 (1.42,	1.51 (0.72,	3.11 (1.36,	2.22 (1.22,	1.92 (0.70,

Bibliographic reference (Ref ID)	Zhao et al 2013 – HbA1c and lower-extremity amputation risk in low-income patients with diabetes

7.9%	2.85)	4.80)	4.57)	2.63)	7.18)	3.17)	7.10)	4.03)	5.27)
8 to 8.9%	2.19 (1.40, 3.42)	2.26 (1.04, 4.91)	2.34 (1.25, 4.38)	2.26 (1.22, 4.18)	3.06 (1.18, 7.95)	1.49 (0.66, 3.34)	4.64 (2.02, 10.70)	2.04 (1.05, 3.99)	2.22 (0.81, 6.09)
9 to 9.9%	3.15 (2.04, 4.85)	3.43 (1.63, 7.24)	3.01 (1.63, 5.57)	3.69 (2.10, 6.47)	2.37 (0.80, 7.01)	4.65 (2.24, 9.69)	6.89 (3.12, 15.20)	2.30 (1.18, 4.48)	2.37 (0.79, 7.08)
≥10%	2.84 (1.93, 4.17)	4.96 (2.50, 9.71)	3.93 (2.26, 6.84)	2.89 (1.73, 4.82)	3.19 (1.27, 8.00)	3.73 (1.99, 7.00)	5.79 (2.73, 12.30)	3.38 (1.93, 5.91)	2.28 (0.88, 5.92)

*adjusted for age, sex, race, BMI, LDL-C, systolic blood pressure, glomerular filtration rate, type of insurance, smoking, peripheral arterial disease, ulcer, and foot deformity at baseline and during follow up; and use of antihypertensive drugs, glucose lowering drugs and cholesterol lowering agents other than the variable for stratification

Subgroup analyses: Adjusted HR and 95% CI from Cox proportional hazard models for lower-extremity amputation for total population at baseline:

HbA1c	Use of glucose lowering medication		Blood pressure				LDL-C (mg/dL)			
	Yes (n=12788)	No (n=22580)	<130/80	130-139/80-89	140-159/90-99	≥160/100	<70	70-99.9	100-119.9	≥120
<6.0%	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
6 to 6.9%	1.30 (0.72, 2.33)	1.62 (1.02, 2.59)	1.20 (0.60, 2.40)	1.00 (0.43, 2.36)	2.94 (1.36, 6.37)	1.54 (0.75, 3.16)	1.10 (0.57, 2.15)	1.58 (0.87, 2.86)	1.08 (0.43, 2.69)	7.59 (1.76, 32.80)
7 to 7.9%	2.24 (1.26, 3.98)	1.93 (1.20, 3.12)	2.05 (1.02, 4.12)	2.26 (0.91, 5.60)	4.01 (1.84, 8.76)	1.41 (0.67, 2.98)	1.35 (0.65, 2.80)	1.81 (0.97, 3.36)	2.02 (0.88, 4.65)	9.40 (2.15, 41.10)
8 to 8.9%	1.94 (0.97, 3.88)	2.20 (1.36, 3.58)	2.45 (1.17, 5.14)	1.24 (0.47, 3.28)	3.86 (1.70, 8.73)	2.19 (1.01, 4.75)	1.12 (0.52, 2.40)	2.49 (1.30, 4.76)	1.64 (0.65, 4.12)	10.20 (2.31, 45.40)
9 to 9.9%	2.81 (1.43, 5.51)	3.41 (2.14, 5.45)	1.57 (0.70, 3.54)	3.93 (1.66, 9.32)	6.35 (2.91, 13.90)	4.07 (1.91, 7.16)	3.07 (1.58, 5.97)	2.67 (1.34, 5.31)	4.53 (1.96, 10.50)	9.78 (2.21, 43.20)
≥10%	2.73	3.50	3.15	3.01	5.11	3.63	1.68	3.70	3.28	14.90

Bibliographic reference (Ref ID)	Zhao et al 2013 – HbA1c and lower-extremity amputation risk in low-income patients with diabetes
	<table><tr><td></td><td>(1.55, 4.82)</td><td>(2.28, 5.36)</td><td>(1.68, 5.89)</td><td>(1.49, 6.09)</td><td>(2.40, 10.90)</td><td>(1.84, 7.16)</td><td>(0.90, 3.12)</td><td>(2.13, 6.43)</td><td>(1.47, 7.28)</td><td>(3.55, 62.60)</td></tr></table> *adjusted for age, sex, race, BMI, LDL-C, systolic blood pressure, glomerular filtration rate, type of insurance, smoking, peripheral arterial disease, ulcer, and foot deformity at baseline and during follow up; and use of antihypertensive drugs, glucose lowering drugs and cholesterol lowering agents other than the variable for stratification
Funding	Grant from Louisiana State University's Improving Clinical Outcomes Network
Authors' conclusion	There is evidence of a graded association between HbA1c and risk of lower-extremity amputation in African American and white type 2 diabetes people from low income background
Comments	~>60% were female ~2.2% were covered by commercial health insurance

E.4 Review question 4: Should intensive or conventional target values be used to control blood glucose levels in people with type 2 diabetes?

Evidence table (Hemmingsen et al 2013, Cochrane review)

Bibliographic reference (Ref ID)	Hemmingsen et al 2013 – Intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus
Study type & aim	Systematic review To assess the effects of targeting intensive vs conventional glycaemic control in T2D patients
Number and characteristics of patients	**Participants;** Adults aged 18 years and above with T2D were included. The diagnosis of T2D should have been established at randomisation into the trial using standard criteria (for example, ADA 1997; ADA 1999; ADA 2003; ADA 2008; ADAa 2010; NDDG 1979; WHO 1980; WHO 1985; WHO 1998; WHO 2011). Ideally, the diagnostic criteria should have been described. If necessary, the authors' definition of T2D was used.
Interventions	All included trials should have, prior to patient allocation, predefined in the protocol the different glycaemic targets for intensive and conventional glycaemic control. Trials using HbA1c equivalents (for example, total glycosylated haemoglobin) to compare predefined intensive versus conventional glycaemic treatment were included as well. Furthermore, if no HbA1c (or equivalent) target levels were predefined, trials targeting metabolic control as measured by fasting blood or plasma glucose or postprandial blood or plasma glucose also fulfilled the criteria for inclusion. Trials with a prespecified glycaemic target in the intensive group only were also included. However, as outlined, studies with different target levels for fasting or postprandial blood or plasma glucose but with similar HbA1c (or equivalent) target levels between interventions, or no specified target levels, did not fulfil the criterion for inclusion.
Outcomes	**Primary outcome measures:** All-cause mortality Cardiovascular mortality (death from MI, stroke, PVD) (subgroup analysis for primary outcomes and non-fatal MI; - Comparing trials with low risk of bias with high risk of bias - Comparing trials with study duration >2yrs with those of ≤2yrs) **Secondary outcome measures:** Macrovascular complications (non-fatal MI, non-fatal ischaemic stroke, non-fatal haemorrhagic stroke, amputation of lower extremity, cardiac or peripheral revascularisation) Microvascular complications (manifestation and progression of nephropathy, ESRD, manifestation and progression of

Bibliographic reference (Ref ID)	Hemmingsen et al 2013 – Intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus
	retinopathy,retinal photocoagulation) Adverse events CHF Hypoglycaemia; mild (controlled by patients), moderate (daily activities interrupted but self-managed), severe (requiring assistance) Health-related QoL Cost of treatment Macrovascular and microvascular outcomes assessed as a composite outcome and each outcome separately (Planned subgroup analyses; - anti-diabetic intervention used to achieve glycaemic target (drug classes compared to each other, the use of monotherapy compared to combination therapy) - HbA1c <7.0% compared with ≥7.0% - defined target in terms of HbA1c compared with non-HbA1c target - cardiovascular disease at baseline - peripheral revascularisation and retinal photocoagulation - age <65yrs compared with ≥65yrs)
Length of follow up	As specified in the individual RCT'
Location	As specified in the individual RCT'
Comments	

E.5 Review question 5: Should self-monitoring be used to manage blood glucose levels in people with type 2 diabetes?

Evidence table 1: (Malanda et at 2012)

Bibliographic reference (Ref ID)	Malanda et al 2012-Updated Cochrane review (REF ID: 19)
Study type & aim	Cochrane systematic review to assess the effect of self-monitoring of blood glucose (SMBG) in patients with type 2 diabetes who are not using insulin.
Number and characteristics of patients	**Total number of patients**: A total of 3259 randomised patients were from 12 randomised controlled trials (RCTs): Allen 1990 (N=54), Davidson 2005 (N=89), Fontbonne 1989 (N=208), Guerci 2003 (N=2003), Muchmore 1994 (N=23), Schwedes 2002 (N=250), Barnett 2008 (N=610), DiGEM trial 2007 (N=453), Duran 2010 (N=195), Franciosi 2011 (N=62), Kleefstra 2010 (N=41), O'Kane 2008 (N=195) **Inclusion criteria:** published and unpublished RCTs of patients with type 2 diabetes assessing the use of SMBG compared to control. Studies assessing the comparison between SMBG and self-monitoring of urine glucose (SMUG) were also included. **Exclusion criteria:** Studies were excluded from the review because they had a control group with access to SMBG, they had included patients using insulin, they did not explore one of the primary outcome measures, were secondary reports of already included studies or because patients were not randomised **Patient characteristics**: All trials had similar groups at baseline for the most important prognostic indicators, except for Kleefstra (2010). In that study, diabetes duration differed between the intervention and control group. With the exception of SMBG study group Schwedes (2002), co-interventions were similar or avoided in all studies. We evaluated that the SMBG group in SMBG study group 2002 received a co-intervention by means of a structured counselling program every four weeks during the intervention period while the control group only received non-standardised counselling. **Subgroup analyses:** A priori defined subgroups were: • HbA1c level at baseline (subdividing into three groups of low [less than 7.0%], medium [between 7.0% and 11.0%] and high level [11.0% or higher] - based on data) • diabetes duration (up to one year past diagnosis vs. duration over one year) • duration of intervention (short-term [up to six months follow-up], medium-term [between 6 and 12 months follow-up], long term [12 months follow-up or more]) • age groups (below 60 years, over 60 years) • gender • presence of complications (e.g. diabetic complications) • different comparison interventions • type of treatment: oral hypoglycaemic agents, diet, exercise, no treatment • weight (normal [body mass index - BMI: women less than 25, men less than 27], overweight [BMI: women 25 to 30, men 27 to 30] obese [BMI more than 30]).

Bibliographic reference (Ref ID)	Malanda et al 2012-Updated Cochrane review (REF ID: 19)
Outcome measures	**Primary outcome measures**: glycaemic control measured by glycated haemoglobin concentration A1c (HbA1c-level); health-related quality of life, well-being (e.g. by using the SF 36 [Ware 1992] or the well-being questionnaire [Bradley 1994a]); patient satisfaction (e.g. by using the Diabetes Treatment Satisfaction Questionnaire [DTSQ, Bradley 1994b]). **Secondary outcome measures:** fasting plasma glucose level; hypoglycaemic episodes; morbidity; adverse effects and costs
Intervention	SMBG vs. usual care without monitoring: 9 trials (Barnett 2008, Davidson 2005, Duran 2010, Franciosi 2011, Guerci 2003, Kleefstra 2010, Muchmore 1994, O'Kane 2008, SMBG study group 2002) SMBG vs. SMUG: 1 trial (Allen 1990) SMBG vs. SMUG vs. usual care: 1 trial (Fontbonne 1989) Less intensive SMBG vs. more intensive SMBG vs. control group: 1 trial (DiGEM trial 2007)
Comparator	See above
Length of follow up	Intervention duration ranged from 6 months to 12 months.
Location	Allen 1990 (USA), Davidson 2005 (USA), Fontbonne 1989 (France), Guerci 2003 (France), Muchmore 1994 (USA), Schwedes 2002 (Germany/Austria), Barnett 2008 (Czech Republic, Hungary, Iran, Malaysia, Poland, Slovakia, Turkey), DiGEM trial 2007 (UK), Duran 2010 (Spain), Franciosi 2011 (Italy), Kleefstra 2010 (the Netherlands), O'Kane 2008 (Northern Ireland).
Outcomes measures and effect sizes	**Heterogeneity** Included studies differed in baseline characteristics and in delivered SMBG education. Due to clinical heterogeneity it was decided not to conduct a pooled analysis of all trials. A random-effects subgroup meta-analysis on the basis of diabetes duration and follow-up was carried out. Primary outcome measure: changes in Hba1c levels: Table one shows the overall summary estimates for changes in Hba1c levels separated for different follow-up times and patient populations.

Table 1. Overall summary estimates for changes in Hba1c levels (%)

Comparison	Follow-up	Total number of included trials	Total number of participants	Pooled mean difference (95% CI)
SMBG vs. control	6 months	9	2324	-0.26 [-0.39, -0.13]
SMBG vs. control	12 months	2	493	-0.13 [-0.31, 0.04]
SMBG vs. control in newly diagnosed patients	6 months	2	345	-0.53 [-1.06, -0.01]
SMBG vs. control in newly diagnosed	12 months	2	345	-0.52 [-0.89, -0.14]

Bibliographic reference (Ref ID)	Malanda et al 2012-Updated Cochrane review (REF ID: 19)

patients				
SMBG vs. SMUG	6 months	2	194	-0.17 [-0.96, 0.61]

Glycaemic control as measured by change in HbA1c between baseline and endpoint improved in the SMBG groups (Davidson 2005; DiGEM trial 2007; Kleefstra 2010; Muchmore 1994; O'Kane 2008), however this was not statistically different from the improvement seen in the control groups. In the meta-analysis, the overall effect for short-term follow-up (up to six months of follow-up) showed a statistically significant decrease of 0.3% in HbA1c (95% CI -0.4 to -0.1; 2324 participants, 9 trials) in favour of SMBG compared with the control group. For medium term follow-up (between 6 and 12 months of follow-up) analysis revealed a statistically non-significant decrease in HbA1c of 0.1% (95% CI -0.3 to 0.04; 493 participants, 2 trials) and no statistical heterogeneity (I^2 = 0%).

The pooled analysis for short-term follow-up (up to six months of follow-up) in newly diagnosed patients (345 participants, 2 trials) showed notable statistical heterogeneity (I^2 = 68%), indicating a substantial inconsistency in the direction of effect. Therefore, the overall effect estimate for HbA1c for this analysis was not presented. However, the meta-analysis for medium term follow-up (between 6 and 12 months of follow-up) in newly diagnosed patients revealed a statistically significant decrease in HbA1c of 0.5% (95% CI -0.9 to -0.1; 345 participants, 2 trials) accompanied by moderate statistical heterogeneity (I^2 = 44%). The pooled comparison between SMBG and SMUG for short term follow-up (up to six months of follow-up) showed a statistical non-significant decrease in HbA1c of 0.2% (95% CI -1.0 to 0.6; 194 participants, 2 trials, Analysis 5.1) in HbA1c. Statistical heterogeneity was not observed (I^2 = 0%).

Primary outcome measure: changes in fasting plasma glucose levels: 3 trials (Allen 1990, Guerci 2003 and Barnett 2008) measured fasting plasma glucose levels. All three studies found that fasting plasma glucose levels decreased as a result of SMBG, however there were no statistically significant differences between SMBG vs. SMUG and SMBG vs. no monitoring.

Other outcome measures

Changes in weight or BMI: Not reported

Frequency, severity and timing of hypoglycaemic episodes: 6 trials (Guerci 2003, DiGEM trial 2007, Barnett 2008, O'Kane 2008, Durán (2010) and Franciosi (2011) investigated SMBG related hypoglycaemia. In Guerci (2003) 10.4% SMBG group and 5.2% control group patients reported at least one episode of symptomatic or asymptomatic hypoglycaemia during the study (P = 0.003). This significant difference was caused by a between-group difference in patients reporting asymptomatic hypoglycaemia only (P = 0.001). No patients reported serious episodes of hypoglycaemia. In the DiGEM trial (2007) episodes of hypoglycaemia with mild symptoms were reported by 9.2%, 22% and 28.5% of the patients in the control group, less intensive group and more intensive group, respectively (P < 0.001). Episodes of severe hypoglycaemia were reported in one patient in the control group (DiGEM trial 2007). In the Barnett (2008) study a hypoglycaemic event (symptomatic, asymptomatic or SMBG confirmed) was reported in 8.7% and 7% of the patients in the SMBG group and control group, respectively. All reported events were considered mild (grade 1), moderate (grade 2) or were non-graded. No significant between-group differences were found in reported hypoglycaemia at any time point in the

Bibliographic reference (Ref ID)	Malanda et al 2012-Updated Cochrane review (REF ID: 19)
	O'Kane (2008) trial. In the Durán (2010) trial no severe hypoglycaemic episodes requiring third-party or medical assistance were reported in either group. In the Franciosi 2011 trial no adverse events including hypoglycaemic events occurred. Barnett (2008) and Guerci (2003) reported adverse effects, but did not specify them. **Adverse events:** see hypoglycaemic episodes **Mortality and microvascular/macrovascular complications**: The DiGEM trial (2007) and Guerci (2003) reported mortality (death of patients during the trial). None of the studies reported data on morbidity. **Quality of life (including changes in confidence, anxiety, mood and depression):** A total of five trials reported outcomes on either patient satisfaction (DiGEM trial 2007; Kleefstra 2010; O'Kane 2008; SMBG study group 2002), well-being (DiGEM trial 2007; Kleefstra 2010; O'Kane 2008; SMBG study group 2002) and/or health-related quality of life (DiGEM trial 2007; Kleefstra 2010; Muchmore 1994). **Treatment satisfaction:** None of the trials reporting outcomes on treatment satisfaction (DTSQ) found significant between group changes (DiGEM trial 2007; Kleefstra 2010; O'Kane 2008; SMBG study group 2002). **Well-being and depression**: SMBG study group 2002 reported a statistically significant decrease of the 22- item Well Being Questionnaire (WBQ-22) sub scale depression in favour of the SMBG group (-0.83 vs. -0.26; range 0 to 18). O'Kane (2008) reported a 6% increase (1.08 points) in the depression subscale of the WBQ-22 (range 0 to 18) in the SMBG group compared to the control group at 12 months (P = 0.01). Both studies did not find statistically significant differences on general well-being or the other three well-being sub-scales (anxiety, energy, positive well-being). The DiGEM trial 2007 found no between group differences in well-being scores (12-item Well Being Questionnaire [WBQ-12]). Kleefstra (2010) found no significant changes between groups in psychological well-being measured with the 5-item Wellbeing Index (WHO-5). **Health related quality of life**: Outcomes on health-related quality of life were reported by 4 trials (Muchmore 1994, DiGEM trial 2007 and Kleefstra 2010). Muchmore (1994) found no significant differences between the SMBG group and the control group in the four sub-scales (satisfaction, impact, diabetes related worry, and the social/vocational worry) of the Diabetes Quality-of-Life Inventory. The DiGEM trial 2007 found that health-related quality of life as measured with the Euro Qol 5 dimensions (EQ5D) questionnaire showed a statistically significant difference of -0.1, (95% CI -0.127 to -0.017; range 1 to 3) at the end of the trial when comparing the more intensive monitoring group with the control group. Kleefstra (2010) found no significant changes between groups in health related quality of life (36-item Short Form Health Survey [SF-36]). Separate analyses of the SF-36 sub scales identified a statistical significant between groups difference in the sub scale health change at the end of the study in favour of the control group (a 4.2 points decrease in the SMBG group and a 9.7 points increase in the control group; range 0 to 100).

Bibliographic reference (Ref ID)	Malanda et al 2012-Updated Cochrane review (REF ID: 19)
	Subgroup analyses (predetermined groups): Subgroup analyses for diabetes duration and duration of the intervention for the comparison of SMBG versus control and SMBG versus SMUG were carried out (see primary outcome measure change in Hba1c levels). Data available on age groups, gender, presence of complications, different comparison interventions, type of treatment and weight could not be extracted sufficiently or could not be delivered by the original authors to investigate subgroups. In addition, baseline glycaemic control was not investigated because 10 out of 12 studies (Allen 1990; Barnett 2008; Davidson 2005; DiGEM trial 2007; Fontbonne 1989; Franciosi 2011; Guerci 2003; Kleefstra 2010; O'Kane 2008; SMBG study group 2002) were in the a-priori specified medium range (between 7.0% and 11.0% HbA1c). The remaining two studies (Durán 2010; Muchmore 1994) had a baseline HbA1c in the low and the high category, respectively. For all comparisons, six months follow-up data (published or retrieved by contacting the authors) or 12 months follow-up data were used only:
Authors' conclusion	When diabetes duration is over one year, the overall effect of self-monitoring of blood glucose on glycaemic control in patients with type 2 diabetes who are not using insulin is small up to six months after initiation and subsides after 12 months. Furthermore, there is no evidence that SMBG affects patient satisfaction, general well-being or general health-related quality of life. More research is needed to explore the psychological impact of SMBG and its impact on diabetes specific quality of life and well-being, as well as the impact of SMBG on hypoglycaemia and diabetic complications. The main results suggest that long-term SMBG in new-onset patients is beneficial in lowering HbA1c. However, when diabetes duration is over one year, the overall glycaemic effect of SMBG is small and more likely to be present at short-term. Because subgroup meta-analyses could not fully take the presence of clinical heterogeneity into account, clinical interpretation and translation into practice of these results is difficult and should be done with caution.
Source of funding	Not reported
Comments	Most included trials and specifically earlier trials were exposed to selection and attrition bias. With the inclusion of new studies (Barnett 2008; DiGEM trial 2007; Durán 2010; Franciosi 2011; Kleefstra 2010; O'Kane 2008) performed after the first review (Welschen 2005a) the risk of bias was reduced.

Evidence table 2: (Lu et al 2011)

Bibliographic reference (Ref ID)	Lu et al 2011 (REF ID: 41)
Study type & aim	To assess whether self-monitoring of urine glucose or blood glucose is effective, convenient and safe for glycaemic control in non-insulin treated type 2 diabetes
Number and characteristics of patients	**Total number of patients:** 108 patients were randomised with 36 analysed in the SMUG group, 34 analysed in the SMBG group and 33 analysed in the control group. **Inclusion criteria:** patients with type 2 diabetes, aged between 18 and 75 years, managed with diet and/or oral hypoglycaemic agents and with a Hba1c level ≥ 7.0% and post-prandial glucose >11.0mmol/L **Exclusion criteria:** included use of insulin, rapidly progressing diabetic complication, severe concurrent illness that would limit life or require extensive treatment, abnormal renal threshold during screening, women in pregnancy or lactation, alcohol misuse and inability to follow trial procedures. **Patient characteristics:** Five patients were lost to follow-up but this was balanced across the groups. There were no significant

Bibliographic reference (Ref ID)	Lu et al 2011 (REF ID: 41)

differences between groups in baseline personal characteristics or laboratory measurements. The mean age was 54.2 years, mean Hba1c level was 8.6% and median duration of diabetes was 3.0 years. Range of the duration was wide from 0 to 19 years, because no limitation of duration had been set for eligibility.

Table 1. Baseline characteristics of included patients (N=108)

Characteristic	SMUG (n=38)	SMBG (n=35)	Control (n=35)
Gender (M/F)	26/12	20/15	23/12
Age (years)	53.13 ± 9.27	53.03 ± 13.77	57.26 ± 9.71
BMI (kg/m^2)	24.96 ± 3.61	24.67 ± 3.34	25.45 ± 4.67
Waist (cm)	94.50 ± 7.96	90.37 ± 7.63	94.99 ± 11.07
Duration of diabetes (years), median	1.0 (0.0-6.0)	4.0 (0.5-8.0)	3.0 (1.0-8.0)
Hba1c (%)	8.8 ± 1.4	8.5 ± 1.1	8.6 ± 1.7
Fasting plasma glucose (mmol/L)	8.60 ± 1.97	9.33 ± 3.23	9.24 ± 2.65
Postprandial glucose (mmol/L)	15.89 ± 3.25	15.51 ± 2.75	14.98 ± 3.84
Triglyceride (mmol/L), median	1.78 (1.17-2.56)	1.51 (1.04-2.15)	1.46 (0.95-2.20)
Total cholesterol (mmol/L)	4.57 ± 0.91	4.54 ± 0.99	4.73 ± 0.80
Quality of life (scores)	170.50 ± 28.23	174.03 ± 18.62	168.96 ± 28.07
Abbreviations: SMUG self-monitoring of urine glucose; SMBG self-monitoring of blood glucose			

Subgroup analyses: No pre-specified or post-hoc subgroup analyses reported

Monitoring information and definitions

Monitoring: After the run-in patients attended scheduled clinic visits every 4 weeks for 6 months.

Definitions: Self-reported hypoglycaemic episodes were categorised as Grade 1: transitory symptoms not affecting normal activity, Grade 2: temporarily incapacitated but able to treat symptoms without help, Grade 3: incapacitated and required assistance to treat symptoms, Grade 4: required medical attention or glucagon injection

Primary outcome measures: change in Hba1c from baseline

Secondary outcome measures: proportion of patients achieving Hba1c targets of <7.0 or ≤6.5%, incidence of hypoglycaemia, changes in BMI, waist circumference, fasting plasma glucose, triglyceride, total cholesterol, compliance to monitoring modality and quality of life

Other outcome measures: N/A

Bibliographic reference (Ref ID)	Lu et al 2011 (REF ID: 41)
Intervention	**Intervention type:** Group B (SMBG) **Instructions:** Instructed in technique of blood glucose testing and were asked to aim for glucose levels 4.0 to 6.0mmol/L before meals and 6.0 to 8.0mmol/L two hours after meals. **Frequency:** required to monitor at same frequency as group A (see below) **Feedback:** given advice on interpreting and applying the results to lifestyle modification**.** **Education:** All patients had one week run-in period during which structured diabetes self-management education was provided by nurse practitioners, dieticians, diabetes educators and physicians. The education sessions focused on diabetes disease process, lifestyle behaviours, utilisation of medications, as well as prevention and detection of complications. **Diary:** All patients received similar diary books in which they had to report changes about diet and exercises. Groups A and B were also required to record the obtained value of urine or blood glucose. **Intervention type:** Group A (SMUG) **Instructions:** Instructed in technique of urine glucose testing and were asked to aim for glucose levels <50 mg/dl **Frequency:** required to test urine twice every day (fasting, 2h after dinner) with at least two extra tests each week (2h after dinner) **Feedback:** as group B (see above) **Education:** as group B (see above) **Diary:** as group B (see above)
Comparator	**Intervention type:** Group C (control group) **Instructions:** asked not to perform any self-monitoring and were provided with standardised usual care **Frequency:** N/A **Feedback:** not reported **Diary:** as group A (see above)
Length of follow up	Intervention: 6 months Follow-up: 6 months
Location	Korea
Outcomes measures and effect sizes	**Primary outcome measures (Change in blood glucose control):** Table 1 shows changes in all blood glucose measures in all 3 treatment groups. At the end-point 46.3% of patients achieved Hba1c <7.0% (58.3% in SMUG group vs. 41.2% in SMBG group vs. 36% in control group, p=0.172) and 32.6% achieved Hba1c ≤6.5% (38.9% in SMUG vs. 35.3% in SMBG vs. 20% control group, p=0.277).

Table 1. Changes in blood glucose measures

Blood glucose measure	SMUG	SMBG	Control	P-value[2]
Hba1c (%)	-	-	-	-

Bibliographic reference (Ref ID)	Lu et al 2011 (REF ID: 41)				
	Baseline	8.8 ± 1.4	8.5 ± 1.1	8.5 ± 1.7	0.577
	6 months	6.9 ± 1.2	7.0 ± 0.9	7.4 ± 1.1	-
	Mean difference (95% CI)*	-1.9 (-2.5 to -1.3)	-1.5 (-1.9 to -1.1)	-1.0 (-1.9 to -0.2)	-
	p-value[1]	0.000	0.000	0.016	-
	Fasting plasma glucose (mmol/L)	-	-	-	-
	Baseline	8.52 ± 1.98	9.36 ± 3.27	9.30 ± 2.75	-
	6 months	6.95 ± 1.64	7.22 ± 1.71	7.61 ± 1.72	0.419
	Mean difference (95% CI)*	-1.57 (-2.40 to -0.74)	-2.14 (-3.45 to -0.83)	-1.70 (-3.18 to -0.22)	0.753
	p-value[1]	0.001	0.002	0.027	-
	***** 95% CI if for mean difference between baseline and 6 months [1] p-value for differences within each group by least significant difference, Friedman test or paired-samples T test [2] p-value for differences between groups by simple or repeated measures analysis of variance or Kruskal-Wallis test				-1.9 (-2.5

Other outcome measures (Changes in weight or BMI): Table 2 shows changes in all weight measures in all 3 treatment groups

Table 2. Changes in weight measures

Weight measures	SMUG	SMBG	Control	P-value[2]
BMI (kg/m^2)	-	-	-	-
Baseline	24.71 ± 3.47	24.61 ± 3.37	25.90 ± 4.52	-
6 months	24.29 ± 3.47	23.67 ± 2.83	25.83 ± 4.56	0.147
Mean difference (95% CI)*	-0.42 (-0.73 to -0.10)	-0.94 (-1.44 to -0.44)	-0.07 (-1.23 to -1.09)	0.122
p-value[1]	0.012	0.001	0.901	-
Waist circumference (cm)	-	-	-	-
Baseline	93.97 ± 7.61	90.52 ± 7.69	95.62 ± 11.27	-
6 months	89.29 ± 7.72	87.85 ± 7.72	93.74 ± 8.56	0.023
Mean difference (95% CI)*	-4.68 (-6.21 to -3.16)	-2.67 (-5.02 to -0.32)	-1.92 (-4.62 to 0.77)	0.165
p-value[1]	0.000	0.027	0.153	-

Bibliographic reference (Ref ID)	Lu et al 2011 (REF ID: 41)

** 95% CI if for mean difference between baseline and 6 months*
1 p-value for differences within each group by least significant difference, Friedman test or paired-samples T test
2 p-value for differences between groups by simple or repeated measures analysis of variance or Kruskal-Wallis test

-1.9 (-2.5

Changes in lipid levels: table 3 shows changes in lipid measures in all 3 treatment groups

Table 3. Changes in lipid levels

Lipid measures	SMUG	SMBG	Control	P-value[2]
Total cholesterol (mmol/L)	-	-	-	-
Baseline	4.51 ± 0.88	4.59 ± 0.96	4.64 ± 0.76	-
6 months	4.39 ± 0.79	4.45 ± 0.85	4.63 ± 1.06	0.147
Mean difference (95% CI)*	-0.13 (-0.43 to 0.16)	-0.15 (-0.43 to 0.13)	-0.01 (-0.41 to 0.40)	0.122
p-value[1]	0.365	0.292	0.963	-
Triglyceride (mmol/L)	-	-	-	-
Baseline	1.78 (1.20 to 2.37)	1.54 (1.01 to 2.19)	1.38 (0.93 to 2.47)	0.531
6 months	1.39 (1.06 to 1.95)	1.22 (1.01 to 1.74)	1.15 (0.88 to 2.26)	0.544
p-value[1]	0.062	0.345	0.418	-

***** *95% CI if for mean difference between baseline and 6 months*
[1] *p-value for differences within each group by least significant difference, Friedman test or paired-samples T test*
[2] *p-value for differences between groups by simple or repeated measures analysis of variance or Kruskal-Wallis test*

Quality of life: table 4 shows changes in quality of life scores across the 3 treatment groups

Table 4. Changes in quality of life

Quality of life (score)	SMUG	SMBG	Control	P-value[2]
Total cholesterol (mmol/L)	-	-	-	-
Baseline	169.86 ± 25.60	174.06 ± 18.86	172.24 ± 28.84	0.750
6 months	185.08 ± 22.12	187.47 ± 22.27	176.28 ± 27.37	0.184
Mean difference (95% CI)*	15.22 (4.92 to 25.53)	13.41 (6.11 to 20.72)	4.04 (-2.49 to 10.57)	0.140
p-value[1]	0.005	0.001	0.214	-

Bibliographic reference (Ref ID)	**Lu et al 2011 (REF ID: 41)**
	***** *95% CI if for mean difference between baseline and 6 months* *[1] p-value for differences within each group by least significant difference, Friedman test or paired-samples T test* *[2] p-value for differences between groups by simple or repeated measures analysis of variance or Kruskal-Wallis test* **Adverse events:** Few patients reported hypoglycaemic events during the trial, with 2 patients in SMUG group, 1 in SMBG group and 2 in the control group (exact X^2 test, p=0.782). None of the five patients experienced more than grade 3 of hypoglycaemia. **Microvascular and macrovascular complication:** not reported **Subgroup analyses:** N/A
Authors' conclusion	Study suggests that SMUG has comparable efficacy on glycaemic control, and facilitates better compliance than SMBG, without influencing the quality of life of risk of hypoglycaemia.
Source of funding	Part of the Key program of Jiangsu National Science Foundation and was funded by the TANITA corporation, Tokyo Japan.
Comments	Randomly generated allocation code from computer programme was used. During the trial a total of 6 different classes of oral glucose-lowering drugs were prescribed to patients, with high rates of utilisation for metformin, α-glucosidase inhibitors and sulfonylureas. Each class of drug was evenly distributed between the groups, either at baseline or at the final visit. No statistical difference between groups was found in the proportions of patients receiving pharmacological adjustments during follow-up (p=0.184). However, after adjustments of hypoglycaemic drugs, there was a difference in the use of combination therapy between the groups. At the end of the trial, none of the control group was prescribes a combination of three kinds of drugs, compared with 30.6% in the SMUG group and 14.7% in SMBG group (exact X^2-test, p=0.004). 70.6% of the three-drug combination therapy combined metformin, α-glucosidase inhibitors and sulfonylureas.

Evidence table 3: (Wing et al 1986)

Bibliographic reference (Ref ID)	**Wing et al 1986 (REF ID: 1287)**
Study type & aim	Randomised controlled trial evaluating the effect of adding self-monitoring of blood glucose levels to a weight control program for people with type 2 diabetes
Number and characteristics of patients	**Total number of patients:** 50 patients with non-insulin dependent diabetes and overweight **Inclusion criteria:** between the ages of 35 and 65 years, 20% or more above ideal weight for height on the basis of metropolitan Life insurance norms, use of oral hypoglycaemic medication or insulin for control of blood glucose and development of diabetes after the age of 30 years. **Exclusion criteria:** patients with prior experience with home monitoring of blood glucose were excluded from the study **Patient characteristics:** There were no significant differences between treatment groups in baseline characteristics. The average weight was 98.2kg and 63.6% above the ideal weight for height. Pre-treatment fasting blood glucose averaged 210.1 mg/dl and average Hba1c was 10.5%.

Bibliographic reference (Ref ID)	Wing et al 1986 (REF ID: 1287)
	Table 1. Baseline characteristics of included patients (N=50) **Characteristic** / **Weight control** / **SMBG** Number: 25 / 25 Males (%): 20 / 24 Using insulin (%): 48 / 52 Age (years): 54.0 / 53.5 **Subgroup analyses:** No pre-specified or post-hoc subgroup analyses reported
Monitoring information and definitions	**Monitoring:** Physiologic assessments were conducted during the week preceding the start of the program and were repeated at weeks 12 and 62. Those taking oral hypoglycaemic medication omitted their evening and morning dose and those taking insulin administered their morning dose of insulin after blood glucose samples had been taken. **Definitions:** Percentage overweight was calculated by comparing the patient's weight to ideal weight for height specified in the metropolitan Life insurance norms. BMI was calculated as kg/m^2. **Primary outcome measures:** No explicit differentiation between primary and secondary outcomes (see below for all outcomes) **Secondary outcome measures:** outcomes included physiologic assessments of BG levels, weight, BP, total cholesterol and triglyceride levels, C-peptide levels, compliance with weight control and compliance with SMBG using diaries and self-reported depression (using Beck depression inventory) at weeks 0, 12 and 62 **Other outcome measures:** N/A
Intervention	**Intervention type:** treatment including SMBG and focusing on weight-blood glucose relationship **Instructions:** taught to self-monitor and encouraged to keep their blood glucose within normal levels (60 to 120mg/dl) by adjusting their caloric intake and expenditure. **Frequency:** provided with enough supplies to complete 5 fasting blood glucose measurements and 2 pre- and post-prandial measurements per week. After week 12, the monitoring regime was reduced to 5 fasting measurements per week. Free self-monitoring supplied were provided through week 37 and then patients were encouraged to purchase supplies on their own. **Feedback:** changes to insulin or oral medication were not made by patients but were made at weekly treatment meetings on the basis of readings and following the same algorithm as used for the weight control group. **Education:** Patients in both groups attended weekly meetings for 12 weeks, monthly meetings for the next 6 months, and follow up sessions at 9 and 12 months. Each meeting consisted of a weigh in, blood glucose measurement and discussion of behaviour modification for weight control. Patients in the monitoring group were taught to observe relationships between their eating and exercise behaviours, their weight and their blood glucose levels and to make changes in their diet and exercise if blood glucose levels were elevated. Both groups were given a standard behavioural weight control program (see below). **Diary:** see below
Comparator	**Intervention type:** Standard behavioural weight control

Bibliographic reference (Ref ID)	Wing et al 1986 (REF ID: 1287)
	Instructions: given a daily calorie goal, based on pre-treatment weight, with a minimum recommended intake of 1000 calories per day being prescribed. The behavioural weight control group focused on weight reduction as the goal of therapy. Financial contracts were refunded contingent on weight loss, with $2 refunded at each treatment meeting for changes in eating and exercise habits. After the fourth week, patients were required to demonstrate an improvement in blood glucose control of 10% from the previous week or maintain their level within the normal range (60 to 120mg/dl) to receive the $2 refund. **Frequency:** N/A **Feedback:** (see education below) **Education:** Specific goals were introduced later to help limit foods high in sugar and to increase the intake of high fibre foods. Walking was encouraged as a form of exercise, and gradually increasing goals for caloric expenditure were prescribed. Behaviour modification techniques for reducing the stimuli associated with eating, slowing the act of eating pre-planning for holidays and eliciting social support were presented. **Diary:** Calorie books and self-monitoring diaries were distributed and asked to self-monitor their intake during the program, attempting to stay within the calorie goal. Daily self-report diaries were asked to be kept during weeks 1 to 12 of the program. After week 12, patients sent monthly weight reports to the office.
Length of follow up	Intervention: 52 weeks Follow-up: 62 weeks
Location	USA
Outcomes measures and effect sizes	**Primary outcome measures (Change in blood glucose control):** Table 1 shows changes in blood glucose in both treatment groups

Table 1. Changes in blood glucose measures

Blood glucose measure	Weight control	SMBG	P-value (0-12 weeks)*	P-value (0-62 weeks)*
Fasting blood glucose (mg/dl)	(n=22)	(n=22)	<0.06	NS
Week 0	207.5 ± 70.5	209.2 ± 69.7	-	-
Week 12	190.7 ± 65.0	197.3 ± 50.0	-	-
Week 62	210.2 ± 73.1	216.2 ± 58.7	-	-
Hba1c level (%)	(n=21)	(n=22)	<0.001	NS
Week 0	10.86 ± 2.00	10.19 ± 2.51	-	-
Week 12	10.00 ± 2.08	9.68 ± 1.95	-	-
Week 62	10.44 ± 2.16	10.19 ± 2.29	-	-
*p-value of F test for time				

Bibliographic reference (Ref ID)	Wing et al 1986 (REF ID: 1287)

Other outcome measures (Changes in weight or BMI): Table 2 shows changes in all weight measures in both treatment groups

Table 2. Changes in weight measures

Weight measures	Weight control	SMBG	P-value (0-12 weeks)*	P-value (0-62 weeks)*
Weight (kg)	(n=22)	(n=23)	<0.001	<0.001
Week 0	96.35 ± 23.57	99.02 ± 16.13	-	-
Week 12	89.53 ± 21.75	93.19 ± 15.25	-	-
Week 62	88.11 ± 17.79	94.92 ± 16.50	-	-
Percent overweight (%)	(n=22)	(n=23)	<0.001	<0.001
Week 0	61.1 ± 28.1	66.8 ± 32.1	-	-
Week 12	50.0 ± 28.6	56.8 ± 29.9	-	-
Week 62	48.9 ± 26.6	59.9 ± 33.3	-	-
*p-value of F test for time				

Changes in lipid levels and BP: Changes in serum lipid levels and blood pressure did not differ between the weight control and SMBG groups. Triglyceride levels decreased significantly over the course of the program from 219.5 mg/dl before treatment to 175.3 mg/dl at 62 weeks ($p<0.01$), but changes in total cholesterol levels (213.2 mg/dl before treatment; 216.4 mg/dl at 62 weeks) and HDL levels (42.8 before treatment and 44.1 mg/dl at 62 weeks) were not significant. Although no changes were observed for diastolic BP (80.9mmHg before treatment vs. 80.8mmHg at 62 weeks), systolic BP improved significantly over the course of the study (140.51 mmHg vs. 132.37 mmHg, $p<0.01$)

Medication changes: Table 3 shows the percentage of patients who had reductions in insulin or oral hypoglycaemic medications over the course of the study. Chi squared analyses indicated that the proportion of patients with decreases in medication was not significantly different for the two treatment groups.

Table 3. Changes in medication use

Weight measures	Weight control	SMBG	Overall
Weeks 0 to 12	-	-	-
Oral agents	75	67	71
Insulin	92	100	96

Bibliographic reference (Ref ID)	Wing et al 1986 (REF ID: 1287)

Weeks 0 to 62	-	-	-
Oral agents	64	73	68
Insulin	64	83	74

Quality of life: There were significant improvements in mood over the course of the program. Beck scores decreased significantly from pre-treatment (mean 11.8) to 12 weeks (mean 6.6). Although there was a tendency for self-reported depression to increase over the following year (mean 9.5 at 1 year) but remained significantly lower than pre-treatment values ($p<0.05$). ANOVA indicated that the mood changes were not significantly different for patients in the weight control group compared to those in SMBG group.

Compliance: High levels of compliance was defined as monitoring of calories for more than 75% of the weeks and the recording of over 75% of the chemstrips plus detection of more than 75% of the marked items. Weight losses for pre-treatment to 12 months was -11.2kg vs. -10.7kg for highly compliant patients in weight control vs. SMBG groups respectively and -4.9kg and -3.0kg for poorly compliant patients. Similarly, 16/18 highly compliant patients had reduction in insulin or oral medication compared with 16/27 poorly compliant patients ($p<0.05$). There were no differences between patients who were compliant with SMBG or weight control.

Adverse events: not reported

Microvascular and macrovascular complication: not reported

Subgroup analyses: for compliance see above

Authors' conclusion	Behavioural weight control used in the study may be of benefit to patients with type 2 diabetes. However, there was no evidence that the addition of self-monitoring improved the outcome in terms of weight loss, reduction in medication, dietary compliance or mood state.
Source of funding	Not reported
Comments	Patients were required to obtain their physicians permission to participate and to deposit $85.00, which could be earned back in full for meeting treatment contingencies. Patients were blocked according to sex and percent overweight and were randomly assigned from within blocks to one of the two treatment groups. Nurse taking BP was unaware of treatment assignment or weight loss of the patients

Evidence table 4: Lim et al 2011)

Bibliographic reference (Ref ID)	Lim et al 2011 (REF ID: 80)
Study type & aim	Three arm RCT to examine the effectiveness of a u-healthcare service in elderly patients with type 2 diabetes
Number and characteristics of patients	**Total number of patients:** 154 (51 in u-healthcare, 51 in SMBG and 52 in control) were randomised. 49, 47 and 48 in the u-healthcare, SMBG and control groups completed the study **Inclusion criteria:** patient ≥60 years diagnosed with type 2 diabetes for at least one year and with Hba1c levels between 6.5 and 10.5%**Exclusion criteria:** severe diabetes complications (e.g. diabetic foot), liver dysfunction, or renal dysfunction or other medical

Bibliographic reference (Ref ID)	Lim et al 2011 (REF ID: 80)

problems that could affect study results or trial participation

Patient characteristics: No significant differences were noted in anthropometry or biochemical parameters including Hba1c and prescriptions of antidiabetics agents among the three groups

Table 1. Baseline characteristics of included patients (N=154)

Characteristic	U-healthcare group (n=51)	SMBG group (n=51)	Control (n=52)	P-value
Age, years	67.2 (4.1)	67.2 (4.4)	68.1 (5.5)	0.542
Sex, male/female	23/27	22/28	19/31	0.706
Diabetes duration, years	14.1 (10.1)	15.4 (8.3)	15.8 (10.7)	0.695
BMI, kg/m^2	24.7 (2.3)	24.9 (3.0)	25.4 (3.3)	0.408
Systolic blood pressure, mmHg	129.8 (18.2)	127.9 (16.1)	129.2 (17.1)	0.856
Diastolic blood pressure, mmHg	73.2 (10.3)	72.7 (10.3)	74.2 (11.1)	0.778
FPG, mg/dl	137.3 (34.4)	137.8 (40.1)	141.6 (43.0)	0.828
Postprandial 2-h glucose, mg/dl	242.5 (64.7)	242.6 (50.1)	246.3 (55.7)	0.982
Hba1c (%)	7.8 (1.0)	7.9 (0.9)	7.9 (0.8)	0.884
Total cholesterol, mg/dl	173.7 (34.7)	175.3 (28.2)	169.1 (30.0)	0.602
Triglyceride, mg/dl	144.44 (53.0)	151.5 (66.2)	164.2 (84.6)	0.685
HDL cholesterol, mg/dl	49.1 (9.9)	48.0 (10.4)	51.9 (16.4)	0.640
LDL cholesterol, mg/dl	110.4 (28.6)	92.9 (22.9)	101.5 (25.3)	0.104
Aspartate aminotransferase, IU/L	20.9 (6.8)	22.3 (9.1)	22.3 (8.5)	0.644
Creatinine, mg/dL	1.06 (0.19)	1.11 (0.34)	1.16 (0.26)	0.211
Medication for glucose control	-	-	-	-
Sulfonylurea, n (%)	29 (58)	24 (56)	28 (48)	0.317
Metformin, n (%)	34 (68)	30 (65.2)	28 (56)	0.216
Thiazolidinedione, n (%)	4 (8)	8 (16)	3 (6)	0.740
DPP-4, n (%)	6 (12)	11 (22)	6 (12)	0.999
Alpha glucosidase inhibitor, n (%)	9 (18)	13 (26)	12 (22.7)	0.475

Bibliographic reference (Ref ID)	Lim et al 2011 (REF ID: 80)
	<table><tr><td>Insulin, n (%)</td><td>12 (24)</td><td>12 (24)</td><td>19 (38)</td><td>0.123</td></tr><tr><td colspan="5">Data are mean (SD) or n (%)</td></tr></table> **Subgroup analyses:** No pre-specified or post-hoc subgroup analyses reported
Monitoring information and definitions	**Monitoring:** All patients visited the outpatient clinic every 3 months for an interview conducted by their physician and provided a blood sample. **Definitions:** see outcome measure for definitions of hypoglycaemia **Primary outcome measures:** proportion of patients achieving Hba1c <7% without hypoglycaemia at 6 months **Secondary outcome measures:** minor hypoglycaemia was defined as symptoms (e.g. weakness, dizziness, shakiness etc.) coexisting with capillary BG levels <3.5mmol/L. Major hypoglycaemia was defined as BG levels <2.8mmol/L and an episode requiring medical attention or exhibiting markedly depressed levels of consciousness or seizure. Nocturnal hypoglycaemia was defined as a hypoglycaemic event occurring while asleep. **Other outcome measures:** N/A
Intervention	**GROUP1: U-healthcare** **Intervention type:** U-healthcare group (have a wired phone connected glucometer plus mobile phone, in which glucometer data were technically transmitted by wired telephone through public switched telephone network (PSTN) **Instructions:** educated to use PSTN-connected glucometer to measure BG levels and to start short message service (SMS) on their mobile phone to receive messages from the CDSS rule engine server. Buttons were larger and so appropriate for use with elderly adults. Patients were given a lead-in period to ensure they were able to fully apply the system. **Frequency:** advised to measure their BG levels at least 8 times a week (≥3 at fasting, ≥3 postprandial and ≥2 bed-times) **Feedback:** All patients visited the outpatient clinic every 3 months for an interview conducted by their physician and provided a blood sample **Education:** pertinent diabetes education including a therapeutic lifestyle change program to standardise every patient's education level and practice of diabetes management. A specialist diabetes management team consisting of diabetologists, nurses, dietitians and exercise trainers organised and directed patient education in the U-healthcare group. In this group additional education was provided to help patients with usage and message interpretation. **Diary:** not reported **GROUP 2: SMBG** **Intervention type:** SMBG group **Instructions:** see frequency below **Frequency:** the SMBG group were advised to measure their BG levels at least 8 times a week (≥3 at fasting, ≥3 postprandial and ≥2 bed-times) **Feedback:** see U-healthcare group **Education:** pertinent diabetes education including a therapeutic lifestyle change program to standardise every patient's education

Bibliographic reference (Ref ID)	Lim et al 2011 (REF ID: 80)
	level and practice of diabetes management. **Diary:** not reported
Comparator	**Intervention type:** routine care (control group) **Instructions:** After education, patients in the control group did not receive an intervention and were advised to follow-up according to their current medical care **Frequency:** N/A **Feedback:** see U-healthcare group **Education:** as SMBG group **Diary:** not reported
Length of follow up	Intervention: 6 months Follow-up: 6 months
Location	Korea
Outcomes measures and effect sizes	**Primary outcome measures (Change in blood glucose control):** Table 1 shows changes in blood glucose in all treatment groups. The proportion of patients with Hba1c <7% after 6 months of follow-up was not significantly different among the three treatment groups, although there was a trend showing a greater proportion of the u-healthcare group achieved Hba1c <7% compared with control. The proportion of patients that achieved Hba1c <7% without hypoglycaemia was 30.6% in the u-healthcare group, which was significantly higher than in the SMBG group (23.4%) or control group (14%, vs. SMBG p=0.027 and vs. control p=0.019)

Table 1. Changes in outcome measures at baseline and 6 months

Outcome	U-healthcare (n=49)			SMBG (n=47)			Control (n=48)		
	Baseline	6 months	P-value	Baseline	6 months	P-value	baseline	6 months	P-value
Weight, kg	64.3 (8.5)	63.5 (8.5)	0.001	66.8 (11.5)	66.4 (11.6)	0.310	63.6 (9.9)	64.2 (9.4)	0.074
BMI, kg/m^2	24.7 (2.4)	24.4 (2.5)	0.009	25.1 (2.9)	25.0 (3.2)	0.303	25.5 (3.5)	25.8 (3.4)	0.005
FPG, mg/dl	137.3 (32.7)	124.3 (29.7)	0.047	137.6 (40.5)	132.2 (15.6)	0.403	146.8 (48.8)	152.6 (58.0)	0.388
Postprandial 2-h glucose, mg/dl	250.1(68.0)	210.1 (49.0)	0.007	239.3 (42.5)	229.80 (65.2)	0.592	259.1 (64.5)	291.1 (77.9)	0.212
Total cholesterol, mg/dl	174.8 (36.0)	171.8 (34.0)	0.490	177.2 (27.1)	183.4 (28.7)	0.242	169.1 (30.0)	174.1 (30.0)	0.168
Triglyceride, mg/dl	150.1 (58.2)	138.8 (56.5)	0.278	175.8 (71.7)	149.9 (85.0)	0.275	135.2 (45.5)	130.1 (69.5)	0.911

Bibliographic reference (Ref ID)	Lim et al 2011 (REF ID: 80)

HDL cholesterol, mg/dl	51.6 (11.8)	49.7 (8.1)	0.243	43.8 (9.2)	46.2 (10.2)	0.421	43.8 (10.9)	45.0 (9.4)	0.750
LDL cholesterol, mg/dl	115.1 (27.8)	95.6 (26.4)	0.038	92.8 (23.7)	100.8 (31.3)	0.302	109.8 (20.5)	93.2 (15.0)	0.099
Frequency of SMBG, n/week	3.2 (3.5)	10.5 (5.1)	<0.001	3.1 (2.7)	8.2 (4.2)	<0.001	2.7 (4.4)	2.4 (3.3)	0.664
Data are mean (SD) or n (%)									

Other outcome measures (Changes in weight or BMI): Table 2 shows changes in weight measures in all treatment groups

Changes in lipid levels and BP: Table 2 shows changes in lipid measures in all treatment groups

Quality of life: not reported

Adverse events: During the 6 months of this study, the proportion of patients experiencing minor hypoglycaemic seemed to be higher in the u-healthcare group (32.2%) than in the SMBG group (24.5%) or control group (21.8%), but this was not statistically significant. In contrast major and nocturnal hypoglycaemia was smaller in the u-healthcare than in the SMBG or control groups ($p<0.05$). Similar results were obtained with number of hypoglycaemic events

Microvascular and macrovascular complication: not reported

Subgroup analyses: N/A

Authors' conclusion	The u-healthcare system helped diabetic patients achieve target glycaemic control with less hypoglycaemia
Source of funding	Supported by a grant of the Korea Healthcare Technology R&D project, Ministry for Health, Welfare & Family affairs, a research grant from the SNUBH and the Korea Science and Engineering Foundation grants
Comments	Block randomisation used to assign each patient to one of three groups

Evidence table 5: (Del Prato trial et al 2012 ELEONOR study)

Bibliographic reference (Ref ID)	Del Prato et al 2012-ELEONOR study (REF ID: 24)
Study type & aim	To compare telecare and conventional SMBG for titrating the addition of one bolus injection of insulin glulisine in patients with type 2 diabetes uncontrolled on oral hypoglycaemic agents for ≥3 months who were first titrated with basal insulin glargine
Number and characteristics of patients	**Total number of patients:** 291 patients were randomised (142 in telecare and 149 in SMBG). The ITT population comprised of 241 patients and of theses 238 completed the study (114 in telecare and 124 in SMBG) **Inclusion criteria:** men and women, 35-70 years old with BMI >25kg/m^2 with type 2 diabetes for at least 1 year, treated with OHAs or metformin at maximal doses for at least 3 months and Hba1c 7.5 to 11.0% were eligible. **Exclusion criteria:** history of two or more severe hypoglycaemic episodes within the past 3 months or history of hypoglycaemic unawareness, active diabetic retinopathy, impaired renal or liver function, hypersensitivity to insulin, insulin analogues or metformin,

Bibliographic reference (Ref ID)	Del Prato et al 2012-ELEONOR study (REF ID: 24)

mental conditions rendering the subject unable to understand the nature, scope or consequences of the study or any clinically significant major organ system disease, pregnant or lactating women.

Patient characteristics: these were comparable at baseline (see table 1). In the telecare group 76/115 patients received full use of the telecare system, defied as patients transmitting data with telecare and receiving an answer from an investigator. Overall 14 patients in the telecare group and 13 in the conventional SMBG group were withdrawn from the study because of FPG>7mmol/L at the end of titration.

Table 1. Baseline characteristics of included patients (N=241)

Characteristic	Telecare (n=115)	Conventional SMBG (n=126)
Sex (n, %)	-	-
Males	60 (52)	66 (52)
Females	55 (48)	60 (48)
Age (years)	57.9 ± 8.7	58.7 ± 7.9
Weight (Kg)	80.5 ± 14.1	82.5 ± 15.2
BMI (kg/m2)	30.0 ± 4.3	30.3 ± 4.7
Number of daily meals	3.4 ± 0.8	3.5 ± 0.9
Calorie intake	1620 ± 259	1590 ± 223
Diabetes duration	10.5 ± 6.7	11.3 ± 6.9
Hba1c (%)	8.83 ± 0.94	8.89 ± 0.95
Combination therapy	101 (87.8)	114 (90.5)
Metformin (n, %)	76 (66)	69 (55)
Monotherapy	14 (12)	12 (10)
Sulfonylureas	38 (33)	32 (25)
Thiazolidinediones	10 (9)	12 (10)
Insulin (n, %)	9 (8)	5 (4)
Data are mean ± SD or n (%)		

Subgroup analyses: No pre-specified or post-hoc subgroup analyses reported

Monitoring information and definitions	**Monitoring:** there was a 2-4 week run-in period, during which any anti-diabetes medication, with the exception of metformin, was discontinued. Metformin was up-titrated in all patients to 2g/day (1g twice daily) until study completion. The treatment phase began when a patient achieved FPG ≤7mmol/L after 8, 12 or 16 weeks of titration. Patients were withdrawn from the study if FPG remained

Bibliographic reference (Ref ID)	Del Prato et al 2012-ELEONOR study (REF ID: 24)
	>7mmol/L after 16 weeks. There were 7 visits, the first at week one, the second at week 4 (start of titration), the third at week 20 (the start of treatment), the fourth at week 24 (for dose adjustment id required in the SMBG group), the fifth at week 32 (8 weeks of treatment), the sixth at week 44 (end of treatment) and the seventh at week 46 (end of follow-up). **Definitions:** **Primary outcome measures:** change in Hba1c from baseline to end of treatment phase (visits 5) between the two treatment groups. **Secondary outcome measures:** safety analyses included the frequency of hypoglycaemia, changes in SMBG 6 or 8-point glycaemic profiles, insulin dose and body weight from baseline **Other outcome measures:**
Intervention	**Intervention type:** Glucobeep telecare system (transforms glucose levels into tones that are transmitted by phone from the patient's home to a centralised server, from which the results are made available to the investigators computer.) **Instructions:** see education **Frequency:** In weeks 9-12 and 21-24 of treatment phase, all patients were asked to perform 2 eight point (pre- and post-breakfast, lunch, and supper and at 11pm and 3am) glucose profiles on 2 consecutive weekdays**.** Eight point glycaemic profiles at visits 2 and 3 were calculated using available data from the patient's glucometer. Patients were required to test glucose whenever they had symptoms related to hypoglycaemia and to record their blood glucose readings**.** **Feedback:** dose adjustments were discussed at each visit. The investigator can also transmit information (e.g. dose titration) to the centralised server, which is returned to the patient by phone. **Education:** Each patient underwent an education program designed to review either conventional capillary blood glucose reading by standard glucometer or features and mode of use of the Glucobeep telecare system. **Diary:** BG levels were recorded in diary
Comparator	**Intervention type:** standard SMBG using standard glucometer **Instructions:** not reported **Frequency:** as telecare group **Feedback:** dose adjustments discussed at each visit. **Diary:** BG values recorded in a diary
Length of follow up	Intervention: 24 weeks Follow-up: 46 weeks
Location	Italy
Outcomes measures and effect sizes	**Primary outcome measures (Change in blood glucose control):** the change in Hba1c from baseline to end of treatment phase was significant for both telecare (adjusted mean ± SE change from baseline, -0.7 ± 0.06%, p<0.0001) and conventional SMBG (adjusted mean ± SE change from baseline, -0.7 ± 0.06%, p<0.0001), with no difference between groups (point estimate 0.07%, 95% CI -0.10 to 0.25, p=0.40). Almost identical results were obtained from the PP population. The proportion of patient's achieving target Hba1c ≤7% was similar in telecare (45.2%) and SMBG (54.8%). Graphs in the full paper also show time course of Hba1c, FPG and insulin at each visit and eight point glycaemic profile at each visit for the IIT population. Although glargine titration was very effective in

Bibliographic reference (Ref ID)	Del Prato et al 2012-ELEONOR study (REF ID: 24)
	reducing FPG, blood glucose levels increased progressively throughout the day to achieve the highest value at bedtime. Adding one injection of glulisine at the time of the meal with the largest glucose excursion resulted in flattening of the blood glucose profile. Eight point profiles demonstrated similar glycaemic values for both treatment groups, regardless of whether the prandial injection was at breakfast, lunch or supper. Approximately 15% of each group did not inject glulisine. **Other outcome measures (Changes in weight or BMI):** There was no change in body weight from baseline to end-point (telecare 0.4 ± 3.4kg, SMBG 0.4 ± 5.1kg) with no difference between treatment groups. **Changes in lipid levels:** not reported **Quality of life:** not reported **Insulin dose:** At the end of the treatment phase, both the telecare and SMBG groups had received similar doses of glulisine (9.5 ± 8.3 vs. 9.5 ± 6.8 U respectively and glargine (28.6 ± 17.8 vs. 27.8 ± 16.0 U respectively) **Adverse events:** The incidence (events per patient year) of total symptomatic hypoglycaemia (telecare 1.89 and SMBG 1.76), severe hypoglycaemia (telecare 0.04 and SMBG 0.02) and severe nocturnal hypoglycaemia (telecare 0.02 and SMBG 0.01) was low and comparable between the two treatment groups. **Microvascular and macrovascular complication:** not reported **Subgroup analyses:** N/A
Authors' conclusion	In conclusion, the telecare system did not provide an advantage in glycaemic control over conventional monitoring in the study population. Patient adding one dose of glulisine at the meal with the highest postprandial plasma glucose excursion to titrated basal glargine achieved comparable improvements in glycaemic control irrespective of traditional or telecare blood glucose monitoring.
Source of funding	Study was supported by Sanofi-Aventis
Comments	N/A

Evidence table 6: Vigersky et al 2012)

Bibliographic reference (Ref ID)	Vigersky et al 2012 (REF ID: 27)
Study type & aim	To evaluate the utility of real time continuous glucose monitoring (RT-CGM) in people with T2DM on a variety of treatment modalities except prandial insulin.
Number and characteristics of patients	**Total number of patients:** 100 participants **Inclusion criteria:** see evidence table for Ehrhardt (2011) for details **Exclusion criteria:** see evidence table for Ehrhardt (2011) for details **Patient characteristics:** see evidence table for Ehrhardt (2011) for details **Subgroup analyses:** No pre-specified or post-hoc subgroup analyses reported
Monitoring information and	**Monitoring:** see evidence table for Ehrhardt (2011) for details **Definitions:** see evidence table for Ehrhardt (2011) for details

Bibliographic reference (Ref ID)	Vigersky et al 2012 (REF ID: 27)
definitions	**Primary outcome measures:** The primary outcome of the study was A1C over the course of the study **Secondary outcome measures:** **Other outcome measures:**
Intervention	**Intervention type:** RT-CGM **Instructions:** see evidence table for Ehrhardt (2011) for details. After the initial 12 weeks, the RT-CGM group continued with SMBG for the duration of the study, as recommended by their usual provider. All participants continued usual care for their type 2 diabetes and were instructed to contact their primary care provider for all treatment decisions **Frequency:** see evidence table for Ehrhardt (2011) for details **Feedback:** see evidence table for Ehrhardt (2011) for details **Education:** see evidence table for Ehrhardt (2011) for details **Diary:** see evidence table for Ehrhardt (2011) for details
Comparator	**Intervention type:** SMBG **Instructions:** After the initial 12 weeks, they performed SMBG for the duration of the study, as recommended by their usual provider. **Frequency:** see evidence table for Ehrhardt (2011) for details **Feedback:** see evidence table for Ehrhardt (2011) for details **Diary:** see evidence table for Ehrhardt (2011) for details
Length of follow up	Intervention: 12 weeks (This article reports on the 12-week effectiveness) Follow-up: 52 weeks
Location	USA
Outcomes measures and effect sizes	**Primary outcome measures (Change in blood glucose control):** The unadjusted mean Hba1C decreased by 1.0 ± 1.1%, 1.2 ± 1.7%, 0.8 ± 1.7%, and 0.8 ± 1.5% in the RTCGM group vs. 0.5 ± 0.8%, 0.5 ± 1.0%, 0.5 ±1.1%, and 0.2 ± 1.3% in the SMBG group at 12, 24, 38, and 52 weeks, respectively. After statistical adjustment for age, sex, baseline therapies, and whether the subject was started on insulin over the study, the rates of change in Hba1c were 1.16 x (1/time^2) (P , 0.0001) for the RT-CGM group and 0.51 x (1/time2) (P = 0.002) for the SMBG group. In other words, the adjusted decline in Hba1c for the RT-CGM versus SMBG group was 0.9 vs. 0.4% from baseline to 12 weeks, 1.0 vs. 0.5% from baseline to 24 weeks, 1.1 vs. 0.5% from baseline to 38 weeks, and 1.1 vs. 0.5% from baseline to 52 weeks. Age, taking only oral hypoglycemia medications, insulin, noninsulin injectable medications at baseline (vs. diet and exercise), and starting insulin were significant predictors of an increase in Hba1c over time. When adjusted for potential confounders, subjects in the RT-CGM group who wore the sensor for at least 48 days experienced the following decline in Hba1c: 1.0% from baseline to 12 weeks, 1.2% from baseline to 24 weeks, and 1.3% from baseline to 38 and 52 weeks. By comparison, subjects in the RT-CGM group who did not wear the sensor per protocol experienced a decline in Hba1c of 0.7% at 12 weeks, with no further decline for the duration of the study. Age, sex, diabetes therapy at baseline, and starting insulin during the study were not significant in this model. In our analysis of the total number of days of RTCGM and Hba1c over the course

Bibliographic reference (Ref ID)	Vigersky et al 2012 (REF ID: 27)

of the study, we found that for each single day of RT-CGM (a continuous variable), Hba1c declined by 0.02 (P = 0.02).

Other outcome measures (Changes in weight or BMI): Table 1 shows changes in all weight measures (also see table 2)

Table 1. Changes in weight measures

	0-12 weeks			0-52 weeks		
Weight measures	**RT-CGM**	**SMBG**	**P-value**	**RT-CGM**	**SMBG**	**P-value**
Weight loss (> -3 pounds)	20 (40)	9 (18)	0.03	23 (46)	17 (34)	0.37
No weight change	24 (48)	29 (58)	-	16 (32)	15 (30)	-
Weight gain (> +3 pounds)	6 (12)	12 (24)	-	11 (22)	18 (36)	-
Data are n (%). P values are from x^2tests.						

Changes in lipid levels: table 2 shows changes in other outcome measures across 52 follow-up period

Table 2. Changes in all outcomes

Outcome	SMBG	RT-CGM	P-value
Weight (pounds)	-	-	-
Baseline*[‡]	197.3 ± 46.4	206.5 ± 35.7	0.27 [0.43]
12 weeks	196.5 ± 43.1	202.6 ± 32.3	-
52 weeks	195.3 ± 41.1	202.4 ± 34.3	-
BMI (kg/m^2)	-	-	-
Baseline*[‡]	32.7 ± 7.7	31.9 ± 5.8	0.54 [0.61]
12 weeks	31.8 ± 6.2	31.3 ± 5.4	-
52 weeks	31.7 ± 6.3	31.4 ± 6.0	-
Systolic blood pressure (mmHg)	-	-	-
Baseline*[‡]	132.5 ± 19.3	130.8 ± 16.2	0.63 [0.14]
12 weeks	129.5 ± 18.0	129.3 ± 16.7	-
52 weeks	135.2 ± 19.1	128.5 6 17.6	-
Diastolic blood pressure (mmHg)	-	-	-
Baseline*[‡]	77.6 ± 9.8	79.0 ± 8.9	0.52 [0.82]

Bibliographic reference (Ref ID)	Vigersky et al 2012 (REF ID: 27)

12 weeks	76.2 ± 8.3	77.7 ± 11.3	-
52 weeks	78.0 ± 10.8	78.4 ± 10.9	-
PAID questionnaire score			
Baseline*[‡]	23.9 ± 22.3	25.7 ± 20.8	0.96 [0.09]
12 weeks	17.1 ± 18.0	19.9 ± 17.1	-
52 weeks	18.4 ± 20.5	19.6 ± 20.5	-
Hba1C (%)			
Baseline*[‡]	8.2 ± 1.1	8.4 ± 1.3	0.24 [0.04]
12 weeks	7.7 ±1.2	7.4 ± 1.0	-
24 weeks	7.6 ± 1.3	7.3 ± 1.1	-
38 weeks	7.7 ±1.3	7.6 ±1.2	-
52 weeks	7.9 ±1.4	7.7 ± 1.1	-
Data are means ± SD or n (%). For diabetes distress, as measured by the PAID questionnaire, the last observation was not carried forward because of nontrivial missing data. n = 38 in the repeated-measures ANOVA. ‡ P value is from a repeated-measures ANOVA.			

Quality of life: see table 2 for PAID questionnaire score

Glucose-lowering therapy: Although subjects in both groups had an overall intensification of their medication regimen over the course of the study, fewer subjects in the RT-CGM group were started on insulin (6 vs. 14 subjects in the SMBG group) between baseline and the last visit (P = 0.05).

Adverse events: not reported

Microvascular and macrovascular complication: not reported

Subgroup analyses: N/A

Authors' conclusion	Subjects with type 2 diabetes not on prandial insulin who used RT-CGM intermittently for 12 weeks significantly improved glycaemic control at 12 weeks and sustained the improvement without RT-CGM during the 40-week follow-up period, compared with those who used only SMBG
Source of funding	DexCom Inc.
Comments	N/A

Evidence table 7: (Yoo et al 2008)

Bibliographic reference (Ref ID)	Yoo et al 2008 (REF ID: 213)

Bibliographic reference (Ref ID)	Yoo et al 2008 (REF ID: 213)
Study type & aim	To determine whether a real time continuous glucose monitoring in the home setting is useful for poorly controlled type 2 diabetes with a view to modify a patient's diet and exercise habits and improve self-control, thereby inducing better glycaemic control compared with SMBG.
Number and characteristics of patients	**Total number of patients:** 65 **Inclusion criteria:** aged 20-80 years, type 2 diabetes with use of oral hypoglycaemic agents (OHA) or insulin for at least 1 year, Hba1c between 8% and 10%, a stable insulin or OHA regime for the prior 2 months and a stable dose of anti-hypertensive or lipid-lowering drugs for at least 4 weeks Exclusion criteria: severe diabetic complications, corticosteroid use in previous 3 months, liver disease, renal insufficiency with serum creatinine ≥2.0mg/dL and other medical problems that affect study results or trial participation. **Patient characteristics:** see table 1 for details

Table 1. Baseline characteristics of included patients (N=65)

Characteristic	SMBG (n=28)	RT-CGM (n=29)	P-value
Gender (male %)	14 (50)	10(34.5)	0.29
Age	57.5 ± 9.0	54.6 ± 6.8	0.17
Body weight (kg)	65.7 ± 12.3	63.3 ± 12.4	0.46
BMI (kg/m^2)	25.7 ± 3.5	25 ± 3.0	0.43
Waist circumference (cm)	90.7 ± 10.6	89 ± 11.2	0.56
Duration of diabetes (years)	13.3 ± 4.9	11.7 ± 5.8	0.28
OHA (%)	10 (35.7)	13(44.8)	0.59
Insulin	5 (17.9)	4 (13.8)	0.73
Insulin + OHA	12 (42.9)	11 (37.9)	0.79
Smoker	10 (35.7)	9 (31)	0.78
FBG (mmol/l)	6.5 ± 1.3	6.3 ± 1.3	0.57
Postprandial BG (mmol/l)	11.5 ± 3.6	11.3 ± 2.8	0.87
Hba1c (%)	8.7 ± 0.7	9.1 ± 1.0	0.12
Total cholesterol (mmol/l)	4.3 ± 0.2	4.2 ± 0.1	0.56
HDL cholesterol (mmol/l)	1.3 ± 0.1	1.2 ± 0.1	0.19
LDL cholesterol (mmol/l)	2.4 ± 0.1	2.4 ± 0.1	0.95
Triglycerides (mmol/l)	1.7 ± 1.6	1.5 ± 0.9	0.49

Bibliographic reference (Ref ID)	Yoo et al 2008 (REF ID: 213)
	Means ± SD for continuous variables or percentile for categorical variables. **Subgroup analyses:** No pre-specified or post-hoc subgroup analyses reported
Monitoring information and definitions	**Monitoring:** see intervention **Definitions:** N/A **Primary outcome measures:** difference in change in Hba1c levels after 3 months between treatment groups Secondary outcome measures: fasting blood glucose (FBG), postprandial 2h blood glucose, lipid profiles, weight, waist circumference and BMI. The secondary end-point was the difference in the change in diet and exercise habits between the RT-CGM and SMBG groups. **Other outcome measures:** N/A
Intervention	**Intervention type:** real time continuous glucose monitoring (RT-CGM) using Guardian RT **Instructions**: underwent RT-CGM once a month for 3 days for 12 weeks and alarm threshold were set for hyperglycaemia (>30mg/dl) and hypoglycaemia (<60 mg/dl). When hyperglycaemic alarms occurred, patients were instructed to increase their movement and take in little amounts of food. If hypoglycaemic alarms sounded, the patients were instructed to perform confirmatory SMBG before corrective action. During the trial neither modifications of OHA or insulin dosage were permitted in either treatment group except for recurrent episodes of hyperglycaemia. All participants were educated to perform moderate intensity aerobic exercise at 50-70% of maximal heart rate (e.g. brisk walking, swimming) **Frequency:** Only during the RT application, patients had to perform at least three capillary BG tests per day for calibration and during the remaining study period, capillary BG tests were at their convenience **Feedback:** based on information downloaded from the RT-CGM, diabetes educator nurses were consulted about the patient's lifestyle. **Education:** Standard diabetes education was also performed in all participants before the start of the study. **Diary**: participants in both groups maintained diaries covering 3 days of meals and 7 days of physical activity at baseline and 3 months later.
Comparator	**Intervention type:** SMBG **Instructions:** see frequency below and instructions in RT-CGM **Frequency:** instructed to check BG levels at least 4 times a week, including fasting blood glucose and postprandial 2h blood glucose levels for 3 months continuously. The testing frequency in this group was the median frequency of their usual practice prior to the study. **Feedback:** instructed about diet and exercise habits every month based on SMBG values for 1 month **Diary:** see RT-CGM group
Length of follow up	Intervention: 12 weeks Follow-up: 12 weeks
Location	Korea

Bibliographic reference (Ref ID)	Yoo et al 2008 (REF ID: 213)
Outcomes measures and effect sizes	**Primary outcome measures (Change in blood glucose control):** the RT-CGM group had a significant reduction in Hba1c levels after 12 weeks (9.1 ± 1.0% to 8.0 ± 1.2%, p<0.001). There was also a significant reduction of Hba1c level in the SMBG group (8.7 ± 0.7% to 8.3 ± 1.1%, p=0.01). Moreover, there was a significant difference in the amounts of improvement in Hba1c levels existed between the two groups (p=0.004)

Table 2. Changes in outcomes

Outcome	SMBG (n=28)		RT-CGM (n=29)		
	Baseline	After 3 months	Baseline	After 3 months	P-value**
Weight (kg)	65.7 ± 12.3	64.3 ± 12.5	63.3 ± 12.4	61.1 ± 12.2*	0.43
BMI (kg/m^2)	25.7 ± 3.5	25.2 ± 3.8	25 ± 3.0	24.3 ± 3.5†	0.37
Waist circumference (cm)	90.7 ± 10.6	91.5 ± 10.9	89 ± 11.2	86.9 ± 10.4	0.35
FBG (mmol/l)	6.5 ± 1.3	7.2 ± 2.2	6.3 ± 1.3	6.5 ± 1.2	0.48
Postprandial BG (mmol/l)	11.5 ± 3.6	10.9 ± 4.1	11.3 ± 2.8	10.0 ± 2.5*	0.48
Hba1c (%)	8.7 ± 0.7	8.3 ± 1.1*	9.1 ± 1.0	8.0 ± 1.2†	<0.01
Total cholesterol (mmol/l)	4.3 ± 0.2	4.1± 0.9	4.2 ± 0.1	3.9 ± 0.7	0.83
HDL cholesterol (mmol/l)	1.3 ± 0.1	1.4 ± 0.4	1.2 ± 0.1	1.2 ± 0.3	0.46
LDL cholesterol (mmol/l)	2.4 ± 0.1	2.3 ± 0.8	2.4 ± 0.1	2.3 ± 0.6	0.84
Triglycerides (mmol/l)	1.7 ± 1.6	1.9 ± 2.5	1.5 ± 0.9	1.4 ± 0.6	0.87
Total calorie intake (kcal/day)	1871.7 ± 246.3	1757.7 ± 265.2	1858.7 ± 239.4	1690 ± 233.7*	0.49
Fat consumption ratio (%)	20.0 ± 8.1	20.0 ± 10	20.0 ± 1.2	20.0 ± 3.4	0.82
Cholesterol intake (g/day)	259.1 ± 140.8	271.8 ± 116.7	277.6 ± 123.0	277 ± 150.3	0.78
Exercise time per week (min/week)	191.5 ± 98.4	235.0 ± 110.2	188.2 ± 110.2	346.6 ± 252.8†	0.02
* p<0.05 compared with baseline; † p<0.01 compared with baseline; ** p-value between SMBG and RT-CGM compared using repeated measures ANOVA					

Other outcome measures (Changes in weight or BMI): see table 2 for changes in all weight measures in both treatment groups

Changes in lipid levels: table 2 shows changes in lipid measures in both treatment groups

Quality of life: not reported

Adverse events: there were no reports of clinically symptomatic hypoglycaemic events during the study period. Three and five patients in the RT-CGM and SMBG groups dropped out of the study respectively, which was not significantly different (p=0.71).

Bibliographic reference (Ref ID)	Yoo et al 2008 (REF ID: 213)
	Microvascular and macrovascular complication: not reported **Subgroup analyses:** N/A
Authors' conclusion	RT-CGM is useful in modifying patients diet and exercise habits and could induce better glycaemic control than SMBG for patients with type 2 diabetes.
Source of funding	Korean Health21 R&D project
Comments	Random assignment using random number table and allocation process was concealed.

Evidence table 8: (Farmer et al 2007 – DiGEM study)

Bibliographic reference (Ref ID)	Farmer et al 2007-DiGEM study (REF ID: 252)
Study type & aim	To determine whether self-monitoring, alone or with instruction in incorporating the results into self-care, is more effective than usual care in improving glycaemic control in non-insulin treated patients with type 2 diabetes
Number and characteristics of patients	**Total number of patients:** 453 patients with non-insulin treated type 2 diabetes **Inclusion criteria:** type 2 diabetes, were aged 25 years or more at diagnosis, were managed with diet or oral hypoglycaemic agents alone, had an HbA1c level ≥6.2% at the assessment visit, and were independent in activities of daily living **Exclusion criteria:** the use of a blood glucose monitor twice a week or more often over the previous three months, serious disease or limited life expectancy that would make intensive glycaemic control inappropriate, or inability to follow trial procedures. **Patient characteristics:** Baseline personal and clinical characteristics were well balanced between the groups (table 1). The median (interquartile) duration of diabetes was 3.0 years (1.8-6.4 years), mean (SD) age was 65.7 (10.2) years, and mean (SD) level of haemoglobin A1c was 7.5% (1.1). Only 57 (12.6%) patients were lost to follow-up, which did not differ between groups (fig 1). Measurements for high density lipoprotein cholesterol levels were not obtained for 39 patients at baseline

Table 1. Baseline characteristics of included patients (N=)

Characteristic	Control group (n=152)	Less intensive SMBG (n=150)	More intensive SMBG (n=151)
Mean (SD) age (years)	66.3 (10.2)	65.2 (10.6)	65.5 (9.9)
Men	85 (55.9)	88 (58.7)	87 (57.6)
Cigarette consumption:	-	-	-
Never smoked	58 (38.2)	54 (36.2)	54 (35.8)
Former smoker	80 (52.6)	74 (49.7)	77 (51.0)
Current smoker	14 (9.2)	21 (14.1)	20 (13.2)

Bibliographic reference (Ref ID)	Farmer et al 2007-DiGEM study (REF ID: 252)

Median (interquartile range) duration (years) of diabetes	3(2-6)	3(2-7)	3(2-6)
Treatment	-	-	-
Diet only	44 (28.9)	39 (26.0)	41 (27.2)
Monotherapy	57 (37.5)	58 (38.7)	58 (38.4)
Combined oral therapy	51 (33.6)	53 (35.3)	52 (34.4)
Presence of diabetes related complications	32 (21.1)	32 (21.3)	39 (25.8)
Use of blood glucose meter:	-	-	-
Not using	104 (68.4)	110 (73.3)	102 (67.5)
Using once weekly or less	48 (31.6)	40 (26.7)	49 (32.5)
Mean (SD) haemoglobin A1c (%)	7.49 (1.09)	7.41 (1.02)	7.53 (1.12)
Mean (SD) total cholesterol level (mmol/l)	4.7 (1.1)	4.6 (1.1)	4.7 (1.1)
Mean (SD) blood pressure (mm Hg):	-	-	-
Systolic	140 (18)	141 (17)	137 (18)
Diastolic	80 (10)	80 (10)	78 (10)
Mean (SD) body mass index	30.9 (6.1)	31.9 (6.2)	31.0 (5.3)

Subgroup analyses: Pre-specified groups as duration of diabetes (above or below median), current management (oral hypoglycaemic drugs or diet only), heath status (above or below EQ-5D score) and presence or absence of diabetes related complications.

Monitoring information and definitions

Monitoring: intervention was initiated at the first visit after randomisation and continued at the scheduled visits at one, three, six, and nine months.

Definitions: Episodes of hypoglycaemia were categorised as grade 2 (mild symptoms requiring minor intervention), grade 3 (moderate symptoms requiring immediate third party intervention), or grade 4 (unconscious). Increases in hypoglycaemic drugs were defined as an increase in the dose or frequency prescribed, progression from use of a single oral agent to combination oral therapy, or addition of insulin to the treatment regimen.

Primary outcome measures: The primary outcome was the HbA1c level at 12 months**.**

Secondary outcome measures: blood pressure, weight, total cholesterol level, ratio of total cholesterol to high density lipoprotein cholesterol, and body mass index

Bibliographic reference (Ref ID)	Farmer et al 2007-DiGEM study (REF ID: 252)
	Other outcome measures: N/A
Intervention	**LESS INTENSIVE SMBG** **Intervention type:** Patients allocated to the less intensive self-monitoring intervention continued to use the goal setting and review techniques introduced at the assessment visit and were given a blood glucose meter. **Instructions:** see feedback **Frequency:** asked to record three values daily on two days during the week (one after fasting and the other two before meals or two hours after meals) and to aim for glucose levels of 4-6 mmol/l after fasting and before meals and levels of 6-8 mmol/l two hours after meals. **Feedback:** They were advised by the nurse to consider contacting their doctor if readings were consistently high (>15 mmol/l) or low (<4 mmol/l). They were not given information about how to interpret their blood glucose readings. Patients in each arm of the trial received feedback on glycaemic control, which was used to explore success of goals and to set new ones. **Diary:** Separate diaries were used to record identified goals and activity and to record blood glucose results. **MORE INTENSIVE SMBG** **Intervention type:** Patients allocated to the more intensive intervention continued to use goal setting and review and were also given a blood glucose meter. **Instructions:** They were also given training and support in timing, interpreting, and using the results of their blood glucose test to enhance motivation and to maintain adherence to diet, physical activity, and drug regimens. They were encouraged to experiment with monitoring to explore the effect of specific activities, such as exercise, on their blood glucose level and to reflect on abnormal values in an attempt to identify what might have contributed to them. **Frequency:** not explicit but assumed same as less intensive SMBG **Feedback:** see above **Diary:** A single diary was used to record goals, activities, and blood glucose results
Comparator	**Intervention type:** standardised usual care, including the use of goal setting and review **Instructions:** asked not to use a blood glucose meter unless their doctor considered it essential for their clinical management **Frequency:** N/A **Feedback:** Patients allocated to the control intervention had a blood test to measure HbA1c level two weeks before their scheduled visit, the result of which was fed back to them as an indication of the impact of their self-care activities on their glycaemic control (also see above) **Diary:** used to record self-care goals and strategies for achieving them
Length of follow up	Intervention: 52 weeks Follow-up: 4 years
Location	UK
Outcomes	**Primary outcome measures: Hba1c levels at 52 weeks**

Bibliographic reference (Ref ID)	Farmer et al 2007-DiGEM study (REF ID: 252)

measures and effect sizes

Table 2. Changes in BG measures

Blood glucose measure	Control	Less intensive SMBG	More intensive SMBG	P-value for difference between groups*
Hba1c level (%)				
Baseline	7.49 (1.09)	7.41 (1.02)	7.53 (1.12)	0.12
Follow-up	7.49 (1.20)	7.28 (0.88)	7.36 (1.05)	
Change	−0.00 (1.02)	−0.14 (0.82)	−0.17 (0.73)	
*adjusted for baseline values				

Other outcome measures

Changes in weight: see table 3 for changes in BMI

Table 3. Changes in weight

Weight measure	Control	Less intensive SMBG	More intensive SMBG	P-value for difference between groups*
Weight (kg):	-	-	-	-
Baseline	86.7 (18.9)	90.4 (18.9)	86.9 (16.4)	0.37
Follow-up	86.4 (19.4)	89.9 (19.0)	86.1 (15.7)	
Change	−0.3 (2.7)	−0.5 (2.6)	−0.8 (3.3)	
BMI	-	-	-	-
Baseline	30.9 (6.1)	31.9 (6.2)	31.0 (5.3)	0.41
Follow-up	30.8 (6.3)	31.8 (6.3)	30.7 (5.0)	
Change	−0.1 (1.0)	−0.2 (0.9)	−0.3 (1.2)	
*adjusted for baseline values				

Adverse events (hypoglycaemia): During the trial one or more grade 2 hypoglycaemic episodes were experienced by 14 patients in the control group, 33 in the less intensive intervention group, and 43 in the more intensive intervention group ($\chi 2=18.3$, $P<0.001$). Only one patient in the control group experienced a grade 3 hypoglycaemic episode

Change in lipid levels and blood pressure: See table 4 for changes in lipid levels and blood pressure

Bibliographic reference (Ref ID)	Farmer et al 2007-DiGEM study (REF ID: 252)

Table 4. Changes in BP and lipids

Outcome	Control	Less intensive SMBG	More intensive SMBG	P-value for difference between groups*
Systolic BP (mmHg)	-	-	-	-
Baseline	140 (18)	141 (17)	137 (18)	0.77
Follow-up	136 (18)	137 (17)	134 (17)	
Change	−4 (14.)	−3 (16)	−3 (14)	
Diastolic BP (mmHg)	-	-	-	-
Baseline	80 (10)	80 (10)	78 (10)	0.67
Follow-up	77 (10)	78 (10)	76 (10)	
Change	−3 (9)	−2 (9)	−2 (8)	
Total cholesterol (mmol/l)	-	-	-	
Baseline	4.73 (1.02)	4.64 (1.11)	4.67 (1.07)	0.010
Follow-up	4.56 (1.03)	4.42 (0.95)	4.28 (0.84)	
Change	−0.16 (0.84)	−0.22 (0.93)	−0.40 (0.90)	
Ratio of total cholesterol to HDL**	-	-	-	
Baseline	4.33 (1.12)	4.40 (1.33)	4.48 (1.35)	0.013
Follow-up	4.18 (1.12)	4.11 (1.17)	4.02 (1.17)	
Change	−0.15 (0.72)	−0.29 (0.86)	−0.46 (0.91	

*adjusted for baseline values; ** based on 414 participants with paired values (137/152, 136/150 and 141/151)

Microvascular or macrovascular complications: not reported

Quality of life:

Subgroup analyses (predetermined groups): Table 5 shows changes in Hba1c by pre-specific subgroups.

Table 5. Hba1c levels stratified by pre-specified subgroups

Subgroup	Control (n=152)	Less intensive SMBG (n=150)	More intensive SMBG (n=151)	P-value for interaction*

Bibliographic reference (Ref ID)	Farmer et al 2007-DiGEM study (REF ID: 252)				
	Duration of diabetes‡	-	-	-	
	≤36 months:	-	-	-	0.82
	Baseline	7.29 (1.02)	7.35 (1.02)	7.41 (1.03)	
	Follow-up	7.30 (1.24)	7.23 (0.93)	7.25 (1.01)	
	Change	0.01 (1.03)	−0.12 (0.85)	−0.16 (0.73)	
	>36 months:	-	-	-	
	Baseline	7.70 (1.13)	7.48 (1.02)	7.67 (1.20)	
	Follow-up	7.70 (1.11)	7.33 (0.84)	7.49 (1.08)	
	Change	−0.01 (1.01)	−0.15 (0.80)	−0.18 (0.73)	
	Baseline therapy	-	-	-	
	Diet only:	-	-	-	0.90
	Baseline	7.18 (0.98)	6.85 (0.66)	7.18 (1.11)	
	Follow-up	7.21 (1.05)	6.90 (0.70)	7.09 (0.94)	
	Change	0.03 (0.80)	0.04 (0.64)	−0.09 (0.72)	
	Oral drug therapy:	-	-	-	
	Baseline	7.61 (1.11)	7.61 (1.05)	7.66 (1.10)	
	Follow-up	7.61 (1.24)	7.41 (0.91)	7.46 (1.07)	
	Change	−0.01 (1.10)	−0.20 (0.87)	−0.20 (0.73)	
	Health status (EQ-5D)§:	-	-	-	
	Diabetes >36 months:	-	-	-	0.63
	Baseline	7.38 (1.02)	7.30 (0.96)	7.57 (1.21)	
	Follow-up	7.46 (1.16)	7.22 (0.76)	7.43 (1.16)	
	Change	0.07 (0.99)	−0.08 (0.84)	−0.13 (0.77)	
	Diabetes ≤36 months:	-	-	-	
	Baseline	7.54 (1.16)	7.50 (1.09)	7.34 (0.80)	
	Follow-up	7.43 (1.22)	7.37 (1.04)	7.14 (0.78)	
	Change	−0.11 (1.14)	−0.13 (0.80)	−0.20 (0.67)	
	Diabetes related complications	-	-	-	

Bibliographic reference (Ref ID)	Farmer et al 2007-DiGEM study (REF ID: 252)				
	Absent:	-	-	-	0.86
	Baseline	7.53 (1.11)	7.51 (1.09)	7.71 (1.19)	
	Follow-up	7.48 (1.16)	7.32 (0.92)	7.43 (1.13)	
	Change	−0.05 (1.02)	−0.19 (0.88)	−0.28 (0.74)	
	Present:	-	-	-	-
	Baseline	7.32 (1.02)	7.07 (0.63)	7.00 (0.64)	
	Follow-up	7.52 (1.34)	7.12 (0.73)	7.16 (0.73)	
	Change	0.20 (1.02)	0.05 (0.56)	0.16 (0.56)	
	* after adjustment for baseline values; ‡ median 36 months				
Authors' conclusion	Evidence is not convincing of an effect of self-monitoring blood glucose, with or without instruction in incorporating findings into self-care, in improving glycaemic control compared with usual care in reasonably well controlled non-insulin treated patients with type 2 diabetes.				
Source of funding	NHS and NIHR HTA				
Comments	Four year open randomised, three arm, parallel group trial with sequential recruitment of patients from general practices in Oxfordshire and South Yorkshire. Randomised using computerised program and incorporated a partial minimisation procedure to adjust the randomisation probabilities between groups to balance three important covariates collected at baseline: duration of diabetes, HbA1c level, and current treatment (diet, oral monotherapy, or oral combination therapy).				

Evidence table 9: (Scherbaum et al 2008)

Bibliographic reference (Ref ID)	Scherbaum et al 2008 (REF ID: 219)
Study type & aim	RCT to test the effect of the frequency of SMBG without changing the other diabetes management.
Number and characteristics of patients	**Total number of patients:** 202 randomised in oral group (100 to low frequency ad 102 to high frequency) **Inclusion criteria:** Patients with type 2 diabetes treated with one or more OAD (not combined with insulin therapy and stable oral medication for the last three months) aged between 35 and 80 years were enrolled **Exclusion criteria:** type 1 diabetes, advanced renal insufficiency (creatinine level at ≥2.5 mg/dl), at least two episodes of hypoglycaemia requiring external support within the previous three months, one or more severe metabolic events (hypoglycemic shock, hyperosmolar coma, inpatient stay due to severe hyperglycaemic events) within the past three months, pregnancy, severe impairment of vision or communication problems due to language. **Patient characteristics:** The baseline characteristics in the two groups were similar (Table 1). Mean diabetes duration was 7.8 ± 6.4 years in the low and 8.2 ± 6.5 in the high group. There were 12 drop-outs in the low and 11 drop-outs in the high group

Bibliographic reference (Ref ID)	Scherbaum et al 2008 (REF ID: 219)

Table 1. Baseline characteristics of included patients (N=202)

Characteristic	Low (n=100)*	High (n=102)	P-value
Age - years (mean ± SD)	61.7 ± 11.7	61.0 ± 9.0	0.68
Sex	-	-	-
male	60/100 (60%)	65/102 (64%)	0.66
female	40/100 (40%)	37/102 (36%)	
Duration of diabetes - years	7.8 ± 6.4	8.2 ± 6.5	0.71
HbA1c - %	7.2 ± 1.4	7.2 ± 1.0	0.53
History	-	-	-
coronary heart disease	19/100 (19%)	16/101 (16%)	0.58
myocardial infarction	8/100 (8%)	11/102 (11%)	0.63
stroke	2/100 (2%)	2/102 (2%)	1.00
peripheral arterial disease (PAD)	13/100 (13%)	14/102 (14%)	1.00
other serious disease	34/100 (34%)	28/102 (28%)	0.36
diabetic nephropathy	2/100 (2%)	3/102 (3%)	1.00
diabetic neuropathy	25/100 (25%)	21/102 (21%)	0.50
diabetic retinopathy	2/100 (2%)	4/102 (4%)	0.68
relevant hypoglycemia*	3/100 (3%)	4/102 (4%)	1.00
relevant hyperglycemia*	6/100 (6%)	3/102 (3%)	0.32
Medication	-	-	-
Acarbose	1/99 (1%)	3/102 (3%)	0.62
Glibenclamide	23/99 (23%)	19/102 (19%)	0.42
Glimepiride	25/99 (25%)	29/102 (28%)	0.61
Gliquidon	0/99 (0%)	1/102 (1%)	1.00
Glyburide	0/99 (0%)	1/102 (1%)	1.00
Metformin	70/99 (71%)	76/102 (75%)	0.55
Nateglinide	2/99 (2%)	1/102 (1%)	0.62
Pioglitazone	3/99 (3%)	2/102 (2%)	0.68

Bibliographic reference (Ref ID)	Scherbaum et al 2008 (REF ID: 219)

Repaglinide	7/99 (7%)	10/102 (10%)	0.49
Rosiglitazone	9/99 (9%)	5/102 (5%)	0.24

*one person with missing data
Abbreviations: SMUG self-monitoring of urine glucose; SMBG self-monitoring of blood glucose

Subgroup analyses: No pre-specified or post-hoc subgroup analyses reported

Monitoring information and definitions

Monitoring: Patients were evaluated at the initial visit and after 3 and 6 months by clinical investigation, assessment of (serious) adverse events, quality of life (at baseline and at 6 months only), compliance with intervention, change in diabetes treatment, socioeconomic effects and measurement of HbA1c. After 12 months only HbA1c was assessed

Definitions: Hypoglycaemia was defined as an SMBG reading of <3.2 mmol/L (60 mg/dl). Severe hypoglycaemia was defined as any hypoglycaemia with the need for assistance by another person.

Compliance with treatment was defined as: maximal deviation of one measurement from the allocated frequency (e.g. 3 to 5 in the high group, 0 to 2 in the low group).

Primary outcome measures: change in HbA1c levels between baseline and six months after enrolment

Secondary outcome measures: number and type of hypoglycaemic and hyperglycaemic events, quality of life, compliance and satisfaction with interventions, socioeconomic effects and HbA1c after 3 and 12 months (quality of life, satisfaction with intervention and socioeconomic background not presented in this paper)

Other outcome measures: N/A

Intervention

Intervention type: low frequency SMBG

Instructions: SMBG with one measurement a week and additional measurement in the event of suspected hypoglycaemia or severe hyperglycaemia

Frequency: see instructions

Feedback: all patients were asked to report back to their physician in the event of inappropriate diabetes control according to the individual targets

Education: After randomisation, patients were instructed on the strategy of SMBG to be applied for a period of 6 months (formal instruction, written instruction, patient diary, delivery of equipment for measuring blood glucose). Patients were not specifically re-educated after randomisation.

Diary: blood glucose measurements were documented by the patient in a diary,

Comparator

Intervention type: High frequency SMBG

Instructions: four measurements a week on Tuesdays, Thursdays and one day of the weekend before dinner and one additional measurement before lunch, and also additional measurement in the event of suspected hypoglycaemia or severe hyperglycaemia.

Frequency: see instructions

Feedback:

Diary:

Bibliographic reference (Ref ID)	**Scherbaum et al 2008 (REF ID: 219)**
Length of follow up	**Intervention:** 6 months **Follow-up:** 12 months
Location	Germany
Outcomes measures and effect sizes	**Primary outcome measures (Change in blood glucose control):** see table 2 for changes in Hba1c at different time-points

Table 2. Changes in Hba1c

Hba1c (%)	Low frequency	High frequency	P-value*
Baseline, mean ± SD (valid observations)	7.2 ± 1.4 (100)	7.2 ± 1.0 (102)	0.92
3 month, mean ± SD (valid observations)	6.9 ± 1.2 (93)	6.9 ± 0.7 (95)	0.66
6 months, mean ± SD (valid observations)	6.961.2 (87)	7.060.8 (91)	0.53
12 months, mean ± SD (valid observations)	6.961.0 (82)	7.161.0 (86)	0.10
* t-test			

Other outcome measures (Changes in weight or BMI): not reported
Changes in lipid levels: not reported
Quality of life: not reported
Adverse events: The number and type of SAE and AE was similar between the groups except for hypoglycaemia, which was increased in the high group

Adverse events	Low (n=100)	High (n=102)	P-value
Relevant hypoglycaemia	-	-	-
one event	1/100 (1%)	9/102 (9%)	0.02
several events	4/100 (4%)	9/102 (9%)	0.25
Relevant hyperglycaemia	1/100 (1%)	1/102 (1%)	1.00
Deterioration neuropathy	0/100 (0%)	0/102 (0%)	1.00
Deterioration retinopathy	0/100 (0%)	0/102 (0%)	1.00
Deterioration nephropathy	0/100 (0%)	0/102 (0%)	1.00
Multiple	6/100 (6%)	4/102 (4%)	0.54
Other	7/100 (7%)	3/102 (3%)	0.21
Serious adverse event	-	-	-
hypoglycaemic shock	0/100 (0%)	0/102 (0%)	1.00

Bibliographic reference (Ref ID)	Scherbaum et al 2008 (REF ID: 219)

hyperosmolar coma	0/100 (0%)	0/102 (0%)	1.00
Other	20/100 (20%)	15/102 (15%)	0.58
inpatient stay	19/100 (19%)	14/102 (14%)	0.57
death	1/100 (1%)	1/102 (1%)	1.00

Microvascular and macrovascular complication: not reported

Compliance: Compliance in the low group assessed by the doctor was 61% at 3 months and 73% at 6 months. In the high group, compliance to the SMBG regimen assigned was 77% at 3 months and 83% at 6 months. Analysis of each patient's diary revealed compliance in 82–83% (0 to 3 months) and 85–88% (4 to 6 months) in the low group and 87–90% and 84–88% in the high group. A statistical significant difference was observed according to doctor's assessment at 3 months (p<0.03).

Compliance	Low frequency	High frequency	P-value*
Investigator	-	-	-
3 months	57/92 (61%)	71/92 (77%)	0.03
6 months	62/85 (73%)	75/91 (83%)	0.14
Patients diary*	-	-	-
3 months	-	-	-
first week in month 1	72/88 (82%)	83/95 (87%)	0.31
first week in month 2	73/88 (83%)	83/95 (87%)	0.41
first week in month 3	72/88 (82%)	85/95 (90%)	0.30
6 months	-	-	-
first week in month 4	73/86 (85%)	77/92 (84%)	0.84
first week in month 5	73/84 (87%)	80/91 (88%)	1.00
first week in month 6	73/83 (88%)	77/92 (84%)	0.82
* t-test			

Change of medication: Overall, 5/100 (5%) in the low frequency group and 9/102 (9%) in the high frequency group changed from oral agents to insulin (p=0.41). 4/100 and 6/102 in the low and high groups respectively changed medication between 0-3 months (p=0.75). 1/100 and 3/102 in the low and high groups respectively changed medication between 4 and 6 months (p=0.62)

Subgroup analyses: N/A

Other: healthcare utilisation is also reported in full paper but is not reported in this evidence table

Bibliographic reference (Ref ID)	Scherbaum et al 2008 (REF ID: 219)
Authors' conclusion	This study shows that in patients with T2D treated with OAD one SMBG measurement a week is not associated with any deterioration in metabolic control (HbA1c) or therapeutic safety as compared to four measurements a week. Under study conditions compliance for a low frequency of SMBG was surprisingly high.
Source of funding	ROCHE Diagnostics (Mannheim, Germany) provided blood glucose meters and meter strips for patients in the study.
Comments	Originally, it was planned to establish a second trial arm with insulin treated patients, comparing one measurement a week (low group) with 11 measurements a week (high group). Due to poor recruitment this arm was terminated early. The randomization list was generated and centrally applied with concealment by the Coordination Centre for Clinical Trials with the use of randomly selected block sizes of 4, 6 and 8 patients stratified according to centre

Evidence table 10: (Knapp et al 2009)

Bibliographic reference (Ref ID)	Knapp et al 2009 (REF ID: 189)
Study type & aim	To compare glycemic control in fingertip versus forearm sampling methods of self-monitoring of blood glucose (SMBG).
Number and characteristics of patients	**Total number of patients:** 174 were randomised (85 in FT and 89 to AST group) **Inclusion criteria:** 18–70 years of age with type 2 diabetes, using insulin, and performing SMBG measurements **Exclusion criteria:** type 1 diabetes, prior use of AST, pregnancy, and serious comorbid illness (unstable cardiovascular disease or metastatic cancer). Potential subjects were also excluded if, within the past year, they had a hypoglycaemic episode requiring urgent medical attention, resulting in cognitive impairment or a lack of symptoms during a hypoglycaemic episode. **Patient characteristics:** Of those randomized, 71 (83%) in the FT group and 64 (72%) in the AST group completed the study. The higher dropout/withdrawal rate in the AST group approached statistical significance (P=0.07).

Table 1. Baseline characteristics of included patients (N=174)

Characteristic	FT (n=85)	Forearm AST (n=89)	P-value
Age (years)	53.2 ± 9.5	53.1 ± 10.2	0.959
Body mass index (kg=m2)	35.9 ± 9.6	35.9 ± 9.2	0.975
Waist circumference (inches)	44.4 ± 7.2	45.3 ± 6.8	0.412
Female	52 (61%)	42 (47%)	0.064
Baseline HbA1C (%)	8.8 ± 2.2	8.7 ± 2.1	0.649
Years with diabetes	12.0 ± 9.8	12.7 ± 9.1	0.643
SMBG tests prior to study	-	-	-
<1 per day	8 (9%)	10 (11%)	-

Bibliographic reference (Ref ID)	Knapp et al 2009 (REF ID: 189)

1–2 per day	40 (47%)	51 (57%)	0.258
≥3 or more per day	37 (44%)	28 (32%)	-
Frequency of insulin injections	-	-	-
1 per day	12 (14%)	12 (14%)	-
2 per day	37 (44%)	34 (38%)	0.633
≥3 per day	33 (39%)	37 (42%)	
Using oral diabetes agent (plus insulin)	52 (63%)	47 (57%)	0.374
Data are mean ± SD for continuous variables and n (%) for categorical variables. Abbreviations: SMUG self-monitoring of urine glucose; SMBG self-monitoring of blood glucose			

Subgroup analyses: post hoc analyses were performed to compare the difference in HbA1C change between the two groups stratified by initial level of glycaemic control

Monitoring information and definitions

Monitoring: there were 9 visits-Subjects were asked to return for study visits at 1, 2, 3, 4, 5, and 7 months after the randomization/training visit

Definitions: Adherence was measured by counting the number of tests recorded, regardless of timing or method, as well as the number of tests requested for each log sheet (21 for a full week). When a test was repeated at an individual time point because of suspicion of hypoglycemia, only one test was counted.

Primary outcome measures: Hba1c levels

Secondary outcome measures: adverse events and adherence to SMBG schedule

Other outcome measures: N/A

Intervention

Intervention type: alternative testing site (AST)

Instructions: asked to use AST as much as possible; however, because of the potential limitations of AST in detecting hypoglycemia, they were instructed to use FT when experiencing symptoms of hypoglycemia and to repeat any AST reading <5.55 mmol/L using FT. They were also told that if they had difficulties obtaining a blood sample from arm puncture on any particular occasion, it was acceptable to substitute a finger test. As intended, this resulted in a mixture of arm and finger testing in the AST group, which is consistent with actual clinical use of AST.

Frequency: minimum of 3 times per day (see diary)

Feedback: At the 1-,3-, and 5-month visits, subjects were asked to show their SMBG log sheets from the preceding month to the provider who used this information to modify the treatment regimen as part of their routine diabetes care

Education: each subject received a 30-min training session from a qualified diabetes nurse educator in the use of the SMBG device, including device calibration and settings adjustment.

Diary: Subjects were given standardized SMBG log sheets that prompted them to test a minimum of three times per day: before breakfast, before dinner, and 2 h after dinner. The log sheets were designed to allow some flexibility such that the subject or their

Bibliographic reference (Ref ID)	Knapp et al 2009 (REF ID: 189)
	diabetes provider could alter the timing of tests if the individual subject's meal or insulin dosing schedule so required. Space was also provided to record test results for episodes of suspected hypoglycemia
Comparator	**Intervention type:** usual fingertip testing (FT) **Instructions:** not reported **Frequency:** as AST group **Feedback:** as AST group **Diary:** as AST group
Length of follow up	**Intervention:** not explicit but assumed 7 months **Follow-up:** 7 months
Location	USA
Outcomes measures and effect sizes	**Primary outcome measures (Change in blood glucose control):** see table 2 for overview of Hba1c changes. To confirm the lack of difference between FT and AST groups, we categorized subjects into improved, unchanged, or worsened glycemic control by change in HbA1C from baseline to month 7 of 0.25% or more. In the FT group 39 (46%) improved, 19 (22%) were unchanged, and 27 (32%) worsened. In the AST group 39 (44%) improved, 21 (24%) were unchanged, and 29 (33%) worsened. There was no difference in frequencies between groups (P=0.929).

Table 2. Changes in blood glucose measures

Hba1c	n	Baseline (T0)	Month 4	Month 7	Change (month 7-T0)	P-value (change)
All subjects						
FT	85	8.8 ± 2.2	8.4 ± 1.9	8.4 ± 1.7	0.4 ± 1.4	0.008
AST	89	8.7 ± 2.1	8.3 ± 1.8	8.4 ± 1.8	0.3 ± 1.2	0.045
Good initial control (baseline HbA1 ≤ 7.0%)						
FT	18	6.4 ± 0.4	6.7 ± 0.5	6.8 ± 0.5	+0.4 ± 0.7	0.024
AST	21	6.3 ± 0.6	6.5 ± 0.9	6.7 ± 0.7	+0.4 ± 0.6	0.040
Intermediate initial control (baseline HbA1C 7.0–8.5%)						
FT	26	7.8 ± 0.4	7.6 ± 1.0	7.9 ± 1.1	+0.1 ± 1.0	0.705
AST	26	7.8 ± 0.4	7.8 ± 0.8	7.9 ± 0.9	+0.1 ± 0.9	0.493
Poor initial control (baseline HbA1C >8.5%)						
FT	41	10.5 ± 1.9	9.7 ± 1.8	9.5 ± 1.6	1.0 ± 1.6	<0.001
AST	42	10.4 ± 1.6	9.5 ± 1.6	9.6 ± 1.6	0.8 ± 1.4	<0.001

Bibliographic reference (Ref ID)	Knapp et al 2009 (REF ID: 189)
	Other outcome measures (Changes in weight or BMI): not reported **Changes in lipid levels:** not reported **Quality of life:** not reported **Adverse events:** Information on hypoglycemic episodes was collected using a strict definition. Events were only considered to be hypoglycaemic episodes if they consisted of hypoglycemic symptoms followed by an SMBG test that confirmed blood glucose <4.44 mmol/L. As a result, the number of such events was very small and concentrated in a few individuals. The mean number of hypoglycemic episodes per month was 0.183 in the FT group and 0.176 in the AST group with no significant difference between the two (P=0.16, Wilcoxon rank-sum test). Only three subjects in each group reported an average of more than one hypoglycemic episode per month. Because of the small number of recorded hypoglycemic events we did not have adequate power to detect a difference in the number between groups. Four subjects were withdrawn from the study because of a severe hypoglycemic episode requiring urgent medical attention: one in the FT group and three (two including seizures) in the AST group **Microvascular and macrovascular complication:** not reported **Adherence:** In the AST group subjects were encouraged to use AST as much as possible but were asked to use FT for suspected or possible hypoglycemia or if they had difficulty obtaining blood from the arm. Tests were counted as completed regardless of whether they were performed on the arm or finger. Adherence overall was better in the FT compared to the AST group; mean overall adherence was higher in the FT group than in the AST group: 87% for FT (95% CI 83.2% to 90.4%) and 78% for AST (95% CI 73.5% to 82.9%, P=0.003). **Subgroup analyses:** see Hba1c levels above for stratified values
Authors' conclusion	Glycemic control improved in both groups over the course of their participation in the study, primarily because of substantial improvements in subjects who began the study in poor control (HbA1C>8.5%). Presumably, this was caused by an increased attention to their diabetes and increased frequency of SMBG testing through their participation in the study. We did not observe a difference in the degree of improvement between the FT and AST groups.
Source of funding	Financial support for the study was provided by Food and Drug Administration and some SMBG meters and test strips were provided by Lifescan.
Comments	Block randomization was used and stratified by six strata of initial HbA1C to ensure similar mean initial HbA1C in both groups. The strata of HbA1C (%) were <7.0%, 7.0–7.5%, 7.5–8.0%, 8.0–8.5%, 8.5–9.5%, and>9.5%. Subjects were compensated with a total of $170 for participation.

Evidence table 11: (Bonomo et al 2010)

Bibliographic reference (Ref ID)	Bonomo et al 2010 (REF ID: 1307)
Study type & aim	To compare once monthly versus fortnightly SMBG in a way that considered cost and compliance.
Number and	**Total number of patients:** 273 (monthly group A=96 and fortnightly group B=177)

<table>
<tr><td>Bibliographic reference (Ref ID)</td><td>Bonomo et al 2010 (REF ID: 1307)</td></tr>
<tr><td>characteristics of patients</td><td>
Inclusion criteria: Hba1c level>7%, not on insulin and already using SMBG
Exclusion criteria: not reported
Patient characteristics: Except for group A being a little older, there were no differences in gender, known diabetes duration, BMI, waist circumference, Hba1c or hypoglycaemic treatment

Table 1. Baseline characteristics of included patients (N=273)
<table>
<tr><th>Characteristic</th><th>Group A (monthly) (n=96)</th><th>Group B (fortnightly) (n=177)</th><th>P-value</th></tr>
<tr><td>Gender (M/F)</td><td>59/37</td><td>108/69</td><td>0.940</td></tr>
<tr><td>Age (years)</td><td>62.80 ± 9.17</td><td>65.30 ± 9.56</td><td>0.017</td></tr>
<tr><td>Known diabetes duration (years)</td><td>10.38 ± 8.50</td><td>10.76 ± 7.90</td><td>0.712</td></tr>
<tr><td>BMI (kg/m^2)</td><td>29.13 ± 4.55</td><td>28.85 ± 4.47</td><td>0.624</td></tr>
<tr><td>Waist circumference (cm)</td><td>102.80 ± 10.80</td><td>103.35 ± 9.91</td><td>0.672</td></tr>
<tr><td>Hba1c (%)</td><td>8.04 ± 0.80</td><td>8.06 ± 0.82</td><td>0.846</td></tr>
<tr><td>Treatment (%)</td><td>-</td><td>-</td><td>1.00</td></tr>
<tr><td>Diet alone</td><td>6.25</td><td>9.04</td><td>-</td></tr>
<tr><td>Metformin</td><td>18.75</td><td>18.64</td><td>-</td></tr>
<tr><td>Sulfonylureas or glinides</td><td>30.21</td><td>27.68</td><td>-</td></tr>
<tr><td>Sulfonylureas or glinides + metformin</td><td>43.75</td><td>44.63</td><td>-</td></tr>
</table>
Subgroup analyses: pre-specified analyses by compliance
</td></tr>
<tr><td>Monitoring information and definitions</td><td>
Monitoring: followed-up by same team at three monthly intervals
Definitions: compliant patient was defined as one who carried out SMBG as requested and recorded the results in a personal diary at least 70% of the recommended BG measurements.
Primary outcome measures: Hba1c
Secondary outcome measures:
Other outcome measures:
</td></tr>
<tr><td>Intervention</td><td>
Intervention type: Monthly (group A)
Instructions: patients continued usual SMBG
Frequency: perform one BG profile per month with fasting, 2h after breakfast, 2h after lunch and 2h after dinner BG measurements
Feedback: patients were encouraged, when BG levels were not within target, in increase compliance with diet and exercise without altering type or dose of oral agents without consulting the diabetes team at least by phone.
</td></tr>
</table>

<table>
<tr><td>Bibliographic reference (Ref ID)</td><td>Bonomo et al 2010 (REF ID: 1307)</td></tr>
<tr><td></td><td>Education: Physicians used SMBG to implement lifestyle education and id necessary to modify drug prescription both during scheduled visits or when patients phoned for advice.
Diary: SMBG results recorded in personal diary</td></tr>
<tr><td>Comparator</td><td>Intervention type: Fortnightly (group B)
Instructions: not reported
Frequency: perform one BG profile every 2 weeks with fasting, 2h after breakfast, before lunch, 2h after lunch, before dinner and 2h after dinner BG measurements
Feedback: as group A
Diary: as group A</td></tr>
<tr><td>Length of follow up</td><td>Intervention:6 months
Follow-up: 6 months</td></tr>
<tr><td>Location</td><td>Italy</td></tr>
<tr><td>Outcomes measures and effect sizes</td><td>Primary outcome measures (Change in blood glucose control): see table 2 for changes in Hba1c levels in all patients and subgroups of people by compliance. The decrease in Hba1c between baseline and 6 months was -0.19 ± 0.85% in compliant group A patients and -0.5 ± 0.88 in compliant group B patients (p=0.031). In non-compliant patients Hba1c levels decreased more in group A than in group B (p=0.026). Multivariate linear regression of Hba1c related to pre- and post-prandial BG values showed a significant correlation of Hba1c with BG before lunch (standard coefficient =0.246, p=0.001), after lunch (standard coefficient=0.199, p=0.003) and before dinner (standard coefficient=0.146, p=0.03)

Table 2. Changes in blood glucose measures by compliance
<table>
<tr><th>Group</th><th>BG measure</th><th>Baseline</th><th>6 months</th><th>P-value</th></tr>
<tr><td>Group A (all)</td><td>Hba1c (%)</td><td>8.04 ± 0.80</td><td>7.79 ± 1.02</td><td>0.06</td></tr>
<tr><td>Group A (compliant, n=70)</td><td>Hba1c (%)</td><td>7.97 ± 0.72</td><td>7.78 ± 1.05</td><td>0.067</td></tr>
<tr><td></td><td>BG before breakfast (mmol/L)</td><td>7.70 ± 1.45</td><td>7.64 ± 1.78</td><td>0.697</td></tr>
<tr><td></td><td>BG After breakfast (mmol/L)</td><td>8.51 ± 1.68</td><td>8.30 ± 1.80</td><td>0.388</td></tr>
<tr><td></td><td>BG Before lunch (mmol/L)</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td></td><td>BG After lunch (mmol/L)</td><td>8.99 ± 2.05</td><td>8.74 ± 2.00</td><td>0.318</td></tr>
<tr><td></td><td>BG Before dinner (mmol/L)</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td></td><td>BG After dinner (mmol/L)</td><td>8.88 ± 1.82</td><td>9.04 ± 2.21</td><td>0.677</td></tr>
<tr><td>Group A (not compliant, n=26)</td><td>Hba1c (%)</td><td>8.20 ± 0.96</td><td>7.79 ± 0.88</td><td>0.11</td></tr>
<tr><td>Group B (all)</td><td>Hba1c (%)</td><td>8.06 ± 0.82</td><td>7.83 ±0.91</td><td>0.0029</td></tr>
</table></td></tr>
</table>

Bibliographic reference (Ref ID)	Bonomo et al 2010 (REF ID: 1307)

Group B (Compliant, n=78)	Hba1c (%)	8.09 ± 0.84	7.60 ± 0.73	<0.001
	BG before breakfast (mmol/L)	7.63 ± 1.57	7.19 ± 1.52	0.013
	BG After breakfast (mmol/L)	8.79 ± 1.99	8.19 ± 1.63	0.004
	BG Before lunch (mmol/L)	7.49 ± 1.93	6.91 ± 1.43	0.003
	BG After lunch (mmol/L)	9.10 ± 1.91	8.73 ± 1.55	0.122
	BG Before dinner (mmol/L)	7.18 ± 1.82	6.68 ± 1.50	0.037
	BG After dinner (mmol/L)	9.04 ± 1.67	8.50 ± 1.63	0.002
Group B (Not compliant, n=99)	Hba1c (%)	8.03 ± 0.80	8.08 ± 1.02	0.70

Other outcome measures (Changes in weight or BMI): Body weight did not change significantly compared with baseline in compliant patients in either group A (BMI 29.14 ± 4.81 vs. 29.14 ± 4.91) or group B (BMI 28.2 ± 3.59 vs. 28.08 ± 3.53)

Changes in lipid levels: not reported

Quality of life: not reported

Drug changes: this included increases or decreases in drug dose and changes in drug type and were more frequent in compliant group B patients than in group A patients (54% vs. 47%), however, this difference was not statistically significant. Changes to hypoglycaemic drugs specifically targeting post-prandial BG were rare with only 2 [patients in group A and 6 patients in group B starting a glinide.

Adverse events: BG readings <3.3mmol/l were recorded in 3/70 compliant group A patients and 1/78 compliant group B patients while no BG value <3.3mmol/l was recorded in compliant patients.

Microvascular and macrovascular complication: not reported

Subgroup analyses: see blood glucose measures for subgroups by compliance

Authors' conclusion	The more intensive (fortnightly) SMBG policy is associated with improvements in glycaemic control in compliant subjects.
Source of funding	Grant of Regione Piemonte to Mariella Trovati (author)
Comments	N/A

Evidence table 12: (Pimazoni-Netto et al 2011)

Bibliographic reference (Ref ID)	Pimazoni-Netto et al 2011 (REF ID: 932)
Study type & aim	RCT to test the hypothesis that more frequent adjustment of therapy, combined with a multifactorial interdisciplinary approach, could result in more rapid improvement in glycemic control

<table>
<tr><td>Bibliographic reference (Ref ID)</td><td>Pimazoni-Netto et al 2011 (REF ID: 932)</td></tr>
<tr><td>Number and characteristics of patients</td><td>
Total number of patients: 63 (32 in intensive therapy group and 31 in control group)
Inclusion criteria: 35–75 years old and poor glycemic control (HbA1C ≥ 8.0%)
Exclusion criteria: not reported
Patient characteristics: baseline characteristics are relatively balanced across both groups (see table 1).

Table 1. Baseline characteristics of included patients (N=63)
<table>
<tr><th>Characteristic</th><th>Intensive group (n=32)</th><th>Control group (n=31)</th></tr>
<tr><td>Age (years)</td><td>54.5 (1.7)</td><td>58.4 (1.7)</td></tr>
<tr><td>Total patients (n)</td><td>32</td><td>31</td></tr>
<tr><td>% male/% female</td><td>28%/72%</td><td>29%/71%</td></tr>
<tr><td>Time since diagnosis (years)</td><td>11.4 (1.3)</td><td>13.3 (1.2)</td></tr>
<tr><td>Weekly mean glycemia (mg/dL) at Week 0</td><td>216.5 (5.6)</td><td>210.2 (9.3)</td></tr>
<tr><td>A1C (%) at Week 0</td><td>10.3 (0.3)</td><td>10.0 (0.3)</td></tr>
<tr><td>Glycemic variability (mg/dL) at Week 0</td><td>69.4 (4.1)</td><td>66.0 (4.0)</td></tr>
<tr><td>Weight (kg) at Week 0</td><td>86.4 (3.4)*</td><td>76.7 (2.8)</td></tr>
<tr><td>BMI (kg/m2)</td><td>32.1 (1.3)</td><td>30.2 (0.9)</td></tr>
<tr><td colspan="3">Data are mean ± SEM values
*one patient was morbidly obese (184.1kg at baseline)</td></tr>
</table>
Subgroup analyses: No pre-specified or post-hoc subgroup analyses reported
</td></tr>
<tr><td>Monitoring information and definitions</td><td>
Monitoring: see intervention details
Definitions: N/A
Primary outcome measures: Blood glucose measures
Secondary outcome measures: weight and hypoglycaemia
Other outcome measures: N/A
</td></tr>
<tr><td>Intervention</td><td>
Intervention type: Intensive SMBG
Instructions: All subjects were provided with a blood glucose meter and glucose monitoring strips for the study period. Patients were trained in the use of meter. At each visit, all patients in both groups were systematically asked whether or not they had experienced clinical symptoms of hypoglycemia.
Frequency: asked to perform a six- or seven-point glucose profile for three consecutive days on eight occasions: Weeks 0–6 and Week 12.
Feedback: Patients in the intensive therapy group were requested to attend clinic on a weekly basis for 6 weeks with a follow-up visit
</td></tr>
</table>

<table>
<tr><td>Bibliographic reference (Ref ID)</td><td>Pimazoni-Netto et al 2011 (REF ID: 932)</td></tr>
<tr><td></td><td>at 12 weeks. During these visits the patients received evaluation of glycemic control, adjustment of pharmacotherapy, and a total of 10 h of education and training by a multidisciplinary diabetes care team (physicians, nurses, nutritionists, psychologist, and physical therapists) over the seven visits from Week 0 through Week 6. Adjustment of pharmacotherapy was done on a weekly basis by one physician for Weeks 0–6 for subjects in the intensive treatment group
Education: see feedback
Diary: not reported</td></tr>
<tr><td>Comparator</td><td>Intervention type: Control (SMBG without intensive education and feedback)
Instructions: as intensive SMBG above
Frequency: asked to perform a six- or seven-point glucose profile for three consecutive days on three occasions: Weeks 0, 6, and 12.
Feedback: follow-up visits at Weeks 6 and 12 and received only 2 h of education regarding diabetes, nutrition, and exercise at Week 0. Adjustment of therapy was done at Week 0 and Week 6. Download of meter glucose data was performed only at Weeks 0, 6, and 12 in this group, but these data were not made available to the clinician treating the control group patient until Week 12.
Education: see feedback
Diary: not reported</td></tr>
<tr><td>Length of follow up</td><td>Intervention: 12 weeks
Follow-up: 12 weeks</td></tr>
<tr><td>Location</td><td>Brazil</td></tr>
<tr><td>Outcomes measures and effect sizes</td><td>Primary outcome measures (Change in blood glucose control): see table one for changes in blood glucose measure across follow-up period.

Table 1. Changes in outcomes
<table>
<tr><th></th><th colspan="3">Intensive group</th><th colspan="3">Control group</th><th colspan="2">P-value for intensive vs. control</th></tr>
<tr><th>Outcome measures</th><th>Week 0</th><th>Week0-6</th><th>Week 0-12</th><th>Week 0</th><th>Week0-6</th><th>Week 0-12</th><th>6 week</th><th>12 weeks</th></tr>
<tr><td>WMG (mg/dL) *</td><td>216.45 ± 5.57</td><td>-76.65 ± 8.92†</td><td>-60.96 ± 10.55†</td><td>210.20 ± 9.27</td><td>-20.46 ± 8.08**</td><td>-34.11 ± 10.25**</td><td>1x10-5***</td><td>0.038</td></tr>
<tr><td>Glycemic variability as SD (mg/dL)</td><td>69.37 ± 4.12</td><td>-16.30 ± 3.12†</td><td>-15.75 ± 3.00†</td><td>65.95 ± 4.04</td><td>-5.04 ± 3.12NS -</td><td>-7.20 ± 3.52*</td><td>0.010*</td><td>0.036*</td></tr>
<tr><td>A1C (%)</td><td>10.29 ± 0.25</td><td>-1.82 ± 0.16†</td><td>-2.26 ± 0.23†</td><td>10.01 ± 0.25</td><td>-0.66 ± 0.22***</td><td>-1.29 ± 0.24***</td><td>1x10-5***</td><td>0.003</td></tr>
</table></td></tr>
</table>

Bibliographic reference (Ref ID)	Pimazoni-Netto et al 2011 (REF ID: 932)

Weight (kg)	86.42 ± 3.41	-0.10 ± 0.40NS	0.12 ± 0.60NS	6.65 ± 2.76	0.05 ± 0.28NS	0.73 ± 0.35*	0.76	0.39

Data are mean – 1 SEM for baseline values and changes between baseline and Week 12 in weekly mean glycemia (WMG), glycemic variability as SD, glycated hemoglobin (A1C), weight, and percentage of subjects in good glycemic control. *P < 0.05, **P < 0.01, ***P < 0.001, ******P < 1x10- 6. NS, not significant (P > 0.05).

Other outcome measures (Changes in weight or BMI): see table one for changes in weight across the follow-up period

Changes in lipid levels: not reported

Quality of life: not reported

Adverse events: The frequency of hypoglycemic events (% of glucose values ≤ 60 mg/dL) was slightly increased in the intensive treatment group (4.11 ±0.96%) compared with the control group (2.24 ±0.64%), but this difference was not statistically significant (P > 0.05). There were no reports of severe hypoglycaemia in either group.

Microvascular and macrovascular complication: not reported

Subgroup analyses: N/A

Authors' conclusion	This short-term pilot study of an intensive monitoring, educational, and pharmacological interventions program resulted in dramatic improvement of glycemic control within 6 weeks, and these effects are sustained through Week 12
Source of funding	Roche Diagnostics of Brazil provided Accu-Chek Performa glucose meters, monitoring supplies, and the Accu-Chek 360 software
Comments	N/A

Evidence table 13: (Polonsky et al 2011 STEP study)

Bibliographic reference (Ref ID)	Polonsky et al 2011-STEP study (REF ID: 81)
Study type & aim	Cluster RCT To assess the effectiveness of structured blood glucose testing in poorly controlled, noninsulin-treated type 2 diabetes.
Number and characteristics of patients	**Total number of patients:** 34 primary care practices that were then randomized with stratification to ACG (n = 13) or STG (n = 21). 499 patients were eligible and enrolled in the study. Of these, 7 patients (ACG, n = 1; STG, n = 6) withdrew consent, and 9 patients (ACG, n = 2; STG, n = 7) were lost to follow-up. The remaining 483 patients (ACG, n = 227; STG, n = 256) were included in the ITT cohort. An additional 84 patients (ACG, n = 26; STG, n = 58) were excluded from the PP analyses because of protocol nonadherence. Thus, the PP cohort included 161 (71%) ACG patients and 130 (51%) STG patients **Inclusion criteria:** duration of type 2 diabetes >1 year; aged ≥25 years; HbA1C level 7.5–12.0%; currently treated by diet, exercise, oral diabetes medication, and/or injectable incretin mimetic; able to read and write English without assistance; and had not participated in any other research protocol within the last 30 days **Exclusion criteria:** type 1 diabetes; managed with insulin at the start of the study; C-peptide level ≤0.50ng/mL; used systemic oral or inhaled steroids more than 14 days within the last 3 months; treated with chemotherapy or radiation therapy; pregnant or

Bibliographic reference (Ref ID)	Polonsky et al 2011-STEP study (REF ID: 81)

breastfeeding; or had severe depression or other severe psychological conditions

Patient characteristics: table one and two show baseline characteristics of practice sites and patients included in this cluster RCT. During the study, 15 patients discontinued, 24 withdrew consent, and 69 were lost to follow-up, all primarily because of time or other life demands. Dropouts were slightly younger (P < 0.02), more likely to be African American (P < 0.02), had a higher A1C (P < 0.01), and had fewer comorbid conditions at baseline (P < 0.02). Characteristics of the dropouts were not significantly different between the two study groups. Patient demographic and disease-related characteristics at baseline between the two study groups differed only by age and ethnicity. These differences were controlled in all subsequent analyses

Table 1. Baseline characteristics of included practice sites (N=34)

Practice sites	All sites	ACG	STG	P-value
n	34	13	21	-
Physician age: mean (SD) age (years)	44.8 (7.7)	43.3 (6.4)	45.7 (8.4)	0.3867
Gender: male	27 (79.4)	11 (84.6)	16 (76.2)	0.5549
Years in practice: mean (SD) (years)	13.1 (7.9)	11.3 (7.2)	14.1 (8.3)	0.3441
Type of practice	-	-	-	0.4289
Primary care	27 (79.5)	10 (76.9)	17 (81.0)	-
Multispecialty care	6 (17.6)	2 (15.4)	4 (19.0)	-
Primary care/multispecialty care	1 (2.9)	1 (7.7)	0 (0.0)	-
Number of type 2 diabetic patients: mean (SD)	1,084 (1,483)	1,250 (2,023)	978 (1,065)	0.6276
Primary location of practice	-	-	-	0.3024
Rural setting	10 (29.4)	2 (15.4)	8 (38.1)	-
Suburban	17 (50.0)	9 (69.2)	8 (38.1)	-
Urban	6 (17.6)	2 (15.4)	4 (19.0)	-
Urban and suburban	1 (3.0)	0 (0.0)	1 (4.8)	-

Table 2. Baseline characteristics of included patients

Patients	All sites	ACG	STG	P-value
N	483	227	256	-

Bibliographic reference (Ref ID)	Polonsky et al 2011-STEP study (REF ID: 81)

Patient age: mean (SD) age (years)	55.8 (10.7)	57.0 (11.2)	54.8 (10.1)	0.0197
Gender: male	257 (53.2)	122 (53.7)	135 (52.7)	0.8243
Ethnicity	-	-	-	0.0004
African American	150 (31.1)	72 (31.7)	78 (30.5)	-
Caucasian	305 (63.1)	152 (67.0)	153 (59.8)	-
Other	28 (5.8)	3 (1.3)	25 (9.8)	-
Highest level of education	-	-	-	0.1002
No college	253 (52.7)	114 (50.9)	139 (54.3)	-
Some college	98 (20.4)	40 (17.9)	58 (22.7)	-
College graduate	129 (26.9)	70 (31.3)	59 (23.0)	-
A1C: mean (SD) A1C (%)	8.9 (1.2)	8.9 (1.2)	8.9 (1.2)	0.8751
BMI: mean (SD) BMI (kg/m2)	35.1 (7.3)	35.1 (6.7)	35.0 (7.8)	0.8851
Diabetes duration: mean (SD) (years)	7.6 (6.1)	7.7 (6.1)	7.5 (6.1)	0.6547
Values are n (%) unless stated otherwise				

Subgroup analyses: methods specify that STG patients that adhered and did not adhere would be analysed separately

Monitoring information and definitions

Monitoring: patient visits occurring at initial screening and baseline followed by visits at months 1, 3, 6, 9, and 12.

Definitions: GWB was measured using theWHO-5 Well-Being Index assessment tool, a widely used, five-item questionnaire with a total score range of from 0–100 (higher scores indicating more positive well-being).

Recommended pharmacologic modification (defined as the initiation of a new medication, increase or decrease in the dose of an existing medication, or termination of an existing medication) and recommended lifestyle modification (defined as any change in diet, exercise, or other self-care behaviour).

Adherence in the ACG was defined as those who completed the study (with ≥4 visits) and did not use structured SMBG records that were similar to the Accu-Chek 360° View blood glucose analysis system intervention tool. Adherence in the STG was defined as those who completed at least 80%of all blood glucose values on the intervention tool, brought their completed tool to the clinic visit, and reported that their physicians looked at the tool and discussed the results (via the Post-Visit Questionnaire) at ≥4 of the 5 clinic visits

Primary outcome measures: change in HbA1C from screening to 12 months

Secondary outcome measures: general well-being, treatment changes, frequency of SMBG, seven point blood glucose profiles

Other outcome measures: N/A

Intervention

Intervention type: Structured testing group (STG)-enhanced usual care and at least quarterly use of SMBG

Instructions: Patients in both arms received a free blood glucose meter and test strips (Accu-Chek Aviva meter system; Roche

Bibliographic reference (Ref ID)	Polonsky et al 2011-STEP study (REF ID: 81)
	Diagnostics, Indianapolis, IN), and they were instructed in their use. STG participants used the Accu-Chek 360° View blood glucose analysis system (Roche Diagnostics), a validated tool that enabled patients to record/plot a 7- point SMBG profile (fasting, preprandial/ 2-h postprandial at each meal, bedtime) on 3 consecutive days prior to each scheduled study visit (months 1, 3, 6, 9, and 12), to document meal sizes and energy levels, and to comment on their SMBG experiences. STG participants received training in the use of the Accu-Chek system, including instructions for how to identify problematic glycemic patterns and how best to address such problems through changes in physical activity, portion sizes, and/or meal composition **Frequency:** at least quarterly **Feedback:** STG physicians/staff received training on interpreting the structured data and were provided with an algorithm that described various pharmacologic/lifestyle treatment strategies that could be used in response to the specific SMBG patterns identified. Physicians were free to select from these options based on patient/ physician preferences. **Education: see instructions above** **Diary:** not reported but results recorded as per instructions above
Comparator	**Intervention type:** Active control group (ACG)-enhanced usual care **Instructions:** ACG subjects did not receive the Accu-Chek system. ACG patients were instructed to use their meter following their physicians' recommendations but received no additional SMBG prompting, training, or instruction. **Frequency:** not reported **Feedback:** ACG physicians and staff received no additional training. **Diary:** not reported
Length of follow up	Intervention: 12 months Follow-up: 12 months
Location	USA
Outcomes measures and effect sizes	**Primary outcome measures (Change in blood glucose control):** see table 3 for changes in Hba1c at different time-points. ITT analysis revealed that both groups showed significant reductions in A1C levels; however, STG subjects evidenced significantly greater mean (SE) reductions in A1C than ACG subjects over the 12 months: -1.2% (0.09) vs.-0.9% (0.10); Δ= -0.3%; P = 0.04. PP analysis revealed an even greater mean (SE) A1C reduction among those STG subjects who adhered to the intervention compared with ACG subjects: -1.3% (0.11) vs. -0.8% (0.11); Δ = -0.5%; P < 0.003. STG subjects showed significantly lower average preprandial and postprandial glucose levels at all meals and at bedtime from month 1 to month 12 (in all cases, P < 0.001). There was a significant drop from month 1 to month 12 in preprandial to postprandial glucose excursions at all meals: breakfast (44 to 35 mg/dL, P < 0.005), lunch (25 mg/dL to 17 mg/dL, P < 0.03), and supper (34 to 26 mg/dL, P <0.05). Measurements of mean amplitude of glucose excursions indicated significant (P = 0.0003) mean (SE) reductions in glycemic variability among STG subjects from 38.5 mg/dL (0.9) at month 1 to 34.3 mg/dL (1.0) at month 12. **Table 3. Changes in Hba1c across study period** **Treatment group** | **Baseline** | **Month 1** | **Month 3** | **Month 6** | **Month 9** | **Month 12**

Bibliographic reference (Ref ID)	Polonsky et al 2011-STEP study (REF ID: 81)

ITT analysis	-	-	-	-	-	-
ACG	8.9% (0.08)	8.7% (0.1)	8.2% (0.1)	7.9% (0.1)	8.0% (0.1)	8.0% (0.1)
STG (all)	8.9% (0.07)	8.5% (0.09)	7.9% (0.09)	7.6% (0.09)	7.6% (0.09)	7.7% (0.09)
PP analysis	-	-	-	-	-	-
ACG	8.9% (0.1)	8.7% (0.1)	8.3% (0.1)	8.0% (0.1)	8.1% (0.1)	8.0% (0.1)
STG (adherent patients)	8.8% (0.1)	8.5% (0.11)	7.9% (0.11)	7.6% (0.11)	7.5% (0.11)	7.6% (0.11)
STG (nonadherent patients)	8.9% (0.14)	8.5% (0.15)	7.9% (0.15)	7.7% (0.15)	7.7% (0.16)	8.0% (0.15)
All data presented as mean ± SE						

Other outcome measures (Changes in weight or BMI): not reported

Changes in lipid levels: not reported

Quality of life: There was a significant increase in general well-being (GWB) over the study period in both the ACG (P<0.007) and the STG (P<0.0001), as assessed by the WHO-5, with no significant between-group differences over time. PP analyses revealed that adherent STG subjects reported a significantly greater improvement in GWB than adherent ACG subjects (P < 0.04).

Adverse events: There were no intervention-related adverse events. Over the 12 months, no severe hypoglycaemic events were reported. The incidence of hypoglycemia (<70 mg/dL), based on downloaded meter data, was 1.9% in the ACG and 1.8% in the STG (P = NS).

Changes in treatment: significantly more STG patients received a treatment change recommendation at the month 1 visit compared with ACG patients, regardless of the patient's baseline A1C level: 179 (75.5%) vs. 61 (28.0%); P < 0.0001. almost twice as many

STG patients were started on intermediate or long-acting insulin than ACG patients between the month 1 and month 12 visits: 42 vs. 23; P = 0.046. ITT analyses excluding patients who began insulin during the study period also indicated significant decreases in A1C for both the ACG and the STG, with STG patients still demonstrating significantly greater reductions in A1C by month 12 than ACG patients: -1.3% (0.10) vs. -1.0% (0.10); Δ= -0.3%; P = 0.03

Microvascular and macrovascular complication: not reported

Subgroup analyses: see subgroup analysis by adherence as part of changes in blood glucose level

Authors' conclusion	Appropriate use of structured SMBG significantly improves glycaemic control and facilitates more timely/aggressive treatment changes in noninsulin-treated type 2 diabetes without decreasing GWB
Source of funding	Roche Diagnostics, Indianapolis, Indiana.
Comments	Patients were recruited from primary care practice sites across the eastern U.S, which were stratified to STG or ACG. Patients in both groups brought their meters to each subsequent visit for electronic data uploading; physicians and clinic staff were blinded to these data and all other study-collected measures.

Evidence table 14: (Kwon et al 2004)

Bibliographic reference (Ref ID)	**Kwon et al 2004 (REF ID: 1227)**
Study type & aim	RCT investigating the effectiveness of an Internet-based blood glucose monitoring system (IBGMS) on controlling the changes in HbA1c levels
Number and characteristics of patients	**Total number of patients:** 110 randomised (55 in each arm), 51 in intervention group and 50 in control group completed the 12 week study **Inclusion criteria:** Men and women diagnosed with type 2 diabetes for ≥1 year. All enrolled participants in this study had Internet access in their homes for this specialized web based diabetes management system and were ≥30 years of age. **Exclusion criteria:** significant diseases that were likely to affect the outcome and compliance of this study. Such diseases or conditions included heart failure, hepatic dysfunction, renal insufficiency with a creatinine level >1.5 mg/dl, and use of insulin pumps. Patients who had any history of participating in other programs that provided any information or education for diabetes management from specific websites other than ours were also excluded **Patient characteristics:** The dropout rates were very similar between the intervention and control group. There were no significant differences between the two groups with respect to age, BMI, diabetes duration, and glucose control methods or in terms of laboratory data, including baseline HbA1c, fasting plasma glucose, total cholesterol, triglyceride, HDL, blood urea nitrogen, and creatinine. The average frequency of blood glucose monitoring during study period in intervention group was 71.5 ± 36.2 and 38.1 ± 24.8 in control group. **Table 1. Baseline characteristics of study participants (N=110)**

Characteristic	Control group (n=55)	Intervention group (n=55)	P-value
n	55	55	-
Age (years)	54.7 ± 9.4	53.5 ± 8.8	0.507
Sex (M/F)	32/18	35/16	0.623
BMI (kg/m2)	23.9 ± 3.1	24.4 ± 3.4	0.493
Diabetes duration (years)	6.6 ± 5.7	7.0 ± 6.3	0.751
Diagnosis of hypertension (n)	13	17	0.420
Systolic blood pressure (mmHg)	128.5 ± 17.0	124.7 ± 15.8	0.999
Diastolic blood pressure (mmHg)	77.0 ± 9.7	77.5 ± 8.7	0.254
HbA1c (%)	7.19 ± 1.17	7.59 ± 1.43	0.133
Fasting plasma glucose (mg/dl)	136.4 ± 32.3	136.0 ± 35.0	0.826
Total cholesterol (mg/dl)	180.9 ± 28.9	188.8 ± 30.10	0.231
Triglyceride (mg/dl)	136.8 ± 94.0	154.7 ± 98.1	0.358
HDL (mg/dl)	47.9 ± 13.2	47.7 ± 11.0	0.925

Bibliographic reference (Ref ID)	Kwon et al 2004 (REF ID: 1227)

Blood urea nitrogen (mg/dl)	16.2 ± 5.2	15.2 ± 3.8	0.393
Creatinine (mg/dl)	0.9 ± 0.3	0.9 ± 0.2	0.498
Data are means ± SD (unless specified)			

Subgroup analyses: some pre-specified analyses by baseline Hba1c level

Monitoring information and definitions

Monitoring: see intervention details
Definitions: N/A
Primary outcome measures: HbA1c was treated as the major outcome variable
Secondary outcome measures: N/A
Other outcome measures: N/A

Intervention

Intervention type: internet based blood glucose monitoring system (IBGMS)
Instructions: Patients in the intervention group were taught how to use the Internet-based system and used the IBGMS for 12 weeks without outpatient management visits. Patients sent information about their self-monitored blood glucose levels before and after eating (fasting and postprandial) and drug information including the types and dosages of insulin and oral anti-diabetic medication used for diabetes control. when necessary, changes in their blood pressure or weight and any questions or detailed information the patient may have (for example, diet, exercise, hypoglycaemic event, or other factors that can cause changes in the glucose level) were also recorded
Frequency: Before starting this program, we recommended our patients in both groups to check their blood glucose3 days a week (one to three times a day) including postprandial level according to the level of glycemic control. During the study period, patients in the intervention group recorded their glucose level one to three times per day for an average of 20 days a month,
Feedback: For this program, our staff consisted of three endocrinology specialists (one professor and two fellows), three nurses, two dietitians, and four programmers. For the intervention group, two endocrinology fellows checked in with the system daily. They analysed all uploaded blood glucose data or questions regarding medication and hypoglycemic episodes and sent recommendations to the patients in the intervention group according to the diabetes management guidelines. No automated algorithm was used, If there was any need to change the patient's medication or dosage, the two endocrinology fellows referred the case to the professor. Three nurses mainly commented upon lifestyle modification, including exercise, and the two dietitians supplied individually modified medical nutrition therapy. All of the responses from the nurses and dietitians were also monitored by medical staff. The medical staff (two fellows and one professor) had meetings regularly to develop the appropriate individual recommendations
Education: see instructions
Diary: not reported

Comparator

Intervention type: control (clinic visits)
Instructions: Patients in the control group were unaware of any knowledge regarding the new diabetes management system. They visited the diabetes center monthly and received their usual outpatient treatment from their physicians during the study period. Participants in the control group met the professor two or three times during the 12 weeks. As customary in our outpatient clinic for

<table>
<tr><td>Bibliographic reference (Ref ID)</td><td>Kwon et al 2004 (REF ID: 1227)</td></tr>
<tr><td></td><td>diabetic patients, when the patients in the control group visited our center, they were provided recommendations about medication, medication dosage, lifestyle modification, and so on from the endocrinology specialist (professor, not fellows). When the doctor chose to consult for special education or if the patient wished, the dietitian or nurse came to aid with a more individualized and detailed information for lifestyle modification
Frequency: patients in the control group visited the diabetes center two or three times in 12 weeks
Feedback: see instructions
Diary: not reported</td></tr>
<tr><td>Length of follow up</td><td>Intervention: 12 weeks
Follow-up: 12 weeks</td></tr>
<tr><td>Location</td><td>Korea</td></tr>
<tr><td>Outcomes measures and effect sizes</td><td>Primary outcome measures (Change in blood glucose control): see table 2 for changes from baseline at 12 weeks

Table 2. Hba1c levels in both treatment groups
<table>
<tr><th>Patients</th><th>n</th><th>Hba1c</th><th>P-value</th></tr>
<tr><td>Total</td><td>-</td><td>-</td><td>0.001</td></tr>
<tr><td>Control</td><td>50</td><td>7.62 ± 0.13</td><td>-</td></tr>
<tr><td>Intervention</td><td>51</td><td>6.94 ± 0.13</td><td>-</td></tr>
<tr><td>HbA1c <7% at baseline</td><td></td><td></td><td>0.046</td></tr>
<tr><td>Control</td><td>26</td><td>6.99 ± 0.18</td><td>-</td></tr>
<tr><td>Intervention</td><td>18</td><td>6.38 ± 0.22</td><td>-</td></tr>
<tr><td>HbA1c ≥7% at baseline</td><td></td><td></td><td>0.001</td></tr>
<tr><td>Control</td><td>24</td><td>8.12 ± 0.19</td><td>-</td></tr>
<tr><td>Intervention</td><td>33</td><td>7.38 ± 0.16</td><td>-</td></tr>
<tr><td colspan="4">Data are means ± SE. Means were adjusted according to HbA1c at baseline. *P for control vs. intervention</td></tr>
</table>

Table 3. Changes in outcomes at 12 week follow-up
<table>
<tr><th>Outcome</th><th>Δ from baseline in control group</th><th>Δ from baseline in intervention group</th></tr>
<tr><td>n</td><td>50</td><td>51</td></tr>
<tr><td>HbA1c (%)</td><td>+0.33</td><td>0.54*</td></tr>
<tr><td>Fasting blood glucose (mg/dl)</td><td>+9.34</td><td>+7.29</td></tr>
</table></td></tr>
</table>

Bibliographic reference (Ref ID)	Kwon et al 2004 (REF ID: 1227)

Total cholesterol (mg/dl)	+7.30	3.33
Triglyceride (mg/dl)	+13.5	19.5
HDL cholesterol (mg/dl)	+2.70*	+2.91
LDL cholesterol (mg/dl)	+1.88	1.93
*significant difference from baseline (p<0.05)		

Other outcome measures (Changes in weight or BMI): not reported
Changes in lipid levels: see table 3
Quality of life: not reported
Adverse events: not reported
Microvascular and macrovascular complication: not reported
Subgroup analyses: see blood glucose levels

Authors' conclusion	This new IBGMS resulted in a significant reduction of HbA1c during the study period. We propose that this IBGMS be used as a method for improving diabetes control
Source of funding	Supported by the 2001 Korea Health Promotion Research Program and the Korea Health 21 R&D Project, Ministry of Health and Welfare of Republic of Korea Grant
Comments	Randomisation method not reported

Evidence table 15: (Cho et al 2009)

Bibliographic reference (Ref ID)	Cho et al 2009 (REF ID: 195)
Study type & aim	RCT to investigate the effectiveness of the diabetes phone for blood glucose control compared with the effectiveness of the internet based glucose monitoring system (IBGMS)
Number and characteristics of patients	**Total number of patients:** 75 patients were enrolled (69 completed 12 weeks, Internet n=37, phone group n=38) **Inclusion criteria:** patents with type 2 diabetes who were able to access the internet and to communicate through a mobile phone using the SMS **Exclusion criteria:** significant disease conditions such as symptomatic heart failure, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels more than twice the normal level, renal disease and creatinine level>1.5mg/dL. Patients were also excluded if they participated in other programmes that provided information or education about diabetes management from any internet websites or by any mobile phone other than the one being examined in the current study **Patient characteristics:** dropout rates were similar between groups, with 3 participants in each group not completing the study. The

Bibliographic reference (Ref ID)	Cho et al 2009 (REF ID: 195)

groups did not significantly differ in age, BMI, diabetes duration, blood pressure, Hba1c and lipid profiles.

Table 1. Baseline characteristics of included practice sites (N=69)

Practice sites	Internet group (n=34)	Phone group (n=35)	P-value
Age, years (SD)	45.2 (11.3)	51.1 (13.2)	0.11
Male/female	26/8	28/7	0.31
BMI, kg/m^2 (SD)	23.6 (3.0)	25.3 (4.7)	0.06
Diabetes duration, years (SD)	5.3 (4.8)	8.2 (7.8)	0.43
Systolic blood pressure, mmHg (SD)	126.4 (12.8)	131.1 (13.4)	0.17
Diastolic blood pressure, mmHg (SD)	79.5 (10.4)	79.3 (10.9)	0.69
Hba1c, % (SD)	7.6 (1.9)	8.3 (2.3)	0.30
Fasting plasma glucose, mg/dL (SD)	167.5 (73.7)	146.6 (49.7)	0.14
2h post meal glucose	269.2 (99.1)	246.1 (65.0)	0.26
Total cholesterol, mg/dL (SD)	175.0 (38.3)	187.5 (28.6)	0.13
Triglycerides, mg/dL (SD)	4.4 (1.0)	4.7 (0.7)	0.11
HDL cholesterol, mg/dL (SD)	50.8 (14.7)	47.3 (14.4)	0.37
LDL cholesterol, mg/dL (SD)	97.0 (26.9)	109.0 (29.1)	0.055

Subgroup analyses: none pre-specified

Monitoring information and definitions

Monitoring: measurements taken at initial and final interview

Definitions: N/A

Primary outcome measures: satisfaction with medical service and adherence with doctor's recommendations. To assess the degree of satisfaction and adherence, these responses were classified into 5 and 4 levels respectively. For satisfaction (level 1= >90% satisfaction, level 2= >80% satisfaction, level 3= >50% satisfaction, level 4= 30% satisfaction, level 5= >20% satisfaction) and for adherence (level 1=patients obeyed >90% of recommendations, level2=70-90%, level 3=50-70% and level 4=<50%)

Secondary outcome measures:

Other outcome measures: N/A

Intervention

Intervention type: Mobile phone (mobile phone containing device to measure capillary blood glucose on site and transmit blood glucose data to a web server without manual input)

Instructions: see education, feedback and frequency

Frequency: Individual patients were taught about the frequency and timing of SMBG according to the mode of treatment and degree of glycaemic control. All patients were recommended to self-monitor one a day. It was recommended that patients on insulin should

Bibliographic reference (Ref ID)	Cho et al 2009 (REF ID: 195)
	measure SMBG three times a day while patients being treated with oral agents who had not reached their target Hba1c levels, twice daily was recommended. **Feedback:** All patients received recommendations once every other week **Education:** An education team consisting of an endocrinologist, nurse educator and a dietitian provided a diabetes education programme for all participants. Patients were also taught how to perform SMBG and were given information about diet, physical exercise and managing hypoglycaemia. **Diary:** not reported
Comparator	**Intervention type:** IBGMS (given blood glucose meters) **Instructions:** data from patients in the phone group were automatically transmitted to a web server **Frequency:** see details for mobile phone **Feedback:** one doctor reviewed all the information about SMBG data on individual web-based charts at least one every other week and sent recommendations to the internet group through the internet web chart **Education:** Participants in the internet group were taught about accessing and using the specialised, web based diabetes patients management system and how to communicate with a management team through their individualised web-based charts on the internet website, at least once every other week. Also see details for mobile phone **Diary:** not reported
Length of follow up	Intervention: 3 months Follow-up: 3 months
Location	Korea
Outcomes measures and effect sizes	**Primary outcome measures (Change in blood glucose control):** The basal Hba1c values were 7.6% (SD 1.9) in the internet group and 8.3% (SD 2.3) in the phone group (p>0.05). Hba1c levels decreased significantly in both groups after three months intervention (p=0.001) and the mean Hba1c decrement between the two groups was not significantly different (p=0.27). 2h post prandial glucose levels also decreased significantly in both groups after 3 months (p=0.001) but fasting plasma glucose levels did not change (p=0.07). The changes in mean fasting plasma glucose levels (internet vs. phone 167.5 to 148.8 mg/dL vs. 146.6 to 143.4 mg/dL, p=0.33) and 2h postprandial glucose levels (internet vs. phone: 269.2 to 223.5mg/dL vs. 246.1 to 214.6 mg/dL, p=0.48) during the study period were not significantly different between the two groups. **Other outcome measures (Changes in weight or BMI):** not reported **Changes in lipid levels:** not reported **Quality of life:** Satisfaction and adherence changes are shown below in table 2

Bibliographic reference (Ref ID)	Cho et al 2009 (REF ID: 195)
	Table 2. Changes in satisfaction and adherence **Adverse events:** not reported **Microvascular and macrovascular complication:** not reported **Subgroup analyses:** N/A
Authors' conclusion	Results suggest that the telecommunication system using the diabetes phone with a glucometer can be effective for glucose control and good for patient satisfaction and adherence.
Source of funding	Supported by the ministry of Information and Communication, the Seoul R&D programme and the ministry of commerce, Industry and Energy
Comments	N/A

Outcome	Group	Level 1	Level 2	Level 3	Level 4	Level 5	P-value
Satisfaction	Internet group	9 (29)	16 (52)	5 (16)	1 (3)	0 (0)	0.94
	Phone group	10 (35)	13 (45)	5 (17)	0 (0)	1 (3)	-
Adherence	Internet group	8 (26)	16 (52)	6 (19)	1 (3)	-	0.999
	Phone group	7 (24)	17 (59)	5 (17)	0 (0)	-	-

Evidence table 16: (Quinn et al 2011)

Bibliographic reference (Ref ID)	Quinn et al 2011 (REF ID: 451)
Study type & aim	Cluster RCT aiming to test whether adding mobile application coaching and patient/provider web portals to community primary care compared with standard diabetes management would reduce Hba1c levels in patients with type 2 diabetes
Number and characteristics of patients	**Total number of patients:** 26 randomised primary care practices with a total of 163 patients (group 1: control–usual care [UC, n=56]; group 2: coach-only [CO, n=23]; group 3: coach PCP portal [CPP, n=22]; and group 4: coach PCP portal with decision support [CPDS, n=62]. **Inclusion criteria:** type 2 diabetes diagnosed by a physician at least 6 months prior to enrolment, Hba1c ≥7.5% within the most recent 3 months and aged between 18 and 64 years **Exclusion criteria:** Medicare or Medicaid beneficiaries, uninsured, using an insulin pump, pregnant, active substance abuse, psychosis or schizophrenia under active care, uncorrected serve hearing or visual impairment and lack of access to internet or email address **Patient characteristics:** The 163 study patients had a mean baseline Hba1c of 9.4% (range 7.5–15.5) (Table 1). Mean age was 52.8 years, 50.3% were female, 39.3%were African-American, and 31.3% were college-educated. The mean duration of diabetes was 8.2 years. Most participants (76.1%) were obese (BMI ≥30 kg/m^2). Participants had a mean PHQ-9 of 5.2 (minimal to mild depression

Bibliographic reference (Ref ID)	Quinn et al 2011 (REF ID: 451)

scores). Most participants had hypertension (63.2%) and hypercholesterolemia (58.3%). CPDS patients had higher baseline glycated haemoglobin than UC (9.9 vs. 9.2%, P = 0.04). No other baseline patient variables differed significantly among the four study groups.

Table 1. Baseline characteristics of included patients (N=163)

	Group 1: UC (n = 56)		Group 2: CO (n = 23)		Group 3: CPP (n = 22)		Group 4: CPDS (n = 62)	
Characteristic	**n**	**% or mean ± SD**	**n**	**% or mean ± SD**	**n**	**% or mean ± SD**	**n**	**% or mean ± SD**
Glycated hemoglobin (%)	56	9.2 ± 1.7	23	9.3 ± 1.8	22	9.0 ± 1.8	62	9.9 ± 2.1
7.5–8.9	35	62.5	13	56.5	13	59.1	28	45.2
≥9	21	37.5	10	43.5	9	40.9	34	54.8
Age (years)	56	53.2 ± 8.4	23	52.8 ± 8.0	22	53.7 ± 8.2	62	52 ± 8.0
Sex	-	-	-	-	-	-	-	-
Male	28	50	12	52.2	10	45.5	31	50
Female	28	50	11	47.8	12	54.5	31	50
Duration of diabetes diagnosis (years)	56	9.0 ± 7.0	23	7.7 ± 5.6	22	6.8 ± 4.9	62	8.2 ± 5.3
BMI	-	-	-	-	-	-	-	-
BMI (kg/m^2)	56	34.3 ± 6.3	23	36.9 ± 7.5	22	35.5 ± 10.3	62	35.8 ± 7.1
Underweight (16.5–18.4 kg/m^2)	1	1.8	0	0	1	4.5	0	0
Normal (18.5–24.9 kg/m^2)	0	0	0	0	2	9.1	1	1.6
Pre-obese (25–29.9 kg/m^2)	11	19.6	4	17.4	7	31.8	12	19.4
Obese class 1 (30–34.9 kg/m^2)	22	39.3	6	26.1	1	4.5	18	29
Obese class 2 (35–39.9kg/m^2)	10	17.9	5	21.7	3	13.6	17	27.4
Obese class 3 (≥40 kg/m2)	12	21.4	8	34.8	8	36.4	14	22.6
Comorbidities								
Hypertension	29	51.8	18	78.3	13	59.1	43	69.4
Hypercholesterolemia	34	60.7	11	47.8	14	63.6	36	58.1
Coronary artery disease	5 5	8.9	2	8.7	0	0	5	8.1
Microvascular complications, any	8	14.3	1	4.3	2	9.1	6	9.7

Subgroup analyses: Two secondary analyses of glycated hemoglobin were performed as follows: one analysis stratified by baseline

Bibliographic reference (Ref ID)	Quinn et al 2011 (REF ID: 451)
	glycated hemoglobin (≥9.0 vs. <9.0); the other (prespecified analysis) adjusted for baseline glycated haemoglobin as a covariate.
Monitoring information and definitions	**Monitoring:** Measures are recorded at baseline and 12 months, or every 3 months through the one-year intervention **Definitions**: N/A **Primary outcome measures:** mean change in Hba1c comparing group 1 and group 4 Secondary outcome measures: Hba1c comparing all groups, blood pressure, BMI, lipid levels, changes in diabetes symptoms and diabetes distress. Serious adverse events (SAEs) are life-threatening or fatal, require or prolong a hospitalisation or result in a major disability. Both adverse events (AEs) and SAEs are grouped as expected or unexpected. Diabetes stages of change (DStoC) is an 18-item stage of change interview measure created for this study. Interview questions focus on decision making of the individual in five key areas: SMBG, managing carbohydrates, portion control, medication adherence and smoking. Participants were asked about self-management behaviour either less than 6 months (action phase scored as 0) or more than 6 months (maintenance phase scored as 1). If participants scored 0 they were asked about their readiness to change a particular behaviour and confidence in change based on a scale of one to ten with 1 being “not at all ready” and 10 being “extremely ready” The depression module of the Patient Health Questionnaire (PHQ-9) was used to assess depression. Total scores range from 0 to 27 with scores of 1-4 representing minimal symptoms; 5-9 for mild depression; 10-14 for moderate (minor) depression; 15-19 for moderately severe and ≥20 for severe depression. **Other outcome measures:** N/A
Intervention	**GROUP 2-coach only (patient only data and physicians have no web access to patient data)** **Intervention type:** Diabetes coaching system, using mobile phones and patient/physician portals to allow patient-specific treatment and communication. In this group physicians do not have web access to patient data. **Instructions:** patients receive coaching software on the mobile phone. Patients enter BG data, carbohydrates consumed, diabetes medications taken and other comments relating to self-care. **Frequency:** all patients in the intervention groups are given system-driven guidance on when to test their BG based on their disease status, medication regimen, and time of poorest control. **Feedback:** real time messaging is sent back to the patient’s mobile providing feedback on the entered data. The feedback is driven by the patient data, the trend of any recently entered data and the physician’s medication instructions for each patient. Patients may provide primary care practice with printed copies of electronic logbooks and other information because group 2 physicians do not have access to the individual patient portal system. Patient action plans summarising the patient entered data and identifying possible self-management actions for improving their diabetes control are electronically sent to the patients every 2.5 months. Each patient is instructed that action plans also serve as a pre-visit summary for the patient’s next office visit to their primary care providers. **Education:** All physicians receive the most recent ADA guidelines. Active treatment physicians (groups 2, 3 and 4) are informed that their patients receive the mobile phone and web-based Diabetes Manager system. The physicians receive different quantities of analysed data and clinical support depending on which treatment group they are assigned to. After randomisation, patients in the intervention groups are risk stratified based on comorbidities, complexity of the medication regimen and diabetes status. This risk stratification is used to direct the level of diabetes educator interaction with patients. Those with the highest risk level are contacted by

Bibliographic reference (Ref ID)	Quinn et al 2011 (REF ID: 451)
	a diabetes educator via the web-based messaging centre at most, four times a month. Other patients receive communication updates every 2-3 months. **Diary:** see above **GROUP 3-coach PCP portal (patients and primary care providers with access)** As group 2 above except primary care providers are provided access to a web portal where they may choose to review their patient's electronic logbooks-this is 'raw' patient data that have not been analysed **GROUP 4-Coach PCP portal with decision support (patients and primary care providers with access to patients data which are analysed based on treatment algorithms)** As group 2 except primary care providers are provided access to a secure web portal where they can choose to see their patient's electronic logbook. In addition, physicians are provided with data analysis reports, which is a summary of the patients glycaemic and metabolic control (lipids, BP and weight), adherence to medication, self-management skills and compliance with other key measures of care (aspirin use, screening for complications. The study physician is reminded that all data analysis is based on patient-entered, unvalidated data. The physician has the option to use this information and remain responsible for treatment decisions.
Comparator	**Intervention type: Group 1 control-usual care (UC)** **Instructions:** see education **Frequency:** not reported **Feedback:** not reported **Education:** Physicians assigned to the control group are told to care for patients as usual, including checking SMBG log books and downloading blood glucose meter readings if made available by the patient. **Diary:** not reported
Length of follow up	Intervention: 1 year Follow-up: 1 year
Location	USA
Outcomes measures and effect sizes	**Primary outcome measures (Change in blood glucose control):** see table 2 for changes in Hba1c levels across the study in the 4 groups. In a stratified analysis, a greater decline was found with CPDS than UC for the stratum with baseline Hba1c <9.0% (difference in decrease 0.7%, 95% CI 0.2–1.1, P = 0.003) and the stratum with baseline Hba1c at least 9.0% (difference in decrease 1.3%, 0.2–2.4, P = 0.01). The test of interaction was not significant (P = 0.49) for baseline Hba1c stratum and treatment group over time. We obtained the same conclusion whether or not we analysed the baseline to 12-month changes with intermediate Hba1c measures

Table 2. Changes in outcomes across study period

	Group 1: UC (n = 56)		Group 2: CO (n = 23)		Group 3: CPP (n = 22)		Group 4: CPDS (n = 62)	
Outcome	**n**	**% or mean ±**	**n**	**% or mean**	**n**	**% or mean ±**	**n**	**% or mean**

Bibliographic reference (Ref ID)	Quinn et al 2011 (REF ID: 451)								
			SD*		± SD*		SD*		± SD*
	Hba1c(%)†								
	Baseline	56	9.2 ± 1.7	23	9.3 ± 1.8	22	9.0 ± 1.8	62	9.9 ± 2.1
	3 Months	30	8.2 ± 1.2	13	7.6 ± 1.2	9	7.5 ± 0.6	41	7.8 ± 1.3
	6 Months	27	8.6 ± 2.0	15	7.6 ± 1.1	11	7.6 ± 0.7	30	7.5 ± 1.2
	9 Months	43	8.5 ± 1.4	16	7.6 ± 0.9	15	7.9 ± 1.4	48	7.9 ± 2.0
	12 Months	51	8.5 ± 1.8	21	7.7 ± 1.0	21	7.9 ± 1.4	56	7.9 ± 1.7
	Change from baseline to 12 months (mean)‡		-0.7		-1.6		-1.2		-1.9
	Change from baseline to 12 months (95% CI)‡		-1.1 to -0.3		-2.3 to -1.0		-1.8 to -0.5		-2.3 to -1.5
	Secondary outcomes, laboratory values								
	Systolic blood pressure (mmHg)								
	Baseline	56	130 ± 22	23	130 ± 18	22	133 ± 14	62	130 ± 14
	12 Months	45	133 ± 20	21	134 ± 25	20	134 ± 16	51	128 ± 19
	Change from baseline to 12 months (mean)‡		+2		+4		2		22
	Change from baseline to 12 months (95% CI)‡		-3 to +7		-4 to +11		-6 to +10		-6 to +3
	Diastolic blood pressure (mmHg)								
	Baseline	56	78 ± 12	23	79 ± 11	22	79 ± 9	62	79 ± 9
	12 Months	45	79 ± 13	21	82 ± 11	20	78 ± 9	51	78 ± 10
	Change from baseline to 12 months (mean)‡		+1		+2		-2		-1
	Change from baseline to 12 months (95% CI)‡		-2 to 4		-2 to 7		-6 to 3		-4 to 2
	LDL (mg/dL)								
	Baseline	51	102 ± 36	23	103 ± 29	22	103 ± 33	55	106 ± 33
	12 Months	42	91 ± 34	19	94 ± 32	15	94 ± 47	45	102 ± 32
	Change from baseline to 12 months		-6		-8		-14		-5

Bibliographic reference (Ref ID)	Quinn et al 2011 (REF ID: 451)

(mean)‡								
Change baseline to 12 months (95% CI)‡		-15 to 3		-21 to 5		-29 to 0		-13 to 4
HDL (mg/dL)								
Baseline	56	44 ± 11	23	44 ± 11	22	43 ± 11	59	43 ± 11
12 Months	44	45 ± 12	16	42 ± 9	15	44 ± 11	48	45 ± 10
Change from baseline to 12 months (mean)‡		+1		0		0		+2
Change from baseline to 12 months (95% CI)‡		-1 to 3		-4 to 3		-3 to 4		0 to 3
Triglycerides (mg/dL)								
Baseline	56	185 ± 167	23	172 ± 100	22	164 ± 105	59	187 ± 145
12 Months	44	169 ± 124	16	113 ± 42	15	151 ± 74	48	139 ± 91
Change baseline to 12 months (mean)‡		-23		-53		-12		-31
Change baseline to 12 months (95% CI)‡		-58 to 12		-110 to 4		-71 to 47		-65 to 3
Total cholesterol (mg/dL)								
Baseline	56	182 ± 51	23	181 ± 35	22	177 ± 42	59	184 ± 41
12 Months	44	168 ± 40	16	151 ± 34	15	168 ± 52	48	174 ± 42
Change baseline to 12 months (mean)‡		-11		-24		-14		-9
Change baseline to 12 months (95% CI)‡		-22 to 1		-43 to 25		-35 to 5		-21 to 2

n = 163. *Unless otherwise indicated. †Primary outcome, glycated hemoglobin change over 12 months; group 4 (P=0.001) and group 2 (P = 0.003) have significantly larger changes than group 1. No other outcomes are significant. ‡Mean change and CI values are from the mixed-effects model

Other outcome measures (Changes in weight or BMI): not reported

Changes in lipid levels: see table 2

Quality of life: see table 3 below for changes in diabetes distress, diabetes symptoms and depression

Bibliographic reference (Ref ID)	Quinn et al 2011 (REF ID: 451)

Table 3. Changes in diabetes distress, diabetes symptom and depression

	Group 1: UC (n = 56)		Group 2: CO (n = 23)		Group 3: CPP (n = 22)		Group 4: CPDS (n = 62)	
Outcome	**n**	**% or mean ± SD***	**n**	**% or mean ± SD***	**n**	**% or mean ± SD***	**n**	**% or mean ± SD***
Diabetes Distress Scale								
Baseline	56	2.4 ± 0.9	22	2.7 ± 0.9	21	2.8 ± 0.7	58	2.6 ± 0.9
12 Months	46	2.3 ± 0.9	20	2.6 ± 0.9	21	2.4 ± 0.8	61	2.3 ± 0.8
Change from baseline to 12 months (mean)‡		-0.1		-0.1		-0.3		-0.3
Change from baseline to 12 months (95% CI)‡		-0.4 to 0.1		-0.4 to 0.3		-0.7 to 0.0		-0.5 to 0.0
Diabetes symptom inventory								
Baseline	56	15.6 ± 5.6	22	16.4 ± 5.7	22	18.1 ± 6.4	62	17 ± 5.6
12 Months	46	14.6 ± 4.8	21	15.5 ± 4.5	21	16.2 ± 5.8	62	16.7 ± 5.2
Change from baseline to 12 months (mean)‡		22.3		22.8		24.3		21
Change from baseline to 12 months (95% CI)‡		-5.5 to 0.9		-7.7 to 2.0		-9.0 to 0.4		-3.8 to 1.8
Depression (PHQ-9)								
Baseline	56	4.7 ± 5.6	23	5.2 ± 4.8	22	5.5 ± 4.7	62	5.5 ± 5.4
12 Months	44	3.6 ± 4.1	21	4.6 ± 5.0	21	3.9 ± 5.3	62	4.8 ± 4.8
Change from baseline to 12 months (mean)‡		-1.1		-0.6		-1.2		-0.7
Change from baseline to 12 months (95% CI)‡		-3.2 to +3.0		-2.7 to +1.4		-3.3 to +0.8		-1.9 to +0.5

Adverse events: Hypoglycemic events, hospitalizations, and emergency-room visits were infrequent in all groups. One patient in group 4 (CPDS) was hospitalized twice for reasons not reported to the study. The DSMB determined that there were no direct study related adverse events found. No patients died during the 12 months of this study

Microvascular and macrovascular complication: not reported

Bibliographic reference (Ref ID)	**Quinn et al 2011 (REF ID: 451)**
	Subgroup analyses: see blood glucose outcome for stratified analysis based on Hba1c levels at baseline
Authors' conclusion	The combination of behavioural mobile coaching with blood glucose data, lifestyle behaviours, and patient self-management data individually analysed and presented with evidence-based guidelines to providers substantially reduced glycated hemoglobin levels over 1 year
Source of funding	Funded through contributions by WellDoc, CareFirst Blue Cross/Blue Shield of Maryland, LifeScan, and Sprint. Additional funding was provided by the Maryland Industrial Partnerships program through the University of Maryland,
Comments	Randomised at the physician practice level in order to prevent potential contamination of the study intervention. The study biostatistician conducted the randomisation by a pseudo-random number generator in the software package R.

Evidence table 17: (Tildesley et al 2010)

Bibliographic reference (Ref ID)	**Tildesley et al 2010 (REF ID: 50)**
Study type & aim	RCT to assess the effect of an Internet-based glucose monitoring system (IBGMS) on Hba1C levels in patients with type 2 diabetes treated with insulin
Number and characteristics of patients	**Total number of patients:** 50 **Inclusion criteria:** type 2 diabetic patients being treated with insulin alone or in combination with oral antihyperglycemic medications. Inclusion criteria were a recent Hba1C >7.0%, internet access, and prior training in SMBG. **Exclusion criteria:** not reported **Patient characteristics:** baseline characteristics were similar across the two treatment groups

Table 1. Baseline characteristics of included participants (N=50)

Characteristic	Usual care*	Intervention*	P-value
n	23	24	-
Age (years)	62 ± 7.2	57 ± 10	0.081
Male/female	15/8	14/10	-
Duration of diabetes (years)	18.8 ± 6.4	18.8 ± 9.2	0.983
BMI (kg/m2)	33.1 ± 6.0	33.7 ± 6.4	0.732
A1C (%)	8.5 ± 1.2	8.8 ± 1.3	0.425
Blood pressure (mmHg)	132.6 ± 14.4/71.3 ± 9.2	129.5 ± 20.1/74.2 ± 15.5	0.545/0.439
Total cholesterol (mmol/l)	4.3 ± 1.3	4.2 ± 1.0	0.789
HDL cholesterol (mmol/l)	1.0 ± 0.3	1.2 ± 0.4	0.171

Bibliographic reference (Ref ID)	Tildesley et al 2010 (REF ID: 50)

LDL cholesterol (mmol/l)	2.2 ± 1.0	2.2 ± 0.8	0.947
Triglyceride (mmol/l)	2.2 ± 0.9	1.7 ± 0.7	0.058
Total-to-HDL cholesterol ratio	4.4 ± 1.3	3.7 ± 1.0	0.065
Creatinine (mol/l)	98.2 ± 30.1	85.4 ± 39.0	0.225
Daily insulin dosage (IU)	57.9 ± 45.0	60.4 ± 36.0	0.829
Data are means Data are means ± SD. *Two patients in the usual-care group and one patient in the intervention group did not follow protocol and were excluded. *Two patients in the usual-care group and one patient in the intervention group did not follow protocol and were excluded			

Subgroup analyses: none pre-specified

Monitoring information and definitions	**Monitoring:** Hba1c and laboratory tests were collected at 0, 3 and 6 months **Definitions**: N/A **Primary outcome measures:** Hba1c **Secondary outcome measures:** none **Other outcome measures:** N/A
Intervention	**Intervention type:** Internet based blood glucose monitoring system (IBGMS) **Instructions:** All patients were provided with a meter and test strips for testing at least three times daily and were asked to perform a laboratory blood test and visit their endocrinologist every 3 months. The system allowed the patient to input medications, set alarms, view a summary of readings, and send a message to their endocrinologist who then viewed the readings and sent feedback. **Frequency:** all patients provided with enough strips to test at least 3 times daily **Feedback:** The endocrinologist's recommendations included changes in insulin dosage, suggestions on testing frequency, and giving compliments **Education:** not reported **Diary:** asked to upload their SMBG readings every 2 weeks to a secure web site
Comparator	**Intervention type:** conventional treatment **Instructions:** not reported **Frequency:** see IBGMS **Feedback:** not reported but see endocrinologist every 3 months **Education:** not reported **Diary:** asked to keep a diary of SMBG for every visit to their endocrinologist
Length of follow up	Intervention: 6 months Follow-up: 6 months

Bibliographic reference (Ref ID)	**Tildesley et al 2010 (REF ID: 50)**
Location	Canada
Outcomes measures and effect sizes	**Primary outcome measures (Change in blood glucose control):** A comparison of between-group changes was not significant for any of the measurements except A1C. Over the 3- and 6-month period, A1C levels in the IBGMS group dropped from 8.8 ± 1.3 to 8.2 ± 0.91% (P=0.05) and further dropped to 7.6 ± 0.74% (P= 0.001), respectively. The control group, on the other hand, dropped from 8.5 ± 1.2 to 8.3 ± 1.1% (P = 0.42) after 3 months but rose to 8.4 ± 1.4% (P=0.51) after 6 months. Furthermore, the difference between the two groups at 6 months post-intervention was statistically significant even after adjusting for baseline A1C levels (P =0.05). **Other outcome measures (Changes in weight or BMI):** not reported **Changes in lipid levels:** not reported **Quality of life: not reported** **Adverse events:** not reported **Microvascular and macrovascular complication:** not reported **Subgroup analyses:** N/A
Authors' conclusion	The use of IBGMS significantly improved A1C levels in patients with type 2 diabetes treated with insulin
Source of funding	Abbott Diabetes Care donated glucose meters and test strips used in the study
Comments	Patients were randomly assigned to either of the groups using a computer random number generator

Evidence table 18: (Bosi et al 2013)

Bibliographic reference (Ref ID)	**Bosi et al 2013 – PRISMA RCT (REF ID:)**
Study type & aim	RCT to investigate the effects of intensive self monitoring of blood glucose (4-point glycaemic profile, 3 times per week) in type 2 patients not treated with insulin compared to active controls with 4-point glycaemic profiles taken at baseline, 6 and 12 months
Number and characteristics of patients	**Total number of patients:** 50 patients randomised (25 in each arm) with 38 completing the study (intervention n=20, control n=18) **Inclusion criteria:** able to perform SMBG and self-injection of medication, understand the goals, methods and procedures of treatment **Exclusion criteria:** Hba1c levels <7%, mental illness or severe cardiovascular disease or uncontrolled hypertension **Patient characteristics:** There was no significant difference in any of the demographic or clinical characteristics between the two groups **Table 1. Baseline characteristics of included participants (N=50)**

Characteristic	Intervention (n=25)	Control (n=25)	P-value

Bibliographic reference (Ref ID)	Bosi et al 2013 – PRISMA RCT (REF ID:)

Age, years (SD)	59.2 ± 7.2	62.0 ± 5.7	0.133
Male/female	9/16	9/16	1.000
BMI, kg/m^2 (SD)	24.6 ± 2.6	24.4 ± 2.6	0.838
Diabetes duration, months (SD)	158.1 ± 99.3	162.4 ± 83.5	0.871
Hba1c, % (SD)	8.8 ± 1.1	8.3 ± 0.9	0.068
FBG, mg/dl (SD)	178.0 ± 54.2	171.8 ± 54.9	0.689
PP2h, mg/dl (SD)	309.6 ± 95.9	278.3 ± 63.1	0.192
Treatment method*	-	-	1.00
None	1 (4.0)	0 (0)	
OHA	15 (60)	14 (56)	
Insulin	7 (28)	8 (32)	
OHA + insulin	2 (8)	3 (12)	
*Fishers exact test ** sum of total compliance score/20, range 0-100 Data are mean ± SD or n (%)			

Subgroup analyses: none pre-specified

Monitoring information and definitions

Monitoring: data on demographic and laboratory assessments was collected at baseline and 12 weeks

Definitions: N/A

Primary outcome measures: outcomes measures include Hba1c, FBG, 2h postprandial blood glucose and BMI

Secondary outcome measures: N/A

Other outcome measures: N/A

Intervention

Intervention type: telephone intervention

Instructions: the goal of the telephone intervention was to improve blood glucose levels. The target Hba1c was <7%, FBG <120mg/dl and 2 hour postprandial glucose <160mg/dl

Frequency: asked to log BG levels more than twice a day

Feedback: The researcher contacted members at least twice a week for the first month and then at least weekly for the second and third month. The frequency of telephone calls averaged 16 times for each individual. A registered dietitian analysed patients daily food intake and made recommendations for appropriate diabetic dietary control based on the participants diet and exercise patterns. The results and recommendations were mailed to participants. The researcher would adjust medications after reviewing the blood glucose log and discussing blood glucose values with the patients.

Education: Before the intervention the diabetes care booklet and a daily log were introduced. Each patient was instructed about the

Bibliographic reference (Ref ID)	Bosi et al 2013 – PRISMA RCT (REF ID:)
	booklet and daily log for 30 minutes by a researcher. It contained information about the nature of disease, risk factors, diet, exercise, drug therapy, hypoglycaemia and sick day management and how to record a daily log. The 12 week intervention consisted of continuing education and reinforcement of diet, exercise and medication adjustment recommendations as well as frequent SMBG. **Diary:** asked to keep daily diet and exercise logs
Comparator	**Intervention type:** control (usual care) **Instructions:** routine care (visiting a physician every 3 months) **Frequency:** not reported **Feedback:** not reported **Education:** not reported **Diary:** not reported
Length of follow up	Intervention: 12 weeks Follow-up: 12 weeks
Location	Italy
Outcomes measures and effect sizes	**Primary outcome measures (Change in blood glucose control):** see table 2 below for changes in blood glucose measures.

Table 2. Outcomes at baseline and end-point

Outcome	Group	Baseline	Study end	Difference from baseline	Difference between groups	Baseline vs. study end
Hba1c (%)	Intervention	8.9 ± 1.2	7.7 ± 1.0	-1.2 ± 1.5	0.000	0.002
	Control	8.4 ± 1.0	9.0 ± 1.2	0.6 ± 0.9	-	0.005
FBG (mg/dl)	Intervention	176.6 ± 56.0	160.9 ± 56.8	-15.7 ± 52.0	0.245	0.193
	Control	180.2 ± 62.4	173.3 ± 53.4	-6.9 ± 68.5	-	0.675
PP2H	Intervention	302.8 ± 94.0	260.2 ±76.6	-42.6 ± 114.8	0.071	0.114
	Control	278.0 ± 71.7	297.6 ± 89.1	19.6 ± 75.3	-	0.315
BMI (kg/m^2)	Intervention	24.6 ± 2.8	24.9 ± 2.8	0.3 ± 0.6	0.607	0.068
	Control	24.5 ± 2.6	24.7 ± 2.6	0.2 ± 0.6	-	0.278
Intervention group (n=20) and control group (n=18)						

Other outcome measures (Changes in weight or BMI): see table 2 for changes in BMI
Changes in lipid levels: not reported

Bibliographic reference (Ref ID)	Bosi et al 2013 – PRISMA RCT (REF ID:)
	Quality of life: not reported **Adverse events:** not reported **Microvascular and macrovascular complication:** not reported **Subgroup analyses:** N/A
Authors' conclusion	The findings indicated that a telephone intervention would improve Hba1c but would not affect BMI
Source of funding	Not reported
Comments	Randomised using the toss of a coin

E.6 Review question 6: Should aspirin and/ or clopidogrel be used for primary prevention of cardiovascular disease in people with type 2 diabetes? (Evidence tables for antiplatelet therapy, update 2015)

Evidence table 19: (Ogawa et al 2008)

Bibliographic reference (Ref ID)	Ogawa et al 2008-The Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD) trial (REF ID: 81)
Study type & aim	Multicentre, prospective, randomised, open label, blinded, end-point trial examining the efficacy of low-dose aspirin for the primary prevention of atherosclerotic events in patients with type 2 diabetes.
Number and characteristics of patients	**Total number of patients:** Out of the 2567 patients who were screened, 2539 were randomly assigned to groups (1262 in aspirin group and 1277 in the non-aspirin group). A total of 193 patients were lost to follow-up (97 in aspirin group and 96 in non-aspirin group) and data for these patients were censored at the last day of follow up. **Inclusion criteria:** diagnosis of type 2 diabetes, age between 30 and 85 years and ability to provide informed consent. Patients were allowed to use any concurrent treatment. Patients in the non-aspirin group were also allowed to use antiplatelet/thrombotic therapy, including aspirin, if needed and vice versa. **Exclusion criteria:** electrocardiographic changes consisting of ischemic ST-segment depression, ST-segment elevation or pathologic Q waves, a history of coronary heart disease confirmed by coronary angiography, a history of cerebrovascular disease consisting of cerebral infarction, cerebral haemorrhage, sub-arachnoid haemorrhage and transient ischemic attack, a history of arteriosclerotic disease necessitating medical treatment, atrial fibrillation, pregnancy, use of antiplatelet or antithrombotic therapy (defined as aspirin, ticlopidine, cilostazol, dipyridamole, trapidil, warfarin and argatroban), a history of severe gastric or duodenal ulcer, severe liver dysfunction, severe renal dysfunction and allergy to aspirin. **Patient characteristics:** In the aspirin group 1139 received aspirin through completion of the trial and 123 patients stopped taking aspirin. In the non-aspirin group 9 received aspirin (n=6) or other antiplatelet therapy (n=3). Baseline characteristics were similar between the two groups (see table 1 below). Overall, mean age was 65 (SD 10) years, 55% were men and diabetes was well controlled in both groups.

Table 1. Baseline characteristics of included patients (N=2539)

Characteristic	Aspirin group (n=1262)	Non-aspirin group (n=1277)
Age, mean(SD), years	65 (10)	64 (10)
Male	706 (56)	681 (53)
Current smoker	289 (23)	248 (19)
Past smoker	545 (43)	482 (38)

Bibliographic reference (Ref ID)	Ogawa et al 2008-The Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD) trial (REF ID: 81)		
	Body mass index, mean (SD)	24 (4)	24 (4)
	Hypertension	742 (59)	731 (57)
	Dyslipidemia	680 (54)	665 (52)
	Systolic blood pressure, mean (SD), mmHg	136 (15)	134 (15)
	Diastolic blood pressure, mean (SD), mmHg	77 (9)	76 (9)
	Duration of diabetes, median (IQR), years	7.3 (2.8 to 12.3)	6.7 (3.0 to 12.5)
	Diabetic microvascular complication	-	-
	Diabetic retinopathy	187 (15)	178 (14)
	Diabetic nephropathy	169 (13)	153 (12)
	Proteinuria, ≥15mg/dL	222 (18)	224 (18)
	Diabetic neuropathy	163 (13)	137 (11)
	Dermal ulcer	6 (0.5)	6 (0.5)
	Treatment for diabetes	-	-
	Sulphonylureas	737 (58)	710 (56)
	α-glucosidase inhibitors	422 (33)	414 (32)
	Biguanides	168 (13)	186 (15)
	Insulin	166 (13)	160 (13)
	Thiazolidines	63 (5)	65 (5)
	Treatment for hypertension and dyslipidemia	-	-
	Calcium channel blocker	436 (35)	440 (34)
	Angiotensin-II receptor antagonists	269 (21)	266 (21)
	Angiotensin-converting enzyme inhibitors	178 (14)	195 (15)
	Beta blockers	75 (6)	87 (7)
	Alpha blockers	53 (4)	38 (3)
	statins	322 (26)	328 (26)
	Family history	-	-
	Type 2 diabetes	526 (42)	513 (40)
	Ischemic heart disease	147 (12)	143 (11)
	stroke	275 (22)	251 (20)

Bibliographic reference (Ref ID)	Ogawa et al 2008-The Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD) trial (REF ID: 81)

Patient medical history	-	-
Peptic ulcer	83 (7)	96 (8)
Clinical laboratory measurements, mean (SD)	-	-
Haemoglobin A1c level, %	7.1 (1.4)	7.0 (1.2)
Fasting plasma glucose level, mg/dL	148 (50)	146 (48)
Total cholesterol level, mg/dL	202 (34)	200 (34)
Fasting triglyceride level, mg/dL	135 (88)	134 (89)
HDL cholesterol level, mg/dL	55 (15)	55 (15)
Blood urea nitrogen level, mg/dL	16 (5)	16 (5)
Serum creatinine level, mg/dL	0.8 (0.3)	0.8 (0.2)
Red blood cells, x 10^5/mL	45.2 (4.7)	45.0 (4.8)
White blood cells, x 10^3/mL	6.2 (1.6)	6.1 (1.7)
Haemoglobin level, g/dL	14.0 (1.5)	14.0 (1.5)
Abbreviations: IQR interquartile range; HDL high-density lipoprotein BMI calculated as weight in kg divided by height in meters squared.		

Subgroup analyses: conducted for predetermined subgroups: sex (men and women); age (younger than 65 years and 65 years and older); hypertensive status (hypertensive, normotensive); smoking status (current or past smoker, non-smoker); and lipid status (hyperlipidemia, normolipidemia).

Monitoring information and definitions

Monitoring: Patients were followed up at each hospital visit or by telephone if necessary. Follow-up visits were scheduled every 2 weeks for patients to be seen in a clinic setting and every 4 weeks for patients seen in a hospital setting.

Primary outcome measures: Any atherosclerotic event, which was a composite of sudden death; death from coronary, cerebrovascular and aortic causes; nonfatal acute myocardial infarction; unstable angina; newly developed exertional angina; nonfatal ischemic and hemorrhagic stroke; transient ischemic attack; or nonfatal aortic and peripheral vascular disease (arteriosclerosis obliterans, aortic dissection, mesenteric arterial thrombosis)

Secondary outcome measures: these were each primary end point and combinations of primary end points and death from any cause. Adverse events analysed included gastrointestinal (GI) events and any hemorrhagic events other than hemorrhagic stroke.

Other outcome measures: None

Intervention

Drug: aspirin

Dose and timing: 81mg or 100mg once daily

Route: not reported

Comparator

Drug: not reported

Bibliographic reference (Ref ID)	**Ogawa et al 2008-The Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD) trial (REF ID: 81)**
	Dose: not reported **Route:** not reported
Length of follow up	Patient enrolment started in December 2002 and was completed in May 2005; patients were followed up until April 2008. Median follow-up period was 4.37 years (95% CI 4.35 to 4.39)
Location	Japan
Outcomes measures and effect sizes	**Primary outcome measures: Atherosclerotic events** A total of 154 atherosclerotic events occurred but the incidence of the primary endpoint of any atherosclerotic event (see definitions) did not significantly differ in the aspirin group compared with the non-aspirin group (see table 2).

Table 2. Atherosclerotic events

Event	Aspirin group		Non-aspirin group			
	No (%)	No. per 1000 person-years	No (%)	No. per 1000 person-years	Hazard ratio (95% CI)	P value
Primary endpoint: all atherosclerotic events	68 (5.4)	13.6	86 (6.7)	17.0	0.80 (0.58 to 1.10)	0.16
Coronary and cerebrovascular mortality	1 (0.08)	0.2	10 (0.8)	2.0	0.10 (0.01 to 0.79)	0.0037
CHD events (fatal and nonfatal)	28 (2.2)	5.6	35 (2.7)	6.9	0.81 (0.49 to 1.33)	0.40
Fatal MI	0	0	5 (0.4)	1.0	-	-
Nonfatal MI	12 (1.0)	2.4	9 (0.7)	1.8	1.34 (0.57 to 3.19)	0.50
Unstable angina	4 (0.3)	0.8	10 (0.8)	2.0	0.40 (0.13 to 1.29)	0.13
Stable angina	12 (1.0)	2.4	11 (0.9)	2.2	1.10 (0.49 to 2.50)	0.82
Cerebrovascular disease (fatal and nonfatal)	28 (2.2)	5.6	32 (2.5)	6.3	0.84 (0.53 to 1.32)	0.44
Fatal stroke	1 (0.08)	0.2	5 (0.4)	1.0	0.20 (0.024 to 1.74)	0.15
Nonfatal stroke	-	-	-	-	-	-
Ischemic	22 (1.7)	4.4	24 (1.9)	4.6	0.93 (0.52 to 1.66)	0.80
Hemorrhagic	5 (0.4)	1.0	3 (0.2)	0.6	1.68 (0.40 to 7.04)	0.48
Transient ischemic attack	5 (0.4)	1.0	8 (0.6)	1.6	0.63 (0.21 to 1.93)	0.42
Peripheral arterial disease	7 (0.6)	1.4	11 (0.9)	2.2	0.64 (0.25 to 1.65)	
Abbreviations: CHD coronary artery disease; CI confidence interval; MI myocardial infarction						

Bibliographic reference (Ref ID)	Ogawa et al 2008-The Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD) trial (REF ID: 81)

Other outcome measures: Other secondary endpoints (coronary, cerebrovascular and peripheral vascular disease):

Rates are shown in table 2 but there were no significant differences between the aspirin and non-aspirin group for any of these endpoints.

Death from other causes (other than cardiovascular events):

For the aspirin group and the non-aspirin group respectively there were: 15 and 19 deaths due to malignancy, 2 and 5 due to infection, 3 and 0 due to suicide, 2 and 0 due to traffic crashes, 1 and 1 due to liver cirrhosis, 8 and 3 due to unknown causes. Therefore, 23 patients in the aspirin group and 25 patients in the non-aspirin group died from causes other than cardiovascular events. A total of 34 patients in the aspirin group and 38 patients in the non-aspirin group died from any cause (HR 0.90, 95% CI 0.57 to 1.14, log-rank test p=0.67)

Adverse events:

There was no significant difference in the composite of hemorrhagic stroke and severe GI bleeding, which occurred in 10 patients in the aspirin group and in 7 patients in the non-aspirin group.

Table 3. Adverse events

Adverse event	Aspirin group, No.	Non-aspirin group, No.
Bleeding, gastrointestinal[a]	-	-
Hemorrhagic gastric ulcer	5	3
Bleeding from esophageal varices	1	0
Bleeding from colon diverticula	2	0
Gastrointestinal bleeding due to cancer	2	0
Haemorrhoid bleeding	1	0
GI bleeding (causes unknown)	1	1
Bleeding, other	-	-
Retinal bleeding	8	4
Bleeding after tooth extraction	1	0
Subcutaneous haemorrhage	3	0
hematuria	2	1
Nose bleeding	6	1
Chronic subdural hematoma	2	0
Non bleeding GI event	-	-

Bibliographic reference (Ref ID)	Ogawa et al 2008-The Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD) trial (REF ID: 81)

Nonhemorrhagic gastritis	3	0
Nonhemorrhagic gastric ulcer	17	3
Nonhemorrhagic duodenal ulcer	1	1
Only GI symptom	26	0
Other	-	-
Anemia	4	0
asthma	1	0
[a] in the aspirin group, 4 cases of severe GI bleeding required transfusion		

Subgroup analyses (predetermined groups):

In the 1363 patients aged 65 years or older, the incidence of atherosclerotic events was significantly lower in the aspirin group compared with the non-aspirin group (HR 0.68, 95% CI 0.46 to 0.99, p=0.047). In the 1176 patients younger than 65 years, there was no significant difference between the aspirin and non-aspirin group. A formal test of interaction showed with age did not show a significant result (p=0.27). There were no significant differences between the aspirin and non-aspirin group in other subgroup analyses as shown in table 4.

Table 4. subgroup analyses

Subgroup	Aspirin (event no/total no)	Non-aspirin (event no/total no)	Hazard ratio (95% CI)
Age, years	-	-	-
≥65	45/719	59/644	0.68 (0.46 to 0.99)
<65	23/543	27/633	1.00 (0.57 to 1.70)
Sex	-	-	-
Male	40/706	51/681	0.74 (0.49 to 1.12)
female	28/556	35/596	0.88 (0.53 to 1.44)
Hypertensive status	-	-	-
Hypertensive	49/742	55/731	0.88 (0.60 to 1.30)
Normotensive	19/520	31/546	0.64 (0.36 to 1.13)
Lipid status	-	-	-
Dyslipidemia	38/680	43/665	0.88 (0.57 to 1.37)
Normolipidemia	30/582	43/612	0.71 (0.45 to 1.14)
Smoking	-	-	-

Bibliographic reference (Ref ID)	**Ogawa et al 2008-The Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD) trial (REF ID: 81)**
	Current or past: 36/565 vs 42/494; 0.73 (0.47 to 1.14) Non-smoker: 32/697 vs 44/783; 0.83 (0.53 to 1.31) **Change in lipid levels and blood pressure:** not reported **Microvascular or macrovascular complications:** see atherosclerotic events above **Mortality:** see atherosclerotic events above **Health related quality of life:** not reported
Authors' conclusion	Low dose aspirin as primary prevention did not reduce the risk of cardiovascular events. These findings should be interpreted in context with the low incidence of atherosclerotic disease in japan and the current management practice for cardiovascular risk factors.
Source of funding	Ministry of Health, Labour and Welfare of Japan
Comments	Randomisation was performed as non stratified randomisation from a random number table. The study centre prepared the sealed envelopes with random assignments and distributed them by mail to the physicians in charge at the study sites. All outcomes were adjudicated by an independent committee on validation of data and events that were unaware of group assignments. Sample size calculations estimated that 2450 patients would need to be enrolled to detect a 30% relative risk reduction for an occurrence of atherosclerotic disease by aspirin. Efficacy comparisons were performed on the basis of time to first event, according to the intention to treat principle, including all patients in the group to which they were randomised with patients lost to follow-up censored at the day of the last visit. Cumulative incidences of primary and secondary endpoints were estimated by Kaplan-Meier method and differences between groups were assessed with log-rank test. Cox proportional hazards model was used to estimate hazard ratios (HRs) of aspirin use and chi-squared or Fisher exact test was used to evaluate adverse events. The Japanese Pharmaceutical Affairs Law limits the use of placebo in physician initiated studies because it is an unapproved medicine. The overall events rates were low: 17 in 1000 Japanese diabetic patients. This is one third of the event rate anticipated in the sample size calculations, which were based on previous epidemiologic studies in Japan.

Evidence able 20: ETDRS trial

Bibliographic reference (Ref ID)	**ETDRS trial (Ref ID:)-unpublished subgroup analyses of type 2 diabetics without a history of CV disease have been used in the evidence review for this question**
Study type & aim	The ETDRS was designed to evaluate the effects of photocoagulation and aspirin on ocular events. This multicenter, RCT, also provided an opportunity to study the effects of aspirin on cardiovascular complications. The study design provided for the collection
Number and characteristics of patients	**Total number of patients:** 3711 patients (1152 patients with type 2 diabetes) **Inclusion criteria:** clinical diagnosis of diabetes mellitus and one of the following categories of diabetic retinopathy: mild nonproliferative with macular edema, or moderate to severe nonproliferative or early proliferative (less severe than the high-risk proliferative stage, as defined by the Diabetic Retinopathy Study) with or without macular edema. Visual acuity was required to be better than 20/40 in each eye (or 20/400 if acuity was reduced as a result of diabetic macular edema)

Bibliographic reference (Ref ID)	ETDRS trial (Ref ID:)-unpublished subgroup analyses of type 2 diabetics without a history of CV disease have been used in the evidence review for this question

Exclusion criteria: systolic blood pressure over 210 mm Hg and/or diastolic blood pressure over 110 mm Hg despite the use of antihypertensive medication; history of gastrointestinal hemorrhage or diagnosis of active gastrointestinal ulcer in the past 2 years; inability or unwillingness to stop taking anticoagulants or antiplatelet drugs; allergy to aspirin; pregnancy or lactation; or poor prognosis for 5 years of follow-up because of a prior major cardiovascular event, cancer, or another chronic disease.

Patient characteristics: baseline characteristics from the whole study population and from patients with type 2 diabetes alone are shown in tables 1 and 2 respectively. The patients assigned to aspirin were comparable to those assigned to placebo for patients with type 2 diabetes

Table 1. Baseline characteristics of all included patients (N=3711)

Characteristic	Aspirin (N=1856)	Placebo (N=1855)
Age at entry, y	-	-
<30	324 (17.5)	302 (16.3)
30-49	572 (30.8)	596 (32.1)
≥ 50	960 (51.7)	957 (51.6)
Sex (M)	1031 (55.5)	1065 (57.4)
Diabetes		
Type I	559 (30.1)	571 (30.8)
Type II	587 (31.6)	565 (30.5)
Mixed	710 (38.3)	719 (38.9)
Duration of diabetes, y	-	-
<10	306 (16.5)	304 (16.4)
10-19	1084 (58.4)	1035 (55.8)
≥20	466 (25.1)	516 (27.8)
Daily use of insulin	1552 83.6)	1561 (84.2)
Use of oral hypoglycaemic agents	276 (14.9)	257(13.9)
≥120% of desirable weight	793 (42.7)	748 (40.3)
≥6 cigarettes/day	819 (44.1)	822 (44.3)
Serum cholesterol ≥6.20mmol/L*	470 (35.2)	495 (36.0)
Low-density lipoprotein cholesterol ≥4.15 mmol/L*	336 (26.4)	328 (25.0)

Bibliographic reference (Ref ID)	ETDRS trial (Ref ID:)-unpublished subgroup analyses of type 2 diabetics without a history of CV disease have been used in the evidence review for this question		
	Serum creatinine ≥133 μ /L*	114 (6.5)	139 (7.9)
	Hemoglobin Alc ≥10%*	538 (41.0)	584 (42.9)
	Systolic blood pressure, mm Hg	-	-
	≥130	1228 (66.2)	1220(65.8)
	≥160	385 (20.7)	364 (19.6)
	Diastolic blood pressure, mm Hg	-	-
	≥85	735 (39.6)	716 (38.6)
	≥90	552 (29.7)	509 (27.5)
	History of definite or suspected Myocardial infarction	111 (6.0)	99 (5.3)
	Stroke	27 (1.5)	38 (2.0)
	Transient ischemic attack	26 (1.4)	29 (1.6)
	Coronary artery disease	141 (7.6)	145 (7.8)
	Congestive heart failure	48 (2.6)	57 (3.1)
	Intermittent claudication	167 (9.0)	180 (9.7)
	Amputation	55 (3.0)	52 (2.8)
	Elevated blood pressure or prescription for diuretic agents or antihypertensive drugs†	840 (45.3)	806 (43.4)
	Cardiovascular disease history‡	912 49.1)	900 (48.5)
	Proliferative retinopathy in one or both eyes	477 (25.7)	486 (26.2)
	Clinically significant macular edema in one or both eyes	1137 (61.3)	1126 (60.7)
	*These laboratory values were obtained only for some patients; denominators range from 1274 to 1769. † Considered present If the patient had systolic blood pressure of 160 mm Hg or greater or diastolic blood pressure of 95 mm Hg or greater or If the patient reported the use of diuretic or antihypertensive agents at the time of entry. ‡ Cardiovascular disease history was considered present if the patient reported a history of any of the following conditions: coronary artery disease, congestive heart failure, myocardial Infarction, or intermittent claudication. Patients reporting any of the following drug use at the time of entry were		

Bibliographic reference (Ref ID)	ETDRS trial (Ref ID:)-unpublished subgroup analyses of type 2 diabetics without a history of CV disease have been used in the evidence review for this question

also considered to have cardiovascular disease history: long-term antianginal agents, propranolol or other ß-blockers, nitroglycerin or other vasodilators, digitalis, antiarrhythmic agents, or diuretic and other antihypertensive agents. Patients who had systolic blood pressure of 160 mm Hg or greater or diastolic blood pressure of 95 mm Hg or greater were also considered to have cardiovascular disease history.

Table 2. Baseline characteristics of patients with type 2 diabetes only

Characteristic	Aspirin (N=587)	Placebo (N=565)
Age at entry, y	-	-
<30	-	-
30-49	55 (9.4)	40 (7.1)
≥ 50	532 (90.6)	525 (92.9)
Sex (M)	303 (51.6)	275 (48.7)
Duration of diabetes, y	-	-
<10	210 (35.8)	201 (35.6)
10-19	322 (54.9)	299 (52.9)
≥20	55 (9.4)	65 (11.5)
Daily use of insulin	305 (52.0)	294 (52.0)
Use of oral hypoglycaemic agents	250 (42.6)	232 (41.1)
≥120% of desirable weight	462 (78.7)	437 (77.3)
≥6 cigarettes/day	231 (39.4)	202 (35.8)
Serum cholesterol ≥6.20mmol/L	178 (41.4)	189 (46.1)
Low-density lipoprotein cholesterol ≥4.15 mmol/L	121 (29.8)	125 (32.3)
Serum creatinine ≥133 µ /L	49 (8.8)	52 (9.7)
Hemoglobin Alc ≥10%	141 (33.3)	136 (33.3)
Systolic blood pressure, mm Hg		
≥130	491 (83.6)	478 (84.6)
≥160	204 (34.8)	179 (31.7)
Diastolic blood pressure, mm Hg		

Bibliographic reference (Ref ID)	ETDRS trial (Ref ID:)-unpublished subgroup analyses of type 2 diabetics without a history of CV disease have been used in the evidence review for this question

≥85	298 (50.8)	281 (49.7)
≥90	235 (40.0)	210 (37.2)
History of definite or suspected Myocardial infarction	46 (7.8)	40 (7.1)
Stroke	16 (2.7)	16 (2.8)
Transient ischemic attack	11 (1.9)	13 (2.3)
Coronary artery disease	67 (11.4)	67 (11.9)
Congestive heart failure	25 (4.3)	32 (5.7)
Intermittent claudication	63 (10.7)	56 (9.9)
Amputation	21 (3.6)	19 (3.4)
Elevated blood pressure or prescription for diuretic agents or antihypertensive drugs	397 (67.6)	367 (65.0)
Cardiovascular disease history	421 (71.7)	393 (69.6)
Proliferative retinopathy in one or both eyes	94 (16.0)	93(16.5)
Clinically significant macular edema in one or both eyes	467 (79.6)	441 (78.1)

Subgroup analyses: analyses were conducted by type of diabetes and by gender but unclear if these analyses were pre-specified

Monitoring information and definitions

Monitoring: All patients were to be followed up for at least 5 years, with visits scheduled every 4 months to assess visual acuity and drug adherence. During the first 3.5 years of the study, a physical examination, medical history, assessment of drug adherence based on pill count and patient interviews, and battery of biochemical and hematologic determinations were performed at annual intervals following entry into the study.

Primary outcome measures: all-cause mortality

Secondary outcome measures: Other outcome variables specified at the start of the study included cause-specific mortality, cardiovascular events (fatal and nonfatal myocardial infarction and stroke), amputations, and evidence of kidney disease or failure (dialysis, transplantation, and/or death due to kidney failure)

Other outcome measures: N/A

Intervention

Drug: aspirin

Dose and timing: two 325-mg tablets once per day (The daily dose of 650 mg was selected because it is sufficient to ensure complete inhibition of platelet aggregation by blocking cyclooxygenase but not enough to completely inhibit prostacyclin production by endothelial tissue. Patients were expected to have good adherence to a regimen of two 325-mg tablets once per day and to have few side effects. During the course of the trial, lower doses of aspirin were considered because accumulating evidence suggested that a

Bibliographic reference (Ref ID)	ETDRS trial (Ref ID:)-unpublished subgroup analyses of type 2 diabetics without a history of CV disease have been used in the evidence review for this question
	dose of aspirin as low as 80 mg every other day might be sufficient to inhibit platelet aggregation. After review of all available information, including ETDRS data on side effects, the ETDRS investigators decided to continue with the dose of 650 mg/d) **Route:** oral
Comparator	**Drug:** placebo **Dose:** unclear but assumed as aspirin group **Route:** unclear but assumed as aspirin group
Length of follow up	At least 5 years
Location	USA
Outcomes measures and effect sizes	NB: outcomes in this evidence table are reported for type 2 diabetic patients only **Primary outcome measures- Microvascular or macrovascular complications:** see table 3 for details of complications

Table 3. Outcomes for patients with type 2 diabetes

	Deaths and events		5-year life table rates and estimates of relative risk		
Outcome	**Aspirin (N=587)**	**Placebo (N=565)**	**Aspirin (N=587)**	**Placebo (N=565)**	**Relative risk (99% CI)**
Death—all causes	161 (27.4)	162 (28.7)	108(19.2)	115(21.6)	0.92 (0.69 to 1.23)
All cardiovascular	117 (19.9)	124 (21.9)	83(15.1)	87(16.8)	0.88 (0.63 to 1.22)
Sudden coronary death	23 (3.9)	35 (6.2)	-	-	-
Cerebrovascular	14 (2.4)	12 (2.1)	-	-	-
All noncardiovascular	42 (7.2)	36 (6.4)	-	-	-
Cancer	6 (1.0)	9 (1.6)	-		-
Other noncardiovascular	36 (6.1)	27 (4.8)	-	-	-
Cause unknown	2 (0.3)	2 (0.4)	-	-	-
Fatal or nonfatal myocardial Infarction	107 (18.2)	118 (20.9)	72 (13.4)	90 (17.3)	0.83 (0.59 to 1.17)
Fatal or nonfatal stroke	49 (8.3)	34 (6.0)	42 (8.1)	29 (6.0)	1.37 (0.77 to 2.43)

Bibliographic reference (Ref ID)	ETDRS trial (Ref ID:)-unpublished subgroup analyses of type 2 diabetics without a history of CV disease have been used in the evidence review for this question

Amputation	29 (4.9)	37 (6.5)	-	-	-
Hypertension	507 (86.4)	483 (85.5)	-	-	-
Any of the following	67 (11.4)	52 (9.2)	-	-	-
Renal transplantation	34 (5.8	28 (5.0)	-	-	-
Renal dialysis	1 (0.2)	2 (0.4)	-	-	-
Candidate for dialysis	27 (4.6)	25 (4.4)	-	-	-
Death from kidney failure	13 (2.2)	8(1.4)	-	-	-
Cardiovascular death, nonfatal myocardial infarction, or stroke	166 (28.3)	163 (28.8)	123 (22.4)	128 (24.4)	0.95 (0.71 to 1.26)
All deaths, nonfatal myocardial infarction, or stroke	207 (35.3)	198 (35.0)	146 (26.0)	154 (28.7)	0.97 (0.75 to 1.26)

*AII relative risk estimates are based on the entire follow-up. CI indicates confidence interval.
†With 0 indicating "no" and 1 indicating "yes," relative risk estimates were adjusted for the following: age greater than 30 years, age greater than 50 years, male, non-white, type I diabetes mellitus, type II diabetes mellitus, and clinical center.
‡With 0 indicating "no" and 1 indicating "yes," relative risk estimates were adjusted for the following: age greater than 30 years, age greater than 50 years, non-white, type I diabetes mellitus, type II diabetes mellitus, and clinical center.

Adverse events: These results do not relate to patients with type 2 diabetes specifically. At scheduled visits, local laboratory tests were performed when there was an indication of possible toxicity or suspicion of toxicity. The percentage of patients who had one or more laboratory tests scheduled for this reason at any time during follow-up was 10.9% for patients assigned to aspirin and 9.6% for patients assigned to placebo. About 53% of these tests yielded abnormalities. No significant treatment differences were observed for any of these abnormalities. Only a few patients (2%) in both groups had some indication of bleeding; that is, hemoglobin less than 100 g/L or haematocrit less than 0.30, hematuria, or blood in the stool.

Change in lipid levels and blood pressure: see table 3 for hypertension, lipid levels are not reported

Mortality: see table 3

Health related quality of life: not reported

Adherence: At the end of one year, 8.2% of patients assigned to aspirin and 7.4% of patients assigned to placebo were not taking their study medication.20 The numbers of patients not taking study medication, which increased by about 5% per year for the first 5 years, were approximately equal in the two groups. Estimates of adherence to assigned medication based on urine salicylate levels and thromboxane measurements, when available, yielded similar findings. The ETDRS protocol specified discontinuation of therapy with the assigned study medication if any of the following occurred: prescription for a platelet-affecting drug or anticoagulant therapy, pregnancy, hospitalization, or the unmasking of study medication.21 The most common reason for stopping administration of the

Bibliographic reference (Ref ID)	ETDRS trial (Ref ID:)-unpublished subgroup analyses of type 2 diabetics without a history of CV disease have been used in the evidence review for this question
	assigned study medication was patient use of known platelet affecting drugs.
Authors' conclusion	The effects of aspirin on any of the cardiovascular events considered in the ETDRS were not substantially different from the effects observed in other studies that included mainly nondiabetic persons. Furthermore, there was no evidence of harmful effects of aspirin. Aspirin has been recommended previously for persons at risk for cardiovascular disease. The ETDRS results support application of this recommendation to those persons with diabetes at increased risk of cardiovascular disease.
Source of funding	The National Eye Institute.
Comments	The randomization was designed to provide balance in the number of patients assigned to aspirin or placebo within each clinical center. Both the placebo and aspirin (Bayer) were supplied to the ETDRS Drug Distribution Center by Glenbrook Laboratories. Neither the patient nor the clinical center personnel were informed of the patient's drug assignment except in the rare event of a medical emergency. The Mortality and Morbidity Classification Committee (internists and cardiologists who were not ETDRS clinical center investigators) 19 coded the deaths and hospitalizations for cardiovascular events. Coding was performed without knowledge of treatment assignment, according to pre-established criteria. Electrocardiogram Reading Center staff without knowledge of treatment assignment or clinical findings used the Minnesota Code25 to read the baseline and 5-year follow-up electrocardiograms (ECGs) (standard supine 12-lead ECGs). The relative risk of specified events for patients assigned to aspirin compared with patients assigned to placebo was estimated (along with the 99% confidence interval [CI]) using Cox regression with covariates. A relative risk less than 1.0 indicates a reduced risk of the outcome measure for patients assigned to aspirin compared with patients assigned to placebo; a relative risk greater than 1.0 indicates an increased risk for patients assigned to aspirin compared with patients assigned to placebo. A confidence interval including 1.0 indicates that the observed data are consistent with no aspirin effect.

E.7 Review question 7: What pharmacological treatment should be used to manage erectile dysfunction in men with type 2 diabetes?

Evidence table 21: (Hatzchristou et al 2008)

Bibliographic reference (Ref ID)	Hatzichristou et al 2008 (Ref ID: 66)
Study type & aim	Randomised controlled, double blind, multi-centre trial (conducted in 23 out-patient centres). Study included 4 week run-in phase and 12 week treatment phase. Aim was to examine if once daily tadalafil 2.5 mg and 5mg was efficacious for men with diabetes and erectile dysfunction (ED).
Number and characteristics of patients	**Total number of patients:** 298 patients were randomly assigned to placebo or treatment groups. 44 patients (14.8%) discontinued treatment before completion of the 12 week treatment phase. **Inclusion criteria:** Men aged ≥ 18 years with at least 3 month history of Type 1 (T1) or Type 2 (T2) diabetes and erectile dysfunction (ED). All patients had to be in a heterosexual monogamous relationship and not to have used other ED treatment during run in and treatment phase or for 96 hours after final study visit. ED was defined as persistent history of inability to achieve or maintain an erection for satisfactory sexual performance. T1D eligibility defined as disease onset prior to age 30 years. T2D defined as all other patients meeting criteria of symptoms of diabetes **Exclusion criteria:** Exclusion criteria included patients with HBA1c >13.0%, clinically significant renal or hepatic insufficiency or uncontrolled blood pressure. Additional exclusion criteria included current treatment with nitrates, a recent history of serious unstable cardio vascular condition or stroke and history of radical prostatectomy (except bilateral- nerve sparing) or other pelvic surgery resulting in failure to achieve an erection. **Patient characteristics:** Patient demographics and ED were balanced for both treatment and control groups at baseline. Mean age of patients = 57 ± 9 years. 42.6% of patients had severe ED. 88.9% had T2D. Patients in Tadalafil (5mg) group had poorer control and longer duration of diabetes. More patients receiving 5mg Tadalafil had a history of retinopathy (12.2%), neuropathy (4.1%) and nephropathy (8.2%) compared to patients receiving Tadalafil 5mg (8.0%, 2.0% and 3.0%, respectively). **Table 1. Baseline clinical patient characteristics*** **Placebo (n=100)** | **Tadalafil (2.5mg) (n=100)** | **Tadalafil (5mg) (n=98)** Type 1: Type 2 Diabetes Mellitus | 9:91 | 9:91 | 15:83

Bibliographic reference (Ref ID)	Hatzichristou et al 2008 (Ref ID: 66)

Diabetes duration (years)	11.1 (0.4- 36.4)	9.9 (0.3- 49.4)	12.3 (0.4- 34.5)
Diabetes therapy: Insulin only Oral glucose-lowering agents only Insulin and oral agents None	 20 (20.0%) 59 (59.0%) 15 (15.0%) 6 (6.0%)	 24 (24.0%) 56 (56.0%) 12 (12.0%) 8 (8.0%)	 33 (33.7%) 47 (48.0%) 16 (16.3%) 2 (2.0%)
HBA1c (%)	7.7% (4.7-11.6%)	7.5% (4.9-12.6%)	7.9% (4.8-13.0%)
Glycaemic control: Good (HBA1c< 7.0%) Fair (HBA1C ≥ 7.0 - 9.5%) Poor (HBA1c >9.5%)	 35 (35.0%) 54 (54.0%) 11 (11.0%)	 49 (49.0%) 38 (38.0%) 13 (13.0%)	 32 (32.7%) 52 (53.1%) 14 (14.3%)
Serum fructosamine (µmol/mol)	309.1 (196.0 – 533.0)	309.7 (192.0 -630.0)	322.7 (211.0-497.0)
Urinary albumin-creatinine (mg/kg)	151.4	76.8	115.2
History of diabetic complications: Retinopathy Autonomic neuropathy Nephropathy Coronary artery disease Cerebral Ischemia Peripheral vascular disease	 9 (9%) 6 (6%) 2 (2%) 10 (10%) 1 (1%) 9 (9%)	 8 (8%) 2 (2%) 3 (3%) 8 (8%) 3 (3%) 10 (10%)	 12 (12%) 4 (4%) 8 (8%) 7 (7%) 2 (2%) (6%)

*Mean ±SD, mean (range) or n (%)

Table 2. Movement of patients through the study

	Placebo (n=100)	**Tadalafil (2.5mg) (n=100)**	**Tadalafil (5mg) (n=98)**

Bibliographic reference (Ref ID)	Hatzichristou et al 2008 (Ref ID: 66)

Discontinued	19	11	14
Perceived lack of efficacy	7	1	5
Adverse events	4	4	5
Loss to follow up	4	2	3
Patient decision	3	3	2
Entry criteria failure	1	1	1
Completed	81	89	84

Monitoring information and definitions

Primary outcome measures:

1) International Index of Erectile Function Erectile Function (IIEF) Erectile function (EF) domain

The IIEF is a self-administered questionnaire based on 15 questions of domains (Erectile function (EF); orgasmic function (OF); sexual desire (SD); intercourse satisfaction (IS); and overall satisfaction (OS). It was used in prior 4 week period to measure ED. Based on response to each question given a numerical value scale (0-5). 1 = almost never/ never, 2 = a few times (much less than half the time), 3 = sometimes (approximately half the time), 4 = most times (much more than half the time), and 5 = almost always/always.

The EF domain was based on questions 1-5 and 15 of the full questionnaire (see below for all questions). Sum of values calculated to identify a domain score: (No ED ≥ 26; mild ED 17-25; moderate ED 11-16; severe ED 1-10).

- How often were you able to get an erection during sexual activity?
- When you had erection with sexual stimulation how were your erections hard enough for penetration?
- When you attempted sexual intercourse, how often were you able to penetrate your partner?
- During sexual intercourse, how often were you able to maintain your erection to completion of intercourse?
- During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?
- How many times have you attempted sexual intercourse?
- When you attempted sexual intercourse, how often was it satisfactory for you?
- How much have you enjoyed sexual intercourse?
- When you had sexual intercourse, how often did you ejaculate?
- When you had sexual intercourse, how often did you have the feeling of orgasm or climax?
- How often have you felt sexual desire?
- How would you rate your level of sexual desire?
- How satisfied have you been with your overall sex life?
- How satisfied have you been with your sexual relationship?
- How do you rate your confidence that you could get and keep an erection?

Bibliographic reference (Ref ID)	Hatzichristou et al 2008 (Ref ID: 66)
	2) Sexual Encounter Profile (SEP) Addressing patient experiences attempting intercourse. Questions 2 and 3 used only Q1-Were you able to achieve at least some erection (some enlargement of penis?)" Q2- "Were you able to insert your penis into your partners vagina?" Q3- "Did your erection last long enough for you to have sexual intercourse?" Q4- "Were you satisfied with the hardness of your erection"? Q5- "Were you satisfied overall with this sexual experience?" SEP diary was completed after each sexual attempt **Secondary outcome measures:** 3) Global Assessment Questions (GAQ): Q1- "Has the treatment you have had improved your erections"?- if 'yes', then Q2- "Has the treatment improved your ability to engage in sexual activity"? Patient satisfaction was based on IIEF IS and OS domain scores Efficacy also considered percentage of men with no ED (IIEF EF) after 12 weeks of treatment. **Other outcome measures:** 4) Glycaemic control: This included HBA1c m and serum fructosamine concentration. HBA1c glycaemic control was classed as good (<7.0%); fair ≥ 7.0 to ≤ 9.5%); or poor (>9.5%) and was stratified to patient EF scores at endpoint. 5) Urinary ACR 6) Treatment emergent adverse events (TEAEs): These were defined as any adverse event that first occurred or worsened after patient was randomly assigned to treatment.
Intervention	Drug: Tadalafil Dose and timing: 2.5mg or 5mg taken once a day (at approximately same time) Route: Oral
Comparator	Drug: placebo Dose and timing: taken once a day (at approximately same time) Route: Oral
Length of follow up	12 weeks
Location	23 outpatient sites across North America
Outcomes measures and	**Primary outcome measures: Erectile Function** For all 3 primary end-points, Tadalafil (2.5 mg and 9 mg) resulted in significant improvements in EF compared to placebo.

Bibliographic reference (Ref ID)	Hatzichristou et al 2008 (Ref ID: 66)

effect sizes

Table 3. Mean SEP scores for Q2 and Q3 per patient % 'yes' score

	Tadalafil 2.5mg		Tadalafil 5mg		Placebo	
	Baseline	**Change**	**Baseline**	**Change**	**Baseline**	**Change**
SEP Q2 Vaginal penetration	41.8%	62.3%*	32.2%.	61.1%*	37.7%	43.0%
SEP Q3 Successful intercourse	20.1%	46.0%*	16.1%	41.1%*	20.1%	28.2%

*change scores at 12 weeks significant at p≤ 0.005

Table 4. Mean change in IIEF domain scores by ED score at baseline

Mean IIEF EF domain scores for ED						
	Tadalafil 2.5mg		**Tadalafil 5mg**		**Placebo**	
	Baseline	**Change**	**Baseline**	**Change**	**Baseline**	**Change**
All patients	13.5	18.3*	12.7	17.2*	13.4	14.7
Mild score (22-30)	21.9	24.7	21.1	24.4	21.3	22.1
Moderate score (17-21)	13.5	18.7	12.9	17.8	13.4	16.1
Severe score (1-10)	7.6	13.6	7.0	7.8	7.1	12.2

* p≤ 0.005 compared with placebo

Table 5. Mean change in IIEF domain scores by Hba1c score at baseline

Mean IIEF EF domain scores for glycaemic control (HBA1c)						
	Tadalafil 2.5mg		**Tadalafil 5mg**		**Placebo**	
	Baseline	**Change**	**Baseline**	**Change**	**Baseline**	**Change**
All patients	13.5	18.3*	12.7	17.2*	13.4	14.7
Good (<7.0 %)	13.7	17.5	12.7	19.3	14.6	16.0
Fair (≥ 7.0 to ≤ 9.5%)	13.7	17.5	12.7	19.3	13.2	14.6
Poor (> 9.5%)	11.0	11.5	11.4	12.8	14.1	18.8
* p≤ 0.005 compared with placebo						

Bibliographic reference (Ref ID)	Hatzichristou et al 2008 (Ref ID: 66)
	Other outcome measures: Change in blood glucose (including HBA1c) No meaningful change in HBA1c or serum fructosamine concentrations were observed among treatment groups at end-point. **Changes in weight or BMI:** This outcome was not reported in this paper **Frequency, severity and timing of hypoglycaemic episodes:** This outcome was not reported in this paper **Adverse events:** Most TEAEs were mild or moderate Discontinuations to adverse events (placebo= 4.0%, tadalafil 2.5mg= 4.0%, tadalafil 5mg=3.1%) Three patients treated with tadalafil experienced serious adverse events (diabetic ketoacidosis, bleeding diverticulum, colelithiasis) but investigator did not consider these to be related to study drug. **Microvascular or macrovascular complications:** No meaningful change in urinary ACR was observed among treatment groups at end-point. Few patients had overt nephropathy at baseline, defined as an ACR > 300 mg/g (macroalbuminuria) but significant decreases in mean ACR over the 12-week treatment period were observed in the subset of patients receiving tadalafil 2.5 mg and 5 mg with baseline ACR values in the upper tertile (> 32 mg/g) had. Mean change in ACR from baseline –9.87 mg/g (tadalafil 2.5 mg, = −9.87 mg/kg, p<0.034; tadalafil 5 mg = −37.62 mg/g, p<0.004, Placebo = +133.00 mg/g). The changes correspond to reductions from baseline values of –4% for the tadalafil 2.5-mg group and –14% for the tadalafil 5-mg group, and an increase of 36% for the placebo group. **Quality of life (including changes in confidence, anxiety, mood and depression):** This outcome was not reported in this paper
Authors' conclusion	Once daily tadalafil 2.5 and 5mg was efficacious and well tolerated. It may be an alternative option to on demand treatment for some men.
Source of funding	Support provided by Lily (manufacturer)
Comments	N/A

Evidence table 22: (Kamenov 2010)

Bibliographic reference (Ref ID)	Kamenov 2010 (Ref ID: 20)
Study type & aim	Randomised controlled, head to head trial comparing the effect of the first intake of tadalafil and vardenafil in patients with diabetes, diabetic neuropathy (DN) and diabetic erectile dysfunction (DED).
Number and characteristics of	**Total number of participants:** 49 diabetic patients with DN and DED (26 in each arm) were randomly assigned to receive two pills containing one of the two

Bibliographic reference (Ref ID)	Kamenov 2010 (Ref ID: 20)
patients	compounds (tadalafil or vardenafil). **Inclusion criteria:** Men aged between 18 and 65 years with type 1 (T1) or type 2 (T2) diabetes, DN and DED. All patients had to have a stable control of diabetes this was defined as differences between corresponding values of blood glucose in consecutive blood sugar profiles<5 mmol/L. Criteria for DN was defined as presence of symptomatic DN (tingling, burning, pain and numbness in lower extremities that are not a result of other neurological disease; modified neuropathy disability score (NDS) ≥ 3. Criteria for DED was defined as patients wishing to improve erectile function with a score on the IIEF domain of >5 and <26. Patients had to have provided a positive answer to the question “Do you have any difficulties in achieving and/or maintaining erection sufficient enough for a satisfactory sexual intercourse?” Patients had to be in a heterosexual stable relationship for at least 6 months and had to have ED accompanied by psychological discomfort. **Exclusion criteria:** Patients were excluded if they were currently using nitrates for ischaemic heart disease, PDE5 inhibitors, androgens or antiandrogens; Had a history of myocardial infarction, stroke, life-threatening arrhythmia, or unstable angina pectoris in last 6 months; serious peripheral vascular changes with considerably decreased or missing pulsations of the peripheral arteries; Atrial flutter/ fibration with ventricular rate ≥ 100bpm; Predisposition to hypertension (diabetic autonomic neuropathy, use of hypertensives, systolic blood pressure <90) and/or uncontrolled hypertension >170 mm Hg; Elevated liver enzymes; Fasting plasma glucose (FPG) >12 mmol/L; A history of radical prostatectomy, traumatic or other structural damage of spinal cord , anatomic anomalies of the penis.; Presence of other neurological disease or neuropathy; Primary decreased libido and/or absence of permanent sexual partner. **Patient characteristics:** There were no significant differences between the patients in each treatment group. Most patients (80%) had T2 diabetes. Duration of diabetes was approx. 10 years. Control of diabetes was not satisfactory (HBA1c 8.5%, FPG 7.2 mmol/L). Most patients were aged ≥ 30 years (2 patients were aged 25 and 26 respectively). Duration of ED for all participants was 4.6±3.9 years.

Table 1. Baseline demographic data and risk factors

Feature	Tadalafil	Vardenafil	In general
N	24	25	49
Age (years)	50.8 ± 9.2	50.7 ± 9.7	50 ± 10.5
Height (cm)	51 (46-60)	53 (49-56)	53 (46-58)
Weight (kg)	93.2 ± 11.8	90.2 ± 24.3	91.7 ± 19.9
BMI (kg/m2)	29.5 ± 3.1	28.8 ± 7.1	29.2 ± 5.8
Waist circumference (cm)	105.5 ± 8.9	103.0 ± 18.7	104.2 ± 15.6
Hip circumference (cm)	107.1 ± 7.1	103.8 ± 12.4	105.4 ± 11.4

Bibliographic reference (Ref ID)	Kamenov 2010 (Ref ID: 20)			
	W/H ratio	0.98 ± 0.04	0.99 ± 0.07	0.98 ± 0.06
	DM2	18 (75.0)	21 (84.0)	39 (79.6)
	Duration of DM (years)	9.2 ± 5.5	9.9 ±7.5	9.5 ± 6.6
	FPG (mmol/L)	7.1 ± 1.6	7.2 ± 1.7	7.2 ± 1.6
	HBA1c (%)	8.6 ± 1.9	8.5 ± 2.1	8.5 ± 2.0
	Hypertension Of them treated Duration of hypertension	16 (66.7) 15 (62.5) 10.9 ± 8.6	19 (76.0) 17 (76.0) 8.9 ± 9.1	35 (71.4) 32 (91.4) 9.8 ± 8.8
	Systolic BP (mmHg)	134.2 ± 15.0	135.6 ± 14.9	134.9 ± 14.8
	Diastolic BP (mmHg)	84.2 ±10.3	83.8 ± 8.5	84.0 ± 9.3
	Dyslipidemia Of them treated Total cholesterol (mmol/L)	16 (66.7) 9 (56.3) 5.3 ± 1.1	15 (16.0) 7 (46.7) 5.7 ± 1.5	31 (63.3) 16 (51.6) 5.5 +1.4
	HDL (mmol/L)	1.3 ± 0.5 1.1 (1.0-1.4)	1.5 ± 0.4 1.4 (1.1-1.7)	1.4 ± 0.4 1.3 (1.0-1.6)
	LDL (mmol/L)	3.0 ± 0.7 3.0 (2.3-3.6)	3.2 ± 1.2 3.1 (2.3-3.6)	3.1 ± 1.0 3.1 (2.3-3.6)
	Triglycerides (mmol/L)	2.3 ± 1.3 2.1 (1.5-2.3)	2.3 ± 1.7 1.9 (1.2-2.4)	2.3 ± 1.6 1.9 (1.3-2.4)
	Smokers (present and ex)	11 (45.8)	9 (39.1)	20 (40.8)
	Duration of smoking	18.2 ± 7.8	15.8 ± 6.6	17.0 ± 7.2
	Number cigarettes per day	20.7 ± 14.5 20 (15-20)	28.0 ± 11.4 25 (20-40)	24.2 ± 13.3 20 (20-30)
	Data presented as mean ± standard deviation, median (25-75 percentile) or N (%) BP, blood pressure; FPG, fasting plasma glucose,			
Monitoring information and definitions	**Verification of DN:** Patients meeting inclusion criteria were clinically studied for DN with a modified NDS. Four items on both feet 1: Vibration perception; 2:Temperature perception; 3: Pressure perception; 4: Achilles reflex DN diagnosed if patients score ≥ 3. Maximum NDS was 10 points (5 for each foot)			

Bibliographic reference (Ref ID)	Kamenov 2010 (Ref ID: 20)
	Verification of ED: IIEF. Presence of ED assumed if score was ≥26 points. IIEF was adapted for the short treatment period. Post treatment answers were modified to : 1: Never or almost never = no successful attempt out of two 3: Sometimes (half of the attempts) = one successful attempt out of two 5: almost always or always = two successful attempts out of two SEP Q2: "Were you able to insert your penis into your partners' vagina?" Q3- "Was your erection long enough to allow sexual intercourse?" GAQ "Do you think that the treatment improved your erection?"
Intervention	Drug: Tadalafil (Cialis, Lily) Dose and timing: Two tablets of 20 mg taken between 1 and 6 hours before intended sexual activity. Time interval between taking each pill had to be at least 1 day. Route: Oral
Comparator	Drug: Vardenafil (Levitra, Bayer-Schering) Dose and timing: Two tablets of 20 mg taken between 1 and 6 hours before intended sexual activity. Time interval between taking each pill had to be at least 3 days. Route: Oral
Length of follow up	Follow up was after the last tablet had been taken (after at least 1 day for tardenafil group and after at least 3 days for vardenafil treatment group).
Location	Bulgaria
Outcomes measures and effect sizes	**Erectile Function:** Differences between ED before and after treatment use were found to be highly significant in both treatment groups. No patients reported deterioration of the condition.

Table 2. Features of erectile dysfunction before and after the use of tadalafil and vardenafil

ED Indicator	Questions	Tadalafil		Vardenafil		All men	
		Before	After	Before	After	Before	After

Bibliographic reference (Ref ID)	Kamenov 2010 (Ref ID: 20)							
	Duration of ED		3 (2-6) 4.3 ± 2.8		3 (1-9) 5.0 ± 4.3		3 (1-8) 4.6 ± 3.9	
	IIEF	1	2 (1-4) 2.5 ± 1.5	5 (2-5)*** 3.7 ± 1.7	1 (1-3) 2.2 ± 1.5	5 (3-5)*** 3.6 ± 1.7	2 (1-4) 2.3 ± 1.5	5 (3-5)*** 3.7 ± 1.7
		2	2 (1-4) 2.3 ± 1.3	5 (1-5)*** 3.6 ± 1.8	2 (1-3) 2.2 ± 1.5	5 (1-5)*** 3.6 ± 1.8	2 (1-3) 2.3 ±1.4	5 (1-5)*** 3.6 ± 1.8
		3	2 (1-4) 2.4 ± 1.6	5 (2-5)*** 3.6 ± 1.7	2 (1-4) 2.3 ± 1.4	5 (3-5)*** 3.6 ± 1.7	2 (1-4) 2.4 ± 1.5	5 (3-5)*** 3.6 ± 1.7
		4	1 (1-4) 2.0 ± 1.3	3 (1-5)** 2.8 ± 1.8	1 (1-3) 1.9 ± 1.2	3 (1-5)** 3.1 ± 1.9	1 (1-3) 2.0 ± 1.2	3 (1-5)*** 3.0 ± 1.8
		5	2 (1-3) 2 .0 ± 1.2	3 (1-4)** 2.8 ± 1.5	1 (1-2) 1.6 ± 1.0	3 (1-4)*** 2.8 ± 1.6	1 (1-3) 1.8 ± 1.1	3 (1-4)*** 2.8 ± 1.5
		15	1 (1-3) 1.8 ± 1.1	3 (2-5)*** 3.0 ± 1.5	1 (1-3) 1.8 ± 1.0	3 (1-4)*** 3.1 ± 1.6	1 (1-3) 1.8 ± 1.1	3 (1-4)*** 3.0 ± 1.5
		In total	12 (6-20) 13.0 ± 7.2	21*** (11-28) 19.5 ± 9.1	9 (6-18) 12.2 ± 6.5	21*** (10-28) 19.8 ± 9.1	10 (6-19) 12.6 ± 6.8	21***(10-28) 19.6 ± 9.0
		Change in all men (points)		6 (1-10) 6.5 ± 6.3		7 (0-12) 7.6 ± 7.4		6 (1-11) 7.0 ± 6.8
		Change in patients who responded to treatment		8 (6-13) 10.0 ± 5.3		11 (8-17) 11.8 ± 6.0		9 (7-16) 10.9 ± 5.7
		Non responders to treatment		5 (20.8)		8 (32.0)		13 (26.5)
	SEP2	Gave positive answer	14 (58.3)	19 (79.2)*	13 (52.0)	19 (76.0)*	27 (55.1)	38 (77.6)***
		Patients who showed improvement as percentage		5 (20.8)		6 (24.0)		11 (22.4)

Bibliographic reference (Ref ID)	Kamenov 2010 (Ref ID: 20)

	from the whole group						
	Patients who showed improvement as percentage of those who gave negative answer before treatment		5 (50.0)		6 (50.0)		11 (50.0)
SEP3	Gave positive answer	4 (16.7)	15 (62.5)***	3 (12.0)	15 (60.0)***	7 (14.3)	30 (61.2)***
	Patients who showed improvement as percentage from the whole group		11 (45.8)		12 (48.0)		23 (46.9)
	Patients who showed improvement as percentage of those who gave negative answer before treatment		11 (55.0)		12 (54.5)		23 (54.8)
GAQ	Patients who showed improvement		15 (62.5)		16 (64.0)		31 (63.3)

IIEF improvement reported in 37 men (75.5%). No effect was reported in 12 men (24.5%)

Change in weight or BMI:

Only baseline BMI and weight was reported. Change following intervention was not reported

Frequency severity and timing of hypoglycaemic episodes:

This outcome was not reported

Bibliographic reference (Ref ID)	Kamenov 2010 (Ref ID: 20)

Adverse events:

Thirteen side effects were reported by 11 patients

Table 3. Side effects during treatment

Type	Tadalafil	Vardenafil	All men
Headache	2 (8.3)	2 (8.0)	4
Flush	1 (4.2)	2 (8.0)	3
Nasal congestion		1 (8.0)	1
Myalgia	2 (8.4)		2
Dyspepsia	2 (8.4)	1 (4.0)	3
Visual disturbances	_	_	_
Total	7 (29.2)	6 (24.0)	13

Three patients discontinued the trial; 2 in tadalafil group and 1 in vardenafil group (but this was for reasons unrelated to treatment)

Change in glycaemic control including HBA1c and microvascular or macrovascular complications:

Elevated risk of developing diabetic foot (NDS ≥6) was seen in 31. (63.3%) of patients, but there were no significant differences between the treatment groups.

Quality of life (including changes in confidence, anxiety, mood and depression):

This outcome was not reported in this paper

Other reported outcomes:

These factors in table 4 were identified as factors that correlate with the treatment efficacy.

Table 4. Correlations of treatment efficacy of the two PDE5 inhibitors (demonstrated by IIEF,SEP2 and SEP3) and different risk factors

	IIEF after treatment	IIEF treatment efficacy	SEP2 after treatment	SEP2 treatment efficacy	SEP3 after treatment	SEP3 treatment efficacy	GAQ

Bibliographic reference (Ref ID)	Kamenov 2010 (Ref ID: 20)							
	Age	-0.170	-0.119	-0.220	-0.075	-0.156	-0.121	0.025
	Duration of DM	0.007	0.280	0.116	0.277	-0.091	0.049	0.113
	HBA1c	-0.059	0.020	-0.135	-0.079	-0.090	-0.089	0.024
	FPG	0.231	-0.019	0.029	-0.171	0.070	0.073	0.007
	NDS	-0.597***	-0.433**	-0.515***	-0.448*	-0.623***	-0.597***	-0.500***
	Hypertension	-0.230	-0.214	-0.232	-0.146	-0.318	-0.324*	-0.107
	Dyslipidemia	-0.095	-0.124	-0.127	-0.026	-0.118	-0.078	0.002
	Smoking	0.151	0.028	0.071	-0.151	0.181	0.165	-0.024
	Duration of smoking	0.182	0.005	0.094	-0.186	0.186	0.162	-0.037
	Number of cigarettes	0.104	-0.078	0.022	-0.213	0.162	0.147	-0.019
	Duration of ED	-0.221	-0.095	-0.271	-0.316	-0.295*	-0.248	-0.155
	IIEF after treatment		0.712***	0.726***	0.738***	0.820***	0.836***	0.672***
	IIEF treatment efficacy			0.710***	0.897***	0.653***	0.717***	0.842***
	SEP2 after treatment				0.917***	0.676***	0.655***	0.706***
	SEP2 treatment efficacy					-0.502*	0.502*	0.917***
	SEP3 after treatment						-	-0.099
	SEP3 treatment efficacy							0.720***
	*P<0.05, **P<0.01,***P<0.001 ED, Erectile dysfunction; FPG, fasting plasma glucose; NDS, neuropathy disability score; SEP, sexual encounter profile question Correlations between risk factors , IIEF, SEP2, SEP3 and GAQ after using 2 PDE-5 inhibitors (after treatment) and treatment efficacy							
Authors conclusion	This study found that tadalafil and vardenafil are equally effective with the first intake in patients with diabetes and DN and both are well tolerated with no serious adverse events.							
Source of funding	Not reported							
Comments	N/A							

Evidence table 23: (De Young et al 2012)

<table>
<tr><th>Bibliographic reference (Ref ID)</th><th>De Young et al 2012 (Ref ID:7)</th></tr>
<tr><td>Study type & aim</td><td>Double-blind, randomised, placebo controlled trial</td></tr>
<tr><td>Number and characteristics of patients</td><td>Total number of participants and characteristics:
24 men with type 2 diabetes enrolled and were assigned to either 50mg sildenafil (n=12) or placebo (n=12). Mean age 59 years (sildenafil, 59.4 years; placebo, 59.8 years) range 49-75 years. All patients were high risk with diabetic ED recruited from a tertiary referral clinic.
Inclusion and exclusion criteria:
Not reported

Table 1. Baseline characteristics of patients
<table>
<tr><th></th><th>Placebo</th><th>Sildenafil</th></tr>
<tr><td>Mean age (y)</td><td>59.8</td><td>59.4</td></tr>
<tr><td>Body mass index (kg/m2)</td><td>28.4</td><td>30.4</td></tr>
<tr><td>Duration of diabetes (y)</td><td>10.9</td><td>11.4</td></tr>
<tr><td>Duration of ED (y)</td><td>7.25</td><td>6.4</td></tr>
<tr><td>Patients who smoke cigarettes n (%)</td><td>5 (42%)</td><td>5 (42%)</td></tr>
<tr><td>Patients who drink alcohol n (%)</td><td>6 (50%)</td><td>10 (84%)</td></tr>
<tr><td>Patients with hypertension (%)</td><td>3 (25%)</td><td>3 (25%)</td></tr>
<tr><td>Patients with hyperlipidaemia n (%)</td><td>5 (42%)</td><td>6 (50%)</td></tr>
<tr><td>Baseline IIEF-5 scores (questions 3 and 4)</td><td>2.7</td><td>3.3</td></tr>
</table></td></tr>
<tr><td>Monitoring information and definitions</td><td>Outcome measures:
Erectile function was assessed using an abridged version of the IIEF-5 item scale. Patients were monitored at baseline and end-point.</td></tr>
<tr><td>Intervention</td><td>Drug: Sildenafil
Dose and timing: 50mg daily
Route: Oral</td></tr>
<tr><td>Comparator</td><td>Drug: Matched placebo (designed to simulate look and feel of treatment drug)
Dose and timing: 50mg daily
Route: Oral</td></tr>
<tr><td>Length of follow up</td><td>10 weeks</td></tr>
</table>

Bibliographic reference (Ref ID)	De Young et al 2012 (Ref ID:7)
Location	Canada
Outcomes measures and effect sizes	**Erectile function:** The sum of scores for questions 3 and 4 of the IIEF scale was examined: Patients taking sildenafil reported significant differences between baseline and end point scores (p<0.001). Scores were not significantly different between treatment groups at baseline (sildenafil, 9.1; SD, 5.6. SEM, 1.6; placebo, 6.2; SD, 4.4; SEM1.3) **Frequency severity and timing of hypoglycaemic episodes:** This outcome was not considered in the study **Adverse events:** No adverse events were recorded **Microvascular or macrovascular complications:** This outcome was not considered in the study although endothelial function assessed at baseline found that brachial arterial FMD was similar between treatment and placebo groups. At endpoint patients in the sildenafil group reported significant improvements in FMD compared to placebo, reporting a 2-fold increase in brachial artery diameter (p<0.01) **Quality of life (including changes in confidence, anxiety, mood and depression):** This outcome was not considered in the study
Authors' conclusions	Improved erectile rigidity and enhanced vascular circulation were noted after 10 weeks of daily sildenafil use.
Source of funding	Pfizer
Comments	N/A

Evidence table 24: (Vardi & Nini 2009)

Bibliographic reference (Ref ID)	Vardi & Nini 2009 (Ref ID:287)
Study type & aim	Cochrane systematic review to assess the effect of PDE-5 inhibitors on management of erectile dysfunction (ED) in men with diabetes
Selection criteria	Randomised controlled trials comparing treatment with PDE-5 inhibitors to control in patients with diabetes and erectile dysfunction, trials with more than 2 treatment groups, cross-over designs (but no wash out period) and trials with intervention and follow up of any duration. Excluded studies included trials that were not truly randomised or where treatment allocation was not concealed.
Patient demographics	People with diabetes known to have ED and treated in a prospective design. At least one treatment option had to include PDE-5 inhibitor therapy
Search methods	Cochrane library

Bibliographic reference (Ref ID)	Vardi & Nini 2009 (Ref ID:287)
	MEDLINE until October 2005 EMBASE until October 2005 Also searched on-going trial databases
Outcomes measures and effect sizes	Eight studies were included **Erectile Function:** Seven studies reported Erectile dysfunction domain of International Index of Erectile Function. Weighted mean difference (WMD) at endpoint was 6.6 (95% confidence interval (CI,) 5.2 to 7.9) The IIEF questions 3 and 4 were taken from 5 studies. WMD for Q3 was 0.9 95% CI was 0.8 to 1.1 and for Q4 was 1.1 95% CI was 1.0 to 1.2 All studies considered the number of participants answering yes to the Global Efficacy Question (GEQ). Relative risk (RR) was 3.75 95% CI 3.12 to 4.51.Heterogeneity I^2 was 77.4% **Change in glycaemic control including HbA1c and change in weight or BMI** Patients' baseline HBA1c was used to assess heterogeneity of treatment effect. Glycaemic control was considered in 2 studies. One study considered high and low control (HBA1c threshold 8.3%) and found change in IIEF EF domain to be similar in treatment and control groups. The second study applied low medium and high HBA1c thresholds (below 7%, 7% to 9.5% and above 9.5%) and found the response to PDE-5 therapy and glycated haemoglobin was non-significant. **Frequency severity and timing of hypoglycaemic episodes:** This outcome was not considered in the review **Adverse events:** The most frequent adverse event was headache 141 of 1012 patients reporting incidence in the intervention arm compared to 28 0f 755 in control arm (risk ratio 3.66; 95% CI 2.51 to 5.35) The second most frequent event was flushing reported by 103 of 970 patients in treatment arm (RR 13.1 95% CI 6.01 to 29.03) compared to control. **Microvascular or macrovascular complications:** One paper reported treatment related CV events in the intervention arm. Two incidences of chest pain, 2 cases of congestive heart failure and 4 cases of hypertension. **Quality of life (including changes in confidence, anxiety, mood and depression):** Quality of life was addressed by 2 papers. A validated life satisfaction checklist found that Sildenafil was shown to improve scores for sexual life but there were no significant differences in other domains (life as a whole, partnership relations, family life, contact with friends, leisure situation, vocational situation and financial situation).
Authors' conclusion	PDE-5 inhibitors are a valid treatment option for men with diabetes and ED.

Bibliographic reference (Ref ID)	Vardi & Nini 2009 (Ref ID:287)
Source of funding	Not reported
Comments	A fixed effects model was chosen to pool data (due to low number of included studies)
Abbreviations	Abbreviations: ED, Erectile dysfunction; IIEF, International Index of Erectile Function questionnaire; EF, Erectile function domain of IIEF; SEP, Sexual Encounter Profile (diary questions regarding sexual encounter); GEQ Global Efficacy Question; QoL Quality of Life; IS, Intercourse satisfaction domain; Orgasmic function domain; Sexual desire domain; Overall satisfaction domain.

Evidence table 25: (Goldstein et al 2012)

Bibliographic reference (Ref ID)	Goldstein et al 2012 (Ref ID: XXX)
Study type & aim	Double-blind (investigator, participants), multi-centre, randomised, placebo-controlled trial to assess the effects of avanafil (100mg or 200mg) on erectile dysfunction in men with diabetes (89.5% with type 2 diabetes)
Number and characteristics of patients	**Total number of participants:** 390 men with diabetes (349 with type 2 diabetes) **Inclusion criteria:** Men aged ≥18 years with documented type 1 or 2 diabetes, ≥6 month history of mild to severe erectile dysfunction who were in a monogamous, heterosexual relationship for ≥3 months and agreed to make ≥4 attempts at intercourse per month. Following a 4 week run-in period, men were eligible for inclusion if they experienced ≥50% failure rate in maintaining an erection of sufficient duration to facilitate successful intercourse, had an IIEF-EF score of 5 to 25 and made ≥4 attempts at sexual intercourse. **Exclusion criteria:** Uncontrolled diabetes (HbA1c >9%); ED resulting from spinal cord injury or radical prostatectomy; BG levels >270mg/dL; untreated hypogonadism; prostate specific antigen level >4ng/mL; clinically significant cardiac, hepatic or renal disease; orthostatic hypotension; uncontrolled hypertension or hypotension; allergy or hypersensitivity to a PDE-5 inhibitor; history of consistent treatment failure or dose limiting adverse events during therapy with other PDE-5 inhibitors; previous or current antiandrogen therapy; use of organic nitrates or any drugs known to inhibit the activity of cytochrome P450 3A4 in previous 28 days of study drug commencement or during the study **Patient characteristics:** Mean duration of diabetes: 11.3±9.4 years Mean duration of ED: 72.3±55.7 months Mean age 58±9.1 years Mean weight 99.4±18.9kg; mean BMI 31.5±5.6kg/m^2 Ethnicity, *n* (%): White 314 (80.5%); Black 67 (17.2%); Asian 6 (1.5%); Multiple 2 (0.5%); Unknown 1 (0.3%) Severity of ED, *n* (%): Mild 85 (21.8%); Moderate 122 (31.3%); Severe 183 (46.9%) Type of diabetes, *n* (%): Type 1 41 (10.5%); Type 2 349 (89.5%)

<table>
<tr><th>Bibliographic reference (Ref ID)</th><th>Goldstein et al 2012 (Ref ID: XXX)</th></tr>
<tr><td></td><td>History of hypertension, n (%): 260 (67%)
History of coronary artery disease, n (%): 54 (13.9%)
Proportion with dyslipidaemia at baseline, n (%): 224 (57.4%)
Proportion on antihypertensive medication, n (%): 239 (61.6%)
Proportion on α-blockers, n (%): 24 (6.2%)</td></tr>
<tr><td>Monitoring information and definitions</td><td>Outcome measures:
Erectile dysfunction was assessed using the IIEF-EF domain score, SEP-2 and SEP-3.
Other domains on IIEF
Adverse events, ECG, laboratory values, physical examination</td></tr>
<tr><td>Intervention</td><td>Drug: Avanafil
Dose and timing: 100mg or 200mg, taken about 30 minutes before sexual activity; 2 doses in 24 hour period permitted provided that doses were separated by at least 12 hours; no restrictions on food or alcohol and concurrent α-blocker use
Route: Oral</td></tr>
<tr><td>Comparator</td><td>Drug: Placebo
Dose and timing: as per drug regimen
Route: as per drug regimen</td></tr>
<tr><td>Length of follow up</td><td>12 weeks</td></tr>
<tr><td>Location</td><td>USA</td></tr>
<tr><td>Outcomes measures and effect sizes</td><td>Erectile Function

Table 1. LS Mean change scores (± SD) from baseline in IIEF-EF domain at 12 weeks (extracted from clinicaltrials.gov NCT00809471)
<table>
<tr><td></td><td>Placebo</td><td>Avanafil 100mg</td><td>Avanafil 200mg</td></tr>
<tr><td>Number of participants</td><td>125</td><td>125</td><td>125</td></tr>
<tr><td>Follow-up at 12 weeks</td><td>1.8±0.64</td><td>4.5±0.64</td><td>5.4±0.66</td></tr>
</table>
Table 2. Proportion of individuals indicating successful intercourse (SEP-3) at 12 weeks
<table>
<tr><td></td><td>Placebo</td><td>Avanafil 100mg</td><td>Avanafil 200mg</td></tr>
<tr><td>Number of participants</td><td>127</td><td>126</td><td>126</td></tr>
<tr><td>Follow-up at 12 weeks, %</td><td>20.5</td><td>34.4</td><td>40</td></tr>
</table></td></tr>
</table>

Bibliographic reference (Ref ID)	Goldstein et al 2012 (Ref ID: XXX)

Table 3. Proportion of individuals indicating successful vaginal penetration (SEP-2) at 12 weeks

	Placebo	Avanafil 100mg	Avanafil 200mg
Number of participants	127	126	126
Follow-up at 12 weeks, %	42	54	63.5

Frequency severity and timing of hypoglycaemic episodes:

This outcome was not considered in the study

Adverse events:

Table 3. Adverse events at 12 weeks

	Placebo	Avanafil 100mg	Avanafil 200mg
Number of participants	130	127	131
Any treatment-emergent AE, *n*	31	45	42
Any drug-related treatment-emergent AE, *n*	5	9	20
Discontinued study medication because of treatment-emergent AE, *n*	0	1	2
Discontinued study medication because of drug-related treatment-emergent AE, *n*	0	0	1
Serious adverse event, *n*	1	3	4
Drug-related SAE, *n*	0	0	0
Death, *n*	0	0	0
Headache, *n*	2	5	15
Nasopharyngitis, *n*	6	4	4
Flushing, *n*	0	2	5
Sinus congestion, *n*	1	1	4
Back pain, *n*	3	2	1
Sinusitis, *n*	0	4	1
Dyspepsia, *n*	0	0	4
Influenza, *n*	0	3	0

Bibliographic reference (Ref ID)	Goldstein et al 2012 (Ref ID: XXX)
	Microvascular or macrovascular complications: This outcome was not considered in the study **Quality of life (including changes in confidence, anxiety, mood and depression):** This outcome was not considered in the study
Authors' conclusion	Avanafil was safe and effective for treating ED in men with diabetes and was effective as early as 15 minutes and more than 6 hours after dosing. AEs seen with avanafil were similar to those of other PDE-5 inhibitors.
Source of funding	VIVUS Inc
Comments	Stratified randomisation based on severity of ED using centralised, computer-generated system

Evidence table 26: (Hackett et al 2013)

Bibliographic reference (Ref ID)	Hackett et al 2013 (Ref ID: XXX), BLAST study
Study type & aim	Double-blind, multi-centre, randomised, placebo-controlled trial to assess the effects of intramuscular testosterone undecanoate on erectile dysfunction in men with type 2 diabetes
Number and characteristics of patients	**Total number of participants:** 199 men with type 2 diabetes and diagnosed hypogonadism; 84.5% had erectile dysfunction **Inclusion criteria:** Men aged ≥18 years with type 2 diabetes recruited from routine diabetes assessments from 8 general practices with initial findings of either total testosterone (TT) between 8.1 and 12nmol/L or free testosterone (FT) from 0.181 to 0.25nmol/L (mild group) or TT of ≤ 8.0nmol/L or FT of ≤0.18nmol/L (severe group). Mean of two morning fasting blood samples (8 to 11am) taken at baseline and 2 weeks later confirmed the diagnosis of hypogonadism according to European Association of Urology/International Society for Sexual Medicine guidelines. Men were symptomatic on baseline Ageing Male Symptom. Presence of relevant clinical symptoms were ascertained by physicians based on baseline assessment and IIEF, AMS and HADS. **Exclusion criteria:** History of testosterone replacement; history of prostate, breast or hepatic cancer; abnormal digital rectal examination; severe symptoms of prostate hypertrophy; elevated prostate-specific antigen (PSA>4µg/L) or haematocrit >50%; anticoagulation therapy **Patient characteristics (n=190):** Mean age 61.6±9.9 (33-83) years Mean weight 100.9±19 (68-186) kg; mean BMI 32.7±5.8 (23-64) kg/m^2 Mean systolic blood pressure: 138.6±14.5 (104-192) mmHg Mean diastolic blood pressure: 78.4±9.2 (54-100) mmHg

Bibliographic reference (Ref ID)	Hackett et al 2013 (Ref ID: XXX), BLAST study
	Mean total testosterone: 9.1±3.5 (0-21.4) nmol/L Proportion with mild testosterone deficiency (8-12nmol/L): 115 (57.8%) Proportion with severe testosterone deficiency (<8nmol/L): 84 (42.2%) Mean free testosterone: 184.4±60.4 (0.2-340) nmol/L Mean PSA: 1.4±1.3 (0.1-10.6) µg/L Mean IIEF score: 12.44±8.1 (0-29) Severity of ED, *n* (%): None [scores 26-30] 31 (15.5%); Mild [scores 17-21] 9 (4.5%); Mild-moderate [scores 11-16] 38 (19%); Moderate severe [scores <10] 35 (18.6%); Severe [scores 22-25] 21 (10.5%) Proportion on PDE-5 inhibitor medication, *n* (%): 35 (18.6%)
Monitoring information and definitions	**Outcome measures:** Erectile dysfunction was assessed using the IIEF Quality of life assessed on Global Efficacy Question Symptom scores assessed by Aging Male Symptom Depression and anxiety assessed by Hospital Anxiety and Depression Scale
Intervention	Drug: testosterone undecanoate Dose and timing: 1000mg administered over 5 minutes into the upper outer buttock at weeks 0, 6 and 18 Route: Intramuscular
Comparator	Drug: Placebo Dose and timing: as per drug regimen Route: as per drug regimen
Length of follow up	30 weeks, with 52 week open label extension where everyone received testosterone therapy (not extracted)
Location	UK
Outcomes measures and effect sizes	**Erectile Function** Table 1. Outcomes at baseline, 18 and 30 weeks

	N	Testosterone	N	Placebo
IIEF: Erectile function				
Baseline	97	13.24±9.80	102	11.64±10.05
18 weeks	96	13.21±10.77	100	11.18±10.51
30 weeks	91	13.99±10.89	95	10.52±10.43

Bibliographic reference (Ref ID)	Hackett et al 2013 (Ref ID: XXX), BLAST study

IIEF: Intercourse satisfaction				
Baseline	97	5.44±4.77	102	5.30±4.91
18 weeks	96	5.94±5.15	100	4.82±5.10
30 weeks	91	5.95±5.12	95	4.72±5.11
IIEF: Sexual desire				
Baseline	97	5.19±2.03	102	5.29±2.22
18 weeks	96	5.56±2.31	100	4.88±2.28
30 weeks	91	5.69±2.34	95	4.96±2.44
IIEF: Overall satisfaction				
Baseline	97	5.12±2.56	102	5.66±3.00
18 weeks	96	5.52±2.79	100	5.16±3.05
30 weeks	91	5.35±2.81	95	5.28±3.06
IIEF: Orgasm				
Baseline	97	5.68±3.83	102	4.80±4.02
18 weeks	96	5.97±3.97	100	4.42±4.18
30 weeks	91	5.68±4.04	95	3.99±3.92
GEQ: 30 weeks				
Score 1	91	13 (14.3%)	95	1 (1.1%)
Score 2	91	29 (31.9%)	95	16 (16.8%)
Score 3	91	21 (23.1%)	95	25 (26.3%)
Score 4	91	28 (30.8%)	95	53 (55.8%)

*Mean±SD

Frequency severity and timing of hypoglycaemic episodes:
This outcome was not considered in the study

Adverse events:
Table 3. Adverse events at 30 weeks

	Testosterone	Placebo

Bibliographic reference (Ref ID)	Hackett et al 2013 (Ref ID: XXX), BLAST study

Number of participants	97	102
Withdrawals	4	5
Reasons reported by study	Bowel malignancy not related to treatment	Bowel malignancy not related to treatment Death due to septicaemia following elective knee replacement surgery Prostate cancer without rise in PSA, diagnosed by digital rectal examination after reported worsening of urinary symptoms on clinical examination Injection-related pain

Microvascular or macrovascular complications:

This outcome was not considered in the study

Quality of life (including changes in confidence, anxiety, mood and depression):

The study reported that testosterone showed a non-significant reduction of 1.05 in the depression domain of the HADS questionnaire when compared to a reduction of 0.41 in the placebo group over the 30 weeks.

Non-significant reduction in the anxiety domain of HADS questionnaire was also observed in testosterone group vs. placebo (actual figures not reported).

Authors' conclusion	Testosterone therapy significantly improved all domains of the IIEF and patient related quality of life at 30 weeks and after 52 week open label extension. In men with type 2 diabetes, trials fo therapy may need to be given for much longer than 3 to 6 months suggested in current guidelines.
Source of funding	Bayer
Comments	GEQ data was only provided as proportion of people reporting various scores from 1 to 4 – no explanation of interpretation of these scores were given.