National Institute for Health and Care Excellence

Draft for consultation

Type 2 diabetes in adults: management (medicines update)

[E1.2] Evidence reviews for initial pharmacological management of type 2 diabetes: appendix D studies A to K

NICE guideline GID-NG10336

Evidence reviews underpinning recommendations 1.8.6-1.8.32, 1.8.34,1.8.38-1.8.60 and recommendations for research in the NICE guideline

August 2025

Draft for Consultation

This evidence review was developed by NICE

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Appendix D Effectiveness evidence

Note: In the study characteristics tables, if any baseline characteristic is not mentioned in a table, then this is because the value was either not reported by the study or not reported in a way that could be meaningfully extracted by the analyst assigned to review the study and so was not reported in the data extraction. The exception for this are HbA1c, weight and BMI values which are reported in appendix L.

1. Aggarwal, 2018

Bibliographic Reference	Aggarwal, Naresh; Singla, Anuj; Mathieu, Chantal; Montanya, Eduard; Pfeiffer, Andreas F H; Johnsson, Eva; Zhao, June; Iqbal, Nayyar; Bailey, Clifford; Metformin extended-release versus immediate-release: An international, randomized, double-blind, head-to-head trial in pharmacotherapy-naive patients with type 2 diabetes.; Diabetes, obesity & metabolism; 2018; vol. 20 (no. 2); 463-467

1.1. Study details

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	NA
Trial name / registration number	Trial name: CV181-206 registration number: NCT01864174
Study type	Randomised controlled trial (RCT)
Study location	148 sites in North America (USA, Canada, Puerto Rico), Europe (Germany, Hungary, Poland, Romania, UK) and South Africa
Study setting	No additional information
Study dates	June 2013 to June 2016
Sources of funding	Bristol-Myers Squibb
Inclusion criteria	• Men and women, aged ≥18 years • Treatment naive subjects (defined as no prior pharmacotherapy for glucose lowering within 90 days prior to enrolment and no more than 14 days of glucose-lowering medication) with type 2 diabetes mellitus with inadequate glycemic (HbA1c ≥7.0% and ≤9.2% obtained at screening visit) control on diet and lifestyle advice alone. • Key inclusion criteria were: body mass index (BMI) ≤45.0 kg/m2; fasting plasma glucose (FPG) <250 mg/dL (13.9 mmol/L); C-peptide ≥1.0 ng/mL at enrolment.

	• Women must have a negative serum or urine test within 24 hours prior to start of investigational product
Exclusion criteria	• History of ketoacidosis, lactic acidosis or hyperosmolar non-ketonic coma • Symptoms of poorly controlled diabetes, including but not limited to marked polyuria and polydipsia with >10% weight loss during last 3 months • Serum creatinine ≥1.50 mg/dL (133 µmol/L) for male subjects; serum creatinine ≥1.40 mg/dL (124 µmol/L for female subjects)
Recruitment / selection of participants	Patients were recruited from 148 sites worldwide. Method of recruitment is not reported.
Intervention(s)	Metformin Extended Release (XR) Metformin Immediate Release (IR) Eligible participants entered a 4-week, single-blind, placebo lead-in period, followed by a 24-week, randomized, double-blind treatment period. Patients were randomized to 1:1 to Metformin XR metformin IR for 24 weeks. Doses were titrated from 500 to 2000 mg/d over the first 3 weeks of treatment. Participants unable to tolerate 2000 mg/d were down-titrated and re-challenge was attempted, if possible, before week 12
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear
Strata 2: People with atherosclerotic cardiovascular diseases	Not stated/unclear
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear
Strata 4: People with type 2 diabetes mellitus and high	Not stated/unclear

cardiovascular risk	
Subgroup 1: People with frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Sensitivity analysis category: Enrichment trial status	6) No response criteria
Population subgroups	subgrouped by baseline HbA1c: <8%; ≥8 to <9%; ≥9%
Comparator	Metformin IR Vs. Metformin XR
Number of participants	568 randomized 283 received metformin XR, 268 completed 285 received metformin IR, 271 completed
Duration of follow-up	24 weeks
Method of analysis	Other
Additional comments	

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1.2. Study arms

1.2.1. Metformin extended release (2000mg/d) (N = 268)

Received once daily 2000 mg (dose was titrated from 500 to 2000 mg/d for first 3 weeks of 24 weeks treatment)

1.2.2. Metformin Immediate release (2000mg/d) (N = 271)

Received twice daily 1000 mg (every morning and evening with meals). Dose was titrated from 500 to 2000 mg/d for first 3 weeks of 24 weeks treatment

1.3. Characteristics

1.3.1. Arm-level characteristics

Characteristic	Metformin extended release (2000mg/d) (N = 268)	Metformin Immediate release (2000mg/d) (N = 271)
% Male Sample size	n = 146 ; % = 54.4	n = 149 ; % = 55
Mean age (SD) (years) Mean (SD)	56.8 (10.7)	55.3 (10.3)
White Sample size	n = 227 ; % = 84.7	n = 225 ; % = 83
Black or African American Sample size	n = 22 ; % = 8.2	n = 19 ; % = 7
Asian Sample size	n = 17 ; % = 6.3	n = 20 ; % = 7.4
Others Includes American Indian/Alaska native; native Hawaiian/other Pacific Islander; or other Sample size	n = 2 ; % = 0.7	n = 7 ; % = 2.6
Comorbidities Custom value	NR	NR
Presence of frailty Custom value	NR	NR

Characteristic	Metformin extended release (2000mg/d) (N = 268)	Metformin Immediate release (2000mg/d) (N = 271)
Time since type 2 diabetes diagnosis (years) Mean (SD)	2.04 (2.9)	1.77 (2.5)
HbA1c (%) Mean (SD)	7.58 (0.6)	7.76 (0.5)
Blood pressure Custom value	NR	NR
Heart rate Custom value	NR	NR
Smoking status Custom value	NR	NR
Alcohol consumption Custom value	NR	NR
Presence of severe mental illness Custom value	NR	NR
People with significant cognitive impairment Custom value	NR	NR
People with a learning disability Custom value	NR	NR
Weight (kg) Mean (SD)	92.88 (18.85)	92.24 (19.08)
BMI (kg/m2) Mean (SD)	32.9 (5.5)	32.8 (5.4)
Number of people with obesity Custom value	NR	NR
Total cholesterol Mean (SD)	180.8 (40.88)	184.3 (43.27)
LDL-cholesterol	103.4 (36.08)	106.6 (37.19)

Characteristic	Metformin extended release (2000mg/d) (N = 268)	Metformin Immediate release (2000mg/d) (N = 271)
Mean (SD)		
HDL-cholesterol Mean (SD)	45.7 (11.58)	44.7 (10.59)
Triglycerides Mean (SD)	165.5 (119.61)	172.9 (113.82)
Albumin creatinine ratio Custom value	NR	NR
eGFR (mL/min/1.73m2) Custom value	NR	NR
Other antidiabetic medication used Custom value	NA	NA
Statins/lipid-lowering medication used Custom value	NR	NR
Other treatment being received Custom value	NR	NR

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2. Arjona Ferreira, 2013

Bibliographic Reference	Arjona Ferreira, J. C.; Corry, D.; Mogensen, C. E.; Sloan, L.; Xu, L.; Golm, G. T.; Gonzalez, E. J.; Davies, M. J.; Kaufman, K. D.; Goldstein, B. J.; Efficacy and safety of sitagliptin in patients with type 2 diabetes and ESRD receiving dialysis: a 54-week randomized trial; Am J Kidney Dis; 2013; vol. 61 (no. 4); 579-87

2.1. Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	NCT00509236
Study type	Randomised controlled trial (RCT)
Study location	Multinational
Study setting	No additional information
Study dates	No additional information
Sources of funding	Sponsored by Merck Sharp & Dohme Corp.
Inclusion criteria	≥30 years of age Had type 2 diabetes with end stage renal disease and had been on haemodialysis or peritoneal dialysis therapy for at least 6 months Able to discontinue monotherapy or low-dose combination therapy, if receiving any, during run-in period HbA1c 7-9% prior to run-in (6-week diet and exercise program to lower to acceptable level if not)
Exclusion criteria	Receiving insulin therapy within 12 weeks of screening visit Type 1 diabetics

	History of ketoacidosis, acute kidney disease, kidney transplantation or liver disease Cardiovascular event within 6 months Hepatic transaminase levels >2 times the upper limit of normal Fasting plasma glucose >240 mg/dL Triglyceride level >600 mg/dL
Recruitment / selection of participants	No additional information
Intervention(s)	Participants allocated to receive sitagliptin received 25 mg sitagliptin per day, plus glipizide placebo pills. Placebo pills were titrated in the same fashion as the glipizide therapy in the comparator arm, up to twice daily. Insulin was available after randomization for patients whose glipizide or glipizide placebo tablets had been up titrated to the maximum tolerated dose and who met predefined glycemic parameters as follows: confirmed FPG level >240 mg/dL at any time after randomization until week 6, confirmed FPG level >220 mg/dL after week 6 through week 12, confirmed FPG level >200 mg/dL after week 12 through week 24, and confirmed HbA1c level >8% after week 24.
Strata 1: People with type 2 diabetes mellitus and heart failure	Mixed population
Strata 2: People with atherosclerotic cardiovascular diseases	Not stated/unclear
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear
Strata 4: People with type 2 diabetes mellitus and high	People at higher risk of developing cardiovascular disease

cardiovascular risk	
Subgroup 1: People with frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Sensitivity analysis category: Enrichment trial status	7) Mixed population
Population subgroups	No additional information
Comparator	Participants allocated to the glipizide arm initially received 2.5 mg glipizide per day. The dose of glipizide received was titrated on a two-weekly basis up to a maximum dose of 10 mg twice daily. Upwards titration generally occurred when the prior week's fasting and pre-prandial glucose measurements were ≥120 mg/dL and there were no episodes of hypoglycaemia. However, investigators were allowed to increase the dose of glipizide/glipizide placebo as considered appropriate. Downward titration, including interruption of treatment, could occur if a patient had unexplained hypoglycaemia documented by fingerstick glucose level ≤70 mg/dL or at the clinical judgment of the investigator, to reduce the risk of hypoglycaemia. Insulin was available after randomization for patients whose glipizide or glipizide placebo tablets had been up titrated to the maximum tolerated dose and who met predefined glycemic parameters as follows: confirmed FPG level >240 mg/dL at any time after randomization until week 6, confirmed FPG level >220 mg/dL after week 6 through week 12, confirmed

	FPG level >200 mg/dL after week 12 through week 24, and confirmed HbA1c level >8% after week 24.
Number of participants	129 randomised 64 received sitagliptin, 47 completed 65 received glipizide, 45 completed
Duration of follow-up	54 weeks
Indirectness	None
Method of analysis	ITT
Additional comments	None

2.2. Study arms

2.2.1. Sitagliptin (N = 64)

25 mg sitagliptin once daily plus glipizide placebo

2.2.2. Glipizide (N = 65)

Initially 2.5 mg glipizide per day, titrated up to a maximum of 10 mg twice daily, plus sitagliptin placebo

2.3. Characteristics

2.3.1. Arm-level characteristics

Characteristic	Sitagliptin (N = 64)	Glipizide (N = 65)
% Male Sample size	n = 40 ; % = 63	n = 37 ; % = 57
Mean age (SD) (years) Mean (SD)	60.5 (9.1)	58.5 (9.9)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 16 ; % = 25	n = 18 ; % = 28

Characteristic	Sitagliptin (N = 64)	Glipizide (N = 65)
Black Sample size	n = 5 ; % = 8	n = 1 ; % = 2
Asian Sample size	n = 28 ; % = 44	n = 32 ; % = 49
Multiracial Sample size	n = 15 ; % = 23	n = 14 ; % = 22
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosis Median (IQR)	19 (12 to 24)	16 (11 to 23)
HbA1c Mean (SD)	7.9 (0.7)	7.8 (0.7)
Blood pressure Nominal	NR	NR
Heart rate Nominal	NR	NR
Smoking status Nominal	NR	NR
Alcohol consumption Nominal	NR	NR
Presence of severe mental illness Nominal	NR	NR
People with significant cognitive impairment Nominal	NR	NR
People with a learning disability Nominal	NR	NR
Weight Nominal	NR	NR

Characteristic	Sitagliptin (N = 64)	Glipizide (N = 65)
BMI (kg/m²) Mean (SD)	27.3 (5.7)	26.3 (4.3)
Number of people with obesity Nominal	NR	NR
Cholesterol and lipid levels Nominal	NR	NR
Albumin creatinine ratio Nominal	NR	NR
eGFR (mL/min/1.73m2) Nominal	NR	NR
Other antidiabetic medication used On oral antihyperglycemic therapy at screening Sample size	n = 24 ; % = 38	n = 31 ; % = 48
Blood pressure-lowering medication used Nominal	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

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3. Arjona Ferreira, 2013

Bibliographic Reference	Arjona Ferreira, J. C.; Marre, M.; Barzilai, N.; Guo, H.; Golm, G. T.; Sisk, C. M.; Kaufman, K. D.; Goldstein, B. J.; Efficacy and safety of sitagliptin versus glipizide in patients with type 2 diabetes and moderate-to-severe chronic renal insufficiency; Diabetes Care; 2013; vol. 36 (no. 5); 1067-73

3.1. Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	NCT00509262
Study type	Randomised controlled trial (RCT)
Study location	Multinational
Study setting	No additional information
Study dates	No additional information
Sources of funding	Sponsored by Merck Sharp & Dohme Corp
Inclusion criteria	Type 2 diabetes Moderate to severe chronic renal insufficiency (eGFR ,50 mL/min/1.73 m2 using the Modification of Diet in Renal Disease equation) Not on dialysis and unlikely to require dialysis for the duration of the study A1C 7.0-9.0%, ≥30 years of age
Exclusion criteria	Taking insulin within 12 weeks of the screening visit Type 1 diabetes

	History of ketoacidosis, acute renal disease, history of renal transplant, liver disease Recent (within 3 months) cardiovascular event Hepatic transaminase levels two or more times the upper limit of normal Thyroid stimulating hormone outside the reference range Triglycerides >600 mg/dL Glycemic criteria: visit 2, FPG >260 mg/dL, unlikely to improve with diet/exercise; visit 3, FPG >250 mg/dL consistently (i.e., measurement repeated and confirmed within 7 days); visit 4, FPG >240 mg/dL consistently; and visit 5, finger-stick glucose >240 or <120 mg/dL
Recruitment / selection of participants	No additional information
Intervention(s)	Following a run-in period of 2 weeks where participants received placebo medication, those randomised to the sitagliptin arm received 25 mg sitagliptin per day if they had severe renal insufficiency, or 50 mg (2x25 mg) sitagliptin per day if they had moderate renal insufficiency. The dose of sitagliptin was reduced from 50 to 25 mg per day for participants who's renal status changed from moderate to severe. Participants also received placebo glipizide tablets that were up/down-titrated in the same manner as in the active glipizide arm. Insulin was available for all participants whose glipizide or glipizide placebo tablets had been up-titrated to the maximum tolerated dose and who met predefined glycemic parameters as follows: confirmed repeated fasting plasma glucose level 240 mg/dL at any time after randomization until week 6, confirmed repeated fasting plasma glucose level 220 mg/dL after week 6 through week 12, confirmed repeated fasting plasma glucose level 200 mg/dL after week 12 through week 24, and confirmed HbA1c level 8% after week 24. Investigators were responsible for the management of insulin therapy.
Strata 1: People with type 2 diabetes mellitus and heart failure	Mixed population
Strata 2: People with atherosclerotic cardiovascular diseases	Mixed population
Strata 3: People with	Not stated/unclear

type 2 diabetes mellitus and chronic kidney disease	
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	People at higher risk of developing cardiovascular disease
Subgroup 1: People with frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	People without non-alcoholic fatty liver disease
Subgroup 4: People with obesity	Mixed population
Subgroup 5: eGFR category at baseline	Mixed population
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Sensitivity analysis category: Enrichment trial status	7) Mixed population
Population subgroups	No additional information
Comparator	Following a run-in period of 2 weeks where participants received placebo medication, those randomised to the glipizide arm received 2.5 mg glipizide per day initially. Dosage was titrated in 2-week intervals to a potential maximum dose of 20 mg per day, as considered appropriate by the investigator based on the patient's glycemic control. The dose of glipizide could also be reduced or interrupted to prevent hypoglycaemia

	After maximally tolerated up titration of glipizide, patients had insulin rescue therapy initiated, with the regimen and dose determined by investigator, if they met the following criteria: confirmed FPG >240 mg/dL any time from randomization to week 6; confirmed FPG >220 mg/dL from week 6 to 12; confirmed FPG >200 mg/dL from week 12 to 24; and confirmed A1C >8% after week 24. Once insulin rescue therapy was initiated, patients continued to take blinded sitagliptin or matching placebo, but discontinued blinded glipizide or matching placebo.
Number of participants	423 randomised 211 received sitagliptin, 164 completed 212 received glipizide, 170 completed
Duration of follow-up	54 weeks
Indirectness	None
Method of analysis	Per protocol
Additional comments	None

3.2. Study arms

3.2.1. Sitagliptin (N = 211)

50 or 25 mg sitagliptin per day, depending on degree of renal insufficiency, plus glipizide placebo

3.2.2. Glipizide (N = 212)

Initially 2.5 mg per day, titrated to a maximum of 20 mg per day, plus sitagliptin placebo

3.3. Characteristics

3.3.1. Arm-level characteristics

Characteristic	Sitagliptin (N = 211)	Glipizide (N = 212)
% Male	n = 80 ; % = 59	n = 78 ; % = 55

Characteristic	Sitagliptin (N = 211)	Glipizide (N = 212)
Sample size		
Mean age (SD) (years) Mean (SD)	64.8 (10.6)	64.3 (9.2)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 40 ; % = 30	n = 40 ; % = 28
Black Sample size	n = 2 ; % = 2	n = 2 ; % = 1
Asian Sample size	n = 72 ; % = 53	n = 83 ; % = 59
Multiracial Sample size	n = 20 ; % = 15	n = 12 ; % = 9
American Indian or Alaska Native Sample size	n = 1 ; % = 1	n = 5 ; % = 4
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosis (years) Mean (SD)	10.7 (7.5)	10.1 (7.8)
HbA1c (%) Mean (SD)	7.8 (0.7)	7.8 (0.7)
Blood pressure Nominal	NR	NR
Heart rate Nominal	NR	NR
Smoking status Nominal	NR	NR

Characteristic	Sitagliptin (N = 211)	Glipizide (N = 212)
Alcohol consumption Nominal	NR	NR
Presence of severe mental illness Nominal	NR	NR
People with significant cognitive impairment Nominal	NR	NR
People with a learning disability Nominal	NR	NR
Weight (kg) Mean (SD)	68 (14.8)	70.2 (15.9)
BMI (kg/m²) Mean (SD)	26.5 (4.8)	27 (4.8)
Number of people with obesity Nominal	NR	NR
Cholesterol and lipid levels Nominal	NR	NR
Albumin creatinine ratio Nominal	NR	NR
eGFR (mL/min/1.73m2) Nominal	NR	NR
Other antidiabetic medication used On oral antihyperglycemic therapy at screening Sample size	n = 94 ; % = 71	n = 93 ; % = 65
Blood pressure-lowering medication used Nominal	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

1 Characteristics based off per-protocol population (sitagliptin n= 135, glipizide n= 142)

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4. Aroda, 2019

Bibliographic Reference	Aroda, V. R.; Rosenstock, J.; Terauchi, Y.; Altuntas, Y.; Lalic, N. M.; Morales Villegas, E. C.; Jeppesen, O. K.; Christiansen, E.; Hertz, C. L.; Haluzik, M.; Investigators, Pioneer; PIONEER 1: Randomized Clinical Trial of the Efficacy and Safety of Oral Semaglutide Monotherapy in Comparison With Placebo in Patients With Type 2 Diabetes; Diabetes Care; 2019; vol. 42 (no. 9); 1724-1732

4.1. Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.
Trial name / registration number	NCT02906930. PIONEER-1 trial.
Study type	Randomised controlled trial (RCT)
Study location	Multicentre trial (9 countries - Algeria, Bulgaria, Czech Republic, Japan, Mexico, Russia, Serbia, Turkey and the U.S.).
Study setting	Outpatient follow-up.
Study dates	No additional information.
Sources of funding	The trial was funded by Novo Nordisk A/S. In addition, authors received consultancy fees, grants and research support from a range of pharmacological industries.
Inclusion criteria	Informed consent; male or female, age at least 18 years (Japan at least 20 years, Algeria at least 19 years); diagnosed with type 2 diabetes mellitus and on treatment with diet/exercise for at least 30 days before screening; glycated haemoglobin 7.0-9.5% (both inclusive).
Exclusion criteria	Treatment with glucose-lowering agent in 90 days prior to screening (short term no more than 14 days, insulin treatment excepted); proliferative retinopathy or maculopathy requiring acute treatment; personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2; estimated glomerular filtration rate <60mL/min/1.73m2; history of pancreatitis; acute coronary or cerebrovascular event within 180 days before randomisation; heart failure New York Heart Association class

	IV; malignant neoplasms within the last 5 years (except basal and squamous cell skin cancer and in-situ carcinomas).
Recruitment / selection of participants	No additional information.
Intervention(s)	Semaglutide N=525 Semaglutide 3mg once daily with dose escalations every 4 weeks until the randomised dose was achieved. The group is made up of three randomised groups: group 1 = 3mg (n=175), group 2 = 7mg (n = 175), group 3 = 14mg (n = 175).
Cointervention	Concomitant therapy: Rescue medication was provided for people with persistent hyperglycaemia if fasting blood glucose was >240mg/dL from weeks 8-13 or >200mg/dL from weeks 14 onward with the type prescribed being at the investigator's discretion (excluding GLP-1 receptor agonists, DPP-4 inhibitors and amylin analogues). People continued in the trial after receiving rescue medication and also if discontinuing the trial product and receiving other glucose-lowering medications.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear
Strata 2: People with atherosclerotic cardiovascular diseases	People without other cardiovascular diseases
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with frailty	Not stated/unclear
Subgroup 2: Onset of type	Not stated/unclear

2 diabetes mellitus	
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Sensitivity analysis category: Enrichment trial status	6) No response criteria
Population subgroups	No additional information.
Comparator	Placebo N=178 Placebo once daily.
Number of participants	703
Duration of follow-up	26 weeks.
Indirectness	No additional information.
Method of analysis	ACA Full analysis set, including all participants that were randomised
Additional comments	No additional information.

4.2. Study arms

4.2.1. Semaglutide (N = 525)

Semaglutide 3mg once daily with dose escalations every 4 weeks until the randomised dose was achieved. The group is made up of three randomised groups: group 1 = 3mg (n=175), group 2 = 7mg (n = 175), group 3 = 14mg (n = 175). Concomitant therapy: Rescue medication was provided for people with persistent hyperglycaemia if fasting blood glucose was >240mg/dL from weeks 8-13 or

>200mg/dL from weeks 14 onward with the type prescribed being at the investigator's discretion (excluding GLP-1 receptor agonists, DPP-4 inhibitors and amylin analogues). People continued in the trial after receiving rescue medication and also if discontinuing the trial product and receiving other glucose-lowering medications.

4.2.2. Placebo (N = 178)

Placebo once daily. Concomitant therapy: Rescue medication was provided for people with persistent hyperglycaemia if fasting blood glucose was >240mg/dL from weeks 8-13 or >200mg/dL from weeks 14 onward with the type prescribed being at the investigator's discretion (excluding GLP-1 receptor agonists, DPP-4 inhibitors and amylin analogues). People continued in the trial after receiving rescue medication and also if discontinuing the trial product and receiving other glucose-lowering medications.

4.3. Characteristics

4.3.1. Arm-level characteristics

Characteristic	Semaglutide (N = 525)	Placebo (N = 178)
% Male Sample size	n = 268 ; % = 51	n = 89 ; % = 50
Mean age (SD) (years) Mean (SD)	55 (11)	54 (11)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosis (years) Mean (SD)	3.6 (5)	3.4 (4.6)
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Semaglutide (N = 525)	Placebo (N = 178)
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR
Other antidiabetic medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Blood pressure-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Statins/lipid-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR

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5. Aronoff, 2000

Bibliographic Reference	Aronoff, S.; Rosenblatt, S.; Braithwaite, S.; Egan, J. W.; Mathisen, A. L.; Schneider, R. L.; Pioglitazone hydrochloride monotherapy improves glycemic control in the treatment of patients with type 2 diabetes: a 6-month randomized placebo-controlled dose-response study. The Pioglitazone 001 Study Group; Diabetes Care; 2000; vol. 23 (no. 11); 1605-11

5.1. Study details

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	None
Trial name / registration number	Pioglitazone 001
Study type	Randomised controlled trial (RCT)
Study location	USA
Study setting	Primary and secondary care, academic and non-academic sites.
Study dates	NR
Sources of funding	Funded by Takeda America.
Inclusion criteria	- HbA1C >= 7% - FPG >= 140 mg/dl - Fasting C-peptide > 1ng/ml
Exclusion criteria	- Use of insulin chronically - History of Ketoacidosis - Unstable or rapidly progressive diabetic retinopathy, nephropathy, or neuropathy

	- Impaired liver function (AST, ALT, total bilirubin or alkaline phosphatase > 2.5 upper limit of normal [ULN]) - Impaired kidney function (serum creatine >1.8mg/dl) - Anaemia - Myocardial infarction, coronary angioplasty, bypass graft, unstable angina, transient ischaemic attacks, or documented cerebrovascular accident within 6 mo. of study
Recruitment / selection of participants	Participants recruited from 35 centres in USA. 6-8 week washout period, including 2 weeks for baseline measurements. Patients who had never received pharmacological antiadiabetic therapy were enrolled in the study and entered a 6-week blind run in period. Patients randomized to one of five parallel treatment groups: pioglitazone 7.5, 15, 30 45mg or placebo. During the double-blind period, patients were seen every 2 weeks for first 6 weeks and every 4 weeks for remaining twenty weeks. No modifications of dietary regimen was required.
Intervention(s)	Patients randomized to one of five parallel treatment groups: pioglitazone 7.5, 15, 30 or 45mg
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear - Myocardial infarction, coronary angioplasty, bypass graft, unstable angina, transient ischaemic attacks, or documented cerebrovascular accident within 6 mo. of study will include some with Heart failure
Strata 2: People with atherosclerotic cardiovascular diseases	Not stated/unclear - Myocardial infarction, coronary angioplasty, bypass graft, unstable angina, transient ischaemic attacks, or documented cerebrovascular accident within 6 mo. of study will include some with Heart failure
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear creatinine level has to be below <1.8 mg/dl but no EGFR or creatinine ratio measures. IS this enough?
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear - Myocardial infarction, coronary angioplasty, bypass graft, unstable angina, transient ischaemic attacks, or documented cerebrovascular accident within 6 mo. of study not enough to stratify.

	Not enough baseline characteristics provided to calculate Qrisk score.
Subgroup 1: People with frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Sensitivity analysis category: Enrichment trial status	7) Mixed population 125 naive to 273 non-naive with washout. Separated in results.
Population subgroups	None
Comparator	Placebo
Number of participants	N= 408
Duration of follow-up	26 weeks
Indirectness	Study conducted in the US, 23 years ago, potential shift in demographics but not enough to downgrade for indirectness.
Method of analysis	Per protocol "Also measured FPG for those patients who completed the study. there were no differences between completers and intention to treat analysis" Technically completer analysis

	ITT
Additional comments	Subset of patients naive to therapy

5.2. Study arms

5.2.1. Placebo (N = 79)

5.2.2. Pioglitazone 7.5mg (N = 79)

5.2.3. Pioglitazone 15mg (N = 79)

5.2.4. Pioglitazone 30mg (N = 85)

5.2.5. Pioglitazone 45mg (N = 76)

5.3. Characteristics

5.3.1. Study-level characteristics

Characteristic	**Study (N = 408)**
% Male Sample size	n = 237 ; % = 58
Mean age (SD) Nominal	53.7
Mean age (SD) Range	29 to 75
Ethnicity Sample size	% = 78
Caucasian Sample size	% = 78

Characteristic	Study (N = 408)
African-American Sample size	% = 8
Asian Sample size	% = 2
Other races Sample size	% = 1
Hispanic Sample size	% = 12
Time since type 2 diabetes diagnosis Nominal	NR
Blood pressure Nominal	NR
Heart rate Nominal	NR
Smoking status Nominal	NR
Alcohol consumption Nominal	NR
Presence of severe mental illness Nominal	NR
People with significant cognitive impairment Nominal	NR
People with a learning disability Nominal	NR
BMI Nominal	NR
Number of people with obesity Nominal	NR
Albumin creatinine ratio Nominal	NR

Characteristic	Study (N = 408)
eGFR (mL/min/1.73m2) Nominal	NR
None Sample size	n = 127 ; % = 31
One prior medication Sample size	n = 228 ; % = 56
Two or more prior medications Sample size	n = 53 ; % = 13
Blood pressure-lowering medication used Nominal	NR
Statins/lipid-lowering medication used Nominal	NR
Other treatment being received Nominal	NR

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2 ### 5.3.2. Arm-level characteristics

Characteristic	Placebo (N = 79)	Pioglitazone 7.5mg (N = 79)	Pioglitazone 15mg (N = 79)	Pioglitazone 30mg (N = 85)	Pioglitazone 45mg (N = 76)
HbA1c (%) Nominal	79	79	79	85	76
HbA1c (%) Mean (SD)	10.4 (0.22)	10 (0.22)	10.2 (0.22)	10.2 (0.21)	10.3 (0.22)
Naive to therapy Nominal	25	27	26	26	21
Naive to therapy Mean (SD)	9 (0.38)	9.3 (0.37)	9.9 (0.37)	9.3 (0.38)	10 (0.43)
Previously treated Nominal	54	53	53	58	55

Characteristic	Placebo (N = 79)	Pioglitazone 7.5mg (N = 79)	Pioglitazone 15mg (N = 79)	Pioglitazone 30mg (N = 85)	Pioglitazone 45mg (N = 76)
Previously treated Mean (SD)	10.9 (0.26)	10.3 (0.26)	10.4 (0.26)	10.4 (0.25)	10.6 (0.26)
Weight (kg) Mean (SD)	90.4 (1.47)	93.5 (1.59)	91.2 (1.8)	90.3 (1.58)	90.8 (1.56)
Triglycerides mg/dl Nominal	79	80	79	84	77
Triglycerides mg/dl Mean (SD)	262.8 (34.35)	319 (34.23)	283.8 (34.4)	261.1 (33.44)	259.7 (34.87)
HDL-cholesterol mg/dl Nominal	79	79	79	83	77
HDL-cholesterol mg/dl Mean (SD)	41.7 (1.24)	40.5 (1.2)	40.4 (1.24)	40.8 (1.21)	40.7 (1.25)
Total cholesterol mg/dl Nominal	79	80	79	84	77
Total cholesterol mg/dl Mean (SD)	224.6 (5.44)	214.5 (5.42)	220 (5.45)	222.7 (5.29)	213.7 (5.52)
LDL-cholesterol mg/dl Nominal	66	67	64	74	65
LDL-cholesterol mg/dl Mean (SD)	138.8 (4.54)	122.9 (4.52)	131.9 (4.64)	135.6 (4.33)	126.8 (4.6)

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6. Aschner, 2010

Bibliographic Reference	Aschner, P.; Katzeff, H. L.; Guo, H.; Sunga, S.; Williams-Herman, D.; Kaufman, K. D.; Goldstein, B. J.; Efficacy and safety of monotherapy of sitagliptin compared with metformin in patients with type 2 diabetes; Diabetes Obes Metab; 2010; vol. 12 (no. 3); 252-61

6.1. Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.
Trial name / registration number	NCT00449930. The study name is the Sitagliptin Study 049.
Study type	Randomised controlled trial (RCT)
Study location	Multicentre trial (23 countries).
Study setting	Outpatient follow-up.
Study dates	No additional information.
Sources of funding	The study was funded by Merck & Co., Whitehouse Station, NJ, USA.
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%.
Exclusion criteria	Type 1 diabetes; fasting plasma glucose <120mg/dL or >250mg/dL; unstable cardiac disease; significant renal impairment (creatinine at least 1.4mg/dL for males, at least 1.3mg/dL for females or creatinine clearance <60mL/min); elevated ALT, AST or creatinine phosphokinase (more than 2 times the upper limit of normal) or triglycerides >600mg/dL.
Recruitment / selection of participants	No additional information.
Intervention(s)	Sitagliptin N=528 Sitagliptin 100mg once daily for 24 weeks.

	Concomitant therapy: Everyone had a 2 week placebo run-in period.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear
Strata 2: People with atherosclerotic cardiovascular diseases	Not stated/unclear
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	People at higher risk of developing cardiovascular disease Based on BMI, age and presence of diabetes.
Subgroup 1: People with frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	People without non-alcoholic fatty liver disease
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria	Not stated/unclear

category at baseline	
Sensitivity analysis category: Enrichment trial status	6) No response criteria
Population subgroups	No additional information.
Comparator	Metformin N=522 Metformin 1000mg twice daily for 24 weeks. Concomitant therapy: Everyone had a 2 week placebo run-in period.
Number of participants	1050
Duration of follow-up	24 weeks.
Indirectness	No additional information.
Method of analysis	Per protocol Other Safety analysis with all patients as treated population (all people who received at least one dose of the study medication)
Additional comments	No additional information.

6.2. Study arms

6.2.1. Sitagliptin (N = 528)

Sitagliptin 100mg once daily for 24 weeks. Concomitant therapy: Everyone had a 2 week placebo run-in period.

6.2.2. Metformin (N = 522)

Metformin 1000mg twice daily for 24 weeks. Concomitant therapy: Everyone had a 2 week placebo run-in period.

6.3. Characteristics

6.3.1. Arm-level characteristics

Characteristic	Sitagliptin (N = 528)	Metformin (N = 522)
% Male Sample size	n = 217 ; % = 48	n = 194 ; % = 44
Mean age (SD) (years) Mean (SD)	56.3 (10.7)	55.7 (10.3)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosis (years) Mean (SD)	2.6 (3.9)	2.1 (3.5)
HbA1c (%) Mean (SD)	7.2 (0.7)	7.2 (0.7)
Blood pressure Mean (SD)	NR (NR)	NR (NR)
Heart rate Mean (SD)	NR (NR)	NR (NR)
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Sitagliptin (N = 528)	Metformin (N = 522)
Sample size		
Weight Mean (SD)	NR (NR)	NR (NR)
BMI (kg/m2) Mean (SD)	30.7 (4.7)	30.9 (4.9)
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR
Cholesterol and lipid levels Mean (SD)	NA (NA)	NA (NA)
Total cholesterol Mean (SD)	187.1 (40.3)	189.5 (42.2)
HDL cholesterol Mean (SD)	47 (11.9)	47.8 (11.2)
LDL cholesterol Mean (SD)	109 (35.8)	110.9 (37.6)
Triglycerides Mean (SD)	136 (NR)	136 (NR)
Albumin creatinine ratio Mean (SD)	NR (NR)	NR (NR)
eGFR (mL/min/1.73m2) Mean (SD)	NR (NR)	NR (NR)
Other antidiabetic medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Blood pressure-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Statins/lipid-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR

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7. Aschner, 2006

Bibliographic Reference	Aschner, P.; Kipnes, M. S.; Lunceford, J. K.; Sanchez, M.; Mickel, C.; Williams-Herman, D. E.; Effect of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy on glycemic control in patients with type 2 diabetes; Diabetes Care; 2006; vol. 29 (no. 12); 2632-7

7.1. Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	NCT00087516
Study type	Randomised controlled trial (RCT)
Study location	Multinational
Study setting	No additional information
Study dates	No additional information
Sources of funding	Sponsored by Merck
Inclusion criteria	18-75 years old A1C 7-10% if not receiving antihyperglycemic agents for 8 weeks (those with an A1C >10% and not on antihyperglycemic agents entered a 6-week run-in, those with an A1C 6-10% on an antihyperglycemic agent discontinued the agent and entered a 6-12 week washout period until A1C was 7-10%) Adequate adherence (>75%) during the placebo run-in period
Exclusion criteria	Type 1 diabetes

	Unstable cardiac disease Significant renal impairment (creatinine clearance <50 ml/min) Elevated (>2 x upper limit of normal) alanine aminotransferase, aspartate aminotransferase or creatine phosphokinase
Recruitment / selection of participants	No additional information
Intervention(s)	Participants were allocated to receive either 100 or 200 mg of sitagliptin. 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. *Two study arms containing 100 and 200 mg sitagliptin were combined for this review*
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear
Strata 2: People with atherosclerotic cardiovascular diseases	Not stated/unclear
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	People at higher risk of developing cardiovascular disease

Subgroup 1: People with frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Sensitivity analysis category: Enrichment trial status	7) Mixed population
Population subgroups	No additional information
Comparator	Participants allocated to the comparator received once daily placebo 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.
Number of participants	741 randomised 488 received sitagliptin, 423 completed 253 received placebo, 216 completed
Duration of follow-up	24 weeks
Indirectness	None
Method of analysis	Modified ITT

	All participants who received at least one dose of study medication and provided at least one follow-up measurement
Additional comments	None

7.2. Study arms

7.2.1. Sitagliptin (N = 488)

100 or 200 mg sitagliptin per day

7.2.2. Placebo (N = 253)

7.3. Characteristics

7.3.1. Arm-level characteristics

Characteristic	Sitagliptin (N = 488)	Placebo (N = 253)
% Male Sample size	n = 253 ; % = 52	n = 130 ; % = 51
Mean age (SD) (years) Mean (SD)	54.2 (9.8)	54.3 (10.1)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Asian Sample size	n = 69 ; % = 14	n = 34 ; % = 13
Black Sample size	n = 22 ; % = 5	n = 16 ; % = 6
Hispanic Sample size	n = 111 ; % = 23	n = 64 ; % = 25
Caucasian Sample size	n = 254 ; % = 52	n = 127 ; % = 50
Other Sample size	n = 32 ; % = 7	n = 12 ; % = 5

Characteristic	Sitagliptin (N = 488)	Placebo (N = 253)
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosis (years) Mean (SD)	4.3 (4.8)	4.6 (4.7)
HbA1c (%) Mean (SD)	8.1 (0.9)	8 (0.8)
Blood pressure Nominal	NR	NR
Heart rate Nominal	NR	NR
Smoking status Nominal	NR	NR
Alcohol consumption Nominal	NR	NR
Presence of severe mental illness Nominal	NR	NR
People with significant cognitive impairment Nominal	NR	NR
People with a learning disability Nominal	NR	NR
Weight (kg) Mean (SD)	84.3 (18.8)	85 (18.1)
BMI (kg/m²) Mean (SD)	30.3 (5.3)	30.8 (5.5)
Number of people with obesity Nominal	NR	NR
Cholesterol and lipid levels Nominal	NR	NR

Characteristic	Sitagliptin (N = 488)	Placebo (N = 253)
Albumin creatinine ratio Nominal	NR	NR
eGFR (mL/min/1.73m2) Nominal	NR	NR
Other antidiabetic medication used Using antihyperglycaemic agents at screening Sample size	n = 239 ; % = 49	n = 124 ; % = 49
Blood pressure-lowering medication used Nominal	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

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8. Bailey, 2012

Bibliographic Reference	Bailey, C. J.; Iqbal, N.; T'Joen, C.; List, J. F.; Dapagliflozin monotherapy in drug-naïve patients with diabetes: a randomized-controlled trial of low-dose range; Diabetes Obes Metab; 2012; vol. 14 (no. 10); 951-9

8.1. Study details

Secondary publication of another included study- see primary study for details	No information available.
Other publications associated with this study included in review	No information available.
Trial name / registration number	Not reported
Study type	Randomised controlled trial (RCT)
Study location	USA Canada Mexico Russia India South Africa Puerto Rico
Study setting	Clinic
Study dates	09/2008 to 01/2010
Sources of funding	Bristol-Myers Squibb and AstraZeneca
Inclusion criteria	• Men and women aged 18–77 years with inadequate glycaemic control (HbA1c ≥7.0 and ≤10%), and were drug-naive to prescribed antidiabetic medication (defined as never having received medication or having received it for <24 weeks since the original diagnosis, no antihyperglycaemic therapy for >14 days during the

	12 weeks prior to enrolment and no antihyperglycaemic therapy during the 4 weeks prior to enrolment). Patients were also required to have a body mass index ≤45.0 kg/m2 and C-peptide ≥0.34 nmol/l (≥1.0 ng/ml) at enrolment.
Exclusion criteria	• High serum creatinine that would contraindicate the use of metformin as a rescue medication [≥133.0 µmol/l (≥1.50 mg/dl) for men and ≥124.0 µmol/l (≥1.40 mg/dl) for women]. • Urine albumin : creatinine ratio >1800 mg/g, serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3 times the upper limit of the normal range (ULN), total bilirubin >34.20 µmol/l (>2 mg/dl) or creatine kinase >3 times ULN at time of enrolment. • Patients with a history of diabetes insipidus or symptoms indicative of poorly controlled diabetes mellitus (e.g. polyuria, polydipsia) were excluded, as were patients with clinically significant renal, hepatic, haematological, oncological, endocrine, psychiatric or rheumatic disease. • Patients who had been diagnosed with a cardiovascular disease or event within 6 months prior to enrolment or severe uncontrolled hypertension (defined as ≥180 systolic and/or ≥110 diastolic mm Hg).
Recruitment / selection of participants	• Drug-naive patients with type 2 diabetes with inadequate glycaemic control [haemoglobin A1c (HbA1c) ≥7.0 and ≤10.0%]. were recruited to receive dapagliflozin or placebo. • A qualification period (which lasted 14 days) was used to evaluate eligibility. This was followed by a lead-in period which consisted of single-blind placebo treatment for 14 days. Qualifying patients were provided with a blood glucose metre and instructions for self-monitoring, as well as diet and exercise counselling consistent with recommendations of the American Diabetes Association or similar local guidelines. Patients who completed the placebo lead-in regimen with compliance of ≥70 and ≤130% were eligible for entry into the double-blind treatment period.
Intervention(s)	Dapagliflozin 1 mg once daily, administered orally with the morning meal Dapagliflozin 2.5 mg once daily, administered orally with the morning meal Dapagliflozin 5 mg once daily, administered orally with the morning meal
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear
Strata 2: People with atherosclerotic cardiovascular diseases	People without other cardiovascular diseases

Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	People without chronic kidney disease
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	People at higher risk of developing cardiovascular disease
Subgroup 1: People with frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	People with type 2 diabetes first diagnosed above 40 years of age
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Sensitivity analysis category: Enrichment trial status	7) Mixed population
Population subgroups	None.
Comparator	Placebo once daily with the morning meal.
Number of participants	N=282 (A total of 497 patients were enrolled but only 282 were randomised).
Duration of follow-up	24-week study and 4-week follow-up period.

Indirectness	Study sites did not include the UK which may limit the generalisability of the results to a UK population.
Method of analysis	ACA
Additional comments	• Randomized patients who received ≥1 dose of double-blind study medication and had both a baseline and post-baseline measurement were included in the efficacy analyses. • There were no restrictions on the use of concomitant antihypertensive medications during the trial. • Patients with poor glycaemic control were eligible to receive open-label metformin as a rescue medication. Rescue eligibility was based on confirmed fasting plasma glucose (FPG) measured by a central laboratory [>15.0 mmol/l (>270 mg/dl) at weeks 4–7, >13.3 mmol/l (>240 mg/dl) at weeks 8–11 and >11.1 mmol/l (200 mg/dl) at weeks 12–24].

8.2. Study arms

8.2.1. Placebo once daily (N = 68)

Administered with morning meal

8.2.2. dapagliflozin 1 mg (N = 72)

Administered with morning meal

8.2.3. dapagliflozin 2.5 mg (N = 74)

Administered with morning meal

8.2.4. dapagliflozin 5 mg (N = 68)

Administered with morning meal

8.3. Characteristics

8.3.1. Arm-level characteristics

Characteristic	Placebo once daily (N = 68)	Dapagliflozin 1 mg (N = 72)	Dapagliflozin 2.5 mg (N = 74)	Dapagliflozin 5 mg (N = 68)
% Male No of events	n = 37 ; % = 54.4	n = 38 ; % = 52.8	n = 34 ; % = 45.9	n = 32 ; % = 47.1

Characteristic	Placebo once daily (N = 68)	Dapagliflozin 1 mg (N = 72)	Dapagliflozin 2.5 mg (N = 74)	Dapagliflozin 5 mg (N = 68)
Mean age (SD) (years) Mean (SD)	53.5 (11.08)	53.7 (9.04)	53.5 (10.61)	51.3 (11.51)
Ethnicity Nominal	NR	NR	NR	NR
Comorbidities Nominal	NR	NR	NR	NR
Presence of frailty Nominal	NR	NR	NR	NR
Time since type 2 diabetes diagnosis Mean (SD)	1.1 (1.95)	1.6 (2.55)	1.5 (2.19)	1.4 (3.24)
Heart rate Nominal	NR	NR	NR	NR
Smoking status Nominal	NR	NR	NR	NR
Alcohol consumption Nominal	NR	NR	NR	NR
Presence of severe mental illness Nominal	NR	NR	NR	NR
People with significant cognitive impairment Nominal	NR	NR	NR	NR
People with a learning disability Nominal	NR	NR	NR	NR
Number of people with obesity Nominal	NR	NR	NR	NR

Characteristic	Placebo once daily (N = 68)	Dapagliflozin 1 mg (N = 72)	Dapagliflozin 2.5 mg (N = 74)	Dapagliflozin 5 mg (N = 68)
Albumin creatinine ratio Nominal	NR	NR	NR	NR
eGFR (mL/min/1.73m2) Nominal	NR	NR	NR	NR
Other antidiabetic medication used Nominal	NR	NR	NR	NR
Blood pressure-lowering medication used Nominal	NR	NR	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR	NR	NR
Other treatment being received Nominal	NR	NR	NR	NR

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9. Banerji, 1995

Bibliographic Reference	Banerji, M. A.; Chaiken, R. L.; Lebovitz, H. E.; Prolongation of near-normoglycemic remission in black NIDDM subjects with chronic low-dose sulfonylurea treatment; Diabetes; 1995; vol. 44 (no. 4); 466-70

9.1. Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	USA
Study setting	No additional information
Study dates	No additional information
Sources of funding	Supported by Pfizer
Inclusion criteria	Black Americans Near-normoglycaemic remission, defined as fasting glucose ≤125 mg/dL with a HbA1c within or at the upper limit of normal, after several months of intensive glycaemic regulation with either insulin or oral hypoglycaemic agents No longer receiving any anti-diabetic medication
Exclusion criteria	None
Recruitment / selection of participants	No additional information
Intervention(s)	Participants randomised to the intervention initially received 0.625 mg glipizide (one-quarter of a tablet), and increased at intervals of several days to one-half, and finally one tablet which contained 2.5 mg glipizide

Cointervention	All people were receiving several months of intensive glycaemic regulation with either insulin or oral hypoglycaemic agents, then became near-normoglycaemic and discontinued all pharmacological therapy before starting the study.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear
Strata 2: People with atherosclerotic cardiovascular diseases	Not stated/unclear
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria	Not stated/unclear

category at baseline	
Sensitivity analysis category: Enrichment trial status	6) No response criteria
Population subgroups	No additional information
Comparator	Participants allocated to the comparator received once-daily placebo *Additional study arm providing no treatment (n=10) was excluded from this review due to not containing a relevant comparator*
Number of participants	20 randomised 10 received glipizide, 8 completed 10 received placebo, 10 completed
Duration of follow-up	3 years
Indirectness	None
Method of analysis	Not stated/unclear
Additional comments	No additional information.

9.2. Study arms

9.2.1. Glipizide (N = 10)

9.2.2. Placebo (N = 10)

9.3. Characteristics

9.3.1. Arm-level characteristics

Characteristic	Glipizide (N = 10)	Placebo (N = 10)
% Male Sample size	n = 7 ; % = 70	n = 3 ; % = 30

Characteristic	Glipizide (N = 10)	Placebo (N = 10)
Mean age (SD) (years) Mean (SD)	NR (NR)	NR (NR)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosis Mean (SD)	NR (NR)	NR (NR)
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR
Other antidiabetic medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Blood pressure-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Statins/lipid-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR

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10. Barzilai, 2011

Bibliographic Reference	Barzilai, N.; Guo, H.; Mahoney, E. M.; Caporossi, S.; Golm, G. T.; Langdon, R. B.; Williams-Herman, D.; Kaufman, K. D.; Amatruda, J. M.; Goldstein, B. J.; Steinberg, H.; Efficacy and tolerability of sitagliptin monotherapy in elderly patients with type 2 diabetes: a randomized, double-blind, placebo-controlled trial; Curr Med Res Opin; 2011; vol. 27 (no. 5); 1049-58

10.1. Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	NCT 00305604
Study type	Randomised controlled trial (RCT)
Study location	USA
Study setting	Community
Study dates	March 2006 - March 2008
Sources of funding	Sponsored by Merck & Co Inc.
Inclusion criteria	Community dwelling elderly adults (>65 years of age) Type 2 diabetes that was inadequately controlled by diet and exercise alone, or receiving AHA monotherapy or AHA combination therapy (HbA1c 7-10%, after washout if on medication)
Exclusion criteria	Received insulin or exenatide within 8 weeks People with type 1 diabetes, acute liver disease, recent change in cardiovascular status (such as acute coronary syndrome, coronary artery intervention, worsening congestive heart failure, a transient ischemic

	neurological event, a stroke, or worsening symptoms of coronary artery disease) Estimated creatinine clearance <35 mL/min
Recruitment / selection of participants	Method not reported
Intervention(s)	Participants randomised to the intervention received 50 mg sitagliptin tablets which were taken once daily. Participants with estimated creatinine clearance >50 mL/min received two tablets per day, totalling 100 mg sitagliptin per day. Participants with estimated creatinine clearance 35-50 mL/min received one tablet per day. Medication compliance was assessed by tablet counting at the end of the study
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear
Strata 2: People with atherosclerotic cardiovascular diseases	People without other cardiovascular diseases Exclusion criteria defined as a recent change to cardiovascular status
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	People at higher risk of developing cardiovascular disease
Subgroup 1: People with frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic	Not stated/unclear

fatty liver disease	
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Sensitivity analysis category: Enrichment trial status	7) Mixed population
Population subgroups	No additional information
Comparator	Participants randomised to the comparison group received identical placebo tablets which were taken once daily. Participants with estimated creatinine clearance >50 mL/min received two tablets per day and those with estimated creatinine clearance 35-50 mL/min received one tablet per day. Medication compliance was assessed by tablet counting at the end of the study.
Number of participants	206 randomised 102 received sitagliptin, 70 completed 104 received placebo, 57 completed
Duration of follow-up	24 weeks
Indirectness	None
Method of analysis	ITT
Additional comments	None

10.2. Study arms

10.2.1. Sitagliptin (N = 102)

Either one or two 50 mg sitagliptin tablets, equalling 50 (estimated creatinine clearance 35-50 mL/min) or 100 (estimated creatinine clearance >50 mL/min) mg per day

10.2.2. Placebo (N = 104)

Image-matched placebo administered with same regimen as intervention

10.3. Characteristics

10.3.1. Arm-level characteristics

Characteristic	Sitagliptin (N = 102)	Placebo (N = 104)
% Male Sample size	n = 54 ; % = 53	n = 55 ; % = 53
Mean age (SD) Mean (SD)	71.6 (6.1)	72.1 (6)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 76 ; % = 75	n = 86 ; % = 83
Black Sample size	n = 10 ; % = 10	n = 9 ; % = 9
Hispanic Sample size	n = 9 ; % = 9	n = 6 ; % = 6
Asian Sample size	n = 3 ; % = 3	n = 3 ; % = 3
Other Sample size	n = 4 ; % = 4	n = 0 ; % = 0
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosis (years) Mean (SD)	7.2 (7.3)	7 (7.5)
HbA1c (%) Mean (SD)	7.8 (0.8)	7.8 (0.7)

Characteristic	Sitagliptin (N = 102)	Placebo (N = 104)
Blood pressure Nominal	NR	NR
Heart rate Nominal	NR	NR
Smoking status Nominal	NR	NR
Alcohol consumption Nominal	NR	NR
Presence of severe mental illness Nominal	NR	NR
People with significant cognitive impairment Nominal	NR	NR
People with a learning disability Nominal	NR	NR
Weight (kg) Mean (SD)	85.6 (16.6)	85.8 (16.5)
BMI (kg/m²) Mean (SD)	30.8 (5.9)	31.1 (7.2)
Number of people with obesity Nominal	NR	NR
Cholesterol and lipid levels Nominal	NR	NR
Albumin creatinine ratio Nominal	NR	NR
eGFR (mL/min/1.73m2) Nominal	NR	NR
Other antidiabetic medication used Using an antihyperglycaemic agent at screening Sample size	n = 59 ; % = 58	n = 64 ; % = 62
Blood pressure-lowering medication used	NR	NR

Characteristic	Sitagliptin (N = 102)	Placebo (N = 104)
Nominal		
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

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11. Bi, 2013

Bibliographic Reference	Bi, Y.; Tong, G. Y.; Yang, H. J.; Cai, M. Y.; Ma, J. H.; Liang, J.; Xin, B.; Miao, H.; Peng, Z. H.; Zhu, D. L.; The beneficial effect of metformin on beta-cell function in non-obese Chinese subjects with newly diagnosed type 2 diabetes; Diabetes Metab Res Rev; 2013; vol. 29 (no. 8); 664-672

11.1. Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.
Trial name / registration number	ChiCTR-TRC10000941
Study type	Randomised controlled trial (RCT)
Study location	China.
Study setting	Outpatient follow up in five centres.
Study dates	1st July 2010 to 1st July 2011.
Sources of funding	Sponsored by grants from Pfizer Inc, the National Natural Science Foundation of China Grant Award (81270906, 81070636, 81000338), the China Postdoctoral Science Foundation (2012M521050), the Jiangsu Province's Key Discipline of Medicine (XK201105), Guangdong Natural Science Foundation (10151008901000033), Jiangsu Province's Key Provincial Talents Program (RC2011011) and the Key Project of Nanjing Medical Science and Technology Development Foundation (ZKX11017).
Inclusion criteria	Newly diagnosed people with type 2 diabetes (according to the World Health Organisation diagnostic criteria); age 25-75 years; fasting plasma glucose 7.0-13.0 mmol/L and body mass index (BMI) <30kg/m2.
Exclusion criteria	People receiving anti-diabetic treatment before the study; having acute or severe chronic diabetic complications; impaired renal function; positive for glutamic acid decarboxylase antibody.
Recruitment / selection of participants	No additional information.

Intervention(s)	Glipizide N=70 Glipizide GITS (gastrointestinal therapeutics systems) extended-release formulation for 24 weeks. The initial dose was 500mg daily, gradually titrated to a maximum of 15mg daily to achieve a fasting capillary plasma glucose level of less than 6.1 mmol/L. In the event of significant hypoglycaemia (<3.9 mmol/L), frequent nausea or vomiting, interventions were sequentially back titrated. Concomitant therapy: No changes in agents known to affect beta cell function and inflammatory cytokines (such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, statins, or NSAIDs) were allowed in the study.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear
Strata 2: People with atherosclerotic cardiovascular diseases	Not stated/unclear
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	People at higher risk of developing cardiovascular disease Based on higher lipid levels, age and history of diabetes
Subgroup 1: People with frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic	Not stated/unclear

fatty liver disease	
Subgroup 4: People with obesity	People who do not have obesity
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Sensitivity analysis category: Enrichment trial status	5) All treatment naïve
Population subgroups	Reports lean and overweight groups (people with a BMI <25 or people with a BMI 25-30).
Comparator	Metformin N=68 Metformin for 24 weeks. The initial dose was 500mg daily, gradually titrated to a maximum dose of 1500mg daily to achieve a fasting capillary plasma glucose level of less than 6.1 mmol/L. In the event of significant hypoglycaemia (<3.9 mmol/L), frequent nausea or vomiting, interventions were sequentially back titrated. Concomitant therapy: No changes in agents known to affect beta cell function and inflammatory cytokines (such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, statins, or NSAIDs) were allowed in the study.
Number of participants	160
Duration of follow-up	24 weeks.
Indirectness	No additional information.
Method of analysis	Per protocol Completers only
Additional comments	No additional information.

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11.2. Study arms

11.2.1. Glipizide (N = 80)

Glipizide GITS (gastrointestinal therapeutics systems) extended-release formulation for 24 weeks. The initial dose was 500mg daily, gradually titrated to a maximum of 15mg daily to achieve a fasting capillary plasma glucose level of less than 6.1 mmol/L. In the event of significant hypoglycaemia (<3.9 mmol/L), frequent nausea or vomiting, interventions were sequentially back titrated. Concomitant therapy: No changes in agents known to affect beta cell function and inflammatory cytokines (such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, statins, or NSAIDs) were allowed in the study.

11.2.2. Metformin (N = 80)

Metformin for 24 weeks. The initial dose was 500mg daily, gradually titrated to a maximum dose of 1500mg daily to achieve a fasting capillary plasma glucose level of less than 6.1 mmol/L. In the event of significant hypoglycaemia (<3.9 mmol/L), frequent nausea or vomiting, interventions were sequentially back titrated. Concomitant therapy: No changes in agents known to affect beta cell function and inflammatory cytokines (such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, statins, or NSAIDs) were allowed in the study.

11.3. Characteristics

11.3.1. Arm-level characteristics

Characteristic	Glipizide (N = 80)	Metformin (N = 80)
% Male Sample size	n = NR ; % = NR	n = NR ; % = NR
Mean age (SD) (years) Mean (SE)	54.5 (1.2)	55.6 (1.2)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosis Mean (SD)	NR (NR)	NR (NR)

Characteristic	Glipizide (N = 80)	Metformin (N = 80)
HbA1c Mean (SE)	8.1 (0.2)	8 (0.2)
Blood pressure Mean (SD)	NA (NA)	NA (NA)
Heart rate Mean (SD)	NA (NA)	NA (NA)
Smoking status Mean (SD)	NA (NA)	NA (NA)
Alcohol consumption Sample size	n = NA ; % = NA	n = NA ; % = NA
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR
Weight (kg) Mean (SE)	67.2 (1.2)	68.6 (1.2)
BMI (kg/m2) Mean (SE)	24.6 (0.3)	25.2 (0.3)
Number of people with obesity Sample size	n = NA ; % = NA	n = NA ; % = NA
Cholesterol and lipid levels (mmol/L) Mean (SE)	NA (NA)	NA (NA)
Triglycerides Mean (SE)	2.2 (0.2)	2 (0.2)
Total cholesterol Mean (SE)	5.2 (0.1)	5.2 (0.1)
LDL cholesterol Mean (SE)	2.9 (0.1)	3 (0.1)

Characteristic	Glipizide (N = 80)	Metformin (N = 80)
Albumin creatinine ratio Mean (SD)	NA (NA)	NA (NA)
eGFR (mL/min/1.73m2) Mean (SD)	NA (NA)	NA (NA)
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Blood pressure-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Statins/lipid-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Other treatment being received Sample size	n = NA ; % = NA	n = NA ; % = NA

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12. Birkeland, 1994

Bibliographic Reference	Birkeland, K I; Furuseth, K; Melander, A; Mowinckel, P; Vaaler, S; Long-term randomized placebo-controlled double-blind therapeutic comparison of glipizide and glyburide. Glycemic control and insulin secretion during 15 months.; Diabetes care; 1994; vol. 17 (no. 1); 45-9

12.1. Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	Norway
Study setting	No additional information
Study dates	No additional information
Sources of funding	Supported by Farmitalia Carlo Erba
Inclusion criteria	Non-insulin dependent diabetes mellitus HbA1c 7-11% C-peptide concentration 6 minutes after intravenous injection of 1 mg glucagon >0.7 nM
Exclusion criteria	Severe intercurrent illness Signs of chronic cardiac, hepatic, pulmonary or renal disease
Recruitment / selection of participants	No additional information
Intervention(s)	Following a 3-6 month run-in during which participants were given dietary advice and taught self-monitoring of glucose, those randomised to the intervention received 2.5 mg glipizide per day. Treatment started with one

	tablet (2.5 mg) per morning, and was adjusted weekly by adding one tablet per time to achieve fasting glucose <8.0 mM and HbA1c <7.5% without hypoglycaemia. The maximum dose allowed was 6 tablets per day, with a limit of 4 before breakfast and 2 with dinner. *Additional study arm containing 1.75 mg glyburide not included in this review due to not being a protocol-listed intervention*
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure
Strata 2: People with atherosclerotic cardiovascular diseases	People without other cardiovascular diseases
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Mixed population
Subgroup 1: People with frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear

Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Sensitivity analysis category: Enrichment trial status	5) All treatment naïve
Population subgroups	No additional information
Comparator	Following a 3-6 month run-in during which participants were given dietary advice and taught self-monitoring of glucose, those randomised to the comparator received once-daily placebo.
Number of participants	31 randomised 15 received glipizide 16 received placebo
Duration of follow-up	15 months
Indirectness	None
Method of analysis	Per protocol
Additional comments	None

12.2. Study arms

12.2.1. Glipizide (N = 15)

2.5 mg glipizide per day, titrated up to a maximum of 15 mg per day

12.2.2. Placebo (N = 16)

Image-matched placebo

12.3. Characteristics

12.3.1. Study-level characteristics

Characteristic	Study (N = 46)
% Male Sample size	n = 22 ; % = 48
Mean age (SD) (years) Mean (SD)	59 (7)
Ethnicity Nominal	NR
Comorbidities Nominal	NR
Presence of frailty Nominal	NR
Time since type 2 diabetes diagnosis (years) Mean (SD)	3.5 (3.1)
HbA1c Nominal	NR
Blood pressure Nominal	NR
Heart rate Nominal	NR
Smoking status Nominal	NR
Alcohol consumption Nominal	NR
Presence of severe mental illness Nominal	NR
People with significant cognitive impairment Nominal	NR
People with a learning disability	NR

Characteristic	Study (N = 46)
Nominal	
Weight Nominal	NR
BMI (kg/m²) Mean (SD)	26.4 (3.9)
Number of people with obesity Nominal	NR
Cholesterol and lipid levels Nominal	NR
Albumin creatinine ratio Nominal	NR
eGFR (mL/min/1.73m2) Nominal	NR
Other antidiabetic medication used Nominal	NR
Blood pressure-lowering medication used Nominal	NR
Statins/lipid-lowering medication used Nominal	NR
Other treatment being received Nominal	NR

Characteristics reported narratively - includes participants allocated to glyburide that are not included in this review

13. Bosi, 2009

Bibliographic Reference	Bosi, E.; Dotta, F.; Jia, Y.; Goodman, M.; Vildagliptin plus metformin combination therapy provides superior glycaemic control to individual monotherapy in treatment-naive patients with type 2 diabetes mellitus; Diabetes Obes Metab; 2009; vol. 11 (no. 5); 506-15

13.1. Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.
Trial name / registration number	NCT00382096 and NCT00468039 (NCT00468039 refers to a substudy within the trial where people who did not achieve the inclusion criteria could enter an open label single arm trial that is not included in this data extraction)
Study type	Randomised controlled trial (RCT)
Study location	250 centres in the USA, Canada, Europe, South America and India
Study setting	Outpatient follow up
Study dates	No additional information.
Sources of funding	Supported by Novartis Pharmaceutical Corporation.
Inclusion criteria	Diagnosed with type 2 diabetes mellitus for at least 4 weeks; people (including women who were non-fertile, or using a medically approved birth control method); treatment-naïve people aged 18-78 years with a body mass index of 22-40 kg/m2; FPG <15 mmol/L (270 mg/dL) and HbA1c 7.5-11%. Treatment naïve was defined as people who had never received an antidiabetic agent or had not taken any antidiabetic agent for at least 12 weeks before screening and for no longer than 3 months at any time.
Exclusion criteria	Pregnant or lactating people; patients with a history of type 1 diabetes; diabetes or acute metabolic diabetic complications within the past 6 months; 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 pharmacological 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 other investigational drugs within 30 days of visit 1; alanine aminotransferase or aspartate aminotransferase >2 times the upper limit of the normal range; total bilirubin >2 times upper limit of normal or direct bilirubin greater than the upper limit of normal; clinically significant renal dysfunction or any other clinically significant laboratory abnormalities.
Recruitment / selection of participants	No additional information.
Intervention(s)	Vildagliptin and metformin (combination) N=585 Combination of two arms: Vildagliptin plus high-dose metformin (50mg + 1000mg twice daily) (n=295) and vildagliptin plus low-dose metformin (50mg + 500mg twice daily) (n=290). Metformin was initiated at 500mg once daily and then increased in 500mg increments at weeks 2, 4 and 6. Concomitant therapy: No additional information. Vildagliptin N=300 Vildagliptin monotherapy (50mg twice daily). Concomitant therapy: No additional information.
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure
Strata 2: People with atherosclerotic cardiovascular diseases	Not stated/unclear
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear
Strata 4: People with type 2 diabetes	Not stated/unclear Likely high based on mean BMI, but ranges provided make it unclear

mellitus and high cardiovascular risk	
Subgroup 1: People with frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Mixed population Based on age ranges provided
Subgroup 3: People with non-alcoholic fatty liver disease	People without non-alcoholic fatty liver disease
Subgroup 4: People with obesity	Mixed population
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Sensitivity analysis category: Enrichment trial status	6) No response criteria
Population subgroups	No additional information.
Comparator	Metformin N=294 Metformin monotherapy (1000mg twice daily). Metformin was initiated at 500mg once daily and then increased in 500mg increments at weeks 2, 4 and 6. Concomitant therapy: No additional information.
Number of participants	1179
Duration of follow-up	24 weeks
Indirectness	No additional information.

Method of analysis	ITT
Additional comments	No additional information.

13.2. Study arms

13.2.1. Vildagliptin + metformin (combination) (N = 585)

Combination of two arms: Vildagliptin plus high-dose metformin (50mg + 1000mg twice daily) (n=295) and vildagliptin plus low-dose metformin (50mg + 500mg twice daily) (n=290). Metformin was initiated at 500mg once daily and then increased in 500mg increments at weeks 2, 4 and 6. Concomitant therapy: No additional information.

13.2.2. Vildagliptin (N = 300)

Vildagliptin monotherapy (50mg twice daily). Concomitant therapy: No additional information.

13.2.3. Metformin (N = 294)

Metformin monotherapy (1000mg twice daily). Metformin was initiated at 500mg once daily and then increased in 500mg increments at weeks 2, 4 and 6. Concomitant therapy: No additional information.

13.3. Characteristics

13.3.1. Arm-level characteristics

Characteristic	Vildagliptin + metformin (combination) (N = 585)	Vildagliptin (N = 300)	Metformin (N = 294)
% Male Sample size	n = 333 ; % = 57	n = 180 ; % = 60	n = 171 ; % = 58.2
Mean age (SD) (years) Mean (SD)	52.7 (10.5)	53.5 (11)	52.4 (10.7)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Caucasian Sample size	n = 430 ; % = 74	n = 225 ; % = 75	n = 212 ; % = 72.1

Characteristic	Vildagliptin + metformin (combination) (N = 585)	Vildagliptin (N = 300)	Metformin (N = 294)
Black Sample size	n = 26 ; % = 4	n = 8 ; % = 2.7	n = 14 ; % = 4.8
Asian Sample size	n = 62 ; % = 11	n = 30 ; % = 10	n = 30 ; % = 10.2
Hispanic or Latino Sample size	n = 55 ; % = 9	n = 31 ; % = 10.3	n = 27 ; % = 9.2
Others Sample size	n = 12 ; % = 2	n = 6 ; % = 2	n = 11 ; % = 3.7
Comorbidities Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Presence of frailty Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Time since type 2 diabetes diagnosis (Months) Mean (SD)	22.78 (33.67)	25.48 (39.82)	26.26 (39.92)
HbA1c (%) Mean (SD)	8.64 (1.02)	8.68 (1.02)	8.62 (0.93)
Blood pressure Mean (SD)	NA (NA)	NA (NA)	NA (NA)
Heart rate Mean (SD)	NA (NA)	NA (NA)	NA (NA)
Smoking status Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Alcohol consumption Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Presence of severe mental illness Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
People with significant cognitive impairment	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Vildagliptin + metformin (combination) (N = 585)	Vildagliptin (N = 300)	Metformin (N = 294)
Sample size			
People with a learning disability Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Weight (kg) Mean (SD)	88.37 (17.74)	87.84 (17.93)	88.43 (17.39)
BMI (kg/m2) Mean (SD)	31.22 (4.83)	31.26 (4.82)	31.31 (4.58)
Number of people with obesity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Cholesterol and lipid levels Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Albumin creatinine ratio Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
eGFR (mL/min/1.73m2) Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Blood pressure-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Statins/lipid-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Other treatment being received Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA

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14. Camerini-Davalos, 1988

Bibliographic Reference	Camerini-Davalos, R A; Velasco, C A; Glasser, M; Bloodworth, J M Jr; Sulfonylurea-induced decrease of muscle capillary basement membrane thickness in diabetes.; Diabetes research and clinical practice; 1988; vol. 5 (no. 2); 113-23

14.1. Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	USA
Study setting	No additional information
Study dates	No additional information
Sources of funding	Supported by Pfizer, the Diabetes Research Fund and the Veterans Administration Research Fund
Inclusion criteria	Met the National Diabetes Data Group criteria for diagnosis of type 2 diabetes At least 3 consecutive fasting glucose measurements about 140 mg White ethnicity 21-55 years of age BMI ≤25 for women and ≤27 for men Untreated, or treated with diet alone - if receiving oral hypoglycaemic compound, medication was discontinued 3 months prior to enrolment

	No vascular or neurological diabetic complications No renal, hepatic or thyroid disease
Exclusion criteria	Females with child-bearing potential, who were pregnant or known to use unreliable methods of contraception Requiring long-term therapy with drugs that affect glucose metabolism or sulfonylurea kinetics Any abnormal laboratory or clinical finding
Recruitment / selection of participants	Recruited from the Metropolitan Hospital Center Diabetes Clinic
Intervention(s)	Participants allocated to the intervention received 20-40 mg glipizide per day
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear
Strata 2: People with atherosclerotic cardiovascular diseases	Not stated/unclear
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Mixed population
Subgroup 1: People with frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear

Subgroup 3: People with non-alcoholic fatty liver disease	People without non-alcoholic fatty liver disease
Subgroup 4: People with obesity	People who do not have obesity
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Sensitivity analysis category: Enrichment trial status	5) All treatment naïve
Population subgroups	No additional information
Comparator	Participants allocated to the comparator received placebo, taken twice per day
Number of participants	77 randomised 46 received glipizide, 35 completed 31 received placebo, 18 completed
Duration of follow-up	24 months
Indirectness	None
Method of analysis	Per protocol
Additional comments	None

14.2. Study arms

14.2.1. Glipizide (N = 35)

20-40 mg glipizide per day

14.2.2. Placebo (N = 18)

14.3. Characteristics

14.3.1. Arm-level characteristics

Characteristic	Glipizide (N = 35)	Placebo (N = 18)
% Male Sample size	n = 15 ; % = 41	n = 6 ; % = 36
Mean age (SD) (years) Nominal	47.9	46.5
Mean age (SD) (years) Range	31 to 55	21 to 55
Ethnicity White Sample size	n = 35 ; % = 100	n = 18 ; % = 100
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosis (years) Nominal	4.8	6.1
Time since type 2 diabetes diagnosis (years) Range	1 to 19	1 to 20
HbA1c (%) Nominal	12.8	12.4
Blood pressure Nominal	NR	NR
Heart rate Nominal	NR	NR
Smoking status Nominal	NR	NR
Alcohol consumption Nominal	NR	NR

Characteristic	Glipizide (N = 35)	Placebo (N = 18)
Presence of severe mental illness Nominal	NR	NR
People with significant cognitive impairment Nominal	NR	NR
People with a learning disability Nominal	NR	NR
Weight Nominal	NR	NR
BMI (kg/m²) Nominal	25.5	24.9
Number of people with obesity Nominal	NR	NR
Cholesterol and lipid levels Nominal	NR	NR
Albumin creatinine ratio Nominal	NR	NR
eGFR (mL/min/1.73m2) Nominal	NR	NR
Other antidiabetic medication used Sample size	n = 4 ; % = 11	n = 3 ; % = 17
Blood pressure-lowering medication used Nominal	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

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15. Campbell, 1994

Bibliographic Reference	Campbell, I. W.; Menzies, D. G.; Chalmers, J.; McBain, A. M.; Brown, I. R.; One year comparative trial of metformin and glipizide in type 2 diabetes mellitus; Diabete Metab; 1994; vol. 20 (no. 4); 394-400

15.1. Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.
Trial name / registration number	No additional information.
Study type	Randomised controlled trial (RCT)
Study location	United Kingdom.
Study setting	Outpatient follow-up.
Study dates	No additional information.
Sources of funding	No additional information.
Inclusion criteria	People with diabetes; aged 40-69 years; uncontrolled by diet; fasting plasma glucose >8mmol/L reported on two occasions two weeks apart.
Exclusion criteria	Ketosis; evidence of cardiac failure; abnormal urea or electrolytes, creatinine and liver function tests; drinking alcohol in excess or taking steroids, salicylates, warfarin or monoaminoxidase inhibitors.
Recruitment / selection of participants	No additional information.
Intervention(s)	Glipizide N=24 Glipizide 5mg once a day increased in increments of 5mg to a maximum daily dose of 30mg if the fasting plasma glucose was >8mmol/L.

	Concomitant therapy: If the fasting glucose became 4mmol/L or less, the dose of either drug was reduced by a single increment.
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure
Strata 2: People with atherosclerotic cardiovascular diseases	Not stated/unclear
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	People at higher risk of developing cardiovascular disease Based on triglycerides, HbA1c, age and presence of diabetes.
Subgroup 1: People with frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	People with obesity "Most people were obese"
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear

Sensitivity analysis category: Enrichment trial status	8) Not reported
Population subgroups	No additional information.
Comparator	Metformin N=24 Metformin 500mg twice daily increased in increments of 500mg at each visit to a maximum of 300mg, if the fasting plasma glucose remained >8mmol/L. Concomitant therapy: If the fasting glucose became 4mmol/L or less, the dose of either drug was reduced by a single increment.
Number of participants	48
Duration of follow-up	1 year.
Indirectness	No additional information.
Method of analysis	Not stated/unclear
Additional comments	No additional information.

15.2. Study arms

15.2.1. Glipizide (N = 24)

Glipizide 5mg once a day increased in increments of 5mg to a maximum daily dose of 30mg if the fasting plasma glucose was >8mmol/L. Concomitant therapy: If the fasting glucose became 4mmol/L or less, the dose of either drug was reduced by a single increment.

15.2.2. Metformin (N = 24)

Metformin 500mg twice daily increased in increments of 500mg at each visit to a maximum of 300mg, if the fasting plasma glucose remained >8mmol/L. Concomitant therapy: If the fasting glucose became 4mmol/L or less, the dose of either drug was reduced by a single increment.

15.3. Characteristics

15.3.1. Arm-level characteristics

Characteristic	Glipizide (N = 24)	Metformin (N = 24)
% Male Sample size	n = 8 ; % = 33	n = 8 ; % = 33
Mean age (SD) (years) Mean (SD)	57 (9)	57 (10)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosis (years) Sample size	n = 2.8 ; % = 3.9	n = 2.3 ; % = 3.4
HbA1c (%) Mean (SD)	11.8 (2.11)	11.5 (1.9)
Blood pressure Mean (SD)	NR (NR)	NR (NR)
Heart rate Mean (SD)	NR (NR)	NR (NR)
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Glipizide (N = 24)	Metformin (N = 24)
Sample size		
Weight (kg) Mean (SD)	82.2 (16.8)	78.2 (15.7)
BMI (kg/m2) Mean (SD)	31.2 (6.6)	29.6 (5.6)
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR
Cholesterol and lipid levels Mean (SD)	NA (NA)	NA (NA)
Cholesterol (total) Mean (SD)	6.39 (1.39)	6.52 (1.27)
HDL cholesterol Mean (SD)	0.93 (0.22)	0.92 (0.29)
Triglycerides Mean (SD)	2.06 (0.69)	2.15 (1.47)
Albumin creatinine ratio Mean (SD)	NR (NR)	NR (NR)
eGFR (mL/min/1.73m2) Mean (SD)	NR (NR)	NR (NR)
Other antidiabetic medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Blood pressure-lowering medication used Sample size	n = 4 ; % = 17	n = 3 ; % = 13
Statins/lipid-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR
Diuretics Sample size	n = 4 ; % = 17	n = 3 ; % = 13

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16. Chakraborty, 2011

Bibliographic Reference	Chakraborty, A.; Chowdhury, S.; Bhattacharyya, M.; Effect of metformin on oxidative stress, nitrosative stress and inflammatory biomarkers in type 2 diabetes patients; Diabetes Res Clin Pract; 2011; vol. 93 (no. 1); 56-62

16.1. Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.
Trial name / registration number	No additional information.
Study type	Randomised controlled trial (RCT)
Study location	India.
Study setting	Outpatient follow up, people in the IPGMER/SSKM hospital, Kolkata, India.
Study dates	No additional information.
Sources of funding	Funding from the UGC-RFSMS programme for a fellowship for the first author and RSSDI for financial support. Instruments and funding provided by UGC-CAS (Phase-I) and DST-FIST.
Inclusion criteria	30-55 year old; BMI 23-29 kg/m2; HbA1c >7%; type 2 diabetes for at least 1 year but no longer than 6 years; able to carry out self-monitoring of blood glucose concentration; people who have been treated with hypoglycaemic agents, had been free from therapeutic drugs for at least 2 weeks before screening.
Exclusion criteria	Noticeable abnormal renal function (serum creatinine >125 micromol/L); smoking; previous history of severe cardiomyopathy; taking vitamin capsules and calcium supplements.
Recruitment / selection of participants	No additional information.
Intervention(s)	Metformin N=110

	Metformin 850mg-2000mg per day. Medications were taken once daily during the first week and twice daily during the second week. Amendment of medications was performed if the mean daily glucose level was greater than 130 mg/dL and the HbA1C was greater than 7.5%. The maximum allowable daily doses of metformin was 2000mg. Concomitant therapy: Lifestyle was not changed during the study.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear
Strata 2: People with atherosclerotic cardiovascular diseases	Not stated/unclear
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	People at higher risk of developing cardiovascular disease Based on triglycerides and BMI
Subgroup 1: People with frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear

Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Sensitivity analysis category: Enrichment trial status	6) No response criteria
Population subgroups	No additional information.
Comparator	Placebo N=98 Matching placebo. Concomitant therapy: Lifestyle was not changed during the study.
Number of participants	208
Duration of follow-up	24 weeks
Indirectness	No additional information.
Method of analysis	Not stated/unclear Appears to be no dropouts, but not clearly reported
Additional comments	No additional information.

16.2. Study arms

16.2.1. Metformin (N = 110)

Metformin 850mg-2000mg per day. Medications were taken once daily during the first week and twice daily during the second week. Amendment of medications was performed if the mean daily glucose level was greater than 130 mg/dL and the HbA1C was greater than 7.5%. The maximum allowable daily doses of metformin was 2000mg. Concomitant therapy: Lifestyle was not changed during the study.

16.2.2. Placebo (N = 98)

Matching placebo. Concomitant therapy: Lifestyle was not changed during the study.

16.3. Characteristics

16.3.1. Arm-level characteristics

Characteristic	Metformin (N = 110)	Placebo (N = 98)
% Male Sample size	n = NR ; % = NR	n = NR ; % = NR
Mean age (SD) (years) Mean (SD)	NR (NR)	NR (NR)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosis Mean (SD)	NR (NR)	NR (NR)
HbA1c (%) Mean (SD)	8.7 (1.4)	8.7 (1.5)
Blood pressure (mmHg) Mean (SD)	NA (NA)	NA (NA)
Systolic blood pressure Mean (SD)	140 (5.9)	141 (5.1)
Diastolic blood pressure Mean (SD)	89 (2.6)	89 (2.1)
Heart rate Mean (SD)	NR (NR)	NR (NR)
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Metformin (N = 110)	Placebo (N = 98)
Sample size		
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR
Weight Mean (SD)	NR (NR)	NR (NR)
BMI (kg/m2) Mean (SD)	27 (2.4)	27 (1.3)
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR
Cholesterol and lipid levels (mg/dL) Mean (SD)	NR (NR)	NR (NR)
Total cholesterol Mean (SD)	202 (29.49)	203 (29.5)
HDL Mean (SD)	39 (5.33)	38 (5.3)
LDL Mean (SD)	124 (13)	124 (13.4)
Triglycerides Mean (SD)	210 (20.85)	211 (20.87)
Albumin creatinine ratio Mean (SD)	NR (NR)	NR (NR)
eGFR (mL/min/1.73m2) Mean (SD)	NR (NR)	NR (NR)
Other antidiabetic medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Blood pressure-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Metformin (N = 110)	Placebo (N = 98)
Statins/lipid-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR

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17. Charbonnel, 2005

Bibliographic Reference	Charbonnel, B H; Matthews, D R; Schernthaner, G; Hanefeld, M; Brunetti, P; A long-term comparison of pioglitazone and gliclazide in patients with Type 2 diabetes mellitus: a randomized, double-blind, parallel-group comparison trial.; Diabetic medicine : a journal of the British Diabetic Association; 2005; vol. 22 (no. 4); 399-405

17.1. Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.
Trial name / registration number	No additional information.
Study type	Randomised controlled trial (RCT)
Study location	Multicentre trial including 209 centres in 14 European countries, Australia, Canada, South Africa and Israel.
Study setting	Outpatient follow-up.
Study dates	No additional information.
Sources of funding	Funded by Takeda Euro R&D and Eli Lilly, Indianapolis, IN, USA.
Inclusion criteria	People aged 35-75 years; types 2 diabetes inadequately treated with diet alone; HbA1c between 7.5% and 11%; stable or worsening glycaemic control over a period of at least 3 months.
Exclusion criteria	Previous use of glucose-lowering pharmacotherapy at any time; specific contraindications to either drug; long-term treatment with corticosteroids and the start of beta-blockers during the study or within 4 weeks prior to screening (if anti-hypertensive treatment was indicated during the study, people were started with ACE inhibitors or calcium antagonists, which have a minimal effect on glucose homeostasis).
Recruitment / selection of participants	No additional information.

Intervention(s)	Pioglitazone N=635 Pioglitazone up to 45 mg once daily with matching placebo. Number of participants assumed as not explicitly stated.
Cointervention	Concomitant therapy: Dietary advice was given at baseline. Further intensive dietary advice was given if body weight increased by more than 5% or HbA1c increased to greater than 9% during dose titration.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear
Strata 2: People with atherosclerotic cardiovascular diseases	Not stated/unclear
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear

Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Sensitivity analysis category: Enrichment trial status	5) All treatment naïve
Population subgroups	No additional information.
Comparator	Gliclazide N=635 Gliclazide up to 160mg twice daily with matching placebo. Number of participants assumed as not explicitly stated.
Number of participants	1270
Duration of follow-up	52 weeks.
Indirectness	No additional information.
Method of analysis	Not stated/unclear
Additional comments	No additional information.

17.2. Study arms

17.2.1. Pioglitazone (N = 635)

Pioglitazone up to 45 mg once daily with matching placebo. Number of participants assumed as not explicitly stated. Concomitant therapy: Dietary advice was given at baseline. Further intensive dietary advice was given if body weight increased by more than 5% or HbA1c increased to greater than 9% during dose titration.

17.2.2. Gliclazide (N = 635)

Gliclazide up to 160mg twice daily with matching placebo. Number of participants assumed as not explicitly stated. Concomitant therapy: Dietary advice was given at baseline. Further intensive dietary advice was given if body weight increased by more than 5% or HbA1c increased to greater than 9% during dose titration.

17.3. Characteristics

17.3.1. Arm-level characteristics

Characteristic	Pioglitazone (N = 635)	Gliclazide (N = 635)
% Male Sample size	n = NR ; % = NR	n = NR ; % = NR
Mean age (SD) Mean (SD)	NR (NR)	NR (NR)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosis Mean (SD)	NR (NR)	NR (NR)

18. Chen, 2023

Bibliographic Reference	Chen, Xiaoping; Jiang, Hongwei; Li, Hongmei; Kuang, Hongyu; Chen, Li; Ma, Jianhua; Zhang, Qiu; Pan, Tianrong; Yang, Wenying; Saxagliptin combined with additional oral antihyperglycaemic agents in drug-naive diabetic patients with high glycosylated haemoglobin: A 24-week, multicentre, randomized, open-label, active parallel-controlled group clinical trial in China (SUCCESS).; Diabetes, obesity & metabolism; 2023; vol. 25 (no. 1); 272-281

18.1. Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.
Trial name / registration number	ChiCTR-IPR-14005716
Study type	Randomised controlled trial (RCT)
Study location	China.
Study setting	Outpatient follow-up.
Study dates	30 December 2014 to 1 November 2017.
Sources of funding	AstraZeneca.
Inclusion criteria	Drug-naive Chinese people with type 2 diabetes mellitus aged between 18 and 80 years, with a body mass index of 19-40 kg/m2; HbA1c 8.0-11.0% (local laboratory testing).
Exclusion criteria	Fasting triglycerides >4.5mmol/L when screening; severe hepatic and renal dysfunction; congestive heart failure NYHA classes III-IV; major cardiovascular events within 6 months before screening; women who are pregnant, intending to become pregnant during the study period, currently lactating females, or women of child-bearing potential not using highly effective, medically approved birth control methods; diagnosis of history of: type 1 diabetes mellitus, diabetes resulting from pancreatic injury or secondary forms of diabetes, acute metabolic diabetic complications such as ketoacidosis or diabetic nonketotic hyperosmolar coma within the past 6 months; previous treatment with any DPP-4 inhibitor or GLP-1 receptor

	agonist; history of hypersensitivity reaction to DPP-4 inhibitors, acarbose, gliclazide MR or metformin; current using weight loss drugs within 3 months at screening; treatment with systemic glucocorticoids for more than 7 consecutive days within the past 6 months; treatment with strong cytochrome P450 3A4/5 inhibitors; history of chronic pancreatitis or idiopathic acute pancreatitis; history of gastrointestinal disease; history of genetic galactose intolerance, lapp lactase deficiency and glucose-galactose malabsorption; history of medullary thyroid carcinoma; diagnosed and/or treated malignancy within the past 5 years; history of organ transplant or AIDS; history of alcohol abuse or illegal drug abuse within the past 12 months; potentially unreliable patients and those judged by the investigator to be unsuitable for the study; clinically significant haematologic, renal disease; family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2; uncontrolled hypertension (SBP >159 mmHg and/or DBP >99mmHg); history of laser treatment for proliferative retinopathy within 6 months; any symptoms and signs which indicate endocrinology disorders; stress condition; chronic oxygen deficiency diseases; participation in any drug clinical trials during the past 3 months before enrolment; mental disorders.
Recruitment / selection of participants	No additional information.
Intervention(s)	Saxagliptin + Gliclazide N=216 Saxagliptin 5mg/day for 24 weeks and Gliclazide modified release increased during weeks 1-4 from 30mg, to 60mg, to 90mg to 120mg all once a day, then 120mg once a day for the remaining 20 weeks.
Cointervention	Concomitant therapy: No additional information.
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure
Strata 2: People with atherosclerotic cardiovascular diseases	People without other cardiovascular diseases
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear
Strata 4: People with type 2 diabetes mellitus and	Not stated/unclear

high cardiovascular risk	
Subgroup 1: People with frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	People without non-alcoholic fatty liver disease
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Sensitivity analysis category: Enrichment trial status	5) All treatment naïve
Comparator	Saxagliptin + Metformin N=216 Saxagliptin 5mg/day for 24 weeks and Metformin increased during weeks 1-2 from 500mg twice daily to 500mg three times daily, then 1000mg twice daily for the remaining 21 weeks. A third arm received saxagliptin + acarbose (n=216). This arm is not extracted as acarbose is rarely used in the United Kingdom and so is not used in the analysis.
Number of participants	432
Duration of follow-up	24 weeks.
Indirectness	No additional information.
Method of analysis	Per protocol ITT

Additional comments	No additional information.

18.2. Study arms

18.2.1. Saxagliptin + Gliclazide (N = 216)

Saxagliptin 5mg/day for 24 weeks and Gliclazide modified release increased during weeks 1-4 from 30mg, to 60mg, to 90mg to 120mg all once a day, then 120mg once a day for the remaining 20 weeks. Concomitant therapy: No additional information.

18.2.2. Saxagliptin + Metformin (N = 216)

Saxagliptin 5mg/day for 24 weeks and Metformin increased during weeks 1-2 from 500mg twice daily to 500mg three times daily, then 1000mg twice daily for the remaining 21 weeks. Concomitant therapy: No additional information.

18.3. Characteristics

18.3.1. Arm-level characteristics

Characteristic	Saxagliptin + Gliclazide (N = 216)	Saxagliptin + Metformin (N = 216)
% Male Sample size	n = 150 ; % = 69.4	n = 150 ; % = 69.4
Mean age (SD) (years) Mean (SD)	51 (11.5)	50.4 (10.9)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosis (Months) Mean (SD)	10.9 (28.2)	11.8 (28.2)
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Saxagliptin + Gliclazide (N = 216)	Saxagliptin + Metformin (N = 216)
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR
Other antidiabetic medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Blood pressure-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Statins/lipid-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR

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19. Chen, 2018

Bibliographic Reference	Chen, Y. H.; Huang, C. N.; Cho, Y. M.; Li, P.; Gu, L.; Wang, F.; Yang, J.; Wang, W. Q.; Efficacy and safety of dulaglutide monotherapy compared with glimepiride in East-Asian patients with type 2 diabetes in a multicentre, double-blind, randomized, parallel-arm, active comparator, phase III trial; Diabetes Obes Metab; 2018; vol. 20 (no. 9); 2121-2130

19.1. Study details

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	None
Trial name / registration number	NCT01644500
Study type	Randomised controlled trial (RCT) Double blind, double-dummy, non-inferiority phase III trial
Study location	International (48 centres in China, South Korea and Taiwan)
Study setting	Community
Study dates	07/2012 to 08/2014
Sources of funding	Funded by Eli Lilly & Co.
Inclusion criteria	• Aged ≥18 years (≥20 years in Taiwan) • Adult men or adult non-pregnant, non-breastfeeding women • Diagnosis of type 2 diabetes mellitus • Naive to oral antihyperglycaemic medication (OAM-naïve) or on OAM monotherapy ≥3 months • HbA1c level 7.0-10.5% inclusive for OAM-naïve participants or 6.5-10.0% inclusive for those on OAM monotherapy, at screening • Stable weight (±5%) ≥3 months prior to screening • BMI≥19.0 to ≤35.0 kg/m2
Exclusion criteria	• Diagnosis of type 1 diabetes mellitus • Previous treatment with GLP-1RA, GLP-1 analogue, or any other incretin mimetic≤3 months before screening

	• Current treatment with DPP-4 inhibitor and thiazolidinediones≤3 months before screening • Gastric emptying abnormality • Cardiac disorder defined as unstable angina, myocardial infarction, coronary artery bypass graft surgery, percutaneous coronary intervention, heart failure, arrhythmia, transient ischemic attack, or stroke • Poorly controlled hypertension (systolic blood pressure>160 mmHg or diastolic blood pressure>95 mmHg) • Impaired liver function • Impaired kidney function • History of chronic pancreatitis or acute pancreatitis • Serum calcitonin ≥20 pg/mL • Personal or family history of medullary C-cell hyperplasia, focal hyperplasia, carcinoma or multiple endocrine neoplasia type 2
Recruitment / selection of participants	Participants recruited from 48 centres in China, South Korea and Taiwan. Initial 2-week screening period, 2-wk washout/lead-in period (discontinuation of previous oral antihyperglycaemic medication [OAM]), 26-wk treatment period and 30-day safety follow up. Random assignment 1:1:1 to one of 3 arms by computer-generated random sequence using interactive voice response system, stratified by country, baseline HbA1c (<8.5%, ≥8.5%) and pretrial oral antihyperglycaemic medication. Participants taught injection techniques/glucose monitoring before randomisation. Trained caregiver could assist participants in administering study drug injections,
Intervention(s)	• Dulaglutide 1.5 mg once weekly • Dulaglutide 0.75 mg once weekly Participants received subcutaneous injections of dulaglutide once weekly, either 1.5 mg or 0.75 mg. Participants, investigators, and trial staff masked to treatment assignment. Participants in these groups also received oral placebo capsules once daily.
Cointervention	Both arms received placebo (oral capsules for dulaglutide arm and subcutaneous injection for glimepiride arm).
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear
Strata 2: People with atherosclerotic cardiovascular diseases	People without other cardiovascular diseases Exclusion criteria: Cardiac disorder defined as unstable angina, myocardial infarction, coronary artery bypass graft surgery, percutaneous coronary intervention, heart failure, arrhythmia, transient ischemic attack, or stroke
Strata 3: People with type 2 diabetes mellitus and	Not stated/unclear

chronic kidney disease	
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Sensitivity analysis category: Enrichment trial status	7) Mixed population Includes participants naive to oral anti-hyperglycaemic medication with HbA1c 7-10.5% inclusive, and those who had been on oral anti-hyperglycaemic medication for at least 3 months before screening with HbA1c 6.5-10% inclusive
Comparator	• Glimepiride 1-3 mg once weekly Participants received oral glimepiride capsules once daily, starting with one capsule of 1 mg/day at randomisation, subsequently increased if no tolerability/safety issues to 2 x 1 mg capsules/day at week 4 and 3 x 1 mg capsule at week 8 and maintained if tolerated. Participants, investigators, and trial staff masked to treatment assignment. Participants in this group received single placebo subcutaneous injection each week.
Number of participants	N=737

Duration of follow-up	26 weeks
Method of analysis	Modified ITT Efficacy analysis on all randomised participants who received ≥1 study drug dose and with both baseline HbA1c and ≥1 postbaseline HbA1c measurement. Other As-treated analysis for safety analysis set including all participants who received ≥1 dose of study drug, analysed according to drug actually received regardless of assignment.

19.2. Study arms

19.2.1. Dulaglutide 1.5 mg once weekly (N = 244)

Subcutaneous injection of dulaglutide 1.5 mg once weekly for 26 weeks.

19.2.2. Dulaglutide 0.75 mg once weekly (N = 248)

Subcutaneous injection of dulaglutide 0.75 mg once weekly for 26 weeks.

19.2.3. Glimepiride 1-3 mg once daily (N = 245)

Oral glimepiride capsules 1 to 3 mg once daily for 26 weeks.

19.3. Characteristics

19.3.1. Arm-level characteristics

Characteristic	Dulaglutide 1.5 mg once weekly (N = 244)	Dulaglutide 0.75 mg once weekly (N = 248)	Glimepiride 1-3 mg once daily (N = 245)
% Male Sample size	n = 134 ; % = 56.1	n = 127 ; % = 46.9	n = 112 ; % = 46.3
Mean age (SD) (years) Mean (SD)	52.7 (10.75)	53.8 (10.09)	52 (10.05)
Ethnicity Ethnicity not reported, only by participating country Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Dulaglutide 1.5 mg once weekly (N = 244)	Dulaglutide 0.75 mg once weekly (N = 248)	Glimepiride 1-3 mg once daily (N = 245)
China Sample size	n = 184 ; % = 77	n = 186 ; % = 77.8	n = 186 ; % = 76.9
South Korea Sample size	n = 26 ; % = 10.9	n = 25 ; % = 10.5	n = 27 ; % = 11.2
Taiwan Sample size	n = 29 ; % = 12.1	n = 28 ; % = 11.7	n = 29 ; % = 12
Comorbidities Custom value	NR	NR	NR
Presence of frailty Custom value	NR	NR	NR
Time since type 2 diabetes diagnosis (years) Glimepiride, n=241 Mean (SD)	4 (4.44)	3.5 (4.06)	3.8 (4.09)
HbA1c (%) Mean (SD)	8 (0.95)	8 (1.03)	7.9 (1.01)
Blood pressure (mmHg) Obtained in sitting position Mean (SD)	NA (NA)	NA (NA)	NA (NA)
Systolic blood pressure Mean (SD)	128 (13.3)	128 (13.7)	126 (14.7)
Diastolic blood pressure Mean (SD)	79 (8.7)	79 (9.3)	78 (8.6)
Heart rate (BPM) Obtained in sitting position Mean (SD)	76 (9.6)	75 (9.3)	77 (9.7)
Smoking status Current use; Dulaglutide 1.5. n=237 Sample size	n = 70 ; % = 29.5	n = 46 ; % = 19.2	n = 60 ; % = 24.9

Characteristic	Dulaglutide 1.5 mg once weekly (N = 244)	Dulaglutide 0.75 mg once weekly (N = 248)	Glimepiride 1-3 mg once daily (N = 245)
Alcohol consumption Current use; Glimepiride, n=241 Sample size	n = 56 ; % = 23.4	n = 43 ; % = 18	n = 40 ; % = 16.6
Presence of severe mental illness Custom value	NR	NR	NR
People with significant cognitive impairment Custom value	NR	NR	NR
People with a learning disability Custom value	NR	NR	NR
Weight Custom value	NR	NR	NR
BMI (kg/m2) Dulaglutide 0.75, n=238 Mean (SD)	25.8 (3.43)	26.2 (3.49)	25.7 (3.14)
Number of people with obesity Custom value	NR	NR	NR
Cholesterol and lipid levels Custom value	NR	NR	NR
Albumin creatinine ratio Custom value	NR	NR	NR
eGFR (mL/min/1.73m2) Custom value	NR	NR	NR
Other antidiabetic medication used Previous use of one or more oral antidiabetic medications Sample size	n = 135 ; % = 56.5	n = 136 ; % = 56.9	n = 139 ; % = 57.4

Characteristic	Dulaglutide 1.5 mg once weekly (N = 244)	Dulaglutide 0.75 mg once weekly (N = 248)	Glimepiride 1-3 mg once daily (N = 245)
Blood pressure-lowering medication used Custom value	NR	NR	NR
Statins/lipid-lowering medication used Custom value	NR	NR	NR
Other treatment being received Custom value	NR	NR	NR

Number of participants by groups for all baseline characteristics, unless otherwise stated in notes, are as follows: Dulaglutide, 1.5 mg, n=239; Dulaglutide 0.75 mg, n=239; Glimepiride 1-3 mg, n=242.

20. Chen, 2015

Bibliographic Reference	Chen, Y.; Ning, G.; Wang, C.; Gong, Y.; Patel, S.; Zhang, C.; Izumoto, T.; Woerle, H. J.; Wang, W.; Efficacy and safety of linagliptin monotherapy in Asian patients with inadequately controlled type 2 diabetes mellitus: A multinational, 24-week, randomized, clinical trial; J Diabetes Invest; 2015; vol. 6 (no. 6); 692-8

20.1. Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	NCT01214239
Study type	Randomised controlled trial (RCT)
Study location	China, Malaysia and the Philippines
Study setting	No additional information
Study dates	November 2010 - May 2012
Sources of funding	Supported by Boehringer Ingelheim, Pharma GmbH & Co
Inclusion criteria	Aged 18-80 years Insufficiently controlled type 2 diabetes (HbA1c between 7-10%) BMI <45 kg/m2 Received no prior anti-diabetes medication, or been treated with one drug which had remained unchanged for at least 6 weeks prior to screening
Exclusion criteria	Myocardial infarction, stroke or transient ischemic attack in the past 6 months

	Unstable or acute congestive heart failure Impaired hepatic function (liver function tests >3 times the upper limit of normal) Confirmed hyperglycaemia (>240 mg/dL) after an overnight fast Treated with a thiazolidinedione, GLP-1 analogue, DPP-4 inhibitor, insulin or anti-obesity drug in the past 3 months Treated with systemic steroids at screening
Recruitment / selection of participants	Not reported
Intervention(s)	5 mg linagliptin administered orally once per day. Rescue metformin was allowed during the first 12 weeks of the trial if fasting glucose >240 mg/dL or >200 mg/dL during the second 12 weeks of the trial, or non-fasting glucose >400 mg/dL at any time in the study. If a participant's fasting glucose remained above these thresholds despite rescue metformin use, they were withdrawn from the study.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear
Strata 2: People with atherosclerotic cardiovascular diseases	Not stated/unclear
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	People at higher risk of developing cardiovascular disease

Subgroup 1: People with frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	eGFR ≥30mL/min/1.73m2
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Sensitivity analysis category: Enrichment trial status	7) Mixed population
Population subgroups	No additional information
Comparator	Placebo administered orally once per day. Rescue metformin was allowed during the first 12 weeks of the trial if fasting glucose >240 mg/dL or >200 mg/dL during the second 12 weeks of the trial, or non-fasting glucose >400 mg/dL at any time in the study. If a participant's fasting glucose remained above these thresholds despite rescue metformin use, they were withdrawn from the study.
Number of participants	299 randomised 200 received linagliptin, 182 completed 99 received placebo, 87 completed
Duration of follow-up	24 weeks
Indirectness	None
Method of analysis	ITT

Additional comments	None

20.2. Study arms

20.2.1. Linagliptin (N = 200)

Once daily 5 mg oral linagliptin

20.2.2. Placebo (N = 99)

Once daily placebo

20.3. Characteristics

20.3.1. Arm-level characteristics

Characteristic	Linagliptin (N = 200)	Placebo (N = 99)
% Male Sample size	n = 84 ; % = 42	n = 40 ; % = 40
Mean age (SD) Mean (SD)	54.6 (10.1)	54.1 (9.3)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosis Time since diagnosis Sample size	n = NA ; % = NA	n = NA ; % = NA
<1 year Sample size	n = 98 ; % = 50	n = 49 ; % = 52
>1 to 5 years Sample size	n = 62 ; % = 32	n = 30 ; % = 32

Characteristic	Linagliptin (N = 200)	Placebo (N = 99)
5+ years Sample size	n = 36 ; % = 18	n = 15 ; % = 16
HbA1c (%) Mean (SD)	7.95 (0.89)	8.09 (0.91)
Blood pressure Nominal	NR	NR
Heart rate Nominal	NR	NR
Smoking status Nominal	NR	NR
Alcohol consumption Nominal	NR	NR
Presence of severe mental illness Nominal	NR	NR
People with significant cognitive impairment Nominal	NR	NR
People with a learning disability Nominal	NR	NR
Weight (kg) Mean (SD)	69 (11.6)	68.2 (10.4)
BMI (kg/m²) Mean (SD)	25.5 (3.3)	25.1 (3.4)
Number of people with obesity Nominal	NR	NR
Cholesterol and lipid levels Nominal	NR	NR
Albumin creatinine ratio Nominal	NR	NR
eGFR (mL/min/1.73m2) Sample size	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Linagliptin (N = 200)	Placebo (N = 99)
>90 Sample size	n = 118 ; % = 59	n = 66 ; % = 67
60-90 Sample size	n = 79 ; % = 40	n = 31 ; % = 31
30-60 Sample size	n = 3 ; % = 2	n = 2 ; % = 2
≤30 Sample size	n = 0 ; % = 0	n = 0 ; % = 0
Other antidiabetic medication used Nominal	NR	NR
Blood pressure-lowering medication used Nominal	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

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21. Chiasson, 2001

Bibliographic Reference	Chiasson, J. L.; Naditch, L.; The synergistic effect of miglitol plus metformin combination therapy in the treatment of type 2 diabetes; Diabetes Care; 2001; vol. 24 (no. 6); 989-94

21.1. Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.
Trial name / registration number	No additional information.
Study type	Randomised controlled trial (RCT)
Study location	Multicentre (location unclear).
Study setting	Outpatient follow up.
Study dates	No additional information.
Sources of funding	An unrestricted research grant from Bayer Canada, Inc. and additional financial support from Sanofi-Synthelabo.
Inclusion criteria	People with type 2 diabetes; >40 years of age; diabetes with inadequately controlled with diet alone (HbA1c between 7.2 and 9.5).
Exclusion criteria	Type 1 diabetes; presence of major debilitating diseases; recent cardiovascular events; gastrointestinal diseases; medications likely to affect intestinal motility or the absorption of nutrients; hypersensitivity to miglitol or metformin; history of lactic acidosis.
Recruitment / selection of participants	No additional information.
Intervention(s)	Metformin N=83 Metformin 500mg three times a day for 36 weeks.

	Concomitant therapy: People who were taking either sulfonylurea or metformin below the maximum dose before the trial were eligible as long as the drug was discontinued. Everyone went through a single blind, 8 week placebo run-in period. All people saw a dietician before the run-in period and were advised on their diet. They were also advised regarding exercise, mainly walking 20-30 minutes at least three times per week. The diet was reinforced after 1 month.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear
Strata 2: People with atherosclerotic cardiovascular diseases	Not stated/unclear
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	People at higher risk of developing cardiovascular disease Based on BMI, age and presence of diabetes
Subgroup 1: People with frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear

Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Sensitivity analysis category: Enrichment trial status	7) Mixed population 50% truly treatment naïve, the remainder receiving treatment but stopped with no response criteria (including people who received this study drug and may not have responded as they entered a trial)
Population subgroups	No additional information.
Comparator	Placebo N=83 Matching placebo. Concomitant therapy: People who were taking either sulfonylurea or metformin below the maximum dose before the trial were eligible as long as the drug was discontinued. Everyone went through a single blind, 8 week placebo run-in period. All people saw a dietician before the run-in period and were advised on their diet. They were also advised regarding exercise, mainly walking 20-30 minutes at least three times per week. The diet was reinforced after 1 month. A third arm (n=82) and fourth arm (n=76) where people received miglitol and a combination of miglitol and metformin respectively were also reported in the study. However, these arms are not relevant to the protocol so are not included in this data extraction and the analysis in this report.
Number of participants	324
Duration of follow-up	36 weeks.
Indirectness	Outcome indirectness - Withdrawal from study as only withdrawal due to adverse events was reported.
Method of analysis	ITT
Additional comments	No additional information.

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21.2. Study arms

21.2.1. Metformin (N = 83)

Metformin 500mg three times a day for 36 weeks. Concomitant therapy: People who were taking either sulfonylurea or metformin below the maximum dose before the trial were eligible as long as the drug was discontinued. Everyone went through a single blind, 8 week placebo run-in period. All people saw a dietician before the run-in period and were advised on their diet. They were also advised regarding exercise, mainly walking 20-30 minutes at least three times per week. The diet was reinforced after 1 month.

21.2.2. Placebo (N = 83)

Matching placebo. Concomitant therapy: People who were taking either sulfonylurea or metformin below the maximum dose before the trial were eligible as long as the drug was discontinued. Everyone went through a single blind, 8 week placebo run-in period. All people saw a dietician before the run-in period and were advised on their diet. They were also advised regarding exercise, mainly walking 20-30 minutes at least three times per week. The diet was reinforced after 1 month.

21.3. Characteristics

21.3.1. Arm-level characteristics

Characteristic	Metformin (N = 83)	Placebo (N = 83)
% Male Sample size	n = 61 ; % = 73	n = 56 ; % = 68
Mean age (SD) (years) Mean (SD)	57.9 (8.6)	57.7 (9.9)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Caucasian Sample size	n = 73 ; % = 88	n = 76 ; % = 91.6
Black Sample size	n = 1 ; % = 1.2	n = 1 ; % = 1.2
Asian Sample size	n = 6 ; % = 7.2	n = 4 ; % = 4.8
Other	n = 3 ; % = 3.6	n = 2 ; % = 2.4

Characteristic	Metformin (N = 83)	Placebo (N = 83)
Sample size		
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosis (years) Mean (SD)	7.5 (7.4)	5.1 (4.9)
HbA1c (%) Mean (SD)	8.2 (0.9)	8.1 (0.7)
Blood pressure Mean (SD)	NR (NR)	NR (NR)
Heart rate Mean (SD)	NR (NR)	NR (NR)
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR
Weight (kg) Mean (SD)	89 (17.8)	88.6 (14.1)
BMI (kg/m2) Mean (SD)	30.7 (5.1)	31.1 (4.4)
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Metformin (N = 83)	Placebo (N = 83)
Cholesterol and lipid levels Sample size	n = NR ; % = NR	n = NR ; % = NR
Albumin creatinine ratio Sample size	n = NR ; % = NR	n = NR ; % = NR
eGFR (mL/min/1.73m2) Sample size	n = NR ; % = NR	n = NR ; % = NR
Other antidiabetic medication used Before discontinuing as the trial started Sample size	n = NA ; % = NA	n = NA ; % = NA
None Sample size	n = 55 ; % = 66.3	n = 48 ; % = 57.8
Metformin Sample size	n = 19 ; % = 22.9	n = 22 ; % = 26.5
Sulfonylureas Sample size	n = 43 ; % = 51.8	n = 33 ; % = 39.8
Blood pressure-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Statins/lipid-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR

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22. Chou, 2012

Bibliographic Reference	Chou, H. S.; Truitt, K. E.; Moberly, J. B.; Merante, D.; Choi, Y.; Mun, Y.; Pfützner, A.; A 26-week, placebo- and pioglitazone-controlled monotherapy study of rivoglitazone in subjects with type 2 diabetes mellitus; Diabetes Obes Metab; 2012; vol. 14 (no. 11); 1000-9

22.1. Study details

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	NA
Trial name / registration number	NCT00484198
Study type	Randomised controlled trial (RCT)
Study location	USA, Europe, India, South America, South Africa
Study setting	No additional information
Study dates	No additional information
Sources of funding	This study was funded by Daiichi Sankyo, Inc.
Inclusion criteria	- Age >= 18 years - Diagnosis of T2DM - HbA1c > 7.0% and <= 8.5% - Nonfasting c-peptide > 0.5 ng/ml - Treatment naive (not having taken any antidiabetic medication within 2 months of screening or stable on non-thiazolidinedione oral antidiabetic monotherapy (a sulphonylurea, meglitinide, metformin, or α-glucosidase inhibitor) for ≥3months prior to screening)

Exclusion criteria	- History of type 1 diabetes and/or ketoacidosis - Insulin therapy > 2 months - Prior treatment failure with, or intolerance of, a thiazolidinedione - Any history of congenital heart failure, unstable angina, myocardial infarction, cerebrovascular accident, transient ischaemic attack or revascularization procedures within 6 months of screening - Malignancy - Treatment with fenofibrate or gemfibrozil - Impaired liver function or ongoing infectious liver disease - HIV infection - Weight loss >10% within 6 months of screening - Systolic blood pressure ≥180mmHg and/or diastolic blood pressure ≥110 mmHg - Body mass index (BMI) >45 kg/m2 at screening - Confirmed repeat (≥2) measurements of fasting plasma glucose (FPG) >240 mg/dl during the placebo run-in period Lab exclusions: - haemoglobin <12 g/dl (men) or <10 g/dl (women) - haematocrit <35% (men) or <32% (women) - transaminase [alanine aminotransferase (ALT) and aspartate aminotransferase (AST)] levels >2.0-fold the upper limit of normal (ULN) - alkaline phosphatase, total bilirubin, or blood urea nitrogen levels>1.5-fold the ULN - creatine kinase >3.0-fold the ULN; or serum creatinine levels>1.6mg/dl.
Recruitment / selection of participants	This was a 26-week, randomized, double-blind, placebo and active comparator-controlled, pivotal Phase III study conducted at 254 sites in the USA (97), Europe (83),

	India (35), South America (19) and South Africa (20). The study comprised the following three periods, as shown in figure 1: a 2-week single-blind, placebo run-in period, where subjects discontinued existing antidiabetic treatment; a 26- week double-blind treatment period; and a 2-week safety follow-up period.
Intervention(s)	Subjects were randomized 2 : 4 : 11 : 11 to receive double-blind, double-dummy treatment with placebo, rivoglitazone 1.0 mg, rivoglitazone 1.5 mg or pioglitazone 45 mg per day. Doses of rivoglitazone 1.5 and 1.0 mg were chosen based on results and exposure-response modelling from previous dose ranging and other clinical trials [31,32]. , and subjects were instructed to take the medication in the morning, with or without food. Treatment compliance was assessed by counting unused tablets.
Cointervention	
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear
Strata 2: People with atherosclerotic cardiovascular diseases	Not stated/unclear
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear Almost lower risk, the paper states they've excluded patients of higher cv risk, but plugging characteristics into Q risk score gives score V close to 10% if average across male and female. So not sure it can be reliably put into either category.
Subgroup 1: People with frailty	Not stated/unclear
Subgroup 2: Onset of type	Not stated/unclear

2 diabetes mellitus	
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Sensitivity analysis category: Enrichment trial status	5) All treatment naïve
Population subgroups	None
Comparator	Study medications were provided as active and identical-appearing placebo.
Number of participants	1912
Duration of follow-up	6 months
Indirectness	No additional information
Method of analysis	Modified ITT The primary efficacy analysis population, termed the full analysis population, included all randomized subjects who received ≥1 dose of study medication, and who had a baseline and ≥1 post-baseline efficacy measurement, with subjects analysed according to their assigned treatment at randomization (modified intention-to-treat).

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22.2. Study arms

22.2.1. Placebo (N = 137)

22.2.2. Rivoglitazone 1.0 mg (N = 274)

22.2.3. Rivoglitazone 1.5mg (N = 750)

22.2.4. Pioglitazone 45mg (N = 751)

22.3. Characteristics

22.3.1. Arm-level characteristics

Characteristic	Placebo (N = 137)	Rivoglitazone 1.0 mg (N = 274)	Rivoglitazone 1.5mg (N = 750)	Pioglitazone 45mg (N = 751)
Age (years) Mean (SD)	55.4 (12.32)	55 (10.51)	55.1 (10.59)	55 (10.84)
Gender (male) (n (%)) Sample size	n = 67 ; % = 48.9	n = 132 ; % = 48.2	n = 382 ; % = 50.9	n = 398 ; % = 53
Caucasian Sample size	n = 80 ; % = 58.4	n = 147 ; % = 53.6	n = 406 ; % = 54.1	n = 414 ; % = 55.1
Black Sample size	n = 2 ; % = 1.5	n = 17 ; % = 6.2	n = 33 ; % = 4.4	n = 35 ; % = 4.7
Asian Sample size	n = 42 ; % = 30.7	n = 89 ; % = 32.5	n = 245 ; % = 32.7	n = 243 ; % = 32.4
American Indian Sample size	n = 2 ; % = 1.5	n = 3 ; % = 1.1	n = 11 ; % = 1.5	n = 1 ; % = 0.1
Others Sample size	n = 11 ; % = 8	n = 18 ; % = 6.6	n = 55 ; % = 7.3	n = 58 ; % = 7.7
Weight (kg) Mean (SD)	82 (19.73)	80.5 (19.65)	80.6 (17.67)	81.6 (19.59)

Characteristic	Placebo (N = 137)	Rivoglitazone 1.0 mg (N = 274)	Rivoglitazone 1.5mg (N = 750)	Pioglitazone 45mg (N = 751)
BMI (kg/m2) Mean (SD)	30.1 (5.43)	29.7 (5.63)	29.6 (5.27)	30 (5.8)
Naive to antidiabetic treatment Sample size	n = 34 ; % = 24.8	n = 67 ; % = 24.5	n = 197 ; % = 26.3	n = 192 ; % = 25.6
HbA1c (%) Mean (SD)	7.7 (0.54)	7.7 (0.53)	7.7 (0.57)	7.7 (0.58)
FPG (mg/dL) Mean (SD)	161.8 (45.22)	159.2 (42.54)	161.2 (40.52)	161.6 (42.96)
HOMA-IR Mean (SD)	6.5 (7.86)	5.6 (4.61)	6 (6.6)	6.2 (6.84)
LDL-C (mg/dL) Mean (SD)	108.4 (29.5)	112.9 (32.2)	112 (32.31)	110.7 (33.6)
TC Mean (SD)	189.6 (36)	193.4 (38)	191.3 (38.8)	190.1 (39.8)
TG Mean (SD)	185.6 (110.6)	173.7 (103.9)	169.2 (100.5)	175.2 (97.1)
HDL-C Mean (SD)	45 (11.8)	45.9 (12.4)	45.7 (11.4)	44.6 (10.2)
ApoA-I Mean (SD)	144.9 (25.1)	145.8 (27.5)	144.9 (24.2)	143.3 (23)
Apo-B (mg/dL) Mean (SD)	112.6 (25)	116.2 (26.3)	114.5 (26.9)	114.5 (27.4)
Adiponectin Mean (SD)	7.8 (3.5)	8.3 (4.4)	8.4 (4.8)	8.1 (4.1)
Withdrawal Nominal	41	66	151	172
Patient request Nominal	12	21	47	59

Characteristic	Placebo (N = 137)	Rivoglitazone 1.0 mg (N = 274)	Rivoglitazone 1.5mg (N = 750)	Pioglitazone 45mg (N = 751)
Met discontinuation criteria Nominal	16	17	29	38
Lack of efficacy Nominal	3	2	6	8
Adverse event Nominal	3	11	32	31
Protocol violation Nominal	0	5	6	8
Other Nominal	7	10	31	28

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23. de Boer, 2017

Bibliographic Reference	de Boer, S. A.; Heerspink, H. J. L.; Juarez Orozco, L. E.; van Roon, A. M.; Kamphuisen, P. W.; Smit, A. J.; Slart, R. H. J. A.; Lefrandt, J. D.; Mulder, D. J.; Effect of linagliptin on pulse wave velocity in early type 2 diabetes: A randomized, double-blind, controlled 26-week trial (RELEASE); Diabetes Obes Metab; 2017; vol. 19 (no. 8); 1147-1154

23.1. Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	RELEASE - NCT02015299
Study type	Randomised controlled trial (RCT)
Study location	The Netherlands
Study setting	Secondary care - outpatient clinic of the Vascular Medicine Department
Study dates	No additional information
Sources of funding	Supported by Boehringer Ingelheim BV
Inclusion criteria	Age 30 to 70 years Treatment naïve type 2 diabetes, as defined as documentation of one of the following: Fasting plasma glucose ≥ 7.0 mmol/l, Random plasma glucose ≥ 11.1 mmol/l, or HbA1c ≥6,5% On a stable dose of blood pressure and/or lipid lowering medication for more than 4 weeks
Exclusion criteria	Current or previous use of glycemic control medications, defined as used for a minimal period of 30 consecutive days and within one year prior to inclusion Type 1 diabetes

	Gestational diabetes mellitus Other specific types of diabetes due to other causes, e.g., genetic defects in β-cell function, genetic defects in insulin action, diseases of the exocrine pancreas (such as 2 cystic fibrosis), and drug- or chemical-induced (such as in the treatment of HIV/AIDS or after organ transplantation) Uncontrolled hypertension, defined as persisting systolic blood pressure >160 or a diastolic blood pressure >100 mmHg without evidence of white coat hypertension Severe dyslipidaemia indicating primary dyslipidaemia, defined as total cholesterol >8 mmol/l, triglycerides >10 mmol/l of high density lipoprotein cholesterol <0.6 mmol/l Current use of weight loss medication or previous weight loss surgery History of severe gastrointestinal disease Clinical contraindications to DPP4-inhibitors Previous cardiovascular disease, defined as stable coronary artery disease or acute coronary syndrome, stroke or transient ischemic attack, peripheral artery disease Symptomatic heart failure, New York Heart Association (NYHA) class II-IV Women who are currently pregnant, planning to become pregnant, breastfeeding women, or women with child bearing potential not using appropriate contraceptive measures Clinically significant liver disease or hepatic function greater than 3 times upper limit of normal Known impaired renal function or eGFR <30 ml/min/1.73m2 Patients who are mentally incompetent and cannot sign a Patient Informed Consent Current active malignancy or in the previous 6 months Documented HIV infection Use of rifampicin Known or suspected allergy to 18F-FDG or its component
Recruitment / selection of participants	Potentially eligible participants were selected from the outpatient clinic of the Vascular Medicine Department of the university hospital, and others were recruited by advertisements in a local newspaper and from general practices

Intervention(s)	Participant allocated to the intervention received 5 mg linagliptin, once daily Rescue therapy was initiated if the participant had a fasting plasma glucose level >15 mmol/L or HbA1c >8.0% (64 mmol/mol)
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure
Strata 2: People with atherosclerotic cardiovascular diseases	People without other cardiovascular diseases
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	People at higher risk of developing cardiovascular disease
Subgroup 1: People with frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	People without non-alcoholic fatty liver disease
Subgroup 4: People with obesity	Not stated/unclear

Subgroup 5: eGFR category at baseline	eGFR ≥30mL/min/1.73m2
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Sensitivity analysis category: Enrichment trial status	5) All treatment naïve
Population subgroups	No additional information
Comparator	Participants allocated to the comparator arm received an image-matched placebo once daily Rescue therapy was initiated if the participant had a fasting plasma glucose level >15 mmol/L or HbA1c >8.0% (64 mmol/mol)
Number of participants	45 randomised, one excluded due to health concerns 22 received linagliptin, 21 completed 22 received placebo, 19 completed
Duration of follow-up	26 weeks
Indirectness	None
Method of analysis	ACA
Additional comments	None

23.2. Study arms

23.2.1. Linagliptin (N = 22)

5 mg linagliptin per day

23.2.2. Placebo (N = 22)

Once daily placebo

23.3. Characteristics

23.3.1. Arm-level characteristics

Characteristic	Linagliptin (N = 22)	Placebo (N = 22)
% Male Sample size	n = 13 ; % = 59	n = 14 ; % = 64
Mean age (SD) (years) Median (IQR)	63 (52 to 66)	62 (56 to 69)
Ethnicity White ethnicity Sample size	n = 18 ; % = 82	n = 22 ; % = 100
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosis (years) Median (IQR)	1.5 (0 to 5)	1 (0 to 3.3)
HbA1c (%) Mean (SD)	6.3 (0.4)	6.2 (0.5)
Blood pressure Mean (SD)	NA (NA)	NA (NA)
SBP Mean (SD)	139 (14)	139 (13)
DBP Mean (SD)	88 (10)	88 (9)
Heart rate Nominal	NR	NR
Smoking status Current smokers Sample size	n = 5 ; % = 23	n = 2 ; % = 9
Alcohol consumption Nominal	NR	NR

Characteristic	Linagliptin (N = 22)	Placebo (N = 22)
Presence of severe mental illness Nominal	NR	NR
People with significant cognitive impairment Nominal	NR	NR
People with a learning disability Nominal	NR	NR
Weight (kg) Mean (SD)	97.9 (17.6)	95.3 (13.2)
BMI (kg/m²) Median (IQR)	32.3 (27.8 to 38.2)	29 (27.4 to 34.2)
Number of people with obesity Nominal	NR	NR
Cholesterol and lipid levels (mmol/L) Mean (SD)	NA (NA)	NA (NA)
Total cholesterol Mean (SD)	4.8 (1.1)	4.7 (0.7)
HDL Mean (SD)	1.4 (0.3)	1.4 (0.4)
LDL Mean (SD)	3.2 (1.2)	2.9 (0.9)
Triglycerides Mean (SD)	1.5 (0.6)	1.7 (1)
Albumin creatinine ratio Nominal	NR	NR
eGFR (mL/min/1.73m2) Mean (SD)	88 (12)	81 (16)
Other antidiabetic medication used Nominal	NR	NR
Blood pressure-lowering medication used Sample size	n = 10 ; % = 46	n = 12 ; % = 55

Characteristic	Linagliptin (N = 22)	Placebo (N = 22)
Statins/lipid-lowering medication used Sample size	n = 11 ; % = 50	n = 13 ; % = 59
Other treatment being received Nominal	NR	NR

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24. DeFronzo, 2008

Bibliographic Reference	DeFronzo, R. A.; Fleck, P. R.; Wilson, C. A.; Mekki, Q.; Efficacy and safety of the dipeptidyl peptidase-4 inhibitor alogliptin in patients with type 2 diabetes and inadequate glycemic control: a randomized, double-blind, placebo-controlled study; Diabetes Care; 2008; vol. 31 (no. 12); 2315-7

24.1. Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	NCT00286455
Study type	Randomised controlled trial (RCT)
Study location	No additional information
Study setting	No additional information
Study dates	No additional information
Sources of funding	Supported by Takeda Global Research and Development
Inclusion criteria	Type 2 diabetes Treatment naïve (no current therapy and <7 days treatment in the past 3 months) 18-80 years of age HbA1c 7-10% BMI 23-45 kg/m2 Treated with diet and exercise for at least a month Systolic/diastolic blood pressure <180/110 mmHg

Exclusion criteria	None reported
Recruitment / selection of participants	No additional information
Intervention(s)	Following a single-blind 4-week run-in, those who had fasting plasma glucose <275 mg/ml and ≥75% compliance and were allocated to the intervention received either 12.5 or 25 mg alogliptin per day. Additional antidiabetic agents were prohibited throughout. *12.5 and 25 mg study arms combined for this review*
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear
Strata 2: People with atherosclerotic cardiovascular diseases	Not stated/unclear
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic	Not stated/unclear

fatty liver disease	
Subgroup 4: People with obesity	Mixed population
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Sensitivity analysis category: Enrichment trial status	5) All treatment naïve
Population subgroups	No additional information
Comparator	Following a single-blind 4-week run-in, those who had fasting plasma glucose <275 mg/ml and ≥75% compliance and were allocated to the comparator received once daily placebo. Additional antidiabetic agents were prohibited throughout.
Number of participants	329 randomised 133 received 12.5 mg alogliptin 131 received 25 mg alogliptin 64 received placebo Dropout rates not reported
Duration of follow-up	26 weeks
Indirectness	None
Method of analysis	ITT
Additional comments	ITT analysis with LOCF imputation, however no reporting of dropout rates

24.2. Study arms

24.2.1. Alogliptin (N = 264)

12.5 or 25 mg alogliptin per day

24.2.2. Placebo (N = 64)

24.3. Characteristics

24.3.1. Study-level characteristics

Characteristic	Study (N = 328)
% Male Sample size	n = 174 ; % = 53
Mean age (SD) Mean (SD)	53.4 (11.1)
Ethnicity White Sample size	n = 220 ; % = 67
HbA1c Mean (SD)	7.9 (0.08)

24.3.2. Arm-level characteristics

Characteristic	Alogliptin (N = 264)	Placebo (N = 64)
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosis Nominal	NR	NR
Blood pressure Nominal	NR	NR
Heart rate Nominal	NR	NR
Smoking status Nominal	NR	NR
Alcohol consumption	NR	NR

Characteristic	Alogliptin (N = 264)	Placebo (N = 64)
Nominal		
Presence of severe mental illness Nominal	NR	NR
People with significant cognitive impairment Nominal	NR	NR
People with a learning disability Nominal	NR	NR
Weight Nominal	NR	NR
BMI Nominal	NR	NR
Number of people with obesity Nominal	NR	NR
Cholesterol and lipid levels Nominal	NR	NR
Albumin creatinine ratio Nominal	NR	NR
eGFR (mL/min/1.73m2) Nominal	NR	NR
Other antidiabetic medication used Nominal	NR	NR
Blood pressure-lowering medication used Nominal	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

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25. DeFronzo, 1995

Bibliographic Reference	DeFronzo, R. A.; Goodman, A. M.; Efficacy of metformin in patients with non-insulin-dependent diabetes mellitus. The Multicenter Metformin Study Group; N Engl J Med; 1995; vol. 333 (no. 9); 541-9

25.1. Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.
Trial name / registration number	No additional information.
Study type	Randomised controlled trial (RCT)
Study location	Multicentre study in the United States of America.
Study setting	Outpatient follow up.
Study dates	No additional information.
Sources of funding	A grant from Lipha Pharmaceuticals, Inc.
Inclusion criteria	Moderately obese people who were treated with diet alone that was unable to control symptoms; non-insulin dependent diabetes mellitus based on clinical history and the finding of a fasting plasma glucose concentration above 140mg/dL on two occasions (had to lack acceptable glycaemic control after 8 weeks of dietary therapy); weight that was 120-170% of ideal (on the basis of 1983 Metropolitan Life Insurance tables); age 40-70 years; normal renal function (serum creatinine, no more than 1.4mg/dL in men, and no more than 1.3mg/dL in women and no more than 2+ proteinuria); normal liver function. Therapy with oestrogen and a progestin and chlorthalidone or a thiazide was permitted if the person had already been taking this as long as the dosage was not changed during the study.
Exclusion criteria	Symptomatic diabetes (polyuria, polydipsia, weight loss); symptomatic cardiovascular disease; diastolic blood pressure above 100mmHg during antihypertensive drug treatment; any concurrent medical illness; received insulin therapy within the previous 6 months; used medications known to affect glucose metabolism; drank three or more alcoholic drinks per day; used illicit drugs; had previously received metformin therapy.

Recruitment / selection of participants	No additional information.
Intervention(s)	Metformin N=143 Metformin 850mg initially once a day for two weeks, then twice a day for two weeks, then 850mg three times a day as long as the fasting plasma glucose exceeding 140mg/dL and the side effects were tolerated. After the fifth week, this dose was continued unless side effects meant that a dose reduction was required. People received the treatment for 29 weeks after this time. Concomitant therapy: Both groups received a pre-enrolment dietary therapy involving a hypocaloric diet with 20% fewer calories than previously ingested.
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure
Strata 2: People with atherosclerotic cardiovascular diseases	People without other cardiovascular diseases
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	People without chronic kidney disease
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	People at higher risk of developing cardiovascular disease Based on presence of obesity and diabetes, also triglyceride levels
Subgroup 1: People with frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear

Subgroup 3: People with non-alcoholic fatty liver disease	People without non-alcoholic fatty liver disease
Subgroup 4: People with obesity	People with obesity
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Sensitivity analysis category: Enrichment trial status	5) All treatment naïve
Population subgroups	No additional information.
Comparator	Placebo N=146 Matching placebo. Concomitant therapy: Both groups received a pre-enrolment dietary therapy involving a hypocaloric diet with 20% fewer calories than previously ingested. A second study is reported in the paper where people received glyburide and metformin compared to glyburide alone and metformin alone. This was not included in this data extraction as glyburide is not commonly used in the UK and so only the first trial was included.
Number of participants	189
Duration of follow-up	29 weeks.
Indirectness	No additional information.
Method of analysis	ITT
Additional comments	No additional information.

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25.2. Study arms

25.2.1. Metformin (N = 143)

Metformin 850mg initially once a day for two weeks, then twice a day for two weeks, then 850mg three times a day as long as the fasting plasma glucose exceeding 140mg/dL and the side effects were tolerated. After the fifth week, this dose was continued unless side effects meant that a dose reduction was required. People received the treatment for 29 weeks after this time. Concomitant therapy: Both groups received a pre-enrolment dietary therapy involving a hypocaloric diet with 20% fewer calories than previously ingested.

25.2.2. Placebo (N = 146)

Matching placebo. Concomitant therapy: Both groups received a pre-enrolment dietary therapy involving a hypocaloric diet with 20% fewer calories than previously ingested.

25.3. Characteristics

25.3.1. Arm-level characteristics

Characteristic	Metformin (N = 143)	Placebo (N = 146)
% Male Sample size	n = 62 ; % = 43	n = 62 ; % = 43
Mean age (SD) (years) Mean (SE)	53 (1)	53 (1)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosis (years) Mean (SE)	6 (0.5)	6 (0.6)
HbA1c (%) Mean (SE)	8.4 (0.1)	8.2 (0.2)
Blood pressure	NR (NR)	NR (NR)

Characteristic	Metformin (N = 143)	Placebo (N = 146)
Mean (SD)		
Heart rate Mean (SD)	NR (NR)	NR (NR)
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR
Weight (kg) Mean (SE)	94.4 (1.1)	92.2 (1.2)
BMI (kg/m2) Mean (SE)	29.9 (0.3)	29.2 (0.3)
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR
Cholesterol and lipid levels Mean (SE)	NA (NA)	NA (NA)
Total cholesterol Mean (SE)	211 (3)	212 (4)
LDL cholesterol Mean (SE)	136 (3)	138 (3)
HDL cholesterol Mean (SE)	39 (1)	41 (1)
Triglycerides Mean (SE)	209 (15)	185 (9)

Characteristic	Metformin (N = 143)	Placebo (N = 146)
Albumin creatinine ratio Sample size	n = NR ; % = NR	n = NR ; % = NR
eGFR (mL/min/1.73m2) Sample size	n = NR ; % = NR	n = NR ; % = NR
Other antidiabetic medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Blood pressure-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Statins/lipid-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR

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26. Dejager, 2007

Bibliographic Reference	Dejager, S.; Razac, S.; Foley, J. E.; Schweizer, A.; Vildagliptin in drug-naïve patients with type 2 diabetes: a 24-week, double-blind, randomized, placebo-controlled, multiple-dose study; Horm Metab Res; 2007; vol. 39 (no. 3); 218-23

26.1. Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	USA, Russia and Tunisia
Study setting	No additional information
Study dates	April 2004 - October 2005
Sources of funding	Funded by Novartis Pharmaceuticals Corporation
Inclusion criteria	Diagnosed type 2 diabetes HbA1c 7.5-10.0% Not receiving any pharmacological treatment (no oral antidiabetic drugs taken in the past 3 months, and never for >3 consecutive months in the past) Aged 18-80 years Non-fertile or using birth-control if female BMI 22-45 kg/m2 Fasting plasma glucose <15 mmol/L

Exclusion criteria	History of type 1 diabetes or secondary forms of diabetes Acute metabolic diabetic complications within 6 months Myocardial infarction, unstable angina or coronary bypass surgery within 6 months Congestive heart failure (NYHA class III or IV) Liver disease such as cirrhosis or chronic active hepatitis ALT or AST >3 times the upper limit of normal Direct bilirubin >1.3 times the upper limit of normal Serum creatinine levels >2.5 mg/dL Clinically abnormal thyroid stimulating hormone Fasting triglycerides >700 mg/dL
Recruitment / selection of participants	No additional information
Intervention(s)	Participants allocated to the intervention arms received 50 mg vildagliptin once or twice per day, or 100 mg once per day *Three study arms examining 50 mg Q.D, 50 mg B.I.D and 100 mg Q.D were combined for this review*
Strata 1: People with type 2 diabetes mellitus and heart failure	Mixed population
Strata 2: People with atherosclerotic cardiovascular diseases	Not stated/unclear
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear
Strata 4: People with	People at higher risk of developing cardiovascular disease

type 2 diabetes mellitus and high cardiovascular risk	
Subgroup 1: People with frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	People without non-alcoholic fatty liver disease
Subgroup 4: People with obesity	Mixed population
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Sensitivity analysis category: Enrichment trial status	7) Mixed population
Population subgroups	No additional information
Comparator	Participants allocated to the comparator arm received a placebo
Number of participants	632 randomised 163 received 50 mg once daily, 130 completed 152 received 50 mg twice daily, 128 completed 157 received 100 mg once daily, 134 completed 472 received vildagliptin, 392 completed 160 received placebo, 119 completed
Duration of follow-up	24 weeks

Indirectness	None
Method of analysis	Other Mixture of methods: 'Primary ITT' - those who received at least one dose, had at least one follow-up measurement of HbA1c and had a baseline HbA1c >7.4% ITT - as above, including those with a baseline HbA1c <7.4% or with missing baseline data (due to measurement error at one lab) Randomised population - all as randomised Safety population - those who received at least one dose and had at least one follow-up safety assessment
Additional comments	None

26.2. Study arms

26.2.1. Vildagliptin (N = 284)

vildagliptin 50 mg once or twice daily, or 100 mg once daily - primary ITT population
Study arms containing different doses/frequencies combined for this review

26.2.2. Placebo (N = 94)

Once daily placebo - primary ITT population

26.3. Characteristics

26.3.1. Arm-level characteristics

Characteristic	Vildagliptin (N = 284)	Placebo (N = 94)
% Male Sample size	n = 134 ; % = 47	n = 45 ; % = 48
Mean age (SD) (years) Mean (SD)	54 (10.7)	52.2 (11.2)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Vildagliptin (N = 284)	Placebo (N = 94)
Caucasian Sample size	n = 212 ; % = 75	n = 65 ; % = 69
Hispanic/Latino Sample size	n = 40 ; % = 14	n = 11 ; % = 12
Black Sample size	n = 23 ; % = 8	n = 12 ; % = 13
Other Sample size	n = 11 ; % = 4	n = 6 ; % = 6
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosis (years) Mean (SD)	2.2 (3.7)	1.6 (2.5)
HbA1c (%) Mean (SD)	8.4 (0.8)	8.4 (0.8)
Blood pressure Nominal	NR	NR
Heart rate Nominal	NR	NR
Smoking status Nominal	NR	NR
Alcohol consumption Nominal	NR	NR
Presence of severe mental illness Nominal	NR	NR
People with significant cognitive impairment Nominal	NR	NR
People with a learning disability Nominal	NR	NR

Characteristic	Vildagliptin (N = 284)	Placebo (N = 94)
Weight Nominal	NR	NR
BMI (kg/m²) Mean (SD)	32.9 (5.7)	32.6 (5.6)
Number of people with obesity Nominal	NR	NR
Cholesterol and lipid levels Nominal	NR	NR
Albumin creatinine ratio Nominal	NR	NR
eGFR (mL/min/1.73m2) Nominal	NR	NR
Other antidiabetic medication used Nominal	NR	NR
Blood pressure-lowering medication used Nominal	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

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27. Del Prato, 2011

Bibliographic Reference	Del Prato, S.; Barnett, A. H.; Huisman, H.; Neubacher, D.; Woerle, H. J.; Dugi, K. A.; Effect of linagliptin monotherapy on glycaemic control and markers of ?-cell function in patients with inadequately controlled type 2 diabetes: a randomized controlled trial; Diabetes Obes Metab; 2011; vol. 13 (no. 3); 258-67

27.1. Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	Multinational - Croatia, India, Italy, Israel, Malaysia, Poland, Romania, Slovakia, Ukraine, Thailand and The Netherlands
Study setting	No additional information
Study dates	No additional information
Sources of funding	Supported by Boehringer Ingelheim
Inclusion criteria	Type 2 diabetes, either treatment naïve or previously receiving one oral antidiabetic drug (but not thiazolidinediones), which was washed-out for 6 weeks prior to randomisation 18-80 years BMI <40 kg/m2 HbA1c 6.5-9.0% in previously treated participants, or 7.0-10.0% in treatment naïve participants
Exclusion criteria	Myocardial infarction, stroke or transient ischaemic attack within 6 months of study enrolment

	Impaired hepatic function at screening Receiving rosiglitazone, pioglitazone, GLP-1 analogues, insulin or anti-obesity drugs (e.g. sibutramine, rimonabant or orlistat) within 3 months of enrolment Receiving systemic steroids at enrolment or those who had received dose changes in any thyroid hormone treatment within 6 weeks of screening
Recruitment / selection of participants	Recruited from 66 sites, method not reported
Intervention(s)	Following a 2-week open-label placebo run-in period, those randomised to the intervention arm received 5 mg linagliptin per day
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear
Strata 2: People with atherosclerotic cardiovascular diseases	Not stated/unclear
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	People at higher risk of developing cardiovascular disease
Subgroup 1: People with frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic	Not stated/unclear

fatty liver disease	
Subgroup 4: People with obesity	Mixed population
Subgroup 5: eGFR category at baseline	eGFR ≥30mL/min/1.73m2
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Sensitivity analysis category: Enrichment trial status	7) Mixed population
Population subgroups	No additional information
Comparator	Following a 2-week open-label placebo run-in period, those randomised to the comparator arm received a placebo
Number of participants	503 randomised 336 received linagliptin, 302 completed 167 received placebo, 138 completed
Duration of follow-up	24 weeks
Indirectness	None
Method of analysis	Modified ITT ITT excluding participants who did not have a follow-up HbA1c measurement (missing data imputed by LOCF)
Additional comments	None

27.2. Study arms

27.2.1. Linagliptin (N = 336)

5 mg linagliptin once daily

27.2.2. Placebo (N = 167)

Placebo once daily

27.3. Characteristics

27.3.1. Arm-level characteristics

Characteristic	Linagliptin (N = 336)	Placebo (N = 167)
% Male Sample size	n = 164 ; % = 49	n = 79 ; % = 47
Mean age (SD) (years) Mean (SD)	56.4 (10.1)	54.4 (10.3)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
American Indian/Alaska Native Sample size	n = 0 ; % = 0	n = 1 ; % = 1
Asian Sample size	n = 156 ; % = 46	n = 76 ; % = 46
White Sample size	n = 180 ; % = 54	n = 90 ; % = 54
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosis Nominal	NR	NR
HbA1c (%) Mean (SE)	8 (0.05)	8 (0.07)
Blood pressure Nominal	NR	NR
Heart rate Nominal	NR	NR
Smoking status Nominal	NR	NR

Characteristic	Linagliptin (N = 336)	Placebo (N = 167)
Alcohol consumption Nominal	NR	NR
Presence of severe mental illness Nominal	NR	NR
People with significant cognitive impairment Nominal	NR	NR
People with a learning disability Nominal	NR	NR
Weight KG Mean (SD)	78.53 (16.73)	79.21 (15.95)
BMI (kg/m²) Mean (SD)	29.04 (4.8)	29.08 (4.84)
Number of people with obesity Sample size	n = 135 ; % = 40	n = 66 ; % = 40
Cholesterol and lipid levels Nominal	NR	NR
Albumin creatinine ratio Nominal	NR	NR
eGFR (mL/min/1.73m2) Sample size	n = NA ; % = NA	n = NA ; % = NA
≥90 Sample size	n = 141 ; % = 42	n = 76 ; % = 46
60 to <90 Sample size	n = 165 ; % = 49	n = 83 ; % = 50
30 to <60 Sample size	n = 14 ; % = 4	n = 4 ; % = 2
Other antidiabetic medication used Previously receiving one oral antidiabetic medicine	n = 146 ; % = 43	n = 70 ; % = 42

Characteristic	Linagliptin (N = 336)	Placebo (N = 167)
Sample size		
Blood pressure-lowering medication used Nominal	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

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28. del Prato, 2003

Bibliographic Reference	del Prato, S.; Erkelens, D. W.; Leutenegger, M.; Six-month efficacy of benfluorex vs. placebo or metformin in diet-failed type 2 diabetic patients; Acta Diabetol; 2003; vol. 40 (no. 1); 20-7

28.1. Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.
Trial name / registration number	No additional information.
Study type	Randomised controlled trial (RCT)
Study location	International, multicentre trial (316 centres in France, Italy and the Netherlands).
Study setting	Outpatient follow up.
Study dates	No additional information.
Sources of funding	Funded by IRIS (Institut de Recherches Internationales Servier Courbevoie Cedex, France).
Inclusion criteria	Type 2 diabetes; age 35-70; fasting plasma glucose concentration of 7.8-16.7 mmol/L on diet alone or 7.8-11.1 mmol/L if already receiving an oral antidiabetic drug; body mass index of 25-40 kg/m2.
Exclusion criteria	No additional information.
Recruitment / selection of participants	No additional information.
Intervention(s)	Metformin N=284 Metformin 850mg tablets for 29 weeks. Initially treatment was one tablet for one week, then one tablet twice a day for two weeks, then a maximum of one table three times a day after this, tolerance permitting. People received 850-2550mg/day for the duration of the treatment period.

	Concomitant period: People who had previous treatment with oral antidiabetic therapy had this withdrawn, and everyone entered a 2 month run-in period while receiving placebo on a single-blind basis (2 tablet a day with the evening meal) and a strict diet plan). They were included in the trial if their FPG concentration was between 7.8 and 13.9 mmol/L and HbA1c was between 7.5% and 10% and the placebo compliance was >80%.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear
Strata 2: People with atherosclerotic cardiovascular diseases	Not stated/unclear
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	People at higher risk of developing cardiovascular disease Based on age and presence of diabetes
Subgroup 1: People with frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear

Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Sensitivity analysis category: Enrichment trial status	7) Mixed population
Population subgroups	No additional information.
Comparator	Placebo N=144 Matching placebo. Concomitant period: People who had previous treatment with oral antidiabetic therapy had this withdrawn, and everyone entered a 2 month run-in period while receiving placebo on a single-blind basis (2 tablet a day with the evening meal) and a strict diet plan). They were included in the trial if their FPG concentration was between 7.8 and 13.9 mmol/L and HbA1c was between 7.5% and 10% and the placebo compliance was >80%. A third arm where people received benfluorex (n=294) was reported. However, this arm is not included in this data extraction as this is not a relevant group to the protocol.
Number of participants	722
Duration of follow-up	6 months
Indirectness	No additional information.
Method of analysis	ITT
Additional comments	No additional information.

28.2. Study arms

28.2.1. Metformin (N = 284)

Metformin 850mg tablets for 29 weeks. Initially treatment was one tablet for one week, then one tablet twice a day for two weeks, then a maximum of one table three

times a day after this, tolerance permitting. People received 850-2550mg/day for the duration of the treatment period. Concomitant period: People who had previous treatment with oral antidiabetic therapy had this withdrawn, and everyone entered a 2 month run-in period while receiving placebo on a single-blind basis (2 tablet a day with the evening meal) and a strict diet plan). They were included in the trial if their FPG concentration was between 7.8 and 13.9 mmol/L and HbA1c was between 7.5% and 10% and the placebo compliance was >80%.

28.2.2. Placebo (N = 144)

Matching placebo. Concomitant period: People who had previous treatment with oral antidiabetic therapy had this withdrawn, and everyone entered a 2 month run-in period while receiving placebo on a single-blind basis (2 tablet a day with the evening meal) and a strict diet plan). They were included in the trial if their FPG concentration was between 7.8 and 13.9 mmol/L and HbA1c was between 7.5% and 10% and the placebo compliance was >80%.

28.3. Characteristics

28.3.1. Arm-level characteristics

Characteristic	Metformin (N = 284)	Placebo (N = 144)
% Male Study reports 68 (59%) for the metformin group, but these values do not make sense given there are 284 people in the group. Values for placebo appear accurate. Sample size	n = 68 ; % = 59	n = 91 ; % = 63
Mean age (SD) (years) Mean (SD)	56 (9)	56 (9)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosis Mean (SD)	NR (NR)	NR (NR)
HbA1c	7.79 (1.61)	7.43 (1.48)

Characteristic	Metformin (N = 284)	Placebo (N = 144)
Mean (SD)		
Blood pressure Mean (SD)	NR (NR)	NR (NR)
Heart rate Mean (SD)	NR (NR)	NR (NR)
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR
Weight (kg) Mean (SD)	82.6 (14.6)	84.5 (14.8)
BMI (kg/m2) Mean (SD)	29.8 (4.2)	29.9 (3.9)
Number of people with obesity Sample size	n = NA ; % = NA	n = NA ; % = NA
Cholesterol and lipid levels Mean (SD)	NA (NA)	NA (NA)
Total cholesterol Mean (SD)	5.38 (0.96)	5.26 (0.94)
HDL cholesterol Mean (SD)	1.14 (0.3)	1.15 (0.29)
Triglycerides Mean (SD)	1.82 (1.15)	1.56 (0.99)

Characteristic	Metformin (N = 284)	Placebo (N = 144)
Albumin creatinine ratio Mean (SD)	NA (NA)	NA (NA)
eGFR (mL/min/1.73m2) Mean (SD)	NA (NA)	NA (NA)
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Blood pressure-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Statins/lipid-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Other treatment being received Sample size	n = NA ; % = NA	n = NA ; % = NA

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29. Derosa, 2004

Bibliographic Reference	Derosa, G.; Franzetti, I.; Gadaleta, G.; Ciccarelli, L.; Fogari, R.; Metabolic variations with oral antidiabetic drugs in patients with Type 2 diabetes: comparison between glimepiride and metformin; Diabetes Nutr Metab; 2004; vol. 17 (no. 3); 143-50

29.1. Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.
Trial name / registration number	No additional information.
Study type	Randomised controlled trial (RCT)
Study location	Italy.
Study setting	Outpatient follow-up.
Study dates	No additional information.
Sources of funding	No additional information.
Inclusion criteria	Type 2 diabetes mellitus according to the American Diabetes Association criteria, who had been diagnosed within the last 6 months; normotensive according to the World Health Organisation criteria (systolic blood pressure <130mmHg, diastolic blood pressure <85mmHg); non-smokers; no coronary heart disease; normal renal function (creatinine value <1.5mg/dL).
Exclusion criteria	Abnormal liver or kidney function (elevated transaminases more than twice the upper normal limit, elevated serum creatinine at least 1.5mg/dL); a medical history of chronic insulin treatment; active cardiac problems (i.e. congestive heart failure, unstable angina pectoris, recent myocardial infarction, hypertension); any other disease state that could interfere with participation or outcome; people with known contraindications to sulfonylureas or biguanides; people who were pregnant, breast-feeding or intended to get pregnant; people who were undergoing systemic treatment with corticosteroids.

Recruitment / selection of participants	No additional information.
Intervention(s)	Glimepiride N=81 Glimepiride initially 1mg/day increased over 8 weeks up to a maximum of 4mg/day, split between two doses during the day. The optimisation was obtained aiming for the glycaemic target of FPG <120mg/dL and PPG <160mg/dL. Concomitant therapy: All people followed a recommended controlled-energy diet (1400-1600kcal/day) [55% carbohydrates, 25% proteins, 22% lipids (7% saturated), 105mg cholesterol, 36g fibre] and undertook aerobic activities of at least 30 minutes on 3-4 occasions/week. Dietary intake was reviewed every 3 months as part of a behaviour modification programme.
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure
Strata 2: People with atherosclerotic cardiovascular diseases	People without other cardiovascular diseases
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	People without chronic kidney disease
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	People at higher risk of developing cardiovascular disease Based on triglycerides and presence of diabetes
Subgroup 1: People with frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear

Subgroup 3: People with non-alcoholic fatty liver disease	People without non-alcoholic fatty liver disease
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Sensitivity analysis category: Enrichment trial status	8) Not reported
Population subgroups	No additional information.
Comparator	Metformin N=83 Metformin initially 1000mg/day increased over 8 weeks up to a maximum of 3000mg/day, split between three doses during the day. The optimisation was obtained aiming for the glycaemic target of FPG <120mg/dL and PPG <160mg/dL. Concomitant therapy: All people followed a recommended controlled-energy diet (1400-1600kcal/day) [55% carbohydrates, 25% proteins, 22% lipids (7% saturated), 105mg cholesterol, 36g fibre] and undertook aerobic activities of at least 30 minutes on 3-4 occasions/week. Dietary intake was reviewed every 3 months as part of a behaviour modification programme.
Number of participants	164
Duration of follow-up	12 months.
Indirectness	No additional information.
Method of analysis	Not stated/unclear Appears to be completers only
Additional comments	No additional information.

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29.2. Study arms

29.2.1. Glimepiride (N = 81)

Glimepiride initially 1mg/day increased over 8 weeks up to a maximum of 4mg/day, split between two doses during the day. The optimisation was obtained aiming for the glycaemic target of FPG <120mg/dL and PPG <160mg/dL. Concomitant therapy: All people followed a recommended controlled-energy diet (1400-1600kcal/day) [55% carbohydrates, 25% proteins, 22% lipids (7% saturated), 105mg cholesterol, 36g fibre] and undertook aerobic activities of at least 30 minutes on 3-4 occasions/week. Dietary intake was reviewed every 3 months as part of a behaviour modification programme.

29.2.2. Metformin (N = 83)

Metformin initially 1000mg/day increased over 8 weeks up to a maximum of 3000mg/day, split between three doses during the day. The optimisation was obtained aiming for the glycaemic target of FPG <120mg/dL and PPG <160mg/dL. Concomitant therapy: All people followed a recommended controlled-energy diet (1400-1600kcal/day) [55% carbohydrates, 25% proteins, 22% lipids (7% saturated), 105mg cholesterol, 36g fibre] and undertook aerobic activities of at least 30 minutes on 3-4 occasions/week. Dietary intake was reviewed every 3 months as part of a behaviour modification programme.

29.3. Characteristics

29.3.1. Arm-level characteristics

Characteristic	Glimepiride (N = 81)	Metformin (N = 83)
% Male Sample size	n = 38 ; % = 47	n = 42 ; % = 51
Mean age (SD) (years) Mean (SD)	56 (10)	58 (9)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosis Sample size	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Glimepiride (N = 81)	Metformin (N = 83)
HbA1c (%) Mean (SD)	8.5 (1.2)	8.4 (1)
Blood pressure (mmHg) Mean (SD)	NA (NA)	NA (NA)
Systolic blood pressure Mean (SD)	128 (5)	129 (5)
Diastolic blood pressure Mean (SD)	85 (4)	86 (3)
Heart rate Mean (SD)	NR (NR)	NR (NR)
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR
Weight Mean (SD)	NR (NR)	NR (NR)
BMI (kg/m2) Mean (SD)	27.6 (1.2)	28.1 (1.5)
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR
Cholesterol and lipid levels Mean (SD)	NA (NA)	NA (NA)
Total cholesterol Mean (SD)	210 (40)	223 (45)

Characteristic	Glimepiride (N = 81)	Metformin (N = 83)
HDL cholesterol Mean (SD)	42 (4)	43 (5)
LDL cholesterol Mean (SD)	135 (20)	144 (20)
Triglycerides Mean (SD)	160 (20)	180 (25)
Albumin creatinine ratio Mean (SD)	NR (NR)	NR (NR)
eGFR (mL/min/1.73m2) Mean (SD)	NR (NR)	NR (NR)
Other antidiabetic medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Blood pressure-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Statins/lipid-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR

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30. Derosa, 2009

Bibliographic Reference	Derosa, G.; Maffioli, P.; Salvadeo, S. A.; Ferrari, I.; Gravina, A.; Mereu, R.; Palumbo, I.; D'Angelo, A.; Cicero, A. F.; Direct comparison among oral hypoglycaemic agents and their association with insulin resistance evaluated by euglycemic hyperinsulinemic clamp: the 60's study; Metabolism; 2009; vol. 58 (no. 8); 1059-66

30.1. Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.
Trial name / registration number	No additional information.
Study type	Randomised controlled trial (RCT)
Study location	Italy.
Study setting	Outpatient follow up.
Study dates	No additional information.
Sources of funding	No funding declared.
Inclusion criteria	White people; at least 18 years of age; either sex; type 2 diabetes mellitus according to the European Society of Cardiology and the European Association for the Study of Diabetes guidelines criteria who were naïve and with poor glycaemic control, expressed as glycated haemoglobin level greater than 6.5%; were overweight (BMI between 25 and 30).
Exclusion criteria	History of ketoacidosis; unstable or rapidly progressive diabetic retinopathy, nephropathy or neuropathy; impaired hepatic function (defined as plasma aminotransferase and/or gamma-glutamyl transferase level higher than the upper limit of normal for age and sex); impaired renal function (defined as serum creatinine level higher than the upper limit of normal for age and sex); or severe anaemia; people with serious cardiovascular disease (NYHA class I-IV congestive heart failure or a history of myocardial infarction or stroke) or cerebrovascular conditions within 6 months before study enrolment; women who were pregnant or

	breastfeeding, or of childbearing potential and not taking adequate contraceptive precautions.
Recruitment / selection of participants	No additional information.
Intervention(s)	Pioglitazone N=69 Pioglitazone. Initially 15mg/day, once a day after lunch. Titrated up to 45mg/day over 3 months. Given in total for 12 months. Concomitant therapy: All people began a controlled-energy diet (600 kcal daily deficit) based on the American Diabetes Association recommendations that contained 50% calories from carbohydrates, 30% from fats (6% saturated) and 20% from proteins, with a maximum cholesterol content of 300mg/d and 35g/d of fibre. Dietitians and/or specialists each month provided instructions on dietary intake for the first 3 months and recorded procedures as part of a behaviour-modification program, and then from month 3 the people used food diaries for counselling. During the study, people participated in behaviour modification sessions on weight loss strategies. People were encouraged to increase their physical activity by walking briskly or riding a stationary bicycle for 20-30 minutes, 3-5 times a week.
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure
Strata 2: People with atherosclerotic cardiovascular diseases	People without other cardiovascular diseases
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	People without chronic kidney disease
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	People at higher risk of developing cardiovascular disease Based on age, smoking status, BMI

Subgroup 1: People with frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	People without non-alcoholic fatty liver disease
Subgroup 4: People with obesity	People who do not have obesity BMI <30 and all people are white, but all people are overweight (BMI >25)
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Sensitivity analysis category: Enrichment trial status	5) All treatment naïve
Population subgroups	No additional information.
Comparator	Metformin N=67 Metformin. Initially 1000mg/day, 500mg twice a day, after lunch and dinner. Titrated up to 3000mg/day over 3 months. Given in total for 12 months. Concomitant therapy: All people began a controlled-energy diet (600 kcal daily deficit) based on the American Diabetes Association recommendations that contained 50% calories from carbohydrates, 30% from fats (6% saturated) and 20% from proteins, with a maximum cholesterol content of 300mg/d and 35g/d of fibre. Dietitians and/or specialists each month provided instructions on dietary intake for the first 3 months and recorded procedures as part of a behaviour-modification program, and then from month 3 the people used food diaries for counselling. During the study, people participated in behaviour modification sessions on weight loss strategies. People were encouraged to increase their physical activity by walking briskly or riding a stationary bicycle for 20-30 minutes, 3-5 times a week.

	Pioglitazone and metformin N=69 Pioglitazone and metformin 15 + 850 mg/day, once a day after lunch. Titrated up to 45 + 2550mg over 3 months. Given in total for 12 months. Concomitant therapy: All people began a controlled-energy diet (600 kcal daily deficit) based on the American Diabetes Association recommendations that contained 50% calories from carbohydrates, 30% from fats (6% saturated) and 20% from proteins, with a maximum cholesterol content of 300mg/d and 35g/d of fibre. Dietitians and/or specialists each month provided instructions on dietary intake for the first 3 months and recorded procedures as part of a behaviour-modification program, and then from month 3 the people used food diaries for counselling. During the study, people participated in behaviour modification sessions on weight loss strategies. People were encouraged to increase their physical activity by walking briskly or riding a stationary bicycle for 20-30 minutes, 3-5 times a week. Glimepiride and metformin N=66 Glimepiride and metformin 2 + 850 mg/day, once a day after lunch. Titrated up to 6 + 850mg over 3 months. Given in total for 12 months. Concomitant therapy: All people began a controlled-energy diet (600 kcal daily deficit) based on the American Diabetes Association recommendations that contained 50% calories from carbohydrates, 30% from fats (6% saturated) and 20% from proteins, with a maximum cholesterol content of 300mg/d and 35g/d of fibre. Dietitians and/or specialists each month provided instructions on dietary intake for the first 3 months and recorded procedures as part of a behaviour-modification program, and then from month 3 the people used food diaries for counselling. During the study, people participated in behaviour modification sessions on weight loss strategies. People were encouraged to increase their physical activity by walking briskly or riding a stationary bicycle for 20-30 minutes, 3-5 times a week.
Number of participants	271
Duration of follow-up	3 months titration, then 12 months of therapy (15 months in total).
Indirectness	Outcome indirectness - reports withdrawal from study due to hypoglycaemia rather than all hypoglycaemia events
Method of analysis	ITT

Additional comments	No additional information.

30.2. Study arms

30.2.1. Pioglitazone (N = 69)

Pioglitazone. Initially 15mg/day, once a day after lunch. Titrated up to 45mg/day over 3 months. Given in total for 12 months. Concomitant therapy: All people began a controlled-energy diet (600 kcal daily deficit) based on the American Diabetes Association recommendations that contained 50% calories from carbohydrates, 30% from fats (6% saturated) and 20% from proteins, with a maximum cholesterol content of 300mg/d and 35g/d of fibre. Dietitians and/or specialists each month provided instructions on dietary intake for the first 3 months and recorded procedures as part of a behaviour-modification program, and then from month 3 the people used food diaries for counselling. During the study, people participated in behaviour modification sessions on weight loss strategies. People were encouraged to increase their physical activity by walking briskly or riding a stationary bicycle for 20-30 minutes, 3-5 times a week.

30.2.2. Metformin (N = 67)

Metformin. Initially 1000mg/day, 500mg twice a day, after lunch and dinner. Titrated up to 3000mg/day over 3 months. Given in total for 12 months. Concomitant therapy: All people began a controlled-energy diet (600 kcal daily deficit) based on the American Diabetes Association recommendations that contained 50% calories from carbohydrates, 30% from fats (6% saturated) and 20% from proteins, with a maximum cholesterol content of 300mg/d and 35g/d of fibre. Dietitians and/or specialists each month provided instructions on dietary intake for the first 3 months and recorded procedures as part of a behaviour-modification program, and then from month 3 the people used food diaries for counselling. During the study, people participated in behaviour modification sessions on weight loss strategies. People were encouraged to increase their physical activity by walking briskly or riding a stationary bicycle for 20-30 minutes, 3-5 times a week.

30.2.3. Pioglitazone and metformin (N = 69)

Pioglitazone and metformin 15 + 850 mg/day, once a day after lunch. Titrated up to 45 + 2550mg over 3 months. Given in total for 12 months. Concomitant therapy: All people began a controlled-energy diet (600 kcal daily deficit) based on the American Diabetes Association recommendations that contained 50% calories from carbohydrates, 30% from fats (6% saturated) and 20% from proteins, with a maximum cholesterol content of 300mg/d and 35g/d of fibre. Dietitians and/or specialists each month provided instructions on dietary intake for the first 3 months and recorded procedures as part of a behaviour-modification program, and then from month 3 the people used food diaries for counselling. During the study, people participated in behaviour modification sessions on weight loss strategies. People

were encouraged to increase their physical activity by walking briskly or riding a stationary bicycle for 20-30 minutes, 3-5 times a week.

30.2.4. Glimepiride and metformin (N = 66)

Glimepiride and metformin 2 + 850 mg/day, once a day after lunch. Titrated up to 6 + 850mg over 3 months. Given in total for 12 months Concomitant therapy: All people began a controlled-energy diet (600 kcal daily deficit) based on the American Diabetes Association recommendations that contained 50% calories from carbohydrates, 30% from fats (6% saturated) and 20% from proteins, with a maximum cholesterol content of 300mg/d and 35g/d of fibre. Dietitians and/or specialists each month provided instructions on dietary intake for the first 3 months and recorded procedures as part of a behaviour-modification program, and then from month 3 the people used food diaries for counselling. During the study, people participated in behaviour modification sessions on weight loss strategies. People were encouraged to increase their physical activity by walking briskly or riding a stationary bicycle for 20-30 minutes, 3-5 times a week.

30.3. Characteristics

30.3.1. Arm-level characteristics

Characteristic	Pioglitazone (N = 69)	Metformin (N = 67)	Pioglitazone and metformin (N = 69)	Glimepiride and metformin (N = 66)
% Male Sample size	n = 32 ; % = 46	n = 34 ; % = 51	n = 34 ; % = 49	n = 32 ; % = 49
Mean age (SD) (years) Mean (SD)	54 (6)	55 (5)	57 (7)	57.7 (7)
Ethnicity All white Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Presence of frailty Sample size	n = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosis Mean (SD)	NR (NR)	NR (NR)	NR (NR)	NR (NR)

Characteristic	Pioglitazone (N = 69)	Metformin (N = 67)	Pioglitazone and metformin (N = 69)	Glimepiride and metformin (N = 66)
HbA1c (%) Mean (SD)	9.2 (1.2)	9.1 (1.2)	9.3 (1.4)	9 (1.1)
Blood pressure Mean (SD)	NR (NR)	NR (NR)	NR (NR)	NR (NR)
Heart rate Mean (SD)	NR (NR)	NR (NR)	NR (NR)	NR (NR)
Smoking status Sample size	n = 16 ; % = 23	n = 18 ; % = 27	n = 19 ; % = 28	n = 15 ; % = 23
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Weight (kg) Mean (SD)	75.7 (5.3)	77.7 (5.9)	76.4 (5.1)	77.4 (5.8)
BMI (kg/m2) Mean (SD)	27.5 (1.7)	27.2 (1.5)	27.4 (1.6)	27.1 (1.4)
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Cholesterol and lipid levels Mean (SD)	NR (NR)	NR (NR)	NR (NR)	NR (NR)

Characteristic	Pioglitazone (N = 69)	Metformin (N = 67)	Pioglitazone and metformin (N = 69)	Glimepiride and metformin (N = 66)
Albumin creatinine ratio Mean (SD)	NR (NR)	NR (NR)	NR (NR)	NR (NR)
eGFR (mL/min/1.73m2) Mean (SD)	NR (NR)	NR (NR)	NR (NR)	NR (NR)
Other antidiabetic medication used Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Blood pressure-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Statins/lipid-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR

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31. Derosa, 2013

Bibliographic Reference	Derosa, Giuseppe; Franzetti, Ivano G; Querci, Fabrizio; Carbone, Anna; Ciccarelli, Leonardina; Piccinni, Mario N; Fogari, Elena; Maffioli, Pamela; Variation in inflammatory markers and glycemic parameters after 12 months of exenatide plus metformin treatment compared with metformin alone: a randomized placebo-controlled trial.; Pharmacotherapy; 2013; vol. 33 (no. 8); 817-26

31.1. Study details

Secondary publication of another included study- see primary study for details	

32. Dou, 2018

Bibliographic Reference	Dou, J.; Ma, J.; Liu, J.; Wang, C.; Johnsson, E.; Yao, H.; Zhao, J.; Pan, C.; Efficacy and safety of saxagliptin in combination with metformin as initial therapy in Chinese patients with type 2 diabetes: results from the START study, a multicentre, randomized, double-blind, active-controlled, phase 3 trial; Diab Obes Metab; 2018; vol. 20 (no. 3); 590-598

32.1. Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.
Trial name / registration number	NCT02273050, START trial.
Study location	25 centres in China.
Study setting	Outpatient follow-up.
Study dates	No additional information.
Sources of funding	Funding from AstraZeneca.
Inclusion criteria	Treatment naïve people aged 18 years or older; diagnosis of type 2 diabetes; BMI no more than 40kg/m2; fasting C-peptide no less than 0.3nmol/L; inadequate glycaemic control with diet and exercise (HbA1c 8.0%-12.0%). Treatment naïve was defined as receiving no medical treatment for diabetes or receiving previous treatment for less than 28 days since their original diagnosis but for no more than 3 consecutive days or 7 non-consecutive days in the 8 weeks before screening (with the exception of people with gestational diabetes during pregnancy or people who received a short course of insulin treatment during a period of hospitalisation).
Exclusion criteria	Pregnant and breastfeeding women; people with a cardiovascular event in the 3 months before screening; history of unstable or rapidly progressing renal disease; signs of poorly controlled diabetes; history of diabetic ketoacidosis or hyperosmolar non-ketotic coma; insulin therapy in the year preceding screening; any history of congestive heart failure; unstable

	major psychiatric disorders; active liver disease and/or significant abnormal liver function; other detailed criteria listed in the study appendix.
Recruitment / selection of participants	No additional information.
Intervention(s)	Saxagliptin and metformin N=216 Saxagliptin 5mg fixed dose plus metformin 500mg with titration every 2 weeks for 8 weeks in 500mg increments up to 2000mg/day with people being required to be received 1500mg/day or at the maximum tolerated dose at week 8. Metformin was taken once or twice daily. Concomitant therapy: If additional rescue treatment was required, acarbose was provided (if people exceeding an MFPG of 11.1mmol/L after week 12, or 13.3mmol/L at week 8).
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure
Strata 2: People with atherosclerotic cardiovascular diseases	Not stated/unclear
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear

Subgroup 3: People with non-alcoholic fatty liver disease	People without non-alcoholic fatty liver disease
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Sensitivity analysis category: Enrichment trial status	7) Mixed population
Population subgroups	No additional information.
Comparator	Saxagliptin N=214 Saxagliptin 5mg fixed dose plus matching placebo. Concomitant therapy: If additional rescue treatment was required, acarbose was provided (if people exceeding an MFPG of 11.1mmol/L after week 12, or 13.3mmol/L at week 8). Metformin N=210 Metformin 500mg with titration every 2 weeks for 8 weeks in 500mg increments up to 2000mg/day with people being required to be received 1500mg/day or at the maximum tolerated dose at week 8, plus matching placebo. Metformin was taken once or twice daily. Concomitant therapy: If additional rescue treatment was required, acarbose was provided (if people exceeding an MFPG of 11.1mmol/L after week 12, or 13.3mmol/L at week 8).
Number of participants	640
Duration of follow-up	24 weeks.

Indirectness	No additional information.
Method of analysis	Other Only people who received at least 1 dose of the medication were included in the final analysis
Additional comments	No additional information.

32.2. Study arms

32.2.1. Saxagliptin + metformin (N = 216)

Saxagliptin 5mg fixed dose plus metformin 500mg with titration every 2 weeks for 8 weeks in 500mg increments up to 2000mg/day with people being required to be received 1500mg/day or at the maximum tolerated dose at week 8. Metformin was taken once or twice daily. Concomitant therapy: If additional rescue treatment was required, acarbose was provided (if people exceeding an MFPG of 11.1mmol/L after week 12, or 13.3mmol/L at week 8).

32.2.2. Saxagliptin (N = 214)

Saxagliptin 5mg fixed dose plus matching placebo. Concomitant therapy: If additional rescue treatment was required, acarbose was provided (if people exceeding an MFPG of 11.1mmol/L after week 12, or 13.3mmol/L at week 8).

32.2.3. Metformin (N = 210)

Metformin 500mg with titration every 2 weeks for 8 weeks in 500mg increments up to 2000mg/day with people being required to be received 1500mg/day or at the maximum tolerated dose at week 8, plus matching placebo. Metformin was taken once or twice daily. Concomitant therapy: If additional rescue treatment was required, acarbose was provided (if people exceeding an MFPG of 11.1mmol/L after week 12, or 13.3mmol/L at week 8).

32.3. Characteristics

32.3.1. Arm-level characteristics

Characteristic	Saxagliptin + metformin (N = 216)	Saxagliptin (N = 214)	Metformin (N = 210)
% Male Sample size	n = 136 ; % = 64.8	n = 151 ; % = 70.9	n = 132 ; % = 63.8
Mean age (SD) (years)	50.8 (10.4)	49.5 (10.9)	50.1 (11)

Characteristic	Saxagliptin + metformin (N = 216)	Saxagliptin (N = 214)	Metformin (N = 210)
Mean (SD)			
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosis (years) Mean (SD)	0.97 (2.08)	0.73 (1.56)	0.72 (2.12)
HbA1c (%) Mean (SD)	9.4 (1.1)	9.4 (1)	9.5 (1)
Blood pressure Mean (SD)	NR (NR)	NR (NR)	NR (NR)
Heart rate Mean (SD)	NR (NR)	NR (NR)	NR (NR)
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Weight (kg) Mean (SD)	73.7 (13.1)	74.2 (13.1)	73.5 (13.8)

Characteristic	Saxagliptin + metformin (N = 216)	Saxagliptin (N = 214)	Metformin (N = 210)
BMI (kg/m2) Mean (SD)	26.7 (3.7)	26.5 (3.2)	26.5 (3.6)
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Cholesterol and lipid levels Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Albumin creatinine ratio Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
eGFR (mL/min/1.73m2) Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Other antidiabetic medication used Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Blood pressure-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Statins/lipid-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR

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33. Erem, 2014

Bibliographic Reference	Erem, C.; Ozbas, H. M.; Nuhoglu, I.; Deger, O.; Civan, N.; Ersoz, H. O.; Comparison of effects of gliclazide, metformin and pioglitazone monotherapies on glycemic control and cardiovascular risk factors in patients with newly diagnosed uncontrolled type 2 diabetes mellitus; Exp Clin Endocrinol Diabetes; 2014; vol. 122 (no. 5); 295-302

33.1. Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.
Trial name / registration number	No additional information.
Study type	Randomised controlled trial (RCT)
Study location	Turkey.
Study setting	Outpatient follow-up.
Study dates	No additional information.
Sources of funding	Supported by a research grant from the Karadeniz Technical University (Project No. 2008.114.003.1).
Inclusion criteria	Oral antihyperglycaemic drug-naive newly diagnosed type 2 diabetics; age between 30 and 70 years; fasting plasma glucose at least 140mg/dL or HbA1c at least 8%. In addition, type 2 diabetics with FBP 126-139mg/dL or HbA1c between 7-8% and homeostasis model assessment of insulin resistance index >3 were enrolled.
Exclusion criteria	Type 1 diabetes; ketoacidosis; ketonuria; renal function impairment (serum creatinine >1.4mg/dL for women, >1.5mg/dL for men); liver disease; impairment liver function (AST or ALT at least 2x the upper limit of normal); NYHA class III or IV congestive heart failure; history of lactic acidosis; malignancy; chronic inflammatory diseases; acute malabsorption; chronic pancreatitis; familial polyposis coli; active infection; pregnancy; hoping to conceive; breastfeeding; chronic obstructive pulmonary disease; angina pectoris; myocardial infarction; documented cerebrovascular disease; peripheral vascular disease; rheumatic disease; substance abuse; allergy

	to sulfonylureas, biguanides or thiazolidinediones; thyroid disease; corticosteroid treatment.
Recruitment / selection of participants	No additional information.
Intervention(s)	Pioglitazone N=20 Pioglitazone initiated at a dosage of 15mg/day raised to maximally effective dose of 45mg/day according to glycaemic control. Once optimal dosage has been reached, people were monitored for 12 months (including the 4-8 week titration period) and examined at 2-4 week intervals. Concomitant therapy: All people received diabetes education and individualised dietary and physical activity instructions.
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure
Strata 2: People with atherosclerotic cardiovascular diseases	People without other cardiovascular diseases
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	People without chronic kidney disease
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	People at higher risk of developing cardiovascular disease Based on BMI, presence of hypertension and presence of diabetes
Subgroup 1: People with frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear

Subgroup 3: People with non-alcoholic fatty liver disease	People without non-alcoholic fatty liver disease
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Sensitivity analysis category: Enrichment trial status	5) All treatment naïve
Population subgroups	No additional information.
Comparator	Gliclazide N=20 Gliclazide initiated at a dosage of 30mg once a day and raised to 60-120mg/day in people for reaching maximally effective dose according to glycaemic control. Once optimal dosage has been reached, people were monitored for 12 months (including the 4-8 week titration period) and examined at 2-4 week intervals. Concomitant therapy: All people received diabetes education and individualised dietary and physical activity instructions. Metformin N=20 Metformin initiated at a dosage of 500mg/day, and if no side/adverse effects were observed, increased to 2x 1000mg/day at 1-2 week intervals. Once optimal dosage has been reached, people were monitored for 12 months (including the 4-8 week titration period) and examined at 2-4 week intervals. Concomitant therapy: All people received diabetes education and individualised dietary and physical activity instructions.

Number of participants	60
Duration of follow-up	12 months.
Indirectness	No additional information.
Method of analysis	Not stated/unclear Appears to be completers only.
Additional comments	No additional information.

33.2. Study arms

33.2.1. Pioglitazone (N = 20)

Pioglitazone initiated at a dosage of 15mg/day raised to maximally effective dose of 45mg/day according to glycaemic control. Once optimal dosage has been reached, people were monitored for 12 months (including the 4-8 week titration period) and examined at 2-4 week intervals. Concomitant therapy: All people received diabetes education and individualised dietary and physical activity instructions.

33.2.2. Gliclazide (N = 20)

Gliclazide initiated at a dosage of 30mg once a day and raised to 60-120mg/day in people for reaching maximally effective dose according to glycaemic control. Once optimal dosage has been reached, people were monitored for 12 months (including the 4-8 week titration period) and examined at 2-4 week intervals. Concomitant therapy: All people received diabetes education and individualised dietary and physical activity instructions.

33.2.3. Metformin (N = 20)

Metformin initiated at a dosage of 500mg/day, and if no side/adverse effects were observed, increased to 2x 1000mg/day at 1-2 week intervals. Once optimal dosage has been reached, people were monitored for 12 months (including the 4-8 week titration period) and examined at 2-4 week intervals. Concomitant therapy: All people received diabetes education and individualised dietary and physical activity instructions.

33.3. Characteristics

33.3.1. Arm-level characteristics

Characteristic	Pioglitazone (N = 20)	Gliclazide (N = 20)	Metformin (N = 20)
% Male Sample size	n = 5 ; % = 25	n = 6 ; % = 30	n = 7 ; % = 35
Mean age (SD) (years) Mean (SD)	52.5 (5.2)	55 (8.7)	52.2 (10.5)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Comorbidities Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Hypertension Sample size	n = 9 ; % = 47.4	n = 5 ; % = 42.1	n = 10 ; % = 52.6
Coronary heart disease Sample size	n = 0 ; % = 0	n = 2 ; % = 10.5	n = 2 ; % = 10.5
Hyperlipidaemia Sample size	n = 2 ; % = 15.8	n = 3 ; % = 15.8	n = 2 ; % = 15.8
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosis Mean (SD)	NR (NR)	NR (NR)	NR (NR)
HbA1c (%) Mean (SD)	8.03 (1.7)	8.26 (1.65)	7.62 (1.06)
Blood pressure Mean (SD)	NA (NA)	NA (NA)	NA (NA)
Systolic blood pressure Mean (SD)	130.8 (11.9)	143.4 (14.3)	133.7 (18.6)
Diastolic blood pressure Mean (SD)	82.37 (11)	86.84 (10.6)	86.32 (10.1)

Characteristic	Pioglitazone (N = 20)	Gliclazide (N = 20)	Metformin (N = 20)
Heart rate Mean (SD)	NR (NR)	NR (NR)	NR (NR)
Smoking status Sample size	n = 3 ; % = 15.8	n = 0 ; % = 0	n = 2 ; % = 10.5
Alcohol consumption Sample size	n = 0 ; % = 0	n = 0 ; % = 0	n = 0 ; % = 0
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Weight Mean (SD)	81.93 (13.43)	90.06 (18.13)	87.47 (12.93)
BMI (kg/m2) Mean (SD)	31.31 (4.69)	32.72 (3.86)	33.56 (4.56)
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Cholesterol and lipid levels Mean (SD)	NR (NR)	NR (NR)	NR (NR)
Total cholesterol Mean (SD)	206.4 (43.2)	190.7 (40.8)	197.8 (44.9)
HDL cholesterol Mean (SD)	42.5 (9)	44 (6.9)	43.9 (10.2)
LDL cholesterol Mean (SD)	144.4 (33.3)	121.6 (32.9)	125.3 (36.9)
Triglycerides Mean (SD)	208.3 (89)	187.7 (116.5)	205.5 (132.3)

Characteristic	Pioglitazone (N = 20)	Gliclazide (N = 20)	Metformin (N = 20)
Albumin creatinine ratio Mean (SD)	NR (NR)	NR (NR)	NR (NR)
eGFR (mL/min/1.73m2) Mean (SD)	NR (NR)	NR (NR)	NR (NR)
Other antidiabetic medication used Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Blood pressure-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Statins/lipid-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR

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34. Esposito, 2011

Bibliographic Reference	Esposito, K.; Maiorino, M. I.; Di Palo, C.; Gicchino, M.; Petrizzo, M.; Bellastella, G.; Saccomanno, F.; Giugliano, D.; Effects of pioglitazone versus metformin on circulating endothelial microparticles and progenitor cells in patients with newly diagnosed type 2 diabetes-a randomized controlled trial; Diabetes Obes Metab; 2011; vol. 13 (no. 5); 439-445

34.1. Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.
Trial name / registration number	No additional information.
Study type	Randomised controlled trial (RCT)
Study location	Italy.
Study setting	Outpatient follow-up.
Study dates	No additional information.
Sources of funding	Supported by the Secondary University of Naples and by an unconditional research grant from Takeda Italia Farmaceutici S. p. A.
Inclusion criteria	Age 30-75; body mass index >25 kg/m2; HbA1c 7-10%; 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 (such as systemic glucocorticoids and weight loss drugs); acute disease or infection; recent (within 3 months) cardiovascular events or surgery; immunological disorders and any condition that might compromise adherence to the study; people with positive antibodies to glutamate decarboxylase or C-peptide levels less than 0.25pmol/L (<0.76ng/L); abnormal laboratory test results, including liver enzyme levels (ALT, AST and ALP) greater than three times the upper limit of normal; serum creatinine levels greater than 123.8 micromol/L.

Recruitment / selection of participants	No additional information.
Intervention(s)	Pioglitazone N=55 Pioglitazone 15mg once a day, titrated up to 30-45mg once daily. Concomitant therapy: No additional information.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear
Strata 2: People with atherosclerotic cardiovascular diseases	Not stated/unclear
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear

Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Sensitivity analysis category: Enrichment trial status	5) All treatment naïve
Population subgroups	No additional information.
Comparator	Metformin N=55 Metformin 500mg twice daily, titrated to 1000mg twice daily. Concomitant therapy: No additional information.
Number of participants	110
Duration of follow-up	24 weeks.
Indirectness	No additional information.
Method of analysis	ITT
Additional comments	No additional information.

34.2. Study arms

34.2.1. Pioglitazone (N = 55)

Pioglitazone 15mg once a day, titrated up to 30-45mg once daily. Concomitant therapy: No additional information.

34.2.2. Metformin (N = 55)

Metformin 500mg twice daily, titrated to 1000mg twice daily. Concomitant therapy: No additional information.

34.3. Characteristics

34.3.1. Arm-level characteristics

Characteristic	Pioglitazone (N = 55)	Metformin (N = 55)
% Male Sample size	n = 30 ; % = 54.5	n = 28 ; % = 50.9
Mean age (SD) (years) Mean (SD)	54.2 (6.1)	54.9 (6.6)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosis Mean (SD)	NR (NR)	NR (NR)
HbA1c (%) Mean (SD)	8 (1)	8.1 (1)
Blood pressure (mmHg) Mean (SD)	NA (NA)	NA (NA)
Systolic blood pressure Mean (SD)	134 (10)	135 (11)
Diastolic blood pressure Mean (SD)	86 (7)	85 (7)
Heart rate Mean (SD)	NR (NR)	NR (NR)
Smoking status Sample size	n = 12 ; % = 21.8	n = 10 ; % = 18
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Pioglitazone (N = 55)	Metformin (N = 55)
Sample size		
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR
Weight (kg) Mean (SD)	84.5 (8.6)	83.5 (8.5)
BMI (kg/m2) Mean (SD)	28.9 (3.5)	29.1 (3.3)
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR
Cholesterol and lipid levels (mmol/L) Mean (SD)	NA (NA)	NA (NA)
Total cholesterol Mean (SD)	5.2 (0.8)	5.1 (0.7)
HDL cholesterol Mean (SD)	1.1 (0.2)	1.05 (0.2)
Triglycerides Mean (SD)	1.7 (0.5)	1.7 (0.5)
Albumin creatinine ratio Mean (SD)	NR (NR)	NR (NR)
eGFR (mL/min/1.73m2) Mean (SD)	NR (NR)	NR (NR)
Other antidiabetic medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Blood pressure-lowering medication used Sample size	n = 15 ; % = 27	n = 13 ; % = 24
Statins/lipid-lowering medication used Sample size	n = 11 ; % = 20	n = 13 ; % = 23.6

Characteristic	Pioglitazone (N = 55)	Metformin (N = 55)
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR

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35. Feng, 2019

Bibliographic Reference	Feng, W. H.; Bi, Y.; Li, P.; Yin, T. T.; Gao, C. X.; Shen, S. M.; Gao, L. J.; Yang, D. H.; Zhu, D. L.; Effects of liraglutide, metformin and gliclazide on body composition in patients with both type 2 diabetes and non-alcoholic fatty liver disease: A randomized trial; Journal of Diabetes Investigation; 2019; vol. 10 (no. 2); 399-407

35.1. Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.
Trial name / registration number	NCT03068065.
Study type	Randomised controlled trial (RCT)
Study location	China.
Study setting	Outpatient follow-up.
Study dates	No additional information.
Sources of funding	Grants from the National Natural Science Foundation of China (81570737, 81570736, 81370947); Project of National Key Clinical Division, Jiangsu Province's Key Discipline of Medicine (XK201105); Medical and Health Research Projects of Nanjing Health Bureau in Jiangsu Province of China (YKK14055); Nanjing Outstanding Youth Fund Projects in Jiangsu Province of China (JQX13010); Nanjing Science and Technology Development projects in Jiangsu province of China (2013ZD005); Project of Standardized Diagnosis and Treatment of Key Diseases in Jiangsu province of China (2015604); China Diabetes Young Scientific Talent Research Project (2017-N-05); and Nanjing University Central University Basic Scientific Research (14380296).
Inclusion criteria	People with type 2 diabetes mellitus aged 18-70 years; no hypoglycaemic drug use during the preceding 3 months; glycated haemoglobin (HbA1c) levels of 7.0-14% body mass index (BMI) of 20-38kg/m2; diagnosed with NAFLD (defined as fatty liver on ultrasonography with alcoholic intake <140 and <210 g per week for women and men, respectively, not treated medications affecting hepatic steatosis and no history of autoimmune liver

	disease or viral hepatitis) and weight fluctuations of <10% within the past 3 months.
Exclusion criteria	A history of allergy to any of the investigational drugs; pancreatic or severe gastrointestinal disease(s); abnormal liver function (serum AST at least 2.5 times the upper limit of normal); moderate-to-severe renal function impairment (eGFR <60mL/min/1.73m2; calculated using the modification of diet in renal disease equation); congestive heart failure (NYHA grade III or IV); proliferative retinopathy confirmed by an ophthalmologist; other severe concomitant disease(s); medullary thyroid carcinoma; multiple endocrine neoplasia; pregnancy; planning pregnancy.
Recruitment / selection of participants	Recruited from Drum Tower Hospital, which is affiliated with the Nanjing University Medical School, Nanjing, China.
Intervention(s)	Liraglutide N=30 Liraglutide 0.6mg once a day during the first week, 1.2mg once a day during the second week, 1.8mg once a day during the third week until the end of the study. Concomitant therapy: All people were provided with diet and exercise guidance aiming for at least 150 minutes per week or moderate intensity aerobic activity.
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure
Strata 2: People with atherosclerotic cardiovascular diseases	Not stated/unclear
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	People with chronic kidney disease
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	People at higher risk of developing cardiovascular disease Based on triglycerides, NAFLD and presence of diabetes

Subgroup 1: People with frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	People with non-alcoholic fatty liver disease
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Sensitivity analysis category: Enrichment trial status	6) No response criteria
Comparator	Metformin N=31 Metformin 250mg three times a day during the first week, 500mg three times a day during the second week, 1000mg twice a day during the third week until the end of the study. Concomitant therapy: All people were provided with diet and exercise guidance aiming for at least 150 minutes per week or moderate intensity aerobic activity. Gliclazide N=32 Gliclazide 30mg once a day, which was gradually increased to a maximum of 120mg/day in order to reach the target for a fasting capillary plasma glucose concentration of <7.0mmol/L.

	Concomitant therapy: All people were provided with diet and exercise guidance aiming for at least 150 minutes per week or moderate intensity aerobic activity.
Number of participants	93
Duration of follow-up	24 months.
Indirectness	No additional information.
Method of analysis	Not stated/unclear Appears to be completers only.
Additional comments	No additional information.

35.2. Study arms

35.2.1. Liraglutide (N = 30)

Liraglutide 0.6mg once a day during the first week, 1.2mg once a day during the second week, 1.8mg once a day during the third week until the end of the study. Concomitant therapy: All people were provided with diet and exercise guidance aiming for at least 150 minutes per week or moderate intensity aerobic activity.

35.2.2. Metformin (N = 31)

Metformin 250mg three times a day during the first week, 500mg three times a day during the second week, 1000mg twice a day during the third week until the end of the study. Concomitant therapy: All people were provided with diet and exercise guidance aiming for at least 150 minutes per week or moderate intensity aerobic activity.

35.2.3. Gliclazide (N = 32)

Gliclazide 30mg once a day, which was gradually increased to a maximum of 120mg/day in order to reach the target for a fasting capillary plasma glucose concentration of <7.0mmol/L. Concomitant therapy: All people were provided with diet and exercise guidance aiming for at least 150 minutes per week or moderate intensity aerobic activity.

35.3. Characteristics

35.3.1. Arm-level characteristics

Characteristic	Liraglutide (N = 30)	Metformin (N = 31)	Gliclazide (N = 32)
% Male Sample size	n = 21 ; % = 70	n = 19 ; % = 61	n = 19 ; % = 59
Mean age (SD) (years) Mean (SE)	46.8 (1.87)	46.3 (2.3)	48.2 (2.5)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosis (Months) Range	2 to 39	1 to 12	1 to 24
HbA1c (%) Mean (SE)	8.91 (0.32)	9.36 (0.33)	9.07 (0.23)
Blood pressure (mmHg) Mean (SE)	NA (NA)	NA (NA)	NA (NA)
Systolic blood pressure Mean (SE)	120 (3)	127 (4)	122 (3)
Diastolic blood pressure Mean (SE)	78.8 (2)	79 (2)	76 (2)
Heart rate Mean (SD)	NR (NR)	NR (NR)	NR (NR)
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Liraglutide (N = 30)	Metformin (N = 31)	Gliclazide (N = 32)
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Weight (kg) Mean (SE)	81.1 (2.3)	74.8 (2.5)	78.13 (2.43)
BMI (kg/m2) Mean (SE)	28.1 (0.6)	26.8 (0.7)	27.5 (0.5)
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Cholesterol and lipid levels Mean (SE)	NA (NA)	NA (NA)	NA (NA)
Total cholesterol Mean (SE)	4.86 (0.18)	5.18 (0.17)	5.37 (0.22)
HDL cholesterol Mean (SE)	0.99 (0.04)	1.16 (0.06)	1.11 (0.05)
LDL cholesterol Mean (SE)	2.5 (0.14)	2.81 (0.14)	2.93 (0.18)
Triglycerides Mean (SE)	2.73 (0.25)	2.45 (0.25)	2.86 (0.33)
Albumin creatinine ratio Mean (SD)	NR (NR)	NR (NR)	NR (NR)
eGFR (mL/min/1.73m2) Mean (SD)	NR (NR)	NR (NR)	NR (NR)
Other antidiabetic medication used Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Liraglutide (N = 30)	Metformin (N = 31)	Gliclazide (N = 32)
Blood pressure-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Statins/lipid-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR

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36. Ferrannini, 2010

Bibliographic Reference	Ferrannini, E.; Ramos, S. J.; Salsali, A.; Tang, W.; List, J. F.; Dapagliflozin monotherapy in type 2 diabetic patients with inadequate glycemic control by diet and exercise: a randomized, double-blind, placebo-controlled, phase 3 trial; Diabetes Care; 2010; vol. 33 (no. 10); 2217-24

36.1. Study details

Secondary publication of another included study- see primary study for details	No information available.
Other publications associated with this study included in review	None
Trial name / registration number	NCT00528372
Study type	Randomised controlled trial (RCT)
Study location	US, Canada, Mexico, Russia
Study setting	Not reported
Study dates	09/2007 to 07/2008
Sources of funding	Bristol-Myers Squibb and AstraZeneca.
Inclusion criteria	• Treatment naive patients whose hyperglycaemia was inadequately controlled with diet and exercise alone. • BMI ≤45 kg/m2 and fasting C-peptide ≥1.0 ng/ml
Exclusion criteria	History of type 1 diabetes, serum creatinine ≥133 µmol/l (men) or ≥124 µmol/l (women), urine albumin-to-creatinine ratio >200 mg/ mmol, aspartate transaminase and/or alanine transaminase ≥3 times the upper limits of normal, creatine kinase ≥3 times the upper limit of normal, symptoms of severely uncontrolled diabetes (including marked polyuria and polydipsia with >10% weight loss during the last 3 months before enrolment); significant renal, hepatic, haematological, oncological, endocrine, psychiatric or rheumatic disease, a cardiovascular event (including New York Heart Association class III/IV congestive heart failure) within 6 months of enrolment, and severe uncontrolled blood pressure (systolic blood pressure ≥180 mmHg and/or diastolic blood pressure ≥110 mmHg).

Recruitment / selection of participants	Adults with T2DM aged 18 - 77 years were recruited from 85 sites in the US, Canada, Mexico and Russia. Patients were treatment-naive and had hyperglycaemia which was not controlled by diet and exercise alone.
Intervention(s)	Dapagliflozin 2.5 mg once daily in the morning or evening Dapagliflozin 5 mg once daily in the morning or evening Dapagliflozin 10 mg once daily in the morning or evening
Cointervention	None.
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure
Strata 2: People with atherosclerotic cardiovascular diseases	People without other cardiovascular diseases
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	People at higher risk of developing cardiovascular disease
Subgroup 1: People with frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	People with type 2 diabetes first diagnosed above 40 years of age
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear

Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Mixed population
Sensitivity analysis category: Enrichment trial status	5) All treatment naïve
Population subgroups	None
Comparator	Placebo once daily in the morning or evening
Number of participants	N=559
Duration of follow-up	24-week study period and no follow-up reported.
Indirectness	The study included people with T2DM which is directly applicable to the population of interest. But the study was conducted in the US, Canada, Mexico and Russia which may make the results less generalisable to a UK setting.
Method of analysis	Not stated/unclear The method of analysis is not stated but the presentation of results is suggestive of an ITT analysis.
Additional comments	Patients with fasting plasma glucose (FPG) >270 mg/dl at week 4, >240 mg/dl at week 8, or >200 mg/dl at weeks 12–24 were eligible for open-label rescue medication (500 mg metformin, titrated as needed up to 2,000 mg). Patients with A1C >8.0% for 12 weeks despite a maximum tolerated metformin dose were discontinued. Throughout the study, patients received diet/exercise counselling per American Diabetes Association recommendations.

36.2. Study arms

36.2.1. Placebo once daily (N = 75)

Taken orally in the morning

36.2.2. Dapagliflozin 2.5 mg daily (N = 132)

Taken orally in the morning or evening

36.2.3. Dapagliflozin 5 mg daily (N = 167)

Taken orally in the morning or evening

36.2.4. Dapagliflozin 10 mg daily (N = 185)

Taken orally in the morning or evening

36.3. Characteristics

36.3.1. Arm-level characteristics

Characteristic	Placebo once daily (N = 75)	Dapagliflozin 2.5 mg daily (N = 132)	Dapagliflozin 5 mg daily (N = 167)	Dapagliflozin 10 mg daily (N = 185)
% Male No of events	n = 31 ; % = 41.3	n = 65 ; % = 49	n = 84 ; % = 50.3	n = 86 ; % = 46.5
Mean age (SD) Mean (SD)	52.7 (10.3)	53.7 (11.6)	52.5 (10.87)	50.07 (10.41)
Ethnicity Nominal	NR	NR	NR	NR
Comorbidities Nominal	NR	NR	NR	NR
Presence of frailty Nominal	NR	NR	NR	NR
Time since type 2 diabetes diagnosis Nominal	NR	NR	NR	NR
Blood pressure Nominal	NR	NR	NR	NR
Heart rate Nominal	NR	NR	NR	NR
Smoking status Nominal	NR	NR	NR	NR

Characteristic	Placebo once daily (N = 75)	Dapagliflozin 2.5 mg daily (N = 132)	Dapagliflozin 5 mg daily (N = 167)	Dapagliflozin 10 mg daily (N = 185)
Alcohol consumption Nominal	NR	NR	NR	NR
Presence of severe mental illness Nominal	NR	NR	NR	NR
People with significant cognitive impairment Nominal	NR	NR	NR	NR
People with a learning disability Nominal	NR	NR	NR	NR
Number of people with obesity Nominal	NR	NR	NR	NR
Albumin creatinine ratio Nominal	NR	NR	NR	NR
eGFR (mL/min/1.73m2) Nominal	NR	NR	NR	NR
Other antidiabetic medication used Nominal	NR	NR	NR	NR
Blood pressure-lowering medication used Nominal	NR	NR	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR	NR	NR

Characteristic	Placebo once daily (N = 75)	Dapagliflozin 2.5 mg daily (N = 132)	Dapagliflozin 5 mg daily (N = 167)	Dapagliflozin 10 mg daily (N = 185)
Other treatment being received Nominal	NR	NR	NR	NR

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37. Foley, 2011

Bibliographic Reference	Foley, J. E.; Bunck, M. C.; Möller-Goede, D. L.; Poelma, M.; Nijpels, G.; Eekhoff, E. M.; Schweizer, A.; Heine, R. J.; Diamant, M.; Beta cell function following 1 year vildagliptin or placebo treatment and after 12 week washout in drug-naive patients with type 2 diabetes and mild hyperglycaemia: a randomised controlled trial; Diabetologia; 2011; vol. 54 (no. 8); 1985-91

37.1. Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	NCT00260156
Study type	Randomised controlled trial (RCT)
Study location	The Netherlands
Study setting	No additional information
Study dates	No additional information
Sources of funding	Sponsored by the Novartis Pharmaceutical Cooperation
Inclusion criteria	Diagnosed type 2 diabetes ≥30 years of age HbA1c ≤7.5% BMI 22-45 kg/m2
Exclusion criteria	Treatment with oral antidiabetic drugs within 12 weeks or for >3 consecutive months at any point

Recruitment / selection of participants	Recruited from a single centre, method not reported
Intervention(s)	Those allocated to the intervention arm received 100 mg vildagliptin per day
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear
Strata 2: People with atherosclerotic cardiovascular diseases	Not stated/unclear
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	People at higher risk of developing cardiovascular disease
Subgroup 1: People with frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Mixed population
Subgroup 5: eGFR category at baseline	Not stated/unclear

Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Sensitivity analysis category: Enrichment trial status	5) All treatment naïve
Population subgroups	No additional information
Comparator	Those allocated to the comparator arm received once daily placebo
Number of participants	59 randomised 29 received vildagliptin, 27 completed 30 received placebo, 27 completed
Duration of follow-up	64 weeks
Indirectness	None
Method of analysis	Modified ITT All participants who received one dose of their allocated treatment, and had at least one follow-up measurement
Additional comments	None

37.2. Study arms

37.2.1. Vildagliptin (N = 29)

100 mg vildagliptin per day

37.2.2. Placebo (N = 30)

Once daily placebo

37.3. Characteristics

37.3.1. Arm-level characteristics

Characteristic	Vildagliptin (N = 29)	Placebo (N = 30)
% Male Sample size	n = 17 ; % = 59	n = 18 ; % = 60

Characteristic	Vildagliptin (N = 29)	Placebo (N = 30)
Mean age (SD) (years) Mean (SD)	57.4 (9.4)	57 (6.7)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosis (years) Mean (SD)	1.4 (2.8)	0.6 (1.1)
HbA1c (%) Mean (SD)	6 (1.2)	6 (0.7)
Blood pressure Nominal	NR	NR
Heart rate Nominal	NR	NR
Smoking status Nominal	NR	NR
Alcohol consumption Nominal	NR	NR
Presence of severe mental illness Nominal	NR	NR
People with significant cognitive impairment Nominal	NR	NR
People with a learning disability Nominal	NR	NR
Weight (kg) Mean (SD)	90.2 (15.9)	87.6 (19.1)
BMI (kg/m²) Mean (SD)	29.9 (4.9)	29.2 (4.4)

Characteristic	Vildagliptin (N = 29)	Placebo (N = 30)
Number of people with obesity Nominal	NR	NR
Cholesterol and lipid levels Nominal	NR	NR
Albumin creatinine ratio Nominal	NR	NR
eGFR (mL/min/1.73m2) Nominal	NR	NR
Other antidiabetic medication used Nominal	NR	NR
Blood pressure-lowering medication used Nominal	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

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38. Foley, 2009

Bibliographic Reference	Foley, J. E.; Sreenan, S.; Efficacy and safety comparison between the DPP-4 inhibitor vildagliptin and the sulfonylurea gliclazide after two years of monotherapy in drug-naïve patients with type 2 diabetes; Horm Metab Res; 2009; vol. 41 (no. 12); 905-9

38.1. Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	NCT00102388
Study type	Randomised controlled trial (RCT)
Study location	Multinational - Europe, Latin America and South Africa
Study setting	No additional information
Study dates	No additional information
Sources of funding	Authored by Novartis
Inclusion criteria	Diagnosed with type 2 diabetes HbA1c 7.5-11.0% whilst receiving no pharmacological treatment (no oral antidiabetic drugs for at least 3 months, and never for 3 or more consecutive months) Aged ≥18 years BMI 22-45 kg/m2 Fasting plasma glucose <15 mmol/L
Exclusion criteria	Type 1 diabetes Pregnant or lactating

	Pancreatic injury Secondary forms of diabetes Symptomatic autonomic neuropathy Acute infection Congestive heart failure (NYHA class III or IV) ECG abnormalities Cirrhosis Chronic active hepatitis
Recruitment / selection of participants	Recruited from 151 centres, method not reported
Intervention(s)	Participants received 50 mg vildagliptin twice daily in addition to placebo gliclazide, which was titrated according to FPG values Metformin could be prescribed as rescue medication in addition to blinded study medication according to clinical judgment and the metformin package insert at or after week 24 for patients who had reached the maximum placebo dose and had an unsatisfactory therapeutic effect as defined by a confirmed FPG >13.3 mmol/L or symptoms of worsening hyperglycaemia
Strata 1: People with type 2 diabetes mellitus and heart failure	Mixed population
Strata 2: People with atherosclerotic cardiovascular diseases	Not stated/unclear
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear
Strata 4: People with type 2 diabetes	People at higher risk of developing cardiovascular disease

mellitus and high cardiovascular risk	
Subgroup 1: People with frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Mixed population
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Sensitivity analysis category: Enrichment trial status	7) Mixed population
Population subgroups	No additional information
Comparator	Participants initially received 80 mg gliclazide per daily in addition to placebo vildagliptin. Gliclazide dose was titrated during the first 24 weeks of the trial up to a maximum of 320 mg per day. Patients were titrated to the next dose level (50 mg bid vildagliptin / 160 mg gliclazide after 4 weeks, 50 mg bid vildagliptin / 240 mg gliclazide after 8 weeks, and 50 mg bid vildagliptin / 320 mg gliclazide after 12 weeks), if FPG was >7 mmol/L titration was not contraindicated in the investigator's opinion due to the risk of hypoglycaemia. The dose of gliclazide could be adjusted downward to no less than 80 mg at any time if there were three Grade 1 hypoglycaemic events per week (defined as symptoms suggestive of low blood glucose confirmed by self-monitored blood glucose measurement of <3.1 mmol/L plasma glucose equivalent, not requiring the assistance of another party), if there was a Grade 2 hypoglycaemic event (requiring the assistance of another party) or if there were 3 or more asymptomatic glucose values <3.1 mmol/L per week.

	Metformin could be prescribed as rescue medication in addition to blinded study medication according to clinical judgment and the metformin package insert at or after week 24 for patients who had reached the maximum placebo dose and had an unsatisfactory therapeutic effect as defined by a confirmed FPG >13.3 mmol/L or symptoms of worsening hyperglycaemia
Number of participants	1092 randomised 546 received vildagliptin, 409 completed 546 received gliclazide, 402 completed
Duration of follow-up	104 weeks
Indirectness	None
Method of analysis	ITT
Additional comments	None

38.2. Study arms

38.2.1. Vildagliptin (N = 546)

50 mg vildagliptin, twice daily

38.2.2. Gliclazide (N = 546)

Initially 80 mg gliclazide once per day, titrated up to 320 mg per day depending on fasting glucose response to treatment

38.3. Characteristics

38.3.1. Arm-level characteristics

Characteristic	Vildagliptin (N = 546)	Gliclazide (N = 546)
% Male Sample size	n = 321 ; % = 59	n = 288 ; % = 53
Mean age (SD) (years) Mean (SD)	55.2 (10.6)	54.3 (10.4)

Characteristic	Vildagliptin (N = 546)	Gliclazide (N = 546)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Caucasian Sample size	n = 405 ; % = 74	n = 401 ; % = 73
Hispanic/Latino Sample size	n = 82 ; % = 15	n = 82 ; % = 15
Other Sample size	n = 59 ; % = 11	n = 63 ; % = 12
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosis (years) Mean (SD)	2.4 (4.3)	1.9 (3.1)
HbA1c (%) Mean (SD)	8.6 (1)	8.7 (1.1)
Blood pressure Nominal	NR	NR
Heart rate Nominal	NR	NR
Smoking status Nominal	NR	NR
Alcohol consumption Nominal	NR	NR
Presence of severe mental illness Nominal	NR	NR
People with significant cognitive impairment Nominal	NR	NR

Characteristic	Vildagliptin (N = 546)	Gliclazide (N = 546)
People with a learning disability Nominal	NR	NR
Weight (kg) Mean (SD)	84.2 (16.3)	84.3 (17.6)
BMI (kg/m²) Mean (SD)	30.6 (5)	30.8 (5.5)
Number of people with obesity Sample size	n = 276 ; % = 51	n = 272 ; % = 50
Cholesterol and lipid levels Nominal	NR	NR
Albumin creatinine ratio Nominal	NR	NR
eGFR (mL/min/1.73m2) Nominal	NR	NR
Other antidiabetic medication used Nominal	NR	NR
Blood pressure-lowering medication used Nominal	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

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39. Frederich, 2012

Bibliographic Reference	Frederich, R.; McNeill, R.; Berglind, N.; Fleming, D.; Chen, R.; The efficacy and safety of the dipeptidyl peptidase-4 inhibitor saxagliptin in treatment-naive patients with type 2 diabetes mellitus: A randomized controlled trial; Diabetol Metab Syndr; 2012; vol. 4 (no. 1)

39.1. Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.
Trial name / registration number	NCT00316082.
Study type	Randomised controlled trial (RCT)
Study location	72 sites in the United States, Russia, India and Taiwan.
Study setting	Outpatient follow up.
Study dates	No additional information.
Sources of funding	Funding was provided by Bristol-Myers Squibb and AstraZeneca.
Inclusion criteria	18-77 years; type 2 diabetes mellitus and inadequate glycaemic control (HbA1c 7.0-10.0%) with diet and exercise alone; BMI no more than 40kg/m2; C-peptide no more than 1.0ng/mL.
Exclusion criteria	Symptoms of poorly controlled diabetes; history of diabetic ketoacidosis or hyperosmolar non-ketotic coma; insulin therapy within 1 year of screening; cardiovascular event within 6 months prior to study entry or New York Heart Association stage III/IV congestive heart failure and/or known left ventricular ejection fraction no less than 40%; significant renal history; alcohol or drug abuse within the previous year; treatment with potent CYP3A4 inhibitors or inducers; immunocompromised individuals; active liver disease or clinically significant abnormal results on hepatic, renal, endocrine, metabolic or hematologic screening tests.
Recruitment / selection of participants	No additional information.

Intervention(s)	Saxagliptin N=291 Saxagliptin split into four arms: saxagliptin 2.5mg once in the morning (n=74), saxagliptin 5mg once in the morning (n=74), saxagliptin 2.5mg once in the morning with titration up to 5mg once in the morning (n=71), and saxagliptin 5mg once in the evening (n=72). All were given this for 24 weeks. (The trial also included a 52 week extension phase. However, the placebo group was switched to metformin for this time which makes it hard to compare the saxagliptin arm as the treatment duration is no longer equivalent. Therefore, this time period is not being compared in this analysis).
Cointervention	Concomitant therapy: Rescue therapy was given if the fasting plasma glucose reached >240mg/dL at week 6, >220mg/dL at week 8 and >200mg/dL at weeks 12, 16, 20 and 24.
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure
Strata 2: People with atherosclerotic cardiovascular diseases	People without other cardiovascular diseases 13% of the people in the study
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic	People without non-alcoholic fatty liver disease

fatty liver disease	
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Sensitivity analysis category: Enrichment trial status	7) Mixed population Never received medical treatment or received treatment for a total of <6 months since original diagnosis
Population subgroups	No additional information.
Comparator	Placebo N=74 Matching placebo.
Number of participants	365
Duration of follow-up	24 weeks.
Indirectness	No additional information.
Method of analysis	ITT Last observation carried forward - does not include all of the participants a lot of the time and the analysis is a bit unclear
Additional comments	No additional information.

39.2. Study arms

39.2.1. Saxagliptin (N = 291)

Saxagliptin split into four arms: saxagliptin 2.5mg once in the morning (n=74), saxagliptin 5mg once in the morning (n=74), saxagliptin 2.5mg once in the morning with titration up to 5mg once in the morning (n=71), and saxagliptin 5mg once in the evening (n=72). All were given this for 24 weeks. (The trial also included a 52 week extension phase. However, the placebo group was switched to metformin for this time which makes it hard to compare the saxagliptin arm as the treatment duration is no longer equivalent. Therefore, this time period is not being compared in this analysis). Concomitant therapy: Rescue therapy was given if the fasting plasma

glucose reached >240mg/dL at week 6, >220mg/dL at week 8 and >200mg/dL at weeks 12, 16, 20 and 24.

39.2.2. Placebo (N = 74)

Matching placebo. Concomitant therapy: Rescue therapy was given if the fasting plasma glucose reached >240mg/dL at week 6, >220mg/dL at week 8 and >200mg/dL at weeks 12, 16, 20 and 24.

39.3. Characteristics

39.3.1. Arm-level characteristics

Characteristic	Saxagliptin (N = 291)	Placebo (N = 74)
% Male Sample size	n = 133 ; % = 46	n = 35 ; % = 47
Mean age (SD) (years) Mean (SD)	54.8 (10.37)	55.6 (10.32)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 201 ; % = 69	n = 53 ; % = 72
Black/African American Sample size	n = 20 ; % = 7	n = 4 ; % = 5
Asian Sample size	n = 68 ; % = 23	n = 17 ; % = 23
Other Sample size	n = 2 ; % = 0.7	n = 0 ; % = 0
Comorbidities Sample size	n = NA ; % = NA	n = NA ; % = NA
Congestive heart failure Sample size	n = 25 ; % = 9	n = 7 ; % = 10
Coronary artery disease Sample size	n = 40 ; % = 14	n = 9 ; % = 12

Characteristic	Saxagliptin (N = 291)	Placebo (N = 74)
Hypertension Sample size	n = 165 ; % = 57	n = 47 ; % = 64
Hypercholesterolaemia Sample size	n = 102 ; % = 35	n = 17 ; % = 23
Mixed dyslipidaemia Sample size	n = 55 ; % = 19	n = 9 ; % = 12
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosis (years) Mean (SD)	1.7 (3.3)	1.7 (2.8)
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR
Other antidiabetic medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Blood pressure-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Statins/lipid-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR

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40. Gantz, 2017

Bibliographic Reference	Gantz, I.; Okamoto, T.; Ito, Y.; Okuyama, K.; O'Neill, E. A.; Kaufman, K. D.; Engel, S. S.; Lai, E.; A randomized, placebo- and sitagliptin-controlled trial of the safety and efficacy of omarigliptin, a once-weekly dipeptidyl peptidase-4 inhibitor, in Japanese patients with type 2 diabetes; Diabetes Obes Metab; 2017; vol. 19 (no. 11); 1602-1609

40.1. Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	Omarigliptin Protocol 020; ClinicalTrials.gov: NCT01703221
Study type	Randomised controlled trial (RCT)
Study location	Japan
Study setting	No additional information
Study dates	October 2012 - April 2014
Sources of funding	Funding for this study was provided by MSD K.K., a subsidiary of Merck & Co
Inclusion criteria	Japanese men and women Aged ≥20 years Type 2 diabetes Body mass index 18-40 kg/m2 Participants who were treatment-naïve (never on an oral antihyperglycaemic agent) or off AHA medication for ≥6 weeks and had an HbA1c ≥7.0% and ≤10.0% were eligible for the study; those on oral AHA medication monotherapy with an HbA1c ≥6.5% and ≤9.0%, and after a 6-week AHA wash-out period, HbA1c ≥7.0% and ≤10.0%, were also eligible for the study. At the end of the 2 week screening period participants were

	required to have an HbA1c level between ≥7.0% and ≤10.0% and an FPG level ≤12.8 mmol/L
Exclusion criteria	Type 1 diabetes History of ketoacidosis, active liver disease, significant cardiovascular disease, a history of malignancy or haematological disorders Previously treated with sitagliptin or omarigliptin at any time, or with thiazolidinediones or insulin therapy within 12 weeks prior to the screening visit Estimated glomerular filtration rate <50 mL/min/1.73 m2 Alanine aminotransferase or aspartate aminotransferase >2 times the upper limit of normal Triglycerides >6.78 mmol/L Thyroid-stimulating hormone outside the central laboratory normal range
Recruitment / selection of participants	No additional information
Intervention(s)	Following a 2-week single-blind placebo run-in period, participants allocated to the intervention arm received sitagliptin 50 mg once daily and placebo matching omarigliptin 25 mg once weekly Participants not meeting prespecified glycaemic control criteria post-randomization (from week 4 to week 24, FPG >13.3 mmol/L; after week 24, FPG >11.1 mmol/ L) were discontinued from the trial *Study arm containing omarigliptin plus sitagliptin placebo was excluded from this review due to not being a relevant treatment*
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear
Strata 2: People with atherosclerotic cardiovascular diseases	People without other cardiovascular diseases
Strata 3: People with type 2 diabetes	Not stated/unclear

mellitus and chronic kidney disease	
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	People at higher risk of developing cardiovascular disease
Subgroup 1: People with frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Mixed population
Subgroup 5: eGFR category at baseline	eGFR ≥30mL/min/1.73m2
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Sensitivity analysis category: Enrichment trial status	7) Mixed population
Population subgroups	No additional information
Comparator	Following a 2-week single-blind placebo run-in period, participants allocated to the comparator arm received placebo matching sitagliptin once daily and placebo matching omarigliptin once weekly Participants not meeting prespecified glycaemic control criteria post-randomization (from week 4 to week 24, FPG >13.3 mmol/L; after week 24, FPG >11.1 mmol/ L) were discontinued from the trial

Number of participants	414 randomised 165 received sitagliptin, 161 completed 83 received placebo, 80 completed 166 received omarigliptin (excluded from this review)
Duration of follow-up	24 weeks (28 week open-label period excluded due to inappropriate study design)
Indirectness	None
Method of analysis	ITT
Additional comments	None

40.2. Study arms

40.2.1. Sitagliptin (N = 165)

50 mg sitagliptin once per day, plus omarigliptin placebo once per week

40.2.2. Placebo (N = 83)

Placebo sitagliptin once per day plus placebo omarigliptin once per week

40.3. Characteristics

40.3.1. Arm-level characteristics

Characteristic	Sitagliptin (N = 165)	Placebo (N = 83)
% Male Sample size	n = 115 ; % = 70	n = 57 ; % = 69
Mean age (SD) (years) Mean (SD)	60 (9)	61 (9)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR

Characteristic	Sitagliptin (N = 165)	Placebo (N = 83)
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosis (years) Mean (SD)	7.4 (5.3)	8.6 (5.1)
HbA1c Mean (SD)	8 (0.8)	8.1 (0.7)
Blood pressure Nominal	NR	NR
Heart rate Nominal	NR	NR
Smoking status Nominal	NR	NR
Alcohol consumption Nominal	NR	NR
Presence of severe mental illness Nominal	NR	NR
People with significant cognitive impairment Nominal	NR	NR
People with a learning disability Nominal	NR	NR
Weight (kg) Mean (SD)	69 (14)	64 (12)
BMI (kg/m²) Mean (SD)	25.4 (4.2)	24.3 (3.3)
Number of people with obesity Nominal	NR	NR
Cholesterol and lipid levels Nominal	NR	NR
Albumin creatinine ratio Nominal	NR	NR

Characteristic	Sitagliptin (N = 165)	Placebo (N = 83)
eGFR (mL/min/1.73m2) Nominal	NR	NR
Other antidiabetic medication used Prior antihyperglycaemic medication use Sample size	n = 61 ; % = 37	n = 32 ; % = 39
Blood pressure-lowering medication used Nominal	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

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41. Garber, 2009

Bibliographic Reference	Garber, A.; Henry, R.; Ratner, R.; Garcia-Hernandez, P. A.; Rodriguez-Pattzi, H.; Olvera-Alvarez, I.; Hale, P. M.; Zdravkovic, M.; Bode, B.; Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): a randomised, 52-week, phase III, double-blind, parallel-treatment trial; Lancet; 2009; vol. 373 (no. 9662); 473-81

41.1. Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	NTC00294723
Study type	Randomised controlled trial (RCT)
Study location	USA and Mexico
Study setting	No additional information
Study dates	February 2006 - November 2007
Sources of funding	Funded by Novo Nordisk
Inclusion criteria	Aged 18-80 years BMI ≤45 kg/m2 Diagnosed type 2 diabetes Treated with diet and exercise alone (36.5%), or with up to half the highest dose of oral antidiabetic drug monotherapy (63.5%) HbA1c 7-11% if treated with diet and exercise, or 7-10% if treated with monotherapy
Exclusion criteria	Insulin treatment during the previous 3 months (except short-term treatment for intercurrent illness)

	Treatment with systemic corticosteroids Hypoglycaemia unawareness or recurrent severe hypoglycaemia Impaired liver function (aspartate aminotransferase or alanine aminotransferase concentrations ≥2·5 times upper normal range).
Recruitment / selection of participants	No additional information
Intervention(s)	Participants allocated to the intervention arms received daily subcutaneous liraglutide at a dose of either 1.2 or 1.8 mg. All participants initially received 0.6 mg per day, which was up titrated to either 1.2 or 1.8 mg in 0.6 mg increments per week. Injections were administered at any time of day in the upper arm, abdomen or thigh with a pre-filled pen injection device. Participants also received once-daily placebo glimepiride which was taken orally before the first morning meal. *1.2 and 1.8 mg liraglutide arms combined for this review*
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear
Strata 2: People with atherosclerotic cardiovascular diseases	Not stated/unclear
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	People at higher risk of developing cardiovascular disease
Subgroup 1: People with frailty	Not stated/unclear

Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Mixed population
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Sensitivity analysis category: Enrichment trial status	5) All treatment naïve Referring to those treated with diet and exercise that are of interest to this review
Population subgroups	Study included participants who were treatment naïve, and participants who had been treated previously with monotherapy which was discontinued at study entry, but without a washout period. Only outcomes that report the treatment naïve population alone are included in this analysis.
Comparator	Participants allocated to the comparator received once-daily 8 mg glimepiride administered orally. Glimepiride was initially administered as 2 mg once-daily, which doubled over the following 2 weeks until 8 mg was reached and maintained for the rest of the study. Participant also received once-daily subcutaneous placebo which was self-administered in the same manner as liraglutide.
Number of participants	746 randomised 251 received 1.2 mg liraglutide, 142 completed 246 received 1.8 mg liraglutide, 154 completed 248 received glimepiride, 130 completed
Duration of follow-up	52 weeks
Indirectness	None
Method of analysis	ITT
Additional comments	None

41.2. Study arms

41.2.1. 1.2 mg Liraglutide (N = 251)

Once daily 1.2 mg subcutaneous liraglutide

41.2.2. 1.8 mg Liraglutide (N = 247)

Once daily 1.8 mg subcutaneous liraglutide

41.2.3. Glimepiride (N = 248)

Once daily 8 mg oral glimepiride

41.3. Characteristics

41.3.1. Arm-level characteristics

Characteristic	1.2 mg Liraglutide (N = 251)	1.8 mg Liraglutide (N = 247)	Glimepiride (N = 248)
% Male Sample size	n = 117 ; % = 47	n = 121 ; % = 49	n = 133 ; % = 54
Mean age (SD) (years) Mean (SD)	53.7 (11)	52 (10.8)	53.4 (10.9)
White Sample size	n = 200 ; % = 80	n = 186 ; % = 75	n = 197 ; % = 77
Black Sample size	n = 34 ; % = 14	n = 30 ; % = 12	n = 30 ; % = 12
Asian Sample size	n = 5 ; % = 2	n = 12 ; % = 6	n = 9 ; % = 4
Other Sample size	n = 12 ; % = 5	n = 19 ; % = 7	n = 7 ; % = 7
Comorbidities Nominal	NR	NR	NR
Presence of frailty	NR	NR	NR

Characteristic	1.2 mg Liraglutide (N = 251)	1.8 mg Liraglutide (N = 247)	Glimepiride (N = 248)
Nominal			
Time since type 2 diabetes diagnosis (years) Mean (SD)	5.2 (5.5)	5.3 (5.1)	5.6 (5.1)
HbA1c (%) Mean (SD)	8.3 (1)	8.3 (1.1)	8.4 (1.2)
SBP Mean (SD)	127.6 (14.3)	128.1 (13.9)	130 (16.1)
DBP Mean (SD)	78.5 (8.3)	78.8 (8.4)	79.5 (8.6)
Heart rate Nominal	NR	NR	NR
Smoking status Nominal	NR	NR	NR
Alcohol consumption Nominal	NR	NR	NR
Presence of severe mental illness Nominal	NR	NR	NR
People with significant cognitive impairment Nominal	NR	NR	NR
People with a learning disability Nominal	NR	NR	NR
Weight (kg) Mean (SD)	92.5 (19.2)	92.8 (20.7)	93.4 (19.2)
BMI (kg/m²) Mean (SD)	33.2 (5.6)	32.8 (6.3)	33.2 (5.6)
Number of people with obesity	NR	NR	NR

Characteristic	1.2 mg Liraglutide (N = 251)	1.8 mg Liraglutide (N = 247)	Glimepiride (N = 248)
Nominal			
Cholesterol and lipid levels Nominal	NR	NR	NR
Albumin creatinine ratio Nominal	NR	NR	NR
eGFR (mL/min/1.73m2) Nominal	NR	NR	NR
Other antidiabetic medication used Nominal	NR	NR	NR
Blood pressure-lowering medication used Nominal	NR	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR	NR
Other treatment being received Nominal	NR	NR	NR

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42. Goldner, 1971

Bibliographic Reference	Goldner, MG; Knatterud, GL; Prout, TE; Effects of hypoglycaemic agents on vascular complications in patients with adult-onset diabetes. 3. Clinical implications of UGDP results; JAMA; 1971; vol. 218 (no. 9); 1400-1410

42.1. Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.
Trial name / registration number	No additional information.
Study type	Randomised controlled trial (RCT)
Study location	United States of America.
Study setting	Outpatient follow-up.
Study dates	1961 to 1966.
Sources of funding	No additional information.
Inclusion criteria	Newly diagnosed diabetes.
Exclusion criteria	No additional information.
Recruitment / selection of participants	No additional information.
Intervention(s)	Tolbutamide N=204 1.5 grams per day. Concomitant therapy: No additional information.
Cointervention	No additional information.

Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear
Strata 2: People with atherosclerotic cardiovascular diseases	Not stated/unclear
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Sensitivity analysis	8) Not reported

category: Enrichment trial status	
Population subgroups	No additional information.
Comparator	Insulin N=414 Two groups combined: insulin standard (n=210) and insulin variable (n=204). Insulin standard includes 10 to 16 units of insulin per day depending on the person's estimated body surface area. Insulin variable is a variable amount of insulin required to maintain the normal blood glucose levels. Concomitant therapy: No additional information. Placebo N=205 Matching placebo. Concomitant therapy: No additional information.
Number of participants	823
Duration of follow-up	5 years
Indirectness	No additional information.
Method of analysis	Not stated/unclear
Additional comments	No additional information.

42.2. Study arms

42.2.1. Tolbutamide (N = 204)

1.5 grams per day. Concomitant therapy: No additional information.

42.2.2. Insulin (N = 414)

Two groups combined: insulin standard (n=210) and insulin variable (n=204). Insulin standard includes 10 to 16 units of insulin per day depending on the person's estimated body surface area. Insulin variable is a variable amount of insulin required

to maintain the normal blood glucose levels. Concomitant therapy: No additional information.

42.2.3. Placebo (N = 205)

Matching placebo. Concomitant therapy: No additional information.

42.3. Characteristics

42.3.1. Study-level characteristics

Characteristic	Study (N = 823)
% Male Sample size	n = NA ; % = 72
Mean age (SD) Mean (SD)	53 (NA)
Ethnicity Sample size	n = NA ; % = 53

42.3.2. Arm-level characteristics

Characteristic	Tolbutamide (N = 204)	Insulin (N = 414)	Placebo (N = 205)
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosis Mean (SD)	NR (NR)	NR (NR)	NR (NR)
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Tolbutamide (N = 204)	Insulin (N = 414)	Placebo (N = 205)
Sample size			
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Other antidiabetic medication used Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Blood pressure-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Statins/lipid-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR

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43. Goldstein, 2007

Bibliographic Reference	Goldstein, B. J.; Feinglos, M. N.; Lunceford, J. K.; Johnson, J.; Williams-Herman, D. E.; Effect of initial combination therapy with sitagliptin, a dipeptidyl peptidase-4 inhibitor, and metformin on glycemic control in patients with type 2 diabetes; Diabetes Care; 2007; vol. 30 (no. 8); 1979-87

43.1. Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.
Trial name / registration number	NCT00103857. Sitagliptin 036.
Study type	Randomised controlled trial (RCT)
Study location	Multicentre trial.
Study setting	Outpatient follow-up.
Study dates	No additional information.
Sources of funding	Funded by Merck & Company, Whitehouse Station, New Jersey.
Inclusion criteria	People with type 2 diabetes; 18-78 years of age; either on or not on an oral hyperglycaemic agent at the screening visit.
Exclusion criteria	Type 1 diabetes; unstable cardiac disease; significant renal impairment (estimated creatinine clearance <60mL/min); or elevated (more than twofold the upper limit of normal) ALT or AST.
Recruitment / selection of participants	No additional information.
Intervention(s)	Sitagliptin + Metformin N=372 Two groups: Sitagliptin 50mg and metformin 1000mg twice a day (n=182) and sitagliptin 50mg and metformin 500mg twice a day (n=190).

	Concomitant therapy: No additional information.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear
Strata 2: People with atherosclerotic cardiovascular diseases	Not stated/unclear
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	People at higher risk of developing cardiovascular disease Based on BMI and presence of diabetes
Subgroup 1: People with frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria	Not stated/unclear

category at baseline	
Sensitivity analysis category: Enrichment trial status	7) Mixed population
Population subgroups	No additional information.
Comparator	Metformin N=364 Two groups: Metformin 1000mg twice a day (n=182) and metformin 500mg twice a day (n=182). Concomitant therapy: No additional information. Sitagliptin N=179 Sitagliptin 100mg once a day. Concomitant therapy: No additional information. Placebo N=176 Matching placebo. Concomitant therapy: No additional information.
Number of participants	1091.
Duration of follow-up	24 weeks.
Indirectness	
Method of analysis	Other All people treated (all people who received at least one dose of treatment and who had both a baseline and at least one postbaseline measurement).
Additional comments	No additional information.

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43.2. Study arms

43.2.1. Sitagliptin + Metformin (N = 372)

Two groups: Sitagliptin 50mg and metformin 1000mg twice a day (n=182) and sitagliptin 50mg and metformin 500mg twice a day (n=190). Concomitant therapy: No additional information.

43.2.2. Metformin (N = 364)

Two groups: Metformin 1000mg twice a day (n=182) and metformin 500mg twice a day (n=182). Concomitant therapy: No additional information.

43.2.3. Sitagliptin (N = 179)

Sitagliptin 100mg once a day. Concomitant therapy: No additional information.

43.2.4. Placebo (N = 176)

Matching placebo. Concomitant therapy: No additional information.

43.3. Characteristics

43.3.1. Arm-level characteristics

Characteristic	Sitagliptin + Metformin (N = 372)	Metformin (N = 364)	Sitagliptin (N = 179)	Placebo (N = 176)
% Male Sample size	n = 182 ; % = 49	n = 171 ; % = 47	n = 93 ; % = 52	n = 93 ; % = 53
Mean age (SD) (years) Mean (SD)	53.7 (9.8)	53.3 (9.9)	53.3 (10.2)	53.6 (10)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 197 ; % = 53	n = 171 ; % = 53	n = 93 ; % = 52	n = 81 ; % = 46
Black Sample size	n = 27 ; % = 7	n = 21 ; % = 6	n = 11 ; % = 6	n = 17 ; % = 10
Hispanic	n = 104 ; % = 28	n = 94 ; % = 26	n = 52 ; % = 29	n = 47 ; % = 27

Characteristic	Sitagliptin + Metformin (N = 372)	Metformin (N = 364)	Sitagliptin (N = 179)	Placebo (N = 176)
Sample size				
Asian Sample size	n = 20 ; % = 5	n = 24 ; % = 7	n = 6 ; % = 3	n = 12 ; % = 7
Other Sample size	n = 24 ; % = 7	n = 32 ; % = 9	n = 17 ; % = 10	n = 19 ; % = 11
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosis (years) Mean (SD)	4.5 (4.5)	4.5 (4.2)	4.4 (4.6)	4.6 (4.9)
HbA1c (%) Mean (SD)	8.8 (1)	8.8 (1)	8.9 (1)	8.7 (1)
Blood pressure Mean (SD)	NR (NR)	NR (NR)	NR (NR)	NR (NR)
Heart rate Mean (SD)	NR (NR)	NR (NR)	NR (NR)	NR (NR)
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Sitagliptin + Metformin (N = 372)	Metformin (N = 364)	Sitagliptin (N = 179)	Placebo (N = 176)
Sample size				
Weight Mean (SD)	NR (NR)	NR (NR)	NR (NR)	NR (NR)
BMI (kg/m2) Mean (SD)	32.3 (6.7)	32.2 (7)	31.2 (5.9)	32.5 (6.7)
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Cholesterol and lipid levels Mean (SD)	NR (NR)	NR (NR)	NR (NR)	NR (NR)
Albumin creatinine ratio Mean (SD)	NR (NR)	NR (NR)	NR (NR)	NR (NR)
eGFR (mL/min/1.73m2) Mean (SD)	NR (NR)	NR (NR)	NR (NR)	NR (NR)
Other antidiabetic medication used Sample size	n = 182 ; % = 49	n = 183 ; % = 50	n = 88 ; % = 49	n = 88 ; % = 50
Blood pressure-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Statins/lipid-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR

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44. Grant, 1996

Bibliographic Reference	Grant, P. J.; The effects of high- and medium-dose metformin therapy on cardiovascular risk factors in patients with type II diabetes; Diabetes Care; 1996; vol. 19 (no. 1); 64-6

44.1. Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.
Trial name / registration number	No additional information.
Study type	Randomised controlled trial (RCT)
Study location	United Kingdom.
Study setting	Outpatient follow-up.
Study dates	No additional information.
Sources of funding	Supported by Lipha Pharmaceuticals, West Drayton, Middlesex, U.K.
Inclusion criteria	People with type 2 diabetes.
Exclusion criteria	Insulin therapy; BMI <25; fasting blood glucose on treatment of <6 mmol/L.
Recruitment / selection of participants	No additional information.
Intervention(s)	Metformin N=52 Metformin 1500mg/day (n=25) or 3000mg/day (n=27) for 6 months. People receiving 3000mg of metformin initially received 1500mg daily for 3 weeks, before increasing the dose for the remainder of the study. Concomitant therapy: No additional information.

Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear
Strata 2: People with atherosclerotic cardiovascular diseases	Not stated/unclear
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Sensitivity analysis	8) Not reported

category: Enrichment trial status	
Population subgroups	No additional information.
Comparator	Placebo N=23 Matching placebo. Concomitant therapy: No additional information.
Number of participants	75
Duration of follow-up	6 months
Indirectness	No additional information.
Method of analysis	Not stated/unclear Appears to be completers only
Additional comments	No additional information.

44.2. Study arms

44.2.1. Metformin (N = 52)

Metformin 1500mg/day (n=25) or 3000mg/day (n=27) for 6 months. People receiving 3000mg of metformin initially received 1500mg daily for 3 weeks, before increasing the dose for the remainder of the study. Concomitant therapy: No additional information.

44.2.2. Placebo (N = 23)

Matching placebo. Concomitant therapy: No additional information.

44.3. Characteristics

44.3.1. Arm-level characteristics

Characteristic	Metformin (N = 52)	Placebo (N = 23)
% Male Sample size	n = NR ; % = NR	n = NR ; % = NR
Mean age (SD) Mean (SD)	NR (NR)	NR (NR)

Characteristic	Metformin (N = 52)	Placebo (N = 23)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosis Mean (SD)	NR (NR)	NR (NR)
HbA1c Mean (SD)	NR (NR)	NR (NR)
Blood pressure Mean (SD)	NR (NR)	NR (NR)
Heart rate Mean (SD)	NR (NR)	NR (NR)
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR
Weight Sample size	n = NR ; % = NR	n = NR ; % = NR
BMI Sample size	n = NR ; % = NR	n = NR ; % = NR
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Metformin (N = 52)	Placebo (N = 23)
Cholesterol and lipid levels Sample size	n = NR ; % = NR	n = NR ; % = NR
Albumin creatinine ratio Sample size	n = NR ; % = NR	n = NR ; % = NR
eGFR (mL/min/1.73m2) Sample size	n = NR ; % = NR	n = NR ; % = NR
Other antidiabetic medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Blood pressure-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Statins/lipid-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR

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45. Haak, 2012

Bibliographic Reference	Haak, T.; Meinicke, T.; Jones, R.; Weber, S.; Eynatten, M.; Woerle, H. J.; Initial combination of linagliptin and metformin improves glycaemic control in type 2 diabetes: a randomized, double-blind, placebo-controlled study; Diabetes Obes Metab; 2012; vol. 14 (no. 6); 565-74

45.1. Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.
Trial name / registration number	NCT00798161
Study type	Randomised controlled trial (RCT)
Study location	Multicentre trial in 14 countries.
Study setting	Outpatient follow up.
Study dates	December 2008 to May 2010
Sources of funding	Funded by Boehringer Ingelheim.
Inclusion criteria	18-80 years of age; diagnosis of type 2 diabetes mellitus and a body mass index of no more than 40 kg/m2; either treatment naïve or had been treated with no more than one oral antidiabetic drug (which had to be unchanged for 10 weeks prior to enrolment); at initial screening, HbA1c had to be 7-10.5% for people undergoing washout of previous hypoglycaemic medication and HbA1c 7.5-11.0% for treatment-naïve people; HbA1c at the start of the placebo run-in period had to be 7.5-11%.
Exclusion criteria	Received previous treatment with rosiglitazone, pioglitazone, GLP-1 analogues, insulin or anti-obesity drugs in the previous 3 months; receiving treatment with systemic steroids or had a change in dosage of thyroid hormones in the previous 6 weeks; had undergone gastric bypass; had experienced a myocardial infarction, stroke or transient ischaemic attack in the previous 6 months; had unstable or acute congestive heart failure; had renal failure or renal impairment at screening; had impaired hepatic function; had known hypersensitivity or allergy to linagliptin or its excipients, metformin or placebo; had a history of alcohol or drug abuse in

	the previous 3 months; had acute or chronic metabolic acidosis; had hereditary galactose intolerance; pre-menopausal women who were nursing or pregnant.
Recruitment / selection of participants	No additional information.
Intervention(s)	Linagliptin and metformin N=286 Two groups combined: linagliptin 2.5mg and metformin 500mg twice a day (n=143), linagliptin 2.5mg and metformin 1000mg twice a day (n=143). People randomised to an arm containing metformin underwent a 2 week titration phase during which the metformin dose was gradually increased from 500mg to 1000mg twice a day (if applicable). Concomitant therapy: People whose glycaemia was not adequately controlled received hypoglycaemic rescue therapy (with sulfonylureas, thiazolidinediones or insulin) during the randomized treatment period if the fasting plasma hyperglycaemia confirmed by a second glucose determined was performed on a different day. People meeting criteria for hyperglycaemia were discontinued for lack of efficacy. There was a 4 week drug washout period (for people pretreated with one oral antidiabetic drug only) followed by a 2 week placebo run-in period (for all people).
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure
Strata 2: People with atherosclerotic cardiovascular diseases	People without other cardiovascular diseases
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	People without chronic kidney disease
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear

Subgroup 1: People with frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	People without non-alcoholic fatty liver disease
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Sensitivity analysis category: Enrichment trial status	7) Mixed population
Population subgroups	No additional information.
Comparator	Linagliptin N=142 Linagliptin 5mg once a day. Concomitant therapy: People whose glycaemia was not adequately controlled received hypoglycaemic rescue therapy (with sulfonylureas, thiazolidinediones or insulin) during the randomized treatment period if the fasting plasma hyperglycaemia confirmed by a second glucose determined was performed on a different day. People meeting criteria for hyperglycaemia were discontinued for lack of efficacy. There was a 4 week drug washout period (for people pretreated with one oral antidiabetic drug only) followed by a 2 week placebo run-in period (for all people). Metformin N=291 Two groups combined: Metformin 500mg twice a day (n=144), metformin 1000mg twice a day (n=147) People randomised to an arm containing

	metformin underwent a 2 week titration phase during which the metformin dose was gradually increased from 500mg to 1000mg twice a day (if applicable). Concomitant therapy: People whose glycaemia was not adequately controlled received hypoglycaemic rescue therapy (with sulfonylureas, thiazolidinediones or insulin) during the randomized treatment period if the fasting plasma hyperglycaemia confirmed by a second glucose determined was performed on a different day. People meeting criteria for hyperglycaemia were discontinued for lack of efficacy. There was a 4 week drug washout period (for people pretreated with one oral antidiabetic drug only) followed by a 2 week placebo run-in period (for all people). Placebo N=72 Matching placebo. Concomitant therapy: People whose glycaemia was not adequately controlled received hypoglycaemic rescue therapy (with sulfonylureas, thiazolidinediones or insulin) during the randomized treatment period if the fasting plasma hyperglycaemia confirmed by a second glucose determined was performed on a different day. People meeting criteria for hyperglycaemia were discontinued for lack of efficacy. There was a 4 week drug washout period (for people pretreated with one oral antidiabetic drug only) followed by a 2 week placebo run-in period (for all people).
Number of participants	791
Duration of follow-up	6 months.
Indirectness	No additional information.
Method of analysis	Other Full analysis set - people who received at least one dose of the study medication and had HbA1c measured at baseline and at least once during treatment
Additional comments	No additional information.

45.2. Study arms

45.2.1. Linagliptin + metformin (N = 286)

Two groups combined: linagliptin 2.5mg and metformin 500mg twice a day (n=143), linagliptin 2.5mg and metformin 1000mg twice a day (n=143). People randomised to

an arm containing metformin underwent a 2 week titration phase during which the metformin dose was gradually increased from 500mg to 1000mg twice a day (if applicable). Concomitant therapy: People whose glycaemia was not adequately controlled received hypoglycaemic rescue therapy (with sulfonylureas, thiazolidinediones or insulin) during the randomized treatment period if the fasting plasma hyperglycaemia confirmed by a second glucose determined was performed on a different day. People meeting criteria for hyperglycaemia were discontinued for lack of efficacy. There was a 4 week drug washout period (for people pretreated with one oral antidiabetic drug only) followed by a 2 week placebo run-in period (for all people).

45.2.2. Linagliptin (N = 142)

Linagliptin 5mg once a day. Concomitant therapy: People whose glycaemia was not adequately controlled received hypoglycaemic rescue therapy (with sulfonylureas, thiazolidinediones or insulin) during the randomized treatment period if the fasting plasma hyperglycaemia confirmed by a second glucose determined was performed on a different day. People meeting criteria for hyperglycaemia were discontinued for lack of efficacy. There was a 4 week drug washout period (for people pretreated with one oral antidiabetic drug only) followed by a 2 week placebo run-in period (for all people).

45.2.3. Metformin (N = 291)

Two groups combined: Metformin 500mg twice a day (n=144), metformin 1000mg twice a day (n=147) People randomised to an arm containing metformin underwent a 2 week titration phase during which the metformin dose was gradually increased from 500mg to 1000mg twice a day (if applicable). Concomitant therapy: People whose glycaemia was not adequately controlled received hypoglycaemic rescue therapy (with sulfonylureas, thiazolidinediones or insulin) during the randomized treatment period if the fasting plasma hyperglycaemia confirmed by a second glucose determined was performed on a different day. People meeting criteria for hyperglycaemia were discontinued for lack of efficacy. There was a 4 week drug washout period (for people pretreated with one oral antidiabetic drug only) followed by a 2 week placebo run-in period (for all people).

45.2.4. Placebo (N = 72)

Matching placebo. Concomitant therapy: People whose glycaemia was not adequately controlled received hypoglycaemic rescue therapy (with sulfonylureas, thiazolidinediones or insulin) during the randomized treatment period if the fasting plasma hyperglycaemia confirmed by a second glucose determined was performed on a different day. People meeting criteria for hyperglycaemia were discontinued for lack of efficacy. There was a 4 week drug washout period (for people pretreated with one oral antidiabetic drug only) followed by a 2 week placebo run-in period (for all people).

45.3. Characteristics

45.3.1. Arm-level characteristics

Characteristic	Linagliptin + metformin (N = 286)	Linagliptin (N = 142)	Metformin (N = 291)	Placebo (N = 72)
% Male Sample size	n = 150 ; % = 52	n = 80 ; % = 56	n = 160 ; % = 55	n = 36 ; % = 50
Mean age (SD) (years) Mean (SD)	56 (11)	56.2 (10.8)	54.1 (10.6)	55.7 (11)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Asian Sample size	n = 85 ; % = 30	n = 45 ; % = 31.7	n = 101 ; % = 35	n = 26 ; % = 36.1
Black Sample size	n = 3 ; % = 1	n = 0 ; % = 0	n = 2 ; % = 0.7	n = 0 ; % = 0
Hawaiian/Pacific Islander Sample size	n = 1 ; % = 0.4	n = 0 ; % = 0	n = 0 ; % = 0	n = 0 ; % = 0
White Sample size	n = 197 ; % = 69	n = 97 ; % = 68	n = 188 ; % = 65	n = 46 ; % = 64
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosis (years) Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Less than and equal to 1 year Sample size	n = 103 ; % = 36	n = 54 ; % = 40	n = 106 ; % = 36	n = 20 ; % = 31
>1 to 5 years Sample size	n = 96 ; % = 34	n = 47 ; % = 35	n = 113 ; % = 39	n = 23 ; % = 35

Characteristic	Linagliptin + metformin (N = 286)	Linagliptin (N = 142)	Metformin (N = 291)	Placebo (N = 72)
>5 years Sample size	n = 78 ; % = 27	n = 34 ; % = 25	n = 60 ; % = 21	n = 22 ; % = 34
HbA1c (%) Mean (SD)	8.7 (1)	8.7 (1)	8.6 (0.9)	8.7 (1)
Blood pressure Mean (SD)	NR (NR)	NR (NR)	NR (NR)	NR (NR)
Heart rate Mean (SD)	NR (NR)	NR (NR)	NR (NR)	NR (NR)
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Weight (kg) Mean (SD)	78.8 (17.7)	79.1 (17.3)	80 (18.5)	76.8 (17.5)
BMI (kg/m2) Mean (SD)	29.2 (5.1)	29 (4.7)	29.2 (5.1)	28.6 (5.2)
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Cholesterol and lipid levels Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Linagliptin + metformin (N = 286)	Linagliptin (N = 142)	Metformin (N = 291)	Placebo (N = 72)
Albumin creatinine ratio Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
eGFR (mL/min/1.73m2) Mean (SD)	NR (NR)	NR (NR)	NR (NR)	NR (NR)
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Prior use of 0 Sample size	n = 130 ; % = 46	n = 61 ; % = 45	n = 136 ; % = 47	n = 32 ; % = 49
Prior use of 1 Sample size	n = 147 ; % = 51	n = 74 ; % = 54.8	n = 142 ; % = 49	n = 33 ; % = 51
Prior use of 2 Sample size	n = 0 ; % = 0	n = 0 ; % = 0	n = 1 ; % = 0.3	n = 0 ; % = 0
Blood pressure-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Statins/lipid-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR

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46. Hadjadj, 2016

Bibliographic Reference	Hadjadj, S.; Rosenstock, J.; Meinicke, T.; Woerle, H. J.; Broedl, U. C.; Initial combination of empagliflozin and metformin in patients with type 2 diabetes; Diabetes Care; 2016; vol. 39 (no. 10); 1718-1728

46.1. Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.
Trial name / registration number	NCT01719003
Study type	Randomised controlled trial (RCT)
Study location	Multicentre trial in 21 countries.
Study setting	Outpatient follow-up.
Study dates	October 2012 to December 2014.
Sources of funding	Authors were employees of Boehringer Ingelheim Pharma GmbH & Co. Authors received funding from other companies including AstraZeneca, Bristol-Myers Squibb, Abbott, Eli Lilly, Janssen, Lexicon, Merck Sharp & Dohme, Novartis, Novo Nordisk, Pfizer, Sanofi, Servier and Takeda.
Inclusion criteria	Adults with type 2 diabetes with BMI no more than 45 kg/m2 at screening who were drug-naïve (no oral antidiabetic therapy, glucagon-like peptide-1 analogue or insulin for at least 12 weeks before randomisation).
Exclusion criteria	Uncontrolled hyperglycaemia (plasma glucose >240mg/dL [13.3 mmol/L] after an overnight fast during a 2-week placebo run-in, confirmed by a second measurement); contraindication to metformin according to the local label; renal impairment (eGFR <60mL/min using the Cockcroft-Gault formula) or indication of liver disease (serum ALT, AST or ALP >3 times the upper limit of normal) at screening or during the placebo run-in; treatment with anti-obesity drugs within 3 months before consent; any uncontrolled endocrine disorder except type 2 diabetes.
Recruitment / selection of participants	Before a protocol amendment, people with HbA1c 7-10% at screening were eligible for randomized treatment and people with HbA1c >10% at screening were eligible for open-label treatment. After the protocol

	amendment, people with HbA1c 7.5%-12% at screening were eligible for randomisation treatment, and enrolment in the open-label arm was stopped. However, people already enrolled in the open-label arm were allowed to complete the study.
Intervention(s)	Empagliflozin and metformin N=680 4 groups combined: Empagliflozin 12.5mg twice a day + metformin 1000mg twice a day (n=170), empagliflozin 12.5mg twice a day + metformin 500mg twice a day (n=170), empagliflozin 6mg twice a day + metformin 1000mg twice a day (n=171) and empagliflozin 6mg twice a day + metformin 500mg twice a day (n=169). Concomitant therapy: No additional information.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear
Strata 2: People with atherosclerotic cardiovascular diseases	Not stated/unclear
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	People without chronic kidney disease
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	People at higher risk of developing cardiovascular disease Based on age, BMI, triglycerides and presence of diabetes
Subgroup 1: People with frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic	People without non-alcoholic fatty liver disease

fatty liver disease	
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	eGFR ≥30mL/min/1.73m2
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Sensitivity analysis category: Enrichment trial status	8) Not reported States no drugs for at least 12 weeks before randomisation, but doesn't state if people were truly drug naïve before then. This seems like the more appropriate category than unclear as selection likely did not take place based on the statement made.
Population subgroups	No additional information.
Comparator	Empagliflozin N=339 2 groups combined: Empagliflozin 25mg once a day (n=167) or empagliflozin 10mg once a day (n=172). Concomitant therapy: No additional information. Metformin N=341 2 groups combined: Metformin 1000mg twice a day (n=170) or metformin 500mg twice a day (n=171). Concomitant therapy: No additional information.
Number of participants	1360
Duration of follow-up	24 weeks.
Indirectness	No additional information.
Method of analysis	Other Full analysis set (people treated with at least 1 dose of the study drug who had a baseline and at least 1 on-treatment HbA1c assessment)

Additional comments	No additional information.

46.2. Study arms

46.2.1. Empagliflozin + metformin (N = 680)

4 groups combined: Empagliflozin 12.5mg twice a day + metformin 1000mg twice a day (n=170), empagliflozin 12.5mg twice a day + metformin 500mg twice a day (n=170), empagliflozin 6mg twice a day + metformin 1000mg twice a day (n=171) and empagliflozin 6mg twice a day + metformin 500mg twice a day (n=169). Concomitant therapy: No additional information.

46.2.2. Empagliflozin (N = 339)

2 groups combined: Empagliflozin 25mg once a day (n=167) or empagliflozin 10mg once a day (n=172). Concomitant therapy: No additional information.

46.2.3. Metformin (N = 341)

2 groups combined: Metformin 1000mg twice a day (n=170) or metformin 500mg twice a day (n=171). Concomitant therapy: No additional information.

46.3. Characteristics

46.3.1. Arm-level characteristics

Characteristic	Empagliflozin + metformin (N = 680)	Empagliflozin (N = 339)	Metformin (N = 341)
% Male Sample size	n = 389 ; % = 60	n = 180 ; % = 53	n = 178 ; % = 52
Mean age (SD) (years) Mean (SD)	52.3 (11.1)	53.2 (10.7)	52.5 (10.9)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 361 ; % = 55	n = 197 ; % = 59	n = 188 ; % = 57
Asian Sample size	n = 157 ; % = 24	n = 74 ; % = 22	n = 78 ; % = 24

Characteristic	Empagliflozin + metformin (N = 680)	Empagliflozin (N = 339)	Metformin (N = 341)
American Indian/Alaska Native Sample size	n = 113 ; % = 17	n = 47 ; % = 14	n = 49 ; % = 15
Black/African American Sample size	n = 30 ; % = 5	n = 15 ; % = 5	n = 17 ; % = 5
Native Hawaiian/Pacific Islander Sample size	n = 1 ; % = 0.2	n = 0 ; % = 0	n = 0 ; % = 0
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosis (years) Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Up to 1 year Sample size	n = 378 ; % = 57	n = 172 ; % = 52	n = 191 ; % = 58
More than 1 but up to 5 years Sample size	n = 177 ; % = 27	n = 110 ; % = 33	n = 92 ; % = 28
More than 5 but up to 10 years Sample size	n = 72 ; % = 11	n = 38 ; % = 11	n = 35 ; % = 11
More than 10 years Sample size	n = 35 ; % = 5	n = 13 ; % = 4	n = 14 ; % = 4
HbA1c (%) Mean (SD)	8.71 (1.24)	8.74 (1.27)	8.64 (1.09)
Blood pressure (mmHg) Mean (SD)	NA (NA)	NA (NA)	NA (NA)
Systolic blood pressure Mean (SD)	126.9 (13.7)	128.3 (15.2)	128.2 (14.8)

Characteristic	Empagliflozin + metformin (N = 680)	Empagliflozin (N = 339)	Metformin (N = 341)
Diastolic blood pressure Mean (SD)	78.6 (8.7)	79.2 (9.5)	78.8 (9)
Heart rate Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Weight (kg) Mean (SD)	83 (19.2)	83.5 (20.1)	83.2 (20.7)
BMI (kg/m2) Mean (SD)	30.3 (5.2)	30.5 (5.6)	30.4 (5.9)
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Cholesterol and lipid levels (mmol/L) Mean (SD)	NA (NA)	NA (NA)	NA (NA)
Total cholesterol Mean (SD)	4.91 (1.64)	4.87 (1.54)	5.05 (1.87)
HDL cholesterol Mean (SD)	1.1 (0.16)	1.1 (0.15)	1.11 (0.16)

Characteristic	Empagliflozin + metformin (N = 680)	Empagliflozin (N = 339)	Metformin (N = 341)
LDL cholesterol Mean (SD)	2.25 (0.74)	2.19 (0.76)	2.31 (0.84)
Triglycerides Mean (SD)	1.3 (1.01)	1.29 (1.17)	1.26 (0.84)
Albumin creatinine ratio Mean (SD)	NR (NR)	NR (NR)	NR (NR)
eGFR (mL/min/1.73m2) (ml/min/1.73 m2) Mean (SD)	93.5 (21.1)	93 (20.7)	92.1 (19.7)
Other antidiabetic medication used Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Blood pressure-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Statins/lipid-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR

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47. Hällsten, 2002

Bibliographic Reference	Hällsten, K.; Virtanen, K. A.; Lönnqvist, F.; Sipilä, H.; Oksanen, A.; Viljanen, T.; Rönnemaa, T.; Viikari, J.; Knuuti, J.; Nuutila, P.; Rosiglitazone but not metformin enhances insulin- and exercise-stimulated skeletal muscle glucose uptake in patients with newly diagnosed type 2 diabetes; Diabetes; 2002; vol. 51 (no. 12); 3479-85

47.1. Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	Koffert, J. P., Mikkola, K., Virtanen, K. A. et al. (2017) Metformin treatment significantly enhances intestinal glucose uptake in patients with type 2 diabetes: results from a randomized clinical trial. Diabetes Res Clin Pract 131: 208-216
Trial name / registration number	No additional information.
Study location	Finland.
Study setting	Outpatient follow up.
Study dates	No additional information.
Sources of funding	Grants from the Academy of Finland, the Novo Nordisk Foundation, the Finnish Diabetes Research Society and GlaxoSmithKline.
Inclusion criteria	People with type 2 diabetes, as defined by the new World Health Organisation criteria, and no diabetes complications.
Exclusion criteria	Fasting plasma glucose value <6.1 mmol/L or >11.0 mmol/L after the run-in period; cardiovascular disease; blood pressure >160/100mmHg; previous or present abnormal hepatic or renal function; antidiabetic medication; anaemia; oral corticosteroid use.
Recruitment / selection of participants	People were recruited by advertisement and among clients of the occupational health service in Turku.
Intervention(s)	Metformin N=13 Metformin 500mg twice a day, increased to 1000mg twice a day after 2 weeks. Provided for 26 weeks in total.

	Concomitant therapy: People were provided with written diet instructions for a 4 week run-in period.
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure
Strata 2: People with atherosclerotic cardiovascular diseases	People without other cardiovascular diseases
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	People without chronic kidney disease
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	People at higher risk of developing cardiovascular disease Based on BMI, blood pressure, age and presence of diabetes.
Subgroup 1: People with frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	People without non-alcoholic fatty liver disease
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria	Not stated/unclear

category at baseline	
Sensitivity analysis category: Enrichment trial status	5) All treatment naïve
Population subgroups	No additional information.
Comparator	Placebo N=14 Matching placebo. Concomitant therapy: People were provided with written diet instructions for a 4 week run-in period. A third arm was reported where people received rosiglitazone (n=14). This arm was not included as rosiglitazone is not licensed for use in the United Kingdom.
Number of participants	27
Duration of follow-up	6 months.
Indirectness	No additional information.
Method of analysis	Not stated/unclear
Additional comments	No additional information.

47.2. Study arms

47.2.1. Metformin (N = 13)

Metformin 500mg twice a day, increased to 1000mg twice a day after 2 weeks. Provided for 26 weeks in total. Concomitant therapy: People were provided with written diet instructions for a 4 week run-in period.

47.2.2. Placebo (N = 14)

Matching placebo. Concomitant therapy: People were provided with written diet instructions for a 4 week run-in period.

47.3. Characteristics

47.3.1. Arm-level characteristics

Characteristic	Metformin (N = 13)	Placebo (N = 14)
% Male Sample size	n = 8 ; % = 62	n = 10 ; % = 71
Mean age (SD) (years) Mean (SE)	57.8 (2.2)	57.7 (1.9)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosis Mean (SD)	NR (NR)	NR (NR)
HbA1c Mean (SE)	6.9 (0.2)	6.3 (0.1)
Blood pressure Mean (SE)	NA (NA)	NA (NA)
Systolic blood pressure Mean (SE)	145 (4.1)	147.2 (3.2)
Diastolic blood pressure Mean (SE)	91.4 (2.5)	85.1 (2.3)
Heart rate Mean (SD)	NR (NR)	NR (NR)
Smoking status Sample size	n = 2 ; % = 15	n = 4 ; % = 29
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Metformin (N = 13)	Placebo (N = 14)
Sample size		
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR
Weight Mean (SE)	88.8 (3)	88.3 (2.5)
BMI Mean (SD)	NR (NR)	NR (NR)
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR
Cholesterol and lipid levels Mean (SD)	NR (NR)	NR (NR)
Albumin creatinine ratio Mean (SD)	NR (NR)	NR (NR)
eGFR (mL/min/1.73m2) Mean (SD)	NR (NR)	NR (NR)
Other antidiabetic medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Blood pressure-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Statins/lipid-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR

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48. Henry, 2012

Bibliographic Reference	Henry, R. R.; Murray, A. V.; Marmolejo, M. H.; Hennicken, D.; Ptaszynska, A.; List, J. F.; Dapagliflozin, metformin XR, or both: initial pharmacotherapy for type 2 diabetes, a randomised controlled trial; Int J Clin Pract; 2012; vol. 66 (no. 5); 446-56

48.1. Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.
Trial name / registration number	NCT00643851 (study 1) and NCT00859898 (study 2).
Study type	Randomised controlled trial (RCT)
Study location	Multicentre trial (North America, Latin America, Europe and Asia).
Study setting	Outpatient follow-up.
Study dates	No additional information.
Sources of funding	Funded by Bristol-Myers Squibb and AstraZeneca.
Inclusion criteria	Aged 18-77 years; HbA1c 7.5-12%; BMI no more than 45 kg/m2; C-peptide concentration no less than 0.33 nmol/L; type 2 diabetes uncontrolled by diet and exercise.
Exclusion criteria	Serum creatinine no less than 132.60 micromol/L (men) or no less than 123.76 micromol/L (women) consistent with metformin labelling; urine albumin:creatinine ratio >1800mg/g; serum aspartate transaminase or alanine transaminase >3 times upper limit of normal; creatinine kinase >3 times upper limit of normal; history of diabetes insipidus; symptoms of poorly controlled diabetes (including marked polyuria and polydipsia with >10% weight loss during 3 months before enrolment); clinically significant renal, hepatic, haematological, oncological, endocrine, psychiatric or rheumatic disease; a cardiovascular event within 6 months or New York Heart Association Class III or IV congestive heart failure; and systolic blood pressure at least 180 or diastolic blood pressure at least 110 mmHg.

Recruitment / selection of participants	Withdrawal from the study was required for any episode of major hypoglycaemia (for example: symptomatic episode requiring third party assistance because of severe impairment in consciousness or behaviour, with capillary or plasma glucose <3.00 mmol/L, and prompt recovery after glucose or glucagon administration).
Intervention(s)	Dapagliflozin + metformin (study 1) N=194 Dapagliflozin 5mg plus metformin XR, initially 500mg increased in weekly increments up to a maximum of 2000mg daily. Titration was re-evaluated at weeks 4, 6 and 8 in people not yet at 2000 mg, and was not permitted after this point or allowed if people experienced recurrent episodes of non-major hypoglycaemia. People up-titrated at least once could be down titrated 500mg for recurrent non-major hypoglycaemia or gastrointestinal intolerance. Down-titration was not permitted after week 12. Concomitant therapy: Everyone had a 7 day lead in where they received diet and exercise advice. People lacking glycaemic control could receive open-label rescue with pioglitazone, sitagliptin or acarbose in addition to double-blind treatment, based on fasting plasma glucose >14.99 mmol/L (weeks 6-7), >13.32 mmol/L (weeks 8-11) or >11.10 mmol/L (weeks 12-20). Dapagliflozin + metformin (study 2) N=211 Dapagliflozin 5mg plus metformin XR, initially 500mg increased in weekly increments up to a maximum of 2000mg daily. Titration was re-evaluated at weeks 4, 6 and 8 in people not yet at 2000 mg, and was not permitted after this point or allowed if people experienced recurrent episodes of non-major hypoglycaemia. People up-titrated at least once could be down titrated 500mg for recurrent non-major hypoglycaemia or gastrointestinal intolerance. Down-titration was not permitted after week 12. Concomitant therapy: Everyone had a 7 day lead in where they received diet and exercise advice. People lacking glycaemic control could receive open-label rescue with pioglitazone, sitagliptin or acarbose in addition to double-blind treatment, based on fasting plasma glucose >14.99 mmol/L (weeks 6-7), >13.32 mmol/L (weeks 8-11) or >11.10 mmol/L (weeks 12-20).
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure
Strata 2: People with	People without other cardiovascular diseases

atherosclerotic cardiovascular diseases	
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	People without chronic kidney disease
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Sensitivity analysis category: Enrichment trial status	6) No response criteria
Population subgroups	No additional information.
Comparator	Dapagliflozin (study 1) N=203

	Dapagliflozin 5mg plus matching placebo daily. Concomitant therapy: Everyone had a 7 day lead in where they received diet and exercise advice. People lacking glycaemic control could receive open-label rescue with pioglitazone, sitagliptin or acarbose in addition to double-blind treatment, based on fasting plasma glucose >14.99 mmol/L (weeks 6-7), >13.32 mmol/L (weeks 8-11) or >11.10 mmol/L (weeks 12-20). Metformin (study 1) N=201 Matching placebo plus metformin XR, initially 500mg increased in weekly increments up to a maximum of 2000mg daily. Titration was re-evaluated at weeks 4, 6 and 8 in people not yet at 2000 mg, and was not permitted after this point or allowed if people experienced recurrent episodes of non-major hypoglycaemia. People up-titrated at least once could be down titrated 500mg for recurrent non-major hypoglycaemia or gastrointestinal intolerance. Down-titration was not permitted after week 12. Concomitant therapy: Everyone had a 7 day lead in where they received diet and exercise advice. People lacking glycaemic control could receive open-label rescue with pioglitazone, sitagliptin or acarbose in addition to double-blind treatment, based on fasting plasma glucose >14.99 mmol/L (weeks 6-7), >13.32 mmol/L (weeks 8-11) or >11.10 mmol/L (weeks 12-20). Dapagliflozin (study 2) N=219 Dapagliflozin 5mg plus matching placebo daily. Concomitant therapy: Everyone had a 7 day lead in where they received diet and exercise advice. People lacking glycaemic control could receive open-label rescue with pioglitazone, sitagliptin or acarbose in addition to double-blind treatment, based on fasting plasma glucose >14.99 mmol/L (weeks 6-7), >13.32 mmol/L (weeks 8-11) or >11.10 mmol/L (weeks 12-20). Metformin (study 2) N=208 Matching placebo plus metformin XR, initially 500mg increased in weekly increments up to a maximum of 2000mg daily. Titration was re-evaluated

	at weeks 4, 6 and 8 in people not yet at 2000 mg, and was not permitted after this point or allowed if people experienced recurrent episodes of non-major hypoglycaemia. People up-titrated at least once could be down titrated 500mg for recurrent non-major hypoglycaemia or gastrointestinal intolerance. Down-titration was not permitted after week 12. Concomitant therapy: Everyone had a 7 day lead in where they received diet and exercise advice. People lacking glycaemic control could receive open-label rescue with pioglitazone, sitagliptin or acarbose in addition to double-blind treatment, based on fasting plasma glucose >14.99 mmol/L (weeks 6-7), >13.32 mmol/L (weeks 8-11) or >11.10 mmol/L (weeks 12-20).
Number of participants	598 in study 1, 638 in study 2
Duration of follow-up	24 weeks
Indirectness	No additional information.
Method of analysis	Other Likely full case analysis (people had to have received at least one dose of the medication to be included in the analysis)
Additional comments	No additional information.

48.2. Study arms

48.2.1. Dapagliflozin + metformin (study 1) (N = 194)

Dapagliflozin 5mg plus metformin XR, initially 500mg increased in weekly increments up to a maximum of 2000mg daily. Titration was re-evaluated at weeks 4, 6 and 8 in people not yet at 2000 mg, and was not permitted after this point or allowed if people experienced recurrent episodes of non-major hypoglycaemia. People up-titrated at least once could be down titrated 500mg for recurrent non-major hypoglycaemia or gastrointestinal intolerance. Down-titration was not permitted after week 12. Concomitant therapy: Everyone had a 7 day lead in where they received diet and exercise advice. People lacking glycaemic control could receive open-label rescue with pioglitazone, sitagliptin or acarbose in addition to double-blind treatment, based on fasting plasma glucose >14.99 mmol/L (weeks 6-7), >13.32 mmol/L (weeks 8-11) or >11.10 mmol/L (weeks 12-20).

48.2.2. Dapagliflozin (study 1) (N = 203)

Dapagliflozin 5mg plus matching placebo daily. Concomitant therapy: Everyone had a 7 day lead in where they received diet and exercise advice. People lacking glycaemic control could receive open-label rescue with pioglitazone, sitagliptin or acarbose in addition to double-blind treatment, based on fasting plasma glucose

>14.99 mmol/L (weeks 6-7), >13.32 mmol/L (weeks 8-11) or >11.10 mmol/L (weeks 12-20).

48.2.3. Metformin (study 1) (N = 201)

Matching placebo plus metformin XR, initially 500mg increased in weekly increments up to a maximum of 2000mg daily. Titration was re-evaluated at weeks 4, 6 and 8 in people not yet at 2000 mg, and was not permitted after this point or allowed if people experienced recurrent episodes of non-major hypoglycaemia. People up-titrated at least once could be down titrated 500mg for recurrent non-major hypoglycaemia or gastrointestinal intolerance. Down-titration was not permitted after week 12. Concomitant therapy: Everyone had a 7 day lead in where they received diet and exercise advice. People lacking glycaemic control could receive open-label rescue with pioglitazone, sitagliptin or acarbose in addition to double-blind treatment, based on fasting plasma glucose >14.99 mmol/L (weeks 6-7), >13.32 mmol/L (weeks 8-11) or >11.10 mmol/L (weeks 12-20).

48.2.4. Dapagliflozin + metformin (study 2) (N = 211)

Dapagliflozin 5mg plus metformin XR, initially 500mg increased in weekly increments up to a maximum of 2000mg daily. Titration was re-evaluated at weeks 4, 6 and 8 in people not yet at 2000 mg, and was not permitted after this point or allowed if people experienced recurrent episodes of non-major hypoglycaemia. People up-titrated at least once could be down titrated 500mg for recurrent non-major hypoglycaemia or gastrointestinal intolerance. Down-titration was not permitted after week 12. Concomitant therapy: Everyone had a 7 day lead in where they received diet and exercise advice. People lacking glycaemic control could receive open-label rescue with pioglitazone, sitagliptin or acarbose in addition to double-blind treatment, based on fasting plasma glucose >14.99 mmol/L (weeks 6-7), >13.32 mmol/L (weeks 8-11) or >11.10 mmol/L (weeks 12-20).

48.2.5. Dapagliflozin (study 2) (N = 219)

Dapagliflozin 5mg plus matching placebo daily. Concomitant therapy: Everyone had a 7 day lead in where they received diet and exercise advice. People lacking glycaemic control could receive open-label rescue with pioglitazone, sitagliptin or acarbose in addition to double-blind treatment, based on fasting plasma glucose >14.99 mmol/L (weeks 6-7), >13.32 mmol/L (weeks 8-11) or >11.10 mmol/L (weeks 12-20).

48.2.6. Metformin (study 2) (N = 208)

Matching placebo plus metformin XR, initially 500mg increased in weekly increments up to a maximum of 2000mg daily. Titration was re-evaluated at weeks 4, 6 and 8 in people not yet at 2000 mg, and was not permitted after this point or allowed if people experienced recurrent episodes of non-major hypoglycaemia. People up-titrated at least once could be down titrated 500mg for recurrent non-major hypoglycaemia or

gastrointestinal intolerance. Down-titration was not permitted after week 12. Concomitant therapy: Everyone had a 7 day lead in where they received diet and exercise advice. People lacking glycaemic control could receive open-label rescue with pioglitazone, sitagliptin or acarbose in addition to double-blind treatment, based on fasting plasma glucose >14.99 mmol/L (weeks 6-7), >13.32 mmol/L (weeks 8-11) or >11.10 mmol/L (weeks 12-20).

48.3. Characteristics

48.3.1. Arm-level characteristics

Characteristic	Dapagliflozin + metformin (study 1) (N = 194)	Dapagliflozin (study 1) (N = 203)	Metformin (study 1) (N = 201)	Dapagliflozin + metformin (study 2) (N = 211)	Dapagliflozin (study 2) (N = 219)	Metformin (study 2) (N = 208)
% Male Sample size	n = 78 ; % = 40	n = 92 ; % = 45	n = 95 ; % = 47	n = 106 ; % = 50	n = 105 ; % = 48	n = 97 ; % = 47
Mean age (SD) (years) Mean (SD)	51.7 (9.3)	52.3 (10.2)	51.8 (9.8)	51 (10.1)	51.1 (11.5)	52.7 (10.4)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosis (years) Mean (SD)	1.6 (2.4)	1.6 (3.1)	1.6 (2.6)	2.2 (3.3)	2.1 (3.8)	1.9 (4)
HbA1c (%) Mean (SD)	9.2 (1.3)	9.1 (1.4)	9.2 (1.3)	9.1 (1.3)	9.1 (1.3)	9.1 (1.3)
Blood pressure Mean (SD)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)

Characteristic	Dapagliflozin + metformin (study 1) (N = 194)	Dapagliflozin (study 1) (N = 203)	Metformin (study 1) (N = 201)	Dapagliflozin + metformin (study 2) (N = 211)	Dapagliflozin (study 2) (N = 219)	Metformin (study 2) (N = 208)
Heart rate Mean (SD)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Weight (kg) Mean (SD)	84.24 (19.51)	86.2 (21.13)	85.75 (19.93)	88.56 (19.72)	88.53 (19.33)	87.24 (19.42)
BMI Mean (SD)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Cholesterol and lipid levels Mean (SD)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)

Characteristic	Dapagliflozin + metformin (study 1) (N = 194)	Dapagliflozin (study 1) (N = 203)	Metformin (study 1) (N = 201)	Dapagliflozin + metformin (study 2) (N = 211)	Dapagliflozin (study 2) (N = 219)	Metformin (study 2) (N = 208)
Albumin creatinine ratio Mean (SD)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)
eGFR (mL/min/1.73m2) Mean (SD)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)
Other antidiabetic medication used Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Blood pressure-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Statins/lipid-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR

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49. Henry, 2014

Bibliographic Reference	Henry, R. R.; Staels, B.; Fonseca, V. A.; Chou, M. Z.; Teng, R.; Golm, G. T.; Langdon, R. B.; Kaufman, K. D.; Steinberg, H.; Goldstein, B. J.; Efficacy and safety of initial combination treatment with sitagliptin and pioglitazone-a factorial study; Diabetes Obes Metab; 2014; vol. 16 (no. 3); 223-230

49.1. Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	Study Protocol 102; Clinicaltrials.gov: NCT00722371
Study type	Randomised controlled trial (RCT)
Study location	No additional information
Study setting	No additional information
Study dates	No additional information
Sources of funding	Sponsored by Merck & Co.
Inclusion criteria	18-78 years of age Type 2 diabetes inadequately controlled by diet and exercise Drug naïve or taking metformin or sulfonylurea monotherapy HbA1c ≥7.5 and ≤11.0% within 1 week of the start of the placebo run-in period and a fasting glucose ≥7.2 mmol/L and ≤15.0 mmol/L
Exclusion criteria	History of type 1 diabetes

	Ketoacidosis, or recent (within the past 6 months) acute coronary syndrome (myocardial infarction or unstable angina), coronary artery intervention, stroke, or transient ischaemic neurological disorder Previous treatment with a thiazolidinedione (rosiglitazone or pioglitazone), any DPP-4 inhibitor, or an incretin mimetic Laboratory findings indicative of renal, hepatic, or thyroid dysfunction, or anaemia
Recruitment / selection of participants	No additional information
Intervention(s)	Following a 3-11 run-in period, including an 8-week washout period for those receiving antihyperglycaemic medication and a 2-week single-blind placebo period, participants were randomised to one of seven treatment arms: Sitagliptin monotherapy 100 mg/day, Pioglitazone monotherapy, 15, 30 or 45 mg/day Combination of sitagliptin 100 mg/day with pioglitazone at doses of 15, 30 or 45 mg/day In the study arms receiving 45 mg pioglitazone, either as monotherapy or in combination, participants received pioglitazone 30 mg/day for the first 4 weeks and 45 mg/day thereafter Participants who failed to meet increasingly stringent criteria for glycaemic control were rescued with open-label metformin. The thresholds for initiating rescue were fasting plasma glucose >15.0 mmol/L after day 21, >13.3 mmol/L after day 42, FPG >11.1 mmol/L after day 84, and HbA1c >8.0% after day 168. *Study arms comparing multiple doses were combined for this review protocol*
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear

Strata 2: People with atherosclerotic cardiovascular diseases	Not stated/unclear
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	People at higher risk of developing cardiovascular disease
Subgroup 1: People with frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Mixed population
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Sensitivity analysis category: Enrichment trial status	7) Mixed population
Population subgroups	No additional information
Comparator	See intervention

Number of participants	1615 randomised 183 received 15 mg pioglitazone, 124 completed 194 received 30 mg pioglitazone, 137 completed 188 received 45 mg pioglitazone, 135 completed 193 received 100 mg sitagliptin + 15 mg pioglitazone, 148 completed 190 received 100 mg sitagliptin + 30 mg pioglitazone, 140 completed 198 received 100 mg sitagliptin + 45 mg pioglitazone, 150 completed *283 participants were excluded from all analyses due to receiving over encapsulated pioglitazone/placebo based on evidence that over encapsulated and non-over encapsulated pioglitazone are not bioequivalent*
Duration of follow-up	54 weeks
Indirectness	None
Method of analysis	Modified ITT ITT excluding those who received over encapsulated pioglitazone/placebo
Additional comments	None

49.2. Study arms

49.2.1. Pioglitazone (N = 565)

15-45 mg pioglitazone per day *Three study arms combined for this review*

49.2.2. Sitagliptin (N = 186)

100 mg sitagliptin per day

49.2.3. Pioglitazone + Sitagliptin (N = 581)

100+15, 100+30 and 100+45 mg sitagliptin + pioglitazone combination treatment *Three study arms combined for this review*

49.3. Characteristics

49.3.1. Arm-level characteristics

Characteristic	Pioglitazone (N = 565)	Sitagliptin (N = 186)	Pioglitazone + Sitagliptin (N = 581)
% Male Sample size	n = 319 ; % = 56	n = 112 ; % = 60	n = 328 ; % = 56
Mean age (SD) (years) Nominal	51.6	51	52.4
Mean age (SD) (years) Range	21 to 77	24 to 76	21 to 77
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
American Indian or Native Alaskan Sample size	n = 38 ; % = 7	n = 14 ; % = 8	n = 40 ; % = 7
Asian Sample size	n = 48 ; % = 8	n = 18 ; % = 10	n = 52 ; % = 9
Black or African American Sample size	n = 43 ; % = 8	n = 11 ; % = 6	n = 44 ; % = 8
Multiracial Sample size	n = 55 ; % = 10	n = 22 ; % = 12	n = 58 ; % = 10
Native Hawaiian or other Pacific Islander Sample size	n = 2 ; % = 0	n = 1 ; % = 1	n = 0 ; % = 0
White Sample size	n = 381 ; % = 67	n = 120 ; % = 65	n = 387 ; % = 67
Comorbidities Nominal	NR	NR	NR
Presence of frailty Nominal	NR	NR	NR
Time since type 2 diabetes diagnosis (years)	3.8 (4.1)	4.5 (6.8)	4 (4.1)

Characteristic	Pioglitazone (N = 565)	Sitagliptin (N = 186)	Pioglitazone + Sitagliptin (N = 581)
Mean (SD)			
HbA1c (%) Mean (SD)	8.9 (1.1)	8.7 (1.2)	8.8 (1.1)
Blood pressure Nominal	NR	NR	NR
Heart rate Nominal	NR	NR	NR
Smoking status Nominal	NR	NR	NR
Alcohol consumption Nominal	NR	NR	NR
Presence of severe mental illness Nominal	NR	NR	NR
People with significant cognitive impairment Nominal	NR	NR	NR
People with a learning disability Nominal	NR	NR	NR
Weight Nominal	NR	NR	NR
BMI (kg/m²) Mean (SD)	30.9 (5.3)	31.4 (5.7)	30.8 (5.4)
Number of people with obesity Nominal	NR	NR	NR
Cholesterol and lipid levels Nominal	NR	NR	NR
Albumin creatinine ratio Nominal	NR	NR	NR
eGFR (mL/min/1.73m2) Nominal	NR	NR	NR

Characteristic	Pioglitazone (N = 565)	Sitagliptin (N = 186)	Pioglitazone + Sitagliptin (N = 581)
Other antidiabetic medication used Receiving oral antihyperglycaemic medicine within 8 weeks of screening Sample size	n = 80 ; % = 14	n = 27 ; % = 15	n = 77 ; % = 13
Blood pressure-lowering medication used Nominal	NR	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR	NR
Other treatment being received Nominal	NR	NR	NR

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50. Horton, 2000

Bibliographic Reference	Horton, E. S.; Clinkingbeard, C.; Gatlin, M.; Foley, J.; Mallows, S.; Shen, S.; Nateglinide alone and in combination with metformin improves glycemic control by reducing mealtime glucose levels in type 2 diabetes; Diabetes Care; 2000; vol. 23 (no. 11); 1660-5

50.1. Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.
Trial name / registration number	No additional information.
Study type	Randomised controlled trial (RCT)
Study location	United States of America.
Study setting	Outpatient follow-up.
Study dates	No additional information.
Sources of funding	Financial support from Novartis.
Inclusion criteria	Age at least 30 years; diagnosed with type 2 diabetes for at least 3 months; BMI required to be 20-35 kg/m2; all people had to have been treated with diet alone during the 4 week washout period before enrolment in the 4 week placebo run-in phase. People with HbA1c levels 6.8-11.0% during the run-in phase and with an FPG level at least 15mmol/L were able to proceed.
Exclusion criteria	Type 1 diabetes; secondary forms of diabetes; a history of significant diabetic complications; renal impairment; people who did not discontinue all oral hypoglycaemic agents for at least 4 weeks before the placebo run-in phase.
Recruitment / selection of participants	No additional information.
Intervention(s)	Metformin N=178

	Metformin 500mg three times a day for 24 weeks. Concomitant therapy: Other medications could be taken if their use had been instituted before study entry, but agents that could interfere with study evaluations, including other oral antidiabetic agents and corticosteroids, were not allowed.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear
Strata 2: People with atherosclerotic cardiovascular diseases	Not stated/unclear
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	People without chronic kidney disease
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	People at higher risk of developing cardiovascular disease Based on BMI, age and presence of diabetes.
Subgroup 1: People with frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear

Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Sensitivity analysis category: Enrichment trial status	6) No response criteria
Population subgroups	No additional information.
Comparator	Placebo N=172 Matching placebo for 24 weeks. Concomitant therapy: Other medications could be taken if their use had been instituted before study entry, but agents that could interfere with study evaluations, including other oral antidiabetic agents and corticosteroids, were not allowed. Two other groups were reported in the study. One (n=172) receive nateglinide and metformin while the other (n=179) received nateglinide alone. These arms did not fulfil the protocol for this review and so are not reported in this data extraction.
Number of participants	701 in total (350 including just the metformin and placebo arms).
Duration of follow-up	24 weeks.
Indirectness	No additional information.
Method of analysis	ITT
Additional comments	No additional information.

50.2. Study arms

50.2.1. Metformin (N = 178)

Metformin 500mg three times a day for 24 weeks. Concomitant therapy: Other medications could be taken if their use had been instituted before study entry, but agents that could interfere with study evaluations, including other oral antidiabetic agents and corticosteroids, were not allowed.

50.2.2. Placebo (N = 172)

Matching placebo for 24 weeks. Concomitant therapy: Other medications could be taken if their use had been instituted before study entry, but agents that could interfere with study evaluations, including other oral antidiabetic agents and corticosteroids, were not allowed.

50.3. Characteristics

50.3.1. Arm-level characteristics

Characteristic	Metformin (N = 178)	Placebo (N = 172)
% Male Sample size	n = 121 ; % = 68	n = 104 ; % = 61
Mean age (SD) (years) Mean (SD)	56.8 (10.9)	59.6 (10.9)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Caucasian Sample size	n = 141 ; % = 79.2	n = 135 ; % = 78.5
African-American Sample size	n = 17 ; % = 9.5	n = 29 ; % = 16.9
Asian Sample size	n = 4 ; % = 2.2	n = 1 ; % = 0.6
Other Sample size	n = 16 ; % = 9	n = 7 ; % = 4.1
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosis (years) Mean (SD)	4.5 (5.5)	4.6 (4.7)
HbA1c (%)	8.4 (1.2)	8.3 (1.1)

Characteristic	Metformin (N = 178)	Placebo (N = 172)
Mean (SD)		
Blood pressure Mean (SD)	NR (NR)	NR (NR)
Heart rate Mean (SD)	NR (NR)	NR (NR)
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR
Weight Mean (SD)	NR (NR)	NR (NR)
BMI (kg/m2) Mean (SD)	29.6 (4.3)	29.2 (3.9)
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR
Cholesterol and lipid levels Mean (SD)	NR (NR)	NR (NR)
Albumin creatinine ratio Mean (SD)	NR (NR)	NR (NR)
eGFR (mL/min/1.73m2) Mean (SD)	NR (NR)	NR (NR)
Other antidiabetic medication used Sample size	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Metformin (N = 178)	Placebo (N = 172)
Blood pressure-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Statins/lipid-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR

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51. Inagaki, 2014

Bibliographic Reference	Inagaki, N.; Kondo, K.; Yoshinari, T.; Takahashi, N.; Susuta, Y.; Kuki, H.; Efficacy and safety of canagliflozin monotherapy in Japanese patients with type 2 diabetes inadequately controlled with diet and exercise: A 24-week, randomized, double-blind, placebo-controlled, Phase III study; Expert Opin Pharmacother; 2014; vol. 15 (no. 11); 1501-1515

51.1. Study details

Secondary publication of another included study- see primary study for details	Not applicable.
Other publications associated with this study included in review	None
Trial name / registration number	NCT014 13204
Study type	Randomised controlled trial (RCT)
Study location	Japan
Study setting	Clinic
Study dates	07/2011 to 08/2012
Sources of funding	This study was funded by Mitsubishi Tanabe Pharma Corp.
Inclusion criteria	• Patients aged ≥ 20 years with T2DM diagnosed ≥ 3 months before starting the run-in period • HbA1c of 7.0 -10.0% and on diet and exercise therapy for ≥55 days • Patients using antihyperglycemic drugs were eligible providing they started a washout period of ≥ 55 days after providing informed consent and before starting the run-in period.
Exclusion criteria	• Presence of another form of diabetes (e.g., type 1 diabetes, diabetes caused by pancreatic injury or secondary diabetes) • Current or history of severe diabetic complications (proliferative diabetic retinopathy, stage 3 or later nephropathy, diabetic ketoacidosis or serious diabetic neuropathy) • Fasting PG > 270 mg/dl on ≥ 2 days after providing informed consent and before Week 0

	• Indication for insulin therapy; hereditary glucose-galactose malabsorption or renal glycosuria • Inadequately controlled thyroid abnormality; anorexia or bulimia • Current or history of urinary tract/genital infection < 1 year before the run-in period; triglyceride ≥ 600 mg/dl (≥ 6.72 mmol/l) • Systolic/diastolic blood pressure ≥ 160/≥ 100 mmHg during the run-in period or patients with known hypertension who immediately required the addition/ modification of antihypertensive therapy • New York Heart Association class III or IV cardiac failure • Myocardial infarction or cerebrovascular disorder £6 months before the run-in period; concurrent unstable angina or arteriosclerosis obliterans of Fontaine class III or IV • Serious liver disease (requiring hospitalization or surgery for treatment; hepatitis B or C alanine aminotransferase or aspartate aminotransferase ≥ 2.5 times the upper limit of normal) • Serious kidney disease (requiring hospitalization or surgery for treatment) • Estimated glomerular filtration rate < 50 ml/min/1.73 m2 • Urinary albumin creatinine ratio ≥ 300 mg/g creatinine; history of malignancy • Neuropsychiatric disorder likely to hinder study evaluations • History of drug-related shock or anaphylactic symptoms • Unwilling to use contraception; females who are pregnant, breast feeding or possibly pregnant • Participation in a clinical trial or use of an investigational product < 12 weeks before providing informed consent • Prior use of canagliflozin • Patients deemed unsuitable for study inclusion by the investigator for any other reason not listed above
Recruitment / selection of participants	
Intervention(s)	Canagliflozin 100 mg once daily before breakfast, orally administered Canagliflozin 200 mg once daily before breakfast, orally administered Patients were instructed to continue their diet and exercise therapies unchanged from before the study until the end of the follow-up period.
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure
Strata 2: People with atherosclerotic	People without other cardiovascular diseases

cardiovascular diseases	
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Mixed population
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Mixed population
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	eGFR ≥30mL/min/1.73m2
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Sensitivity analysis category: Enrichment trial status	7) Mixed population
Population subgroups	
Comparator	Placebo once daily before breakfast, orally administered

Number of participants	N=352 (only 272 participants entered the treatment period and were randomized to one of the three arms)
Duration of follow-up	24-week treatment period and 2-week follow-up period
Indirectness	Japanese patients included in the study, the breakdown of ethnicity is not given. As the study was conducted in Japan, the results may be less generalisable to a UK population.
Method of analysis	ACA
Additional comments	

51.2. Study arms

51.2.1. Placebo once daily (N = 93)

Administered orally before breakfast

51.2.2. Canagliflozin 100 mg once daily (N = 90)

Administered orally before breakfast

51.2.3. Canagliflozin 200 mg once daily (N = 89)

Administered orally before breakfast

51.3. Characteristics

51.3.1. Arm-level characteristics

Characteristic	Placebo once daily (N = 93)	Canagliflozin 100 mg once daily (N = 90)	Canagliflozin 200 mg once daily (N = 89)
% Male No of events	n = 60 ; % = 64.5	n = 59 ; % = 65.6	n = 72 ; % = 81.8
Mean age (SD) (years) Mean (SD)	58.2 (11)	58.4 (10.4)	57.4 (11.1)
Ethnicity Nominal	NR	NR	NR
Comorbidities Nominal	NR	NR	NR

Characteristic	Placebo once daily (N = 93)	Canagliflozin 100 mg once daily (N = 90)	Canagliflozin 200 mg once daily (N = 89)
Presence of frailty Nominal	NR	NR	NR
Time since type 2 diabetes diagnosis (years) Mean (SD)	58.2 (11)	58.4 (10.4)	57.4 (11.1)
Heart rate Nominal	NR	NR	NR
Smoking status Nominal	NR	NR	NR
Alcohol consumption Nominal	NR	NR	NR
People with significant cognitive impairment Nominal	NR	NR	NR
People with a learning disability Nominal	NR	NR	NR
Number of people with obesity Nominal	NR	NR	NR
Other antidiabetic medication used No of events	n = 24 ; % = 25.8	n = 20 ; % = 22.2	n = 31 ; % = 35.2
Blood pressure-lowering medication used Nominal	NR	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR	NR
Other treatment being received	NR	NR	NR

Characteristic	Placebo once daily (N = 93)	Canagliflozin 100 mg once daily (N = 90)	Canagliflozin 200 mg once daily (N = 89)
Nominal			

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52. Inagaki, 2015

Bibliographic Reference	Inagaki, N.; Onouchi, H.; Maezawa, H.; Kuroda, S.; Kaku, K.; Once-weekly trelagliptin versus daily alogliptin in Japanese patients with type 2 diabetes: A randomised, double-blind, phase 3, non-inferiority study; Lancet Diabetes Endocrinol; 2015; vol. 3 (no. 3); 191-197

52.1. Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	NCT01632007
Study type	Randomised controlled trial (RCT)
Study location	Japan
Study setting	No additional information
Study dates	May 2012 - November 2012
Sources of funding	Sponsored by Takeda Pharmaceuticals
Inclusion criteria	≥20 years of age Type 2 diabetes Received diet and exercise therapy for at least 4 weeks prior to screening HbA1c 6.9-10.5% 4 weeks after the start of the screening period, with <10% variation from the pre-screening value
Exclusion criteria	Received any antidiabetic drugs within 4 weeks pre screening

	Signs of hepatic impairment (alanine aminotransferase or aspartate aminotransferase >2.5 times the upper limit of normal, or total bilirubin >34.2 mmol/L) Severe renal impairment (creatinine clearance <30 mL/min) ECQ abnormalities (QTcF interval >450 ms)
Recruitment / selection of participants	No additional information
Intervention(s)	Following an 8-week screening period those randomised to the intervention received 25 mg alogliptin once per day. Participants also received placebo trelagliptin once per week. Compliance with diet, exercise and medication was monitored throughout the trial. No rescue therapy was planned. *Study arm including trelagliptin not included in this review - not a protocol intervention*
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear
Strata 2: People with atherosclerotic cardiovascular diseases	Not stated/unclear
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	People at higher risk of developing cardiovascular disease
Subgroup 1: People with frailty	Not stated/unclear

Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Mixed population
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Sensitivity analysis category: Enrichment trial status	7) Mixed population Participants could have been receiving antidiabetic medication up to 4 weeks prior to screening - number of participants who were receiving medication prior to this not reported
Population subgroups	No additional information
Comparator	Following an 8-week screening period those randomised to the comparator received placebo alogliptin once per day and placebo trelagliptin once per week. Compliance with diet, exercise and medication was monitored throughout the trial. No rescue therapy was planned.
Number of participants	245 randomised 92 received alogliptin, 90 completed 51 received placebo, 46 completed 102 received trelagliptin (not included in this review)
Duration of follow-up	24 weeks
Indirectness	None
Method of analysis	ITT
Additional comments	One patient excluded from analyses due to duplicated enrolment (placebo arm)

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52.2. Study arms

52.2.1. Alogliptin (N = 92)

25 mg alogliptin once per day

52.2.2. Placebo (N = 50)

52.3. Characteristics

52.3.1. Arm-level characteristics

Characteristic	Alogliptin (N = 92)	Placebo (N = 50)
% Male Sample size	n = 69 ; % = 75	n = 43 ; % = 86
Mean age (SD) (years) Median (IQR)	60 (53 to 65)	62 (54 to 67)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosis (Months) Mean (SD)	84.8 (71.1)	90.5 (66)
HbA1c (%) Mean (SD)	7.87 (0.86)	7.72 (0.77)
Blood pressure Nominal	NR	NR
Heart rate Nominal	NR	NR
Smoking status Nominal	NR	NR

Characteristic	Alogliptin (N = 92)	Placebo (N = 50)
Alcohol consumption Nominal	NR	NR
Presence of severe mental illness Nominal	NR	NR
People with significant cognitive impairment Nominal	NR	NR
People with a learning disability Nominal	NR	NR
Weight (kg) Mean (SD)	67.37 (13.17)	67.2 (14.72)
BMI (kg/m²) Mean (SD)	24.7 (3.8)	24.6 (4.3)
Number of people with obesity Nominal	NR	NR
Cholesterol and lipid levels Nominal	NR	NR
Albumin creatinine ratio Nominal	NR	NR
eGFR (mL/min/1.73m2) (ml/min) Creatinine clearance rate Mean (SD)	109.1 (41.7)	98.4 (36.3)
Other antidiabetic medication used Nominal	NR	NR
Blood pressure-lowering medication used Nominal	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

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53. Inagaki, 2022

Bibliographic Reference	Inagaki, N.; Takeuchi, M.; Oura, T.; Imaoka, T.; Seino, Y.; Efficacy and safety of tirzepatide monotherapy compared with dulaglutide in Japanese patients with type 2 diabetes (SURPASS J-mono): a double-blind, multicentre, randomised, phase 3 trial; The lancet. Diabetes & endocrinology; 2022; 623-633

53.1. Study details

Secondary publication of another included study- see primary study for details	No
Other publications associated with this study included in review	None
Trial name / registration number	SURPASS J-mono/NCT03861052
Study type	Randomised controlled trial (RCT) Double-blind trial
Study location	Japan
Study setting	Community
Study dates	05/2019 to 03/2021
Sources of funding	Funded by Eli Lilly & Co.
Inclusion criteria	• Aged≥20 years • Diagnosis of type 2 diabetes (WHO classification) ≥8 weeks before screening visit • No previous treatment with anti-hyperglycaemic medication (diet and exercise only) and HbA1c level 7·0-10·0% inclusive at screening; or receiving anti-hyperglycaemic monotherapy (excluding thiazolidinedione) and HbA1c level 6·5-9·0% inclusive at visit 1 and 7·0-10·0% inclusive at visit 2 and willing to discontinue the medication with an 8-week washout period before visit 2 • Stable weight (±5%) for 3 months before visit 1 • BMI ≥23 kg/m2 at visit 1

	• Agreement to not initiate intensive diet or exercise programme during study
Exclusion criteria	• Diagnosis of type 1 diabetes • Previous use of injectable therapy for type 2 diabetes • Chronic or acute pancreatitis • Proliferative diabetic retinopathy • Diabetic maculopathy • Non-proliferative diabetic retinopathy requiring acute treatment • Acute or chronic hepatitis • eGFR<30 mL/min per 1·73 m²
Recruitment / selection of participants	Participants recruited from 46 medical research centres/hospitals in Japan. Randomisation 1:1:1:1 ratio to arms using computer-generated random sequence with interactive web response system and stratified according to baseline HbA1c level (≤8.5%, >8.5%), baseline BMI (<25 kg/m2, ≥25 kg/m2), and whether receiving antidiabetic medication at baseline.
Intervention(s)	• Tirzepatide 15 mg once weekly • Tirzepatide 10 mg once weekly • Tirzepatide 5 mg once weekly Initial 4-week (anti-diabetic medication-naive participants) or 10-week (participants on antidiabetic medication monotherapy) lead-in period followed by subcutaneous injections of tirzepatide once weekly for 52 weeks, and then 4-week safety FU period. In all three groups, participants started on 2.5 mg once weekly for 4 weeks. Subsequently, dose increased by 2.5 mg every 4 weeks in tirzepatide 15 and 10 mg groups until appropriate doses reached; dose increased to 5 mg for tirzepatide 5 mg group. Participants, investigators, and sponsor masked to treatment assignment with study drugs administered using unified single-use pens with identical injection volumes (0.5 mL). Participants asked to use them on same day at same time each week. Concomitant medications allowed that did not interfere with study treatments (e.g. anti-hyperglycaemic medication, weight loss medication, chronic systemic glucocorticoid therapy). Clinical assessments/lab tests performed at each study visit.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear
Strata 2: People with atherosclerotic cardiovascular diseases	Not stated/unclear
Strata 3: People with type 2 diabetes mellitus and	Not stated/unclear

chronic kidney disease	
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	eGFR ≥30mL/min/1.73m2 Exclusion criteria: eGFR<30 mL/min per 1·73 m²
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Sensitivity analysis category: Enrichment trial status	7) Mixed population Participants were naive to anti-diabetic medication (diabetes managed with only diet and exercise) or if on antidiabetic monotherapy there was 8-week washout period before starting on study drugs.
Comparator	• Dulaglutide 0.75 mg once weekly Participants received subcutaneous injection of dulaglutide 0.75 mg once weekly for 52 weeks. Participants, investigators, and sponsor masked to treatment assignment with study drugs administered using unified single-use pens with identical injection volumes (0.5 mL). Participants asked to use them on same day at same time each week. Concomitant medications allowed that did not interfere with study treatments (e.g. anti-hyperglycaemic medication, weight loss medication, chronic systemic glucocorticoid therapy). Clinical assessments/lab tests performed at each study visit.
Number of participants	N=636

Duration of follow-up	52 weeks + 4 week safety follow up
Method of analysis	Modified ITT All randomised participants who received ≥1 dose of study drug used for efficacy and safety analysis
Additional comments	

53.2. Study arms

53.2.1. Tirzepatide 15 mg once weekly (N = 160)

Subcutaneous injection of tirzepatide 15 mg once weekly for 52 weeks.

53.2.2. Tirzepatide 10 mg once weekly (N = 158)

Subcutaneous injection of tirzepatide 10 mg once weekly for 52 weeks.

53.2.3. Tirzepatide 5 mg once weekly (N = 159)

Subcutaneous injection of tirzepatide 5 mg once weekly for 52 weeks.

53.2.4. Dulaglutide 0.75 mg once weekly (N = 159)

Subcutaneous injection of dulaglutide 0.75 mg once weekly for 52 weeks.

53.3. Characteristics

53.3.1. Arm-level characteristics

Characteristic	Tirzepatide 15 mg once weekly (N = 160)	Tirzepatide 10 mg once weekly (N = 158)	Tirzepatide 5 mg once weekly (N = 159)	Dulaglutide 0.75 mg once weekly (N = 159)
% Male Sample size	n = 132 ; % = 83	n = 119 ; % = 75	n = 113 ; % = 71	n = 117 ; % = 74
Mean age (SD) (years) Mean (SD)	56 (10.7)	56.2 (10.3)	56.8 (10.1)	57.5 (10.2)

Characteristic	Tirzepatide 15 mg once weekly (N = 160)	Tirzepatide 10 mg once weekly (N = 158)	Tirzepatide 5 mg once weekly (N = 159)	Dulaglutide 0.75 mg once weekly (N = 159)
Japanese Sample size	n = 160 ; % = 100	n = 158 ; % = 100	n = 159 ; % = 100	n = 159 ; % = 100
Comorbidities Custom value	NR	NR	NR	NR
Presence of frailty Custom value	NR	NR	NR	NR
Time since type 2 diabetes diagnosis (years) Median (IQR)	5.1 (2.2 to 8.4)	5.1 (2.2 to 8.4)	4.5 (2.1 to 7.5)	5 (1.9 to 8.4)
HbA1c (%) Mean (SD)	8.2 (0.9)	8.2 (0.9)	8.2 (0.9)	8.2 (0.9)
Blood pressure (mmHg) Mean (SD)	NA (NA)	NA (NA)	NA (NA)	NA (NA)
Systolic blood pressure Mean (SD)	132.2 (13.8)	130 (15.6)	130.2 (12.7)	130.6 (15.4)
Diastolic blood pressure Mean (SD)	83.9 (10)	82.6 (10)	82.4 (9.7)	82.1 (10.2)
Heart rate (BPM) Mean (SD)	72.8 (9.7)	72.9 (10.2)	72.8 (10.8)	73 (10.8)
Smoking status Custom value	NR	NR	NR	NR
Alcohol consumption Custom value	NR	NR	NR	NR
Presence of severe mental illness Custom value	NR	NR	NR	NR

Characteristic	Tirzepatide 15 mg once weekly (N = 160)	Tirzepatide 10 mg once weekly (N = 158)	Tirzepatide 5 mg once weekly (N = 159)	Dulaglutide 0.75 mg once weekly (N = 159)
People with significant cognitive impairment Custom value	NR	NR	NR	NR
People with a learning disability Custom value	NR	NR	NR	NR
BMI Mean (SD)	28.1 (4.4)	28 (4.1)	28.6 (5.4)	27.8 (3.7)
Number of people with obesity Custom value	NR	NR	NR	NR
Cholesterol and lipid levels Custom value	NR	NR	NR	NR
Albumin creatinine ratio Custom value	NR	NR	NR	NR
eGFR (mL/min/1.73m2) (mL/min per 1·73 m2) Median (IQR)	80 (71 to 86)	80 (72 to 86)	78 (68 to 86)	79 (71 to 86)
Other antidiabetic medication used Custom value	NR	NR	NR	NR
Blood pressure-lowering medication used Custom value	NR	NR	NR	NR
Statins/lipid-lowering medication used Custom value	NR	NR	NR	NR

Characteristic	Tirzepatide 15 mg once weekly (N = 160)	Tirzepatide 10 mg once weekly (N = 158)	Tirzepatide 5 mg once weekly (N = 159)	Dulaglutide 0.75 mg once weekly (N = 159)
Other treatment being received Custom value	NR	NR	NR	NR

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54. Jadzinsky, 2009

Bibliographic Reference	Jadzinsky, M; Pfutzner, A; Paz-Pacheco, E; Xu, Z; Allen, E; Chen, R; Saxagliptin given in combination with metformin as initial therapy improves glycaemic control in patients with type 2 diabetes compared with either monotherapy: a randomized controlled trial.; Diabetes, obesity & metabolism; 2009; vol. 11 (no. 6); 611-22

54.1. Study details

Secondary publication of another included study- see primary study for details	Pfützner, A., Paz-Pacheco, E., Allen, E. et al. (2011) Initial combination therapy with saxagliptin and metformin provides sustained glycaemic control and is well tolerated for up to 76 weeks. Diabetes Obes Metab 13(6): 567-76
Other publications associated with this study included in review	No additional information.
Trial name / registration number	NCT00327015
Study type	Randomised controlled trial (RCT)
Study location	
Study setting	
Study dates	
Sources of funding	Bristol-Myers Squibb and AstraZeneca
Inclusion criteria	Patients aged 18–77 years with T2D, HbA1c >8 and <12% at screening, fasting C-peptide concentration >1.0 ng/ml and body mass index <40 kg/m2; treatment naïve, defined as never having received medical treatment for diabetes or having received medical treatment for diabetes for a total period of <1 month since original diagnosis and not having received antihyperglycemic therapy for more than three consecutive days or for a total of seven non-consecutive days during 8 weeks before screening
Exclusion criteria	poorly controlled diabetes; history of diabetic ketoacidosis or hyperosmolar non-ketotic coma; insulin therapy within 1 year of screening; cardiovascular event within 6 months before study entry or New York Heart Association stage III/IV congestive heart failure and/or known left ventricular ejection fraction <40%; significant renal, liver or psychiatric

	history; history of alcohol or drug abuse within the previous year; treatment with potent CYP3A4 inhibitors or inducers; immunocompromised individuals; active liver disease or clinically significant abnormal hepatic, renal, endocrine, metabolic or haematological screening tests
Recruitment / selection of participants	
Intervention(s)	Saxagliptin 5-10 mg Metformin 500-2000 mg
Cointervention	None
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear
Strata 2: People with atherosclerotic cardiovascular diseases	Not stated/unclear
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	People at higher risk of developing cardiovascular disease
Subgroup 1: People with frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Mixed population
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear

Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Sensitivity analysis category: Enrichment trial status	6) No response criteria
Comparator	
Indirectness	

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55. Ji, 2016

Bibliographic Reference	Ji, L.; Han, P.; Wang, X.; Liu, J.; Zheng, S.; Jou, Y. M.; O'Neill, E. A.; Golm, G. T.; Engel, S. S.; Kaufman, K. D.; Shankar, R. R.; Randomized clinical trial of the safety and efficacy of sitagliptin and metformin co-administered to Chinese patients with type 2 diabetes mellitus; Journal of Diabetes Investigation; 2016; vol. 7 (no. 5); 727-36

55.1. Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.
Trial name / registration number	NCT01076088.
Study type	Randomised controlled trial (RCT)
Study location	China.
Study setting	Outpatient follow-up.
Study dates	No additional information.
Sources of funding	Funded by Merck & Co., Inc., Kenilworth, NJ, USA.
Inclusion criteria	People with type 2 diabetes who had inadequate glycaemic control with diet and exercise alone (HbA1c at least 7.5 and no more than 11.0%) or while on a single oral antihyperglycaemic agent other than a thiazolidinedione (HbA1c at least 7.0 and no more than 10.5%) or on low dose combination antihyperglycaemic agents (less than or equal to 50% maximum labelled dose of each agent) with HbA1c between 7.0 and 10.0%.
Exclusion criteria	Type 1 diabetes; a history of ketoacidosis; active liver disease; significant and active cardiovascular disease or haematological disorders; had been treated with a DPP-4 inhibitor or a GLP-1 receptor agonist; had been treated with a thiazolidinedione or insulin within 12 weeks before screening; people with serum creatinine more than or equal to 1.4mg/dL (men) or 1.3mg/dL (women), eGFR <60mL/min/1.73m2 (calculated using the Modification of Diet in Renal Disease equation), ALT or AST more than two times the upper limit of normal, haemoglobin <11g/dL (men) or

	<10g/dL (women), triglycerides >600mg/dL or thyroid-stimulating hormone outside the normal range.
Recruitment / selection of participants	No additional information.
Intervention(s)	Sitagliptin and metformin N=247 Two groups: Sitagliptin 100mg once a day and metformin 850mg twice a day (n=125) or sitagliptin 100mg once a day and metformin 500mg twice a day (n=122). Concomitant therapy: People who were not taking an antihyperglycaemic agent entered a 2 week single blind placebo run in, while those receiving a single or low-dose combination therapy discontinued that therapy and entered and 8 week washout phase before entering the placebo run in. At week 10, people were given advise on diet and exercise.
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure
Strata 2: People with atherosclerotic cardiovascular diseases	People without other cardiovascular diseases
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear

Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Sensitivity analysis category: Enrichment trial status	7) Mixed population
Population subgroups	No additional information.
Comparator	Metformin N=250 Two groups: Metformin 850mg twice a day (n=124) or metformin 500mg twice a day (n=126). Concomitant therapy: People who were not taking an antihyperglycaemic agent entered a 2 week single blind placebo run in, while those receiving a single or low-dose combination therapy discontinued that therapy and entered and 8 week washout phase before entering the placebo run in. At week 10, people were given advise on diet and exercise. Sitagliptin N=120 Sitagliptin 100mg once a day. Concomitant therapy: People who were not taking an antihyperglycaemic agent entered a 2 week single blind placebo run in, while those receiving a single or low-dose combination therapy discontinued that therapy and entered and 8 week washout phase before entering the placebo run in. At week 10, people were given advise on diet and exercise.

	Placebo N=127 Matching placebo. Concomitant therapy: People who were not taking an antihyperglycaemic agent entered a 2 week single blind placebo run in, while those receiving a single or low-dose combination therapy discontinued that therapy and entered and 8 week washout phase before entering the placebo run in. At week 10, people were given advise on diet and exercise.
Number of participants	744
Duration of follow-up	35 weeks (including an 8 week washout period) - 27 weeks of therapy (minus the washout period).
Indirectness	No additional information.
Method of analysis	Other Full analysis set (all people who received at least one dose of study treatment and had a measurement of the analysis end-point at baseline as well as at one or more post-baseline time-points)
Additional comments	No additional information.

55.2. Study arms

55.2.1. Sitagliptin + metformin (N = 247)

Two groups: Sitagliptin 100mg once a day and metformin 850mg twice a day (n=125) or sitagliptin 100mg once a day and metformin 500mg twice a day (n=122). Concomitant therapy: People who were not taking an antihyperglycaemic agent entered a 2 week single blind placebo run in, while those receiving a single or low-dose combination therapy discontinued that therapy and entered and 8 week washout phase before entering the placebo run in. At week 10, people were given advise on diet and exercise.

55.2.2. Metformin (N = 250)

Two groups: Metformin 850mg twice a day (n=124) or metformin 500mg twice a day (n=126). Concomitant therapy: People who were not taking an antihyperglycaemic agent entered a 2 week single blind placebo run in, while those receiving a single or low-dose combination therapy discontinued that therapy and entered and 8 week washout phase before entering the placebo run in. At week 10, people were given advise on diet and exercise.

55.2.3. Sitagliptin (N = 120)

Sitagliptin 100mg once a day. Concomitant therapy: People who were not taking an antihyperglycaemic agent entered a 2 week single blind placebo run in, while those receiving a single or low-dose combination therapy discontinued that therapy and entered and 8 week washout phase before entering the placebo run in. At week 10, people were given advise on diet and exercise.

55.2.4. Placebo (N = 127)

Matching placebo. Concomitant therapy: People who were not taking an antihyperglycaemic agent entered a 2 week single blind placebo run in, while those receiving a single or low-dose combination therapy discontinued that therapy and entered and 8 week washout phase before entering the placebo run in. At week 10, people were given advise on diet and exercise.

55.3. Characteristics

55.3.1. Arm-level characteristics

Characteristic	Sitagliptin + metformin (N = 247)	Metformin (N = 250)	Sitagliptin (N = 120)	Placebo (N = 127)
% Male Sample size	n = 152 ; % = 62	n = 144 ; % = 58	n = 74 ; % = 62	n = 87 ; % = 69
Mean age (SD) (years) Mean (SD)	52.5 (10.3)	52.8 (9.9)	51.7 (10.2)	53.6 (9.7)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Asian Sample size	n = 247 ; % = 100	n = 250 ; % = 100	n = 120 ; % = 100	n = 127 ; % = 100
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosis (years) Mean (SD)	1.1 (0.3)	1.1 (0.2)	1.1 (0.2)	1.1 (0.2)
HbA1c (%) Different number of participants.	8.6 (1)	8.7 (1.1)	8.7 (1.1)	9 (1.1)

Characteristic	Sitagliptin + metformin (N = 247)	Metformin (N = 250)	Sitagliptin (N = 120)	Placebo (N = 127)
Combination = 232. Metformin = 233. Sitagliptin = 113. Placebo = 117. Mean (SD)				
Blood pressure Mean (SD)	NR (NR)	NR (NR)	NR (NR)	NR (NR)
Heart rate Mean (SD)	NR (NR)	NR (NR)	NR (NR)	NR (NR)
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Weight (kg) Mean (SD)	70.9 (11.6)	71.1 (12.8)	71.8 (12.1)	70.8 (12.5)
BMI (kg/m2) Mean (SD)	25.8 (3.3)	25.9 (3.6)	26 (3.5)	25.4 (3.4)
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Cholesterol and lipid levels Mean (SD)	NR (NR)	NR (NR)	NR (NR)	NR (NR)
Albumin creatinine ratio Mean (SD)	NR (NR)	NR (NR)	NR (NR)	NR (NR)

Characteristic	Sitagliptin + metformin (N = 247)	Metformin (N = 250)	Sitagliptin (N = 120)	Placebo (N = 127)
eGFR (mL/min/1.73m2) Mean (SD)	NR (NR)	NR (NR)	NR (NR)	NR (NR)
Other antidiabetic medication used Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Blood pressure-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Statins/lipid-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR

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56. Ji, 2017

Bibliographic Reference	Ji, L.; Li, L.; Kuang, J.; Yang, T.; Kim, D. J.; Kadir, A. A.; Huang, C. N.; Lee, D.; Efficacy and safety of fixed-dose combination therapy, alogliptin plus metformin, in Asian patients with type 2 diabetes: A phase 3 trial; Diabetes Obes Metab; 2017; vol. 19 (no. 5); 754-758

56.1. Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.
Trial name / registration number	No additional information.
Study type	Randomised controlled trial (RCT)
Study location	China, Malaysia, the Republic of Korea (South Korea) and Taiwan.
Study setting	Outpatient follow-up.
Study dates	No additional information.
Sources of funding	Funded by Takeda Pharmaceutical Company Limited. Some authors received grants from this organisation.
Inclusion criteria	People aged 18 to 75 years; historical diagnosis of type 2 diabetes for which glycemic control was inadequate (HbA1c 7.5%-10% after at least 2 months of diet and exercise prior to screening; receiving any other diabetic therapy for less than 7 days in total during this 2 month period); adequate haemoglobin, creatinine, eGFR; ability and willingness to self-monitor blood glucose levels, keep a hypoglycaemic diary; routinely use adequate contraception (for sexually active women of childbearing potential only).
Exclusion criteria	History of treatment for diabetic gastric paresis, gastric banding of gastric bypass surgery; history of diabetic ketoacidosis or hyperosmolar non-ketotic coma; chronic and/or acute pancreatitis; any hemoglobinopathy or diagnosis of chronic anaemia; angioedema in association with use of angiotensin-converting enzyme inhibitors or angiotensin-II receptor blockers or organ transplantation; NYHA class III or IV heart failure; systolic blood pressure greater than 180 mmHg and/or diastolic blood pressure at least 110 mmHg at screening; clinical evidence of hepatopathy; acute or chronic hepatitis; HIV; ALT 2.5x upper limit of

	normal; people with a history of DPP-4 inhibitor therapy within 3 months of screening; coronary angioplasty, coronary stent placement, coronary bypass surgery, or myocardial infarction within 6 months of screening; alcohol or substance abuse within 2 years of screening; any cancer within 5 years of screening (except non-melanoma skin cancer); use of oral or systemic glucocorticoids or weight-loss drugs within 2 months of screening; women who were pregnant, lactating or intended to be pregnant or donate ova within 4 weeks of study completion.
Recruitment / selection of participants	No additional information.
Intervention(s)	Alogliptin and metformin N=159 Alogliptin 12.5mg twice a day plus metformin 500mg twice a day. Concomitant therapy: No additional information.
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure
Strata 2: People with atherosclerotic cardiovascular diseases	Not stated/unclear
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear

Subgroup 3: People with non-alcoholic fatty liver disease	People without non-alcoholic fatty liver disease
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Sensitivity analysis category: Enrichment trial status	5) All treatment naïve
Population subgroups	No additional information.
Comparator	Alogliptin N=163 Alogliptin 12.5mg twice a day. Concomitant therapy: No additional information. Metformin N=162 Metformin 500mg twice a day. Concomitant therapy: No additional information. Placebo N=163 Matching placebo. Concomitant therapy: No additional information.

Number of participants	643
Duration of follow-up	26 weeks.
Indirectness	No additional information.
Method of analysis	Per protocol Other Full Analysis Set (all people who received at least one dose of the treatment)
Additional comments	No additional information.

56.2. Study arms

56.2.1. Alogliptin + metformin (N = 159)

Alogliptin 12.5mg twice a day plus metformin 500mg twice a day. Concomitant therapy: No additional information.

56.2.2. Alogliptin (N = 163)

Alogliptin 12.5mg twice a day. Concomitant therapy: No additional information.

56.2.3. Metformin (N = 162)

Metformin 500mg twice a day. Concomitant therapy: No additional information.

56.2.4. Placebo (N = 163)

Matching placebo. Concomitant therapy: No additional information.

56.3. Characteristics

56.3.1. Arm-level characteristics

Characteristic	Alogliptin + metformin (N = 159)	Alogliptin (N = 163)	Metformin (N = 162)	Placebo (N = 163)
% Male Sample size	n = 91 ; % = 57.2	n = 98 ; % = 60.1	n = 82 ; % = 50.6	n = 95 ; % = 58.3

Characteristic	Alogliptin + metformin (N = 159)	Alogliptin (N = 163)	Metformin (N = 162)	Placebo (N = 163)
Mean age (SD) (years) Mean (SD)	53.4 (10.46)	55.4 (9.62)	53.6 (9.91)	52.2 (10.17)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Asian Sample size	n = 159 ; % = 100	n = 162 ; % = 99.4	n = 161 ; % = 99.4	n = 161 ; % = 98.8
American Indian or Alaskan Native Sample size	n = 0 ; % = 0	n = 1 ; % = 0.6	n = 0 ; % = 0	n = 2 ; % = 1.2
Multiracial Sample size	n = 0 ; % = 0	n = 0 ; % = 0	n = 1 ; % = 0.6	n = 0 ; % = 0
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosis Mean (SD)	NR (NR)	NR (NR)	NR (NR)	NR (NR)
HbA1c (%) Mean (SD)	8.39 (0.81)	8.48 (0.71)	8.4 (0.78)	8.21 (0.77)
Blood pressure Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Heart rate Mean (SD)	NR (NR)	NR (NR)	NR (NR)	NR (NR)
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Alogliptin + metformin (N = 159)	Alogliptin (N = 163)	Metformin (N = 162)	Placebo (N = 163)
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Weight Mean (SD)	NR (NR)	NR (NR)	NR (NR)	NR (NR)
BMI (kg/m2) Mean (SD)	26.56 (4.22)	26.3 (3.57)	26.16 (3.92)	26.16 (3.51)
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Cholesterol and lipid levels Mean (SD)	NR (NR)	NR (NR)	NR (NR)	NR (NR)
Albumin creatinine ratio Mean (SD)	NR (NR)	NR (NR)	NR (NR)	NR (NR)
eGFR (mL/min/1.73m2) Mean (SD)	NR (NR)	NR (NR)	NR (NR)	NR (NR)
Other antidiabetic medication used Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Blood pressure-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Statins/lipid-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Alogliptin + metformin (N = 159)	Alogliptin (N = 163)	Metformin (N = 162)	Placebo (N = 163)
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR

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57. Ji, 2014

Bibliographic Reference	Ji, L.; Ma, J.; Li, H.; Mansfield, T. A.; T'Joen, C. L.; Iqbal, N.; Ptaszynska, A.; List, J. F.; Dapagliflozin as monotherapy in drug-naive asian patients with type 2 diabetes mellitus: A randomized, blinded, prospective phase III study; Clin Ther; 2014; vol. 36 (no. 1); 84-100.e9

57.1. Study details

Secondary publication of another included study- see primary study for details	No information reported
Other publications associated with this study included in review	No information reported
Trial name / registration number	NCT01095653
Study type	Randomised controlled trial (RCT)
Study location	China Korea Taiwan India
Study setting	Not reported
Study dates	06/10 to 03/12
Sources of funding	Bristol-Myers Squibb and AstraZeneca.
Inclusion criteria	a) Men and woman aged ≥18 years with inadequately controlled T2DM defined as a glycosylated haemoglobin (HbA1c) levels ≥7.5% and ≤10.5% (≥58 and ≤91 mmol/mol) at the enrolment visit and ≥7.0% and r10.5% (≥53 and ≤91 mmol/mol) at the lead-in day -14 visit were included in this study. b) Patients were required to have a C-peptide level ≥1.0 ng/mL (0.34 nmol/L) and a BMI ≤45.0 kg/m2 at the enrolment visit and be drug naive (never received prescription medication, including Chinese

	traditional medicines for diabetes, or have received prescription medication for diabetes for <24 weeks since original diagnosis).
Exclusion criteria	• Patients were excluded from enrolment if they had: aspartate aminotransferase and/or alanine aminotransferase levels 43 times the upper limit of normal (ULN), serum total bilirubin 42 mg/dL (34.2 mmol/L), serum creatinine ≥1.5 mg/dL (132.6 mmol/L) for men or Z1.4 mg/dL (123.8 mmol/L) for women (based on guidance from the rescue therapy [metformin] prescribing information), haemoglobin ≤110 g/L for men and ≤100 g/L for women, creatine kinase ≥3 times the ULN, urine albumin: creatinine ratio 41800 mg/g, severe hypertriglyceridemia (triglyceride 4800 mg/dL [9.3 mmol/L]), urinary excretion of N-acetyl-β-D-glycosaminidase (NAG) 484 mmol/h NAG/mmol creatinine, urinary excretion of α1 microglobulin 428 mg α1 microglobulin/g creatinine, parathyroid hormone value 41.5 times the ULN, calcium or serum phosphate values outside the normal reference range, abnormal free T4 values, and positive hepatitis B surface antigen or positive anti–hepatitis C antibodies. Patients with current unstable or serious vascular, renal, hepatic, hematologic, oncologic, endocrine, psychiatric, or rheumatic diseases were also excluded.
Recruitment / selection of participants	Men and woman aged ≥18 years with inadequately controlled T2DM from 40 sites internationally were recruited.
Intervention(s)	Dapagliflozin 5 mg once daily, administered orally before the first meal of the day Dapagliflozin 10 mg once daily, administered orally before the first meal of the day Changes in the blinded study medication were not permitted during the study.
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure
Strata 2: People with atherosclerotic cardiovascular diseases	People without other cardiovascular diseases
Strata 3: People with type 2 diabetes mellitus and	Not stated/unclear

chronic kidney disease	
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	People at higher risk of developing cardiovascular disease
Subgroup 1: People with frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Mixed population
Subgroup 5: eGFR category at baseline	eGFR ≥30mL/min/1.73m2
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Sensitivity analysis category: Enrichment trial status	7) Mixed population
Population subgroups	
Comparator	Placebo taken orally once per day before breakfast. Changes in the blinded study medication were not permitted during the study.
Number of participants	N=393 (1179 patients were enrolled but only 393 were eligible for randomisation)
Duration of follow-up	24-week treatment period and 28-day follow-up

Indirectness	Patients were recruited from sites outside of the UK, this may limit the generalisability of the results to the wider UK population. However, the results may be more generalisable to people of Chinese, Indian, Korean and Japanese origin living in the UK. Conducted in China, Korea, Taiwan and India but most of the sites were in China (26 sites).
Method of analysis	ACA
Additional comments	• Patients with inadequate glycemic control could remain in the trial and receive open-label rescue therapy with metformin (500 mg daily, titrated to 2000 mg if necessary). • Criteria for inadequate glycaemic control requiring rescue therapy became progressively more stringent over time: during weeks 4 to 12, a central laboratory fasting plasma glucose (FPG) measurement (confirmed with a second measurement within 3–5 days) of 4240 mg/dL (13.3 mmol/L) was required; during weeks 12 to 24, an FPG level 4200 mg/dL (11.1 mmol/L) was required. Patients with FPG values consistently greater than protocol-specified values for 12 weeks despite a maximum tolerated dose of metformin were discontinued from the study.

57.2. Study arms

57.2.1. Placebo (N = 132)

Administered orally before the first meal of the day

57.2.2. Dapagliflozin 5 mg once daily (N = 128)

Administered orally before the first meal of the day

57.2.3. Dapagliflozin 10 mg once daily (N = 133)

Administered orally before the first meal of the day

57.3. Characteristics

57.3.1. Study-level characteristics

Characteristic	Study (N = 393)
Number of people with obesity	n = 84 ; % = 21.4

Characteristic	Study (N = 393)
No of events	

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2 **57.3.2. Arm-level characteristics**

Characteristic	Placebo (N = 132)	Dapagliflozin 5 mg once daily (N = 128)	Dapagliflozin 10 mg once daily (N = 133)
% Male No of events	n = 87 ; % = 65.9	n = 84 ; % = 65.6	n = 86 ; % = 64.7
Mean age (SD) Mean (SD)	49.9 (10.87)	53 (11.07)	51.2 (9.89)
Chinese No of events	n = 117 ; % = 88.6	n = 114 ; % = 89.1	n = 117 ; % = 88
Indian Asian No of events	n = 8 ; % = 6.1	n = 8 ; % = 6.3	n = 9 ; % = 6.8
Korean No of events	n = 5 ; % = 3.8	n = 6 ; % = 4.7	n = 5 ; % = 3.8
Japanese No of events	n = 1 ; % = 0.8	n = 0 ; % = 0	n = 1 ; % = 0.8
Other Asian No of events	n = 1 ; % = 0.8	n = 0 ; % = 0	n = 1 ; % = 0.8
History of dyslipidaemia No of events	n = 53 ; % = 40.2	n = 49 ; % = 38.3	n = 57 ; % = 42.9
History of hypertension No of events	n = 54 ; % = 40.9	n = 49 ; % = 38.3	n = 50 ; % = 37.6
Presence of frailty Nominal	NR	NR	NR
Time since type 2 diabetes diagnosis Mean (SD)	1.3 (2)	1.15 (2.3)	1.67 (2.8)
Heart rate Nominal	NR	NR	NR

Characteristic	Placebo (N = 132)	Dapagliflozin 5 mg once daily (N = 128)	Dapagliflozin 10 mg once daily (N = 133)
Smoking status Nominal	NR	NR	NR
Alcohol consumption Nominal	NR	NR	NR
Presence of severe mental illness Nominal	NR	NR	NR
People with significant cognitive impairment Nominal	NR	NR	NR
People with a learning disability Nominal	NR	NR	NR
Albumin creatinine ratio Nominal	NR	NR	NR
Other antidiabetic medication used Nominal	NR	NR	NR
Blood pressure-lowering medication used Nominal	NR	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR	NR
Other treatment being received Nominal	NR	NR	NR

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58. Jiang, 2021

Bibliographic Reference	Jiang, A.; Feng, Z.; Yuan, L.; Zhang, Y.; Li, Q.; She, Y.; Effect of sodium-glucose co-transporter-2 inhibitors on the levels of serum asprosin in patients with newly diagnosed type 2 diabetes mellitus; Diabetology and Metabolic Syndrome; 2021; vol. 13 (no. 1)

58.1. Study details

Secondary publication of another included study- see primary study for details	No information available.
Other publications associated with this study included in review	No information available.
Trial name / registration number	CTR20131268
Study type	Randomised controlled trial (RCT)
Study location	China
Study setting	Hospital
Study dates	No information available.
Sources of funding	Jiangsu Natural Science Foundation and the Nanjing Medical Science and Technique Development Foundation.
Inclusion criteria	Participants with newly diagnosed type 2 diabetes following the WHO diagnostic criteria and drug-naïve type 2 diabetes, had HbA1c levels between 58 and 85 mmol/mol (7.5%–10%), BMI ≥23.0 kg/m2.
Exclusion criteria	Severe hepatic and renal dysfunction, acute diabetic complication, suffered from acute or chronic pancreatitis at any time, have received or planned to undergo gastric bypass bariatric surgery or restrictive bariatric surgery during the study period, or long-term use of drugs that directly affect the motility of the gastrointestinal tract.
Recruitment / selection of participants	Eligible participants received instructions on a similar level of physical activity and the same nutritional value and equivalent energy intake of meals, the original lipid-lowering and anti-hypertensive programs were maintained during the period.
Intervention(s)	Dapagliflozin 10 mg orally, daily before breakfast.

Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear
Strata 2: People with atherosclerotic cardiovascular diseases	Not stated/unclear
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Sensitivity analysis	5) All treatment naïve

category: Enrichment trial status	
Population subgroups	None.
Comparator	Placebo orally, daily before breakfast.
Number of participants	N=29
Duration of follow-up	24 weeks study duration
Indirectness	Study was conducted in China, this may limit the generalisability to the UK population.
Method of analysis	Not stated/unclear
Additional comments	Median and IQR reported for HbA1c. Median and IQR reported for systolic blood pressure for the placebo group.

58.2. Study arms

58.2.1. Placebo once daily (N = 10)

Taken before breakfast

58.2.2. Dapagliflozin 10 mg once daily (N = 19)

Taken before breakfast

58.3. Characteristics

58.3.1. Arm-level characteristics

Characteristic	Placebo once daily (N = 10)	Dapagliflozin 10 mg once daily (N = 19)
% Male No of events	n = 2 ; % = 20	n = 9 ; % = 47
Mean age (SD) (years) Mean (SD)	59.3 (9.03)	58.32 (8.01)

Characteristic	Placebo once daily (N = 10)	Dapagliflozin 10 mg once daily (N = 19)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosis Nominal	NR	NR
HbA1c (%) Median (IQR)	8.5 (8.05 to 8.92)	8.1 (7.7 to 8.9)
Heart rate Nominal	NR	NR
Smoking status Nominal	NR	NR
Alcohol consumption Nominal	NR	NR
Presence of severe mental illness Nominal	NR	NR
People with significant cognitive impairment Nominal	NR	NR
People with a learning disability Nominal	NR	NR
Number of people with obesity Nominal	NR	NR
Albumin creatinine ratio Nominal	NR	NR
eGFR (mL/min/1.73m2) Nominal	NR	NR

Characteristic	Placebo once daily (N = 10)	Dapagliflozin 10 mg once daily (N = 19)
Other antidiabetic medication used Nominal	NR	NR
Blood pressure-lowering medication used Nominal	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

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59. Kahl, 2019

Bibliographic Reference	Kahl, S.; Gancheva, S.; Strassburger, K.; Herder, C.; Machann, J.; Katsuyama, H.; Kabisch, S.; Henkel, E.; Kopf, S.; Lagerpusch, M.; et, al.; Empagliflozin effectively lowers liver fat content in well-controlled type 2 diabetes: A randomized, double-blind, phase 4, placebo-controlled trial; Diabetes Care; 2019

59.1. Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.
Trial name / registration number	NCT02637973
Study type	Randomised controlled trial (RCT)
Study location	Germany (five centres).
Study setting	Outpatient follow-up.
Study dates	No additional information.
Sources of funding	Funded by the German Federal Ministry of Health and the Ministry of Innovation, Science and Research to the German Center for Diabetes Research.
Inclusion criteria	Age between 18 and 75 years; obtained written informed consent; HbA1c between 6% and 8%; BMI no more than 45 kg/m2; drug naive (no previous antihyperglycaemic treatment or one-month washout period of treatment with oral glucose lowering drugs - no previous treatment with thiazolidinedione drugs allowed); known diabetes duration up to 7 years.
Exclusion criteria	Participation in other interventional trials; uncontrolled hyperglycaemia at screening (glucose level no more than 240mg/dL after an overnight fast); acute coronary syndrome, stroke or transient ischaemic attack within 3 months prior to consent; previous lower limb amputation; severe lower limb infection/ulceration within 3 months prior to consent; evidence for liver disease (other than NAFLD) including chronic viral hepatitis (B or C), alcohol abuse, hemochromatosis, alpha-1 antitrypsin deficiency, autoimmune hepatitis, Wilson's disease, primary sclerosing cholangitis or primary biliary cirrhosis, or liver cirrhosis of any aetiology; AST or ALT >3

	times the upper limit of normal; positive result on hepatitis B, C or HIV-1 and -2 tests; impaired kidney function (eGFR <60 mL/min/1.73m2) during screening; structural or functional urogenital abnormalities that predispose to urogenital infections; gastrointestinal surgeries that induce chronic malabsorption; history of cancer (except basal cell carcinoma) or treatment for cancer within 5 years prior to screening; blood dyscrasias or any disorders causing hemolysis or unstable erythrocytes; treatment with anti-obesity drugs 3 months prior to consent; treatment with immunomodulatory drugs (oral steroids, antihistamines); change in dosage of thyroid hormones within 6 months of consent; pregnancy, lactation period; metal or magnetic implants, devices or objects inside of or on the body, which are not MRI compatible; claustrophobia; cigarette smoking (non-smoker <1 year), alcohol consumption (male >30g/d, female >20g/d); drug abuse or psychiatric disease; night-worker or circumstances not allowing normal day-night rhythm; hypersensitivity to empagliflozin or any of the drug compounds (galactose intolerance, Lapp-lactase deficiency, glucose-galactose malabsorption); pharmaceutical preparations with which interactions can be expected - amiloride, furosemide, indapamide, spironolactone, torasemide, triamterene; use of anti-NASH drugs (vitamin E, ursodeoxycholic acid, S-adenosylmethionine, betaine, silymarine, gemfibrozil, anti-TNF therapies, probiotics) in the 3 months prior to randomisation); women of childbearing potential not using two adequate methods of contraception, including a barrier method and a non-barrier method; people with any kind of dependency on the investigator or employed by the sponsor or investigator; persons held inan institution by legal or official order; legally incapacitated persons.
Recruitment / selection of participants	No additional information.
Intervention(s)	Empagliflozin N=42 Empagliflozin 25mg once daily.
Cointervention	Concomitant therapy: No additional information.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear
Strata 2: People with atherosclerotic cardiovascular diseases	People without other cardiovascular diseases
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear

Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	People with non-alcoholic fatty liver disease 79% - so included in people with because very close to 80%
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Sensitivity analysis category: Enrichment trial status	7) Mixed population
Population subgroups	No additional information.
Comparator	Placebo N=42 Matching placebo.
Number of participants	84
Duration of follow-up	24 weeks.
Indirectness	No additional information.
Method of analysis	ITT

Additional comments	No additional information.

59.2. Study arms

59.2.1. Empagliflozin (N = 42)

Empagliflozin 25mg once daily. Concomitant therapy: No additional information.

59.2.2. Placebo (N = 42)

Matching placebo. Concomitant therapy: No additional information.

59.3. Characteristics

59.3.1. Arm-level characteristics

Characteristic	Empagliflozin (N = 42)	Placebo (N = 42)
% Male Sample size	n = 29 ; % = 69	n = 29 ; % = 69
Mean age (SD) (years) Mean (SD)	62.7 (7)	61.5 (10)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Caucasian Sample size	n = 42 ; % = 100	n = 41 ; % = 98
Hispanic/Latino Sample size	n = 0 ; % = 0	n = 1 ; % = 2
Comorbidities Sample size	n = NA ; % = NA	n = NA ; % = NA
Hepatic steatosis Sample size	n = 33 ; % = 79	n = 33 ; % = 79
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Empagliflozin (N = 42)	Placebo (N = 42)
Time since type 2 diabetes diagnosis (Months) Mean (SD)	36 (27)	40 (27)
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR
Other antidiabetic medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Blood pressure-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Statins/lipid-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR

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60. Kaku, 2018

Bibliographic Reference	Kaku, K.; Haneda, M.; Tanaka, Y.; Lee, G.; Shiki, K.; Miyamoto, Y.; Solimando, F.; Lee, J.; Lee, C.; George, J.; Linagliptin as add-on to empagliflozin in a fixed-dose combination in Japanese patients with type 2 diabetes: glycaemic efficacy and safety profile in a two-part, randomized, placebo-controlled trial; Diab Obes Metab; 2018; vol. 21 (no. 1); 136-145

60.1. Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	NCT02489968
Study type	Randomised controlled trial (RCT)
Study location	Japan
Study setting	No additional information
Study dates	May 2015 - June 2017
Sources of funding	Funded by Boehringer Ingelheim
Inclusion criteria	Aged ≥20 years Diagnosed with type 2 diabetes On a diet and exercise regime for ≥12 weeks Drug naïve (no antidiabetic drug for ≥12 weeks) or using a stable dose of one oral antidiabetic drug for ≥12 weeks (≥18 weeks for thiazolidinedione) that was discontinued at screening BMI ≤40 kg/m2 HbA1c 8.0-10.5% for drug naïve participants, or 7.5-10.0% for drug-treated participants

Exclusion criteria	Uncontrolled hyperglycaemia (fasting glucose >270 mg/dL during the open-label stabilisation period Acute coronary syndrome Previous stroke or transient ischemic attack Undergoing insulin or glucagon-like peptide-1 agonist treatment, anti-obesity or any other treatment leading to unstable weight within 12 weeks Indication of liver disease Estimated GFR <45 mL/min
Recruitment / selection of participants	No additional information
Intervention(s)	All participants underwent an open-label stabilisation period, where they received 10 mg empagliflozin for 16 weeks. Those who completed the stabilisation period entered a placebo run-in period where they continued to receive empagliflozin, plus a placebo for empagliflozin/linagliptin. Those who still fulfilled the inclusion/exclusion criteria were randomised. Those randomised to the intervention arm in study A received 10/5 mg empagliflozin/linagliptin, plus placebo for empagliflozin for 24 weeks. Those randomised to the intervention arm in study B received 25/5 mg empagliflozin/linagliptin, plus placebo for empagliflozin for 52 weeks. Rescue medication could be initiated for patients with confirmed FPG > 270 mg/dL (Weeks 0-8), FPG > 240 mg/ dL (Weeks 8-12), FPG > 200 mg/dL (Weeks 12-24) or FPG > 180 mg/dL and/or HbA1c > 8.0% (Weeks 24-52). The choice of rescue medication and dosage were at the discretion of the investigator, With the exception of DPP-4 inhibitors, SGLT2 inhibitors, and GLP-1 agonists, which were prohibited.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear
Strata 2: People with atherosclerotic cardiovascular diseases	People without other cardiovascular diseases
Strata 3: People with type 2 diabetes mellitus and	People without chronic kidney disease

chronic kidney disease	
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	People at higher risk of developing cardiovascular disease
Subgroup 1: People with frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	People without non-alcoholic fatty liver disease
Subgroup 4: People with obesity	Mixed population
Subgroup 5: eGFR category at baseline	eGFR ≥30mL/min/1.73m2
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Sensitivity analysis category: Enrichment trial status	1) Including only responders
Population subgroups	No additional information
Comparator	Those randomised to the comparator arm in study A received 10 mg empagliflozin, plus placebo for empagliflozin/linagliptin. Those randomised to the comparator arm in study B received 25 mg empagliflozin, plus placebo for empagliflozin/linagliptin. Rescue medication could be initiated for patients with confirmed FPG > 270 mg/dL (Weeks 0-8), FPG > 240 mg/ dL (Weeks 8-12), FPG > 200 mg/dL (Weeks 12-24) or FPG > 180 mg/dL and/or HbA1c > 8.0% (Weeks 24-52). The choice of rescue medication and dosage were at the discretion

	of the investigator, With the exception of DPP-4 inhibitors, SGLT2 inhibitors, and GLP-1 agonists, which were prohibited.
Number of participants	**Study A** 215 randomised 107 received empagliflozin/linagliptin, 105 completed 108 received empagliflozin, 100 completed **Study B** 232 randomised 116 received empagliflozin/linagliptin, 110 completed 116 received empagliflozin, 108 completed
Duration of follow-up	Study A - 24 weeks Study B - 52 weeks
Indirectness	None
Method of analysis	ITT
Additional comments	None

60.2. Study arms

60.2.1. Empagliflozin + linagliptin (N = 107)

10/5 mg empagliflozin/linagliptin plus placebo, once daily

60.2.2. Empagliflozin (N = 108)

10 mg empagliflozin plus placebo, once daily

60.2.3. Empagliflozin + linagliptin (N = 116)

25/5 mg empagliflozin/linagliptin plus placebo, once daily

60.2.4. Empagliflozin (N = 116)

25 mg empagliflozin plus placebo, once daily

60.3. Characteristics

60.3.1. Arm-level characteristics

Characteristic	Empagliflozin + linagliptin (N = 107)	Empagliflozin (N = 108)	Empagliflozin + linagliptin (N = 116)	Empagliflozin (N = 116)
% Male Sample size	n = 85 ; % = 79	n = 85 ; % = 79	n = 87 ; % = 75	n = 79 ; % = 68
Mean age (SD) (years) Mean (SD)	58 (9.3)	56.3 (9.9)	56.8 (10.6)	58.4 (9.2)
Ethnicity Nominal	NR	NR	NR	NR
Comorbidities Nominal	NR	NR	NR	NR
Presence of frailty Nominal	NR	NR	NR	NR
Time since type 2 diabetes diagnosis (years) Mean (SD)	8.4 (5.6)	7.6 (5)	8.5 (5.5)	8.3 (5.7)
HbA1c (%) Mean (SD)	8.34 (0.54)	8.4 (0.68)	8.27 (0.59)	8.26 (0.68)
Blood pressure (mmHg) Mean (SD)	NA (NA)	NA (NA)	NA (NA)	NA (NA)
SBP Mean (SD)	125.7 (12.1)	127.1 (15.1)	124.8 (14)	126 (15.1)
DBP Mean (SD)	77.8 (10.3)	78.5 (9.5)	76.3 (8.8)	76.6 (10.1)
Heart rate Nominal	NR	NR	NR	NR

Characteristic	Empagliflozin + linagliptin (N = 107)	Empagliflozin (N = 108)	Empagliflozin + linagliptin (N = 116)	Empagliflozin (N = 116)
Smoking status Nominal	NR	NR	NR	NR
Alcohol consumption Nominal	NR	NR	NR	NR
Presence of severe mental illness Nominal	NR	NR	NR	NR
People with significant cognitive impairment Nominal	NR	NR	NR	NR
People with a learning disability Nominal	NR	NR	NR	NR
Weight kg Mean (SD)	69 (13)	70.2 (12)	69.1 (14.2)	67.5 (13.8)
BMI (kg/m²) Mean (SD)	24.9 (4)	25.1 (3.6)	25 (4.3)	24.7 (3.7)
Number of people with obesity Nominal	NR	NR	NR	NR
Cholesterol and lipid levels Nominal	NR	NR	NR	NR
Albumin creatinine ratio Nominal	NR	NR	NR	NR
eGFR (mL/min/1.73m2) Mean (SD)	97 (17.6)	96.4 (21.4)	96.4 (19.7)	94.7 (19.8)

Characteristic	Empagliflozin + linagliptin (N = 107)	Empagliflozin (N = 108)	Empagliflozin + linagliptin (N = 116)	Empagliflozin (N = 116)
Other antidiabetic medication used Previous monotherapy Sample size	n = 81 ; % = 76	n = 83 ; % = 77	n = 93 ; % = 80	n = 95 ; % = 82
Blood pressure-lowering medication used Nominal	NR	NR	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR	NR	NR
Other treatment being received Nominal	NR	NR	NR	NR

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61. Kaku, 2014

Bibliographic Reference	Kaku, K.; Kiyosue, A.; Inoue, S.; Ueda, N.; Tokudome, T.; Yang, J.; Langkilde, A. M.; Efficacy and safety of dapagliflozin monotherapy in Japanese patients with type 2 diabetes inadequately controlled by diet and exercise; Diabetes Obes Metab; 2014; vol. 16 (no. 11); 1102-10

61.1. Study details

Secondary publication of another included study- see primary study for details	No information available.
Other publications associated with this study included in review	No information available.
Trial name / registration number	NCT01294423
Study type	Randomised controlled trial (RCT)
Study location	Japan
Study setting	Clinic
Study dates	Not reported
Sources of funding	Funded by AstraZeneca and Bristol-Myers Squibb.
Inclusion criteria	• Patients aged ≥20 years with a confirmed diagnosis of T2DM were eligible for inclusion. • Patients were required to be: (i) drug-naïve (never received medical treatment for diabetes or received treatment for <30 days after diagnosis, and during the 30-day period before screening did not receive oral antidiabetic agents for >3 consecutive or >7 non-consecutive days, or were previously treated for diabetes but not within 6 weeks of enrolment), or (ii) receiving ongoing treatment for diabetes within 6 weeks of enrolment (not drug-naïve). These patients would undergo a washout period before study treatments. • At enrolment, HbA1c values ≥6.5 and ≤10% were required for patients defined as drug-naïve, and HbA1c values ≤8% were required for patients with ongoing treatment. • At 1 week before randomization, HbA1c was required to be ≥6.5 and ≤10% for all patients. The proportion of randomized patients

	with HbA1c ≥6.5%, but ≤7%, 1 week before randomization was required to be ≤25%.
Exclusion criteria	• Patients with type 1 diabetes or FPG >240 mg/dl (13.3 mmol/l) • Pregnant or breastfeeding women and patients with: creatinine kinase >3× upper limit of normal (ULN); an estimated glomerular filtration rate (eGFR) <45 ml/min or a serum creatinine value of >1.5 mg/dl (>133 µmol/l) for men and >1.4 mg/dl (>124 µmol/l) for women; severe hepatic insufficiency and/or significant abnormal liver function (aspartate aminotransferase >3 × ULN and/or alanine aminotransferase >3 × ULN); New York Heart Association class IV congestive heart failure; unstable or acute congestive heart failure; or treatment with thiazolidinediones <6 months before enrolment.
Recruitment / selection of participants	A 2-week screening period, and a 4-week, single-blind, placebo lead-in period. Dapagliflozin 5 or 10 mg, or placebo, was administered orally once daily during the 24-week double-blind period.
Intervention(s)	Dapagliflozin 5 mg once daily orally administered Dapagliflozin 10 mg once daily orally administered
Cointervention	
Strata 1: People with type 2 diabetes mellitus and heart failure	People with heart failure
Strata 2: People with atherosclerotic cardiovascular diseases	Not stated/unclear
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	People with chronic kidney disease
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	People at higher risk of developing cardiovascular disease

Subgroup 1: People with frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	eGFR ≥30mL/min/1.73m2
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Sensitivity analysis category: Enrichment trial status	3) Selection of specific population
Population subgroups	
Comparator	Placebo administered orally once daily
Number of participants	261
Duration of follow-up	24 weeks
Indirectness	Japanese patients were included, the patient population is not directly generalisable to the UK population.
Method of analysis	ACA
Additional comments	• At enrolment, HbA1c values ≥6.5 and ≤10% were required for patients defined as drug-naïve, and HbA1c values ≤8% were required for patients with ongoing treatment. At 1 week before randomization, HbA1c was required to be ≥6.5 and ≤10% for all patients. • Efficacy data were analysed for all randomised individuals who took at least one dose of double-blind study medication, had a non-missing baseline value for ≥1 efficacy variable. • The safety set comprised patients who took ≥1 dose of double-blind study medication and who provided any safety records.

	• The primary efficacy endpoint (change from baseline in HbA1c at week 24) was assessed by an analysis of covariance model with fixed terms for treatment group and gender (stratification factor) and baseline value as a covariate, using last observation carried forward (LOCF) to calculate a least-squares estimate of the treatment difference.

61.2. Study arms

61.2.1. Dapagliflozin 5 mg once daily (N = 86)

Administered orally

61.2.2. Dapagliflozin 10 mg once daily (N = 88)

Administered orally

61.2.3. Placebo (N = 87)

61.3. Characteristics

61.3.1. Arm-level characteristics

Characteristic	Dapagliflozin 5 mg once daily (N = 86)	Dapagliflozin 10 mg once daily (N = 88)	Placebo (N = 87)
% Male No of events	n = 50 ; % = 58.1	n = 53 ; % = 60.2	n = 52 ; % = 59.8
Mean age (SD) Mean (SD)	58.6 (10.4)	57.5 (9.3)	60.4 (9.7)
Ethnicity Nominal	NR	NR	NR
Comorbidities Nominal	NR	NR	NR
Presence of frailty Nominal	NR	NR	NR

Characteristic	Dapagliflozin 5 mg once daily (N = 86)	Dapagliflozin 10 mg once daily (N = 88)	Placebo (N = 87)
Time since type 2 diabetes diagnosis (years) Mean (SD)	4.59 (5.56)	4.93 (4.52)	5.29 (6.17)
Heart rate Nominal	NR	NR	NR
Smoking status Nominal	NR	NR	NR
Alcohol consumption Nominal	NR	NR	NR
Presence of severe mental illness Nominal	NR	NR	NR
People with significant cognitive impairment Nominal	NR	NR	NR
People with a learning disability Nominal	NR	NR	NR
Number of people with obesity Nominal	NR	NR	NR
Albumin creatinine ratio Nominal	NR	NR	NR
Other antidiabetic medication used Nominal	NR	NR	NR
Blood pressure-lowering medication used Nominal	NR	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR	NR

Characteristic	Dapagliflozin 5 mg once daily (N = 86)	Dapagliflozin 10 mg once daily (N = 88)	Placebo (N = 87)
Other treatment being received Nominal	NR	NR	NR

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62. Kikuchi, 2012

Bibliographic Reference	Kikuchi, M.; Kaku, K.; Odawara, M.; Momomura, S.; Ishii, R.; Efficacy and tolerability of rosiglitazone and pioglitazone in drug-naïve Japanese patients with type 2 diabetes mellitus: a double-blind, 28 weeks' treatment, comparative study; Curr Med Res Opin; 2012; vol. 28 (no. 6); 1007-16

62.1. Study details

Secondary publication of another included study- see primary study for details	
Other publications associated with this study included in review	
Trial name / registration number	NCT00297063
Study type	Randomised controlled trial (RCT)
Study location	Japan
Study setting	43 centres in Japan
Study dates	2005 - 2007
Sources of funding	sponsored by GlaxoSmithKline
Inclusion criteria	- Drug naive - 20 - 75 years old - HbA1c > 6.4%
Exclusion criteria	Occurrence of: - serious hepatic disease, - renal impairment, - hemoglobinopathy,

	- edema, - unstable or serious angina, - myocardial infarction in the past year - history of or current heart failure, - serious arrhythmia, - valvular disease, - cardiomyopathy, - serious neuropathy requiring treatment, - pre-proliferative or proliferative retinopathy, - Hyperlipidemia (LDL cholesterol >=120 mg/dL or total cholesterol >=200 mg/dL) without statin treatment, - systolic blood pressure >=160mmHg or diastolic blood pressure >=100 mmHg, - BNP (brain natriuretic peptide) >=60 pg/dL - Fasting plasma glucose (FPG) >=270 mg/dL.
Recruitment / selection of participants	Participants were randomized to receive rosiglitazone, pioglitazone or placebo in a ratio of 3:3:1 for a treatment period of 28 weeks. Randomization was stratified to achieve a comparable ratio of male to female subjects at the start of the treatment period and a comparable ratio of subjects with HbA1c <8.5% to those with HbA1c ≥8.5% on the first day of the baseline period (week 4).
Intervention(s)	Pioglitazone was titrated to maximum dose at fixed time points during the study. The active agents were initiated at the lowest dose (15 mg/day). At week 4, pioglitazone was up-titrated to 30 mg/day, unless any adverse event related to increased circulating plasma volume had occurred (including rapid weight gain, edema or heart failure). If HbA1c was >=6.5% at week 16 and no adverse event related to increased circulating plasma volume had occurred, pioglitazone was up-titrated at week 17 to the maximum dose: 45 mg/day for pioglitazone. If these criteria were not met, dose was maintained at 30 mg/day. No reduction in dose of study drug was allowed during the treatment period. A third arm (n=159) received rosiglitazone. This arm was not included in this data extraction as it was not relevant to the review protocol.
Cointervention	

Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure
Strata 2: People with atherosclerotic cardiovascular diseases	Not stated/unclear
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear

Sensitivity analysis category: Enrichment trial status	5) All treatment naïve
Comparator	Placebo
Number of participants	373
Duration of follow-up	28 weeks
Indirectness	Directly applicable
Method of analysis	Per protocol glycemic responders ITT

62.2. Study arms

62.2.1. Placebo (N = 54)

62.2.2. Piaglitazone (N = 159)

Started 15 mg/day, up titrated to 30mg/day unless AE occurred, if hba1c % >6.5 week 16 and no AE up-titrated to 6.5%

62.3. Characteristics

62.3.1. Arm-level characteristics

Characteristic	Placebo (N = 54)	Piaglitazone (N = 159)
Male (%) Sample size	n = 33 ; % = 61.1	n = 99 ; % = 62.3
Mean age (SD) (years) Mean (SD)	53.9 (10)	55 (10.6)
Ethnicity Sample size	NA	NA
Asian/Japanese Sample size	n = 54; % = 100	n = 159; % = 100

Characteristic	Placebo (N = 54)	Piaglitazone (N = 159)
Comorbidities Sample size	n = NA ; % = NA	n = NA ; % = NA
Presence of frailty Sample size	n = NA ; % = NA	n = NA ; % = NA
Time since type 2 diabetes diagnosis (years) Mean (SD)	4.2 (3.9)	4.2 (4.5)
Smoking status Sample size	NR	NR
Alcohol consumption Sample size	NR	NR
Presence of severe mental illness Sample size	NR	NR
People with significant cognitive impairment Sample size	NR	NR
People with a learning disability Sample size	NR	NR
Number of people with obesity Sample size	NR	NR
Other antidiabetic medication used Sample size	NR	NR
Blood pressure-lowering medication used Sample size	NR	NR
Statins/lipid-lowering medication used Sample size	NR	NR

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63. Kim, 2017

Bibliographic Reference	Kim, Sang Soo; Kim, In Joo; Lee, Kwang Jae; Park, Jeong Hyun; Kim, Young Il; Lee, Young Sil; Chung, Sung Chang; Lee, Sang Jin; Efficacy and safety of sitagliptin/metformin fixed-dose combination compared with glimepiride in patients with type 2 diabetes: A multicenter randomized double-blind study.; Journal of diabetes; 2017; vol. 9 (no. 4); 412-422

63.1. Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	NCT00993187
Study type	Randomised controlled trial (RCT)
Study location	South Korea
Study setting	No additional information
Study dates	May 2010 - October 2013
Sources of funding	Funded by MSD Korea
Inclusion criteria	Aged ≥18 years Type 2 diabetes HbA1c 7.0-9.5% for those not on antihyperglycaemic medication for ≥12 weeks, or 6.5-9.0% for those receiving antihyperglycaemic medication
Exclusion criteria	Pregnant, breast feeding or likely to conceive during the study or follow-up period History of type 1 diabetes or ketoacidosis

	Received insulin ≤12 weeks pre-screening Receiving or required specific weight loss treatments, including weight loss programs Received any glucagon-like peptide-1 analog, peroxisome proliferator-activated receptor agonist within 12 weeks Received oral corticosteroids within 2 weeks, immunomodulating agents, general anesthetic within 30 days, or any investigational drug treatment within 8 weeks Hypersensitivity or contraindication to any sulfonylurea, DPP-4 inhibitor, or biguanide medication Serum creatinine ≥1.5 mg/dL in men and ≥1.4 mg/dL in women Triglycerides >500 mg/dL Thyroid stimulating hormone imbalance Active liver disease (other than fatty liver) Cardiovascular diseases HIV positive Haematological disorders History of malignancy BMI >35 kg/m2 Conditions that could result in non-compliance or may pose a risk to the participant Fasting glucose <110 mg/dL or >300 mg/dL during placebo run-in
Recruitment / selection of participants	Recruited from 21 centres, method not reported
Intervention(s)	Following the placebo run-in period, where participants received three placebo tablets representing sitagliptin, metformin and glimepiride, along with diet and exercise recommendations and instructions on the use of glucose monitors, eligible participants were randomised. Those allocated to the intervention received 50 mg sitagliptin to be taken with the morning meal, and 500 mg metformin to be taken with the evening meal. Metformin was up-titrated to 1000 mg over the initial 4-week period, after which down-titration was possible until week-8 if intolerance occurred, with no change in dose thereafter. Placebo tablets matching glimepiride were taken once per day.

Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear
Strata 2: People with atherosclerotic cardiovascular diseases	People without other cardiovascular diseases
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Mixed population
Subgroup 1: People with frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Sensitivity analysis	7) Mixed population

category: Enrichment trial status	
Population subgroups	No additional information
Comparator	Participants allocated to the comparator initially received 1 mg glimepiride, taken once per day. Over the following 8 weeks this was titrated to 6 mg per day (1 or 2 mg per tablet) as judged appropriate by the investigator and based on ADA guidelines. Placebo tablets matching sitagliptin and metformin were administered twice per day. *Glimepiride doses* Mean: 2.0 mg, Median: 1.4 mg *Final doses:* 1 mg n = 70 2 mg n = 23 3 mg n = 9 4 mg n = 10 5 mg n = 5 6 mg n = 24
Number of participants	292 randomised 147 received sitagliptin/metformin, 121 completed 145 received glimepiride, 108 completed
Duration of follow-up	30 weeks
Indirectness	None
Method of analysis	ITT
Additional comments	None

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63.2. Study arms

63.2.1. Sitagliptin + Metformin (N = 147)

50/500 mg sitagliptin/metformin, twice daily, up-titrated to 50/1000 mg twice daily over a 4-week period, then possible down-titration or maintenance for a further 4-week period followed by a stable dose for the rest of the trial, plus glimepiride placebo

63.2.2. Glimepiride (N = 145)

1 mg glimepiride per day, up-titrated to 6 mg per day over an 8-week period, plus sitagliptin/metformin placebo

63.3. Characteristics

63.3.1. Arm-level characteristics

Characteristic	Sitagliptin + Metformin (N = 147)	Glimepiride (N = 145)
% Male Sample size	n = 81 ; % = 55	n = 84 ; % = 58
Mean age (SD) (years) Mean (SD)	54.8 (8.5)	53.1 (9.2)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosis (years) Mean (SD)	4.6 (4.6)	3.9 (3.7)
HbA1c (%) Mean (SD)	8 (0.9)	8.1 (0.9)
SBP Mean (SD)	125.3 (11.2)	126.3 (13.2)

Characteristic	Sitagliptin + Metformin (N = 147)	Glimepiride (N = 145)
DBP Mean (SD)	76.7 (8.1)	77.7 (8.5)
Heart rate Nominal	NR	NR
Smoking status Nominal	NR	NR
Alcohol consumption Nominal	NR	NR
Presence of severe mental illness Nominal	NR	NR
People with significant cognitive impairment Nominal	NR	NR
People with a learning disability Nominal	NR	NR
Weight (kg) Mean (SD)	67.3 (8.8)	67.7 (10.4)
BMI (kg/m²) Mean (SD)	25.2 (2.7)	25 (2.8)
Number of people with obesity Nominal	NR	NR
TC Mean (SD)	176.1 (34.9)	171 (32.4)
LDL-c Mean (SD)	97.3 (33)	95 (28.1)
HDL-C Mean (SD)	48.2 (11)	48.8 (10.1)
TG Mean (SD)	150.5 (88.2)	134.1 (72.1)

Characteristic	Sitagliptin + Metformin (N = 147)	Glimepiride (N = 145)
Albumin creatinine ratio Nominal	NR	NR
eGFR (mL/min/1.73m2) Mean (SD)	75.9 (11.7)	76.7 (16.2)
Other antidiabetic medication used Prior antihyperglycaemic medication Sample size	n = 90 ; % = 61	n = 82 ; % = 57
Antiplatelet agents Sample size	n = 57 ; % = 39	n = 53 ; % = 37
RAS inhibitors Sample size	n = 43 ; % = 29	n = 43 ; % = 30
Statins/lipid-lowering medication used Lipid-lowering agents Sample size	n = 65 ; % = 44	n = 66 ; % = 46
Other treatment being received Nominal	NR	NR

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64. Koffert, 2017

Bibliographic Reference	Koffert, J. P.; Mikkola, K.; Virtanen, K. A.; Andersson, A. D.; Faxius, L.; Hällsten, K.; Heglind, M.; Guiducci, L.; Pham, T.; Silvola, J. M. U.; et, al.; Metformin treatment significantly enhances intestinal glucose uptake in patients with type 2 diabetes: results from a randomized clinical trial; Diabetes Res Clin Pract; 2017; vol. 131; 208-216

64.1. Study details

Secondary publication of another included study- see primary study for details	Hällsten, K., Virtanen, K. A., Lönnqvist, F. et al. (2002) Rosiglitazone but not metformin enhances insulin- and exercise-stimulated skeletal muscle glucose uptake in patients with newly diagnosed type 2 diabetes. Diabetes 51(12): 3479-85
Other publications associated with this study included in review	No additional information.
Inclusion criteria	

65. Kondo, 2016

Bibliographic Reference	Kondo, Y.; Harada, N.; Hamasaki, A.; Kaneko, S.; Yasuda, K.; Ogawa, E.; Harashima, S. I.; Yoneda, H.; Fujita, Y.; Kitano, N.; Nakamura, Y.; Matsuo, F.; Shinji, M.; Hinotsu, S.; Nakayama, T.; Inagaki, N.; Sitagliptin monotherapy has better effect on insulinogenic index than glimepiride monotherapy in Japanese patients with type 2 diabetes mellitus: A 52-week, multicenter, parallel-group randomized controlled trial; Diabetol Metab Syndr; 2016; vol. 8; 15

65.1. Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.
Trial name / registration number	No additional information.
Study type	Randomised controlled trial (RCT)
Study location	Japan in 18 centres.
Study setting	Outpatient follow up.
Study dates	February 10th 2011 to March 31st 2013.
Sources of funding	The trial was supported by the Japan Diabetes Foundation.
Inclusion criteria	Type 2 diabetes mellitus; age <80 years; HbA1c levels <8.4%; no pharmacological treatment for diabetes for at least 1 month prior to participation in the trial.
Exclusion criteria	Renal or liver dysfunction; pancreatic or haematological operation; severe complications of diabetes; being pregnant or possibly pregnant; malignancy under treatment; medications known to affect glucose metabolism.
Recruitment / selection of participants	No additional information.
Intervention(s)	Glimepiride N=85

	Glimepiride titrated upward to 1.0mg once daily for 52 weeks.
Cointervention	Concomitant therapy: When HbA1c levels exceed 6.9% after 6 months or later, doses were increased to the titrated dose. They were decreased to avoid hypoglycaemia at any point. If they did not meet the glycaemic control conditions at any point, then additional medications, or switching medications was allowed and people discontinued from the trial.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear
Strata 2: People with atherosclerotic cardiovascular diseases	Not stated/unclear
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear

Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Sensitivity analysis category: Enrichment trial status	6) No response criteria Not receiving pharmacological treatment for diabetes for at least 1 month prior to participation.
Population subgroups	No additional information.
Comparator	Sitagliptin N=86 Sitagliptin titrated upward to 100mg once daily for 52 weeks.
Number of participants	171
Duration of follow-up	52 weeks.
Indirectness	No additional information.
Method of analysis	ACA Full analysis set for all people who took the medication as allocated and underwent the oral glucose tolerance test before and after treatment, excluding those with a haemolysed sample, those who were added or changed therapy and those who were withdrawn from the trial before treatment following consent acquisition. Per protocol
Additional comments	No additional information.

65.2. Study arms

65.2.1. Glimepiride (N = 85)

Glimepiride titrated upward to 1.0mg once daily for 52 weeks. Concomitant therapy: When HbA1c levels exceed 6.9% after 6 months or later, doses were increased to the titrated dose. They were decreased to avoid hypoglycaemia at any point. If they did not meet the glycaemic control conditions at any point, then additional medications, or switching medications was allowed and people discontinued from the trial.

65.2.2. Sitagliptin (N = 86)

Sitagliptin titrated upward to 100mg once daily for 52 weeks. Concomitant therapy: When HbA1c levels exceed 6.9% after 6 months or later, doses were increased to the titrated dose. They were decreased to avoid hypoglycaemia at any point. If they did not meet the glycaemic control conditions at any point, then additional

medications, or switching medications was allowed and people discontinued from the trial.

65.3. Characteristics

65.3.1. Arm-level characteristics

Characteristic	Glimepiride (N = 85)	Sitagliptin (N = 86)
% Male Sample size	n = 49 ; % = 72.1	n = 49 ; % = 75.4
Mean age (SD) (years) Mean (SD)	64 (8)	63 (9)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosis Mean (SD)	6 (5.1)	6.2 (6)
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR
Other antidiabetic medication used Sample size	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Glimepiride (N = 85)	Sitagliptin (N = 86)
Blood pressure-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Statins/lipid-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR

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66. Kumar KMP Jain SM Tou CSchützer, 2014

Bibliographic Reference	Kumar KMP Jain SM Tou CSchützer, K-M; Saxagliptin as initial therapy in treatment-naive Indian adults with type 2 diabetes mellitus inadequately controlled with diet and exercise alone: a randomized, double-blind, placebo-controlled, phase IIIb clinical study; International journal of diabetes in developing countries; 2014; vol. 34 (no. 4); 201-209

66.1. Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.
Trial name / registration number	NCT00918879
Study type	Randomised controlled trial (RCT)
Study location	India (12 centres).
Study setting	Outpatient follow-up.
Study dates	No additional information.
Sources of funding	Funded by Bristol-Myers Squibb and AstraZeneca.
Inclusion criteria	At least 18 years of age; diagnosis of type 2 diabetes; treatment naive (no more than 6 month of medical treatment [insulin, oral antihyperglycaemic agents] since original diagnosis and antihyperglycaemic therapy for no more than 3 consecutive days or 7 nonconseuctive days during the past 8 weeks [12 weeks for thiazolidinediones]). Women who had received treatment for gestational diabetes during pregnancy could enroll, as could people who had received short-term insulin therapy during a hospitalisation. C-peptide levels at least 0.33nmol/L, HbA1c 7.0-10.0%, FPG <15mmol/L; fertile people using adequate contraception; women of childbearing potential having a negative pregnancy test.
Exclusion criteria	History of clinically significant cardiovascular disease; NYHA class III/IV congestive heart failure and/or LVEF no more than 40%; active liver disease and/or abnormal liver function tests (AST or ALT >2x upper limit of

	normal or total bilirubin >34 micromol/L); creatine kinase >3x upper limit of normal); anaemia; elevated serum creatinine (at least 132.6 micromol for men; at least 123.8 micromol for women); any clinically significant abnormality on physical examination or electrocardiogram (ECG); pregnancy or breastfeeding; current treatment with a cytochrome P450 3A4 inducer, HIV antiviral drug, or systemic glucocorticoid; abuse of alcohol or illegal drugs within the past 12 months; symptoms of poorly controlled diabetes, diabetic ketoacidosis or hyperosmolar nonketotic coma; previous treatment with any DPP-4 inhibitor or participation in a clinical study within the past 90 days.
Recruitment / selection of participants	No additional information.
Intervention(s)	Saxagliptin N=107 Saxagliptin 5mg once daily for 24 weeks.
Cointervention	Concomitant therapy: People with inadequate glycaemic control at visit 6 (week 4 after randomisation) or later could receive rescue treatment with open-label metformin (500mg/day initially, could increase by 500mg/day increments every 2 weeks to a maximum of 2500mg/day) added to their randomised medication. FPG rescue criteria was >13.3mmol/L at weeks 4-6, >12.2mmol/L at week 8, >11.1mmol/L at weeks 12, 16 and 20.
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure
Strata 2: People with atherosclerotic cardiovascular diseases	Not stated/unclear
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with frailty	Not stated/unclear

Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Sensitivity analysis category: Enrichment trial status	6) No response criteria
Population subgroups	No additional information.
Comparator	Placebo N=106 Matching placebo for 24 weeks.
Number of participants	213
Duration of follow-up	24 weeks
Indirectness	No additional information.
Method of analysis	ACA People who took at least 1 dose of the treatment and had efficacy observations at baseline and at least 1 time afterwards - last observation carried forward. Safety analyses completed based on people who took at least 1 dose of the treatment only.
Additional comments	No additional information

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66.2. Study arms

66.2.1. Saxagliptin (N = 107)

Saxagliptin 5mg once daily for 24 weeks. Concomitant therapy: People with inadequate glycaemic control at visit 6 (week 4 after randomisation) or later could receive rescue treatment with open-label metformin (500mg/day initially, could increase by 500mg/day increments every 2 weeks to a maximum of 2500mg/day) added to their randomised medication. FPG rescue criteria was >13.3mmol/L at weeks 4-6, >12.2mmol/L at week 8, >11.1mmol/L at weeks 12, 16 and 20.

66.2.2. Placebo (N = 106)

Matching placebo for 24 weeks. Concomitant therapy: People with inadequate glycaemic control at visit 6 (week 4 after randomisation) or later could receive rescue treatment with open-label metformin (500mg/day initially, could increase by 500mg/day increments every 2 weeks to a maximum of 2500mg/day) added to their randomised medication. FPG rescue criteria was >13.3mmol/L at weeks 4-6, >12.2mmol/L at week 8, >11.1mmol/L at weeks 12, 16 and 20.

66.3. Characteristics

66.3.1. Arm-level characteristics

Characteristic	Saxagliptin (N = 107)	Placebo (N = 106)
% Male Sample size	n = 57 ; % = 53.3	n = 63 ; % = 59.4
Mean age (SD) (years) Mean (SD)	49.1 (8.8)	48.3 (9.6)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosis (years) Mean (SD)	0.8 (1.2)	1 (1.4)
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Saxagliptin (N = 107)	Placebo (N = 106)
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR
Other antidiabetic medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Blood pressure-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Statins/lipid-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR