National Institute for Health and Care Excellence

Final

Type 2 diabetes in adults: management (medicines update)

[E1.3] Evidence reviews for initial pharmacological management of type 2 diabetes: appendix D studies L to Z

NICE guideline

Evidence reviews underpinning recommendations 1.9.1 to 1.9.5, 1.10.1 to 1.18.4, 1.19.1 to 1.19.3, 1.22.1 to 1.31.2 and recommendations for research in the NICE guideline

February 2026

Final

This evidence review was developed by NICE

NICE accredited
www.nice.org.uk/accreditation

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the Welsh Government, Scottish Government, and Northern Ireland Executive. All NICE guidance is subject to regular review and may be updated or withdrawn.

Copyright

© NICE 2026. All rights reserved. Subject to Notice of Rights.

ISBN: 978-1-4731-9247-8

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.

1. Lambadiari, 2018

Bibliographic Reference	Lambadiari, V.; Pavlidis, G.; Kousathana, F.; Varoudi, M.; Vlastos, D.; Maratou, E.; Georgiou, D.; Andreadou, I.; Parissis, J.; Triantafyllidi, H.; et, al.; Effects of 6-month treatment with the glucagon like peptide-1 analogue liraglutide on arterial stiffness, left ventricular myocardial deformation and oxidative stress in subjects with newly diagnosed type 2 diabetes; Cardiovasc Diabetol; 2018; vol. 17 (no. 1); 8

1.1. 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	NCT03010683.
Study type	Randomised controlled trial (RCT)
Study location	Greece.
Study setting	Outpatient follow-up.
Study dates	No additional information.
Sources of funding	No funding.
Inclusion criteria	Newly diagnosed and treatment-naïve people with type 2 diabetes.
Exclusion criteria	History or clinical evidence of coronary or valvular heart disease; liver or kidney failure; history of alcohol or drug abuse; treatments able to modify glucose metabolism. All women were premenopausal and their investigations were undertaken during the first week of their menstrual cycles. None were taking oral contraceptives.
Recruitment / selection of participants	No additional information.
Intervention(s)	Liraglutide N=30

	Liraglutide 1.8mg once daily (with weekly dose escalation as instructed) as a subcutaneous injection for 6 months. 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	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 smoking, hypertension, dyslipidaemia, family history, age, 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	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	Metformin N=30 Metformin 1000mg twice daily for 6 months. Concomitant therapy: No additional information.
Number of participants	60
Duration of follow-up	6 months.
Indirectness	No additional information.
Method of analysis	Not stated/unclear
Additional comments	No additional information.

1.2. Study arms

1.2.1. Liraglutide (N = 30)

Liraglutide 1.8mg once daily (with weekly dose escalation as instructed) as a subcutaneous injection for 6 months. Concomitant therapy: No additional information.

1.2.2. Metformin (N = 30)

Metformin 1000mg twice daily for 6 months. Concomitant therapy: No additional information.

1.3. Characteristics

1.3.1. Arm-level characteristics

Characteristic	Liraglutide (N = 30)	Metformin (N = 30)
% Male Sample size	n = 20 ; % = 67	n = 20 ; % = 67
Mean age (SD) (years) Mean (SD)	51 (10)	50 (12)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR
Comorbidities Sample size	n = NA ; % = NA	n = NA ; % = NA
Hypertension Sample size	n = 17 ; % = 56.7	n = 16 ; % = 53.3
Dyslipidaemia Sample size	n = 16 ; % = 53.3	n = 15 ; % = 50
Family history of coronary artery disease Sample size	n = 6 ; % = 20	n = 6 ; % = 20
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)	8.6 (2)	8.4 (1.2)
Blood pressure (mmHg) Mean (SD)	NA (NA)	NA (NA)
Systolic blood pressure Mean (SD)	142 (15)	142 (19)
Diastolic blood pressure Mean (SD)	90 (8)	89 (9)
Heart rate (beats per minute)	74 (12)	71 (12)

Characteristic	Liraglutide (N = 30)	Metformin (N = 30)
Mean (SD)		
Smoking status Sample size	n = 11 ; % = 36.7	n = 11 ; % = 36.7
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)	98 (16)	78 (12)
BMI (kg/m2) Mean (SD)	32.9 (5)	27.7 (2)
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)	85 (8)	83 (11)
Other antidiabetic medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Blood pressure-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Beta blockers Sample size	n = 5 ; % = 16.7	n = 6 ; % = 20

Characteristic	Liraglutide (N = 30)	Metformin (N = 30)
Calcium antagonists Sample size	n = 10 ; % = 33.3	n = 8 ; % = 26.7
ACE inhibitors/ARBs Sample size	n = 9 ; % = 30	n = 10 ; % = 33.3
Diuretics Sample size	n = 4 ; % = 13.3	n = 4 ; % = 13.3
Statins/lipid-lowering medication used Sample size	n = 14 ; % = 46.7	n = 12 ; % = 40
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR

2. Lee, 2013

Bibliographic Reference	Lee, Ji; Hong, Soon; Jeong, Han Saem; Joo, Hyung; Park, Jae; Chul-Min, Ahn; Yu, Cheol; Lim, Do-Sun; Effects of a PPAR-γ (Peroxisome Proliferator-Activated Receptor-gamma) Activator on Flow-Mediated Brachial Artery Dilation and Circulating Level of microRNA-21 in Hypertensive Type 2 Diabetic Patients; Journal of the Korean Society of Hypertension; 2013; vol. 19; 99

2.1. Study details

Study location	Korea
Study setting	University hospital cardiovascular centres
Study dates	Recruitment: July 2011 - June 2012
Sources of funding	Grant from Korean Society of Hypertension.
Inclusion criteria	- 45-75 years old - Essential hypertension - Type 2 diabetes - sitting diastolic bp >= 80 mmHg - sitting systolic bp <= 130 mmHg -previously untreated hypertensive diabetes
Exclusion criteria	- use of pioglitazone within 3 months of enrolment - SiSBP > 180 mmHg - SiDBP > 110 mmHg - heart failure (ejection fraction <45% or signs of heart failure) - hepatic dysfunction (serum asparate or alanine aminotransferase levels being above twice the upper limit of normal ranges -serum creatinine > 2.0 mg/dl - pregnant, breastfeeding, "childbearing potential"
Recruitment / selection of participants	Eligible patients (n = 50, 20 women and 30 men) were randomly assigned to receive either pioglitazone 15 mg (25 patients) or control (25 patients) after measuring baFMD.
Intervention(s)	
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
Population subgroups	
Comparator	"Placebo"
Number of participants	50
Duration of follow-up	6 months
Indirectness	Directly applicable
Method of analysis	ITT

2.2. Study arms

2.2.1. Pioglitazone (N = 25)

15mg

2.2.2. Placebo (N = 25)

"control"

2.3. Characteristics

2.3.1. Arm-level characteristics

Characteristic	Pioglitazone (N = 25)	Placebo (N = 25)
Age (yr) Mean (SD)	61.4 (12.4)	59.5 (11.8)
% Male (%) Sample size	n = 16 ; % = 64	n = 14 ; % = 56

3. Lewin, 2015

Bibliographic Reference	Lewin, A.; DeFronzo, R. A.; Patel, S.; Liu, D.; Kaste, R.; Woerle, H. J.; Broedl, U. C.; Initial combination of empagliflozin and linagliptin in subjects with type 2 diabetes; Diabetes Care; 2015; vol. 38 (no. 3); 394-402

3.1. 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	NCT01422876
Study type	Randomised controlled trial (RCT)
Study location	US
Study setting	No information available
Study dates	08/2011 to 09/2013
Sources of funding	Boehringer Ingelheim and Eli Lilly and Company.
Inclusion criteria	This study enrolled subjects aged ≥18 years with type 2 diabetes with BMI ≤45 kg/m2 and HbA1c >7% to ≤10.5% (>53 to ≤91 mmol/mol) at screening despite a diet and exercise regimen who had not received treatment with oral antidiabetic therapy, GLP-1 analogue, or insulin for ≥12 weeks prior to randomisation.
Exclusion criteria	Uncontrolled hyperglycaemia (glucose level >240 mg/dL after an overnight fast during the placebo run-in, confirmed by a second measurement); estimated glomerular filtration rate (eGFR), 60 mL/min/1.73 m2 (using the Modification of Diet in Renal Disease equation); acute coronary syndrome, stroke, or transient ischemic attack within 3 months prior to consent; bariatric surgery in the last 2 years; and treatment with anti-obesity drugs within 3 months prior to consent.
Recruitment / selection of participants	Patients were recruited from 197 centres in 122 countries. All patients had a 2-week placebo run-in period prior to randomisation.

Intervention(s)	Linagliptin 5 mg once daily, taken orally in the morning.
Cointervention	No information available.
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	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	Mixed population
Sensitivity analysis category: Enrichment trial status	3) Selection of specific population
Population subgroups	No information available.
Comparator	Empagliflozin 10 mg once daily, taken orally in the morning. Empagliflozin 5 mg once daily, taken orally in the morning. The study included a further two arms listed below, but data for these interventions has not been extracted because they are outside the scope of this review. • Empagliflozin 25 mg/ linagliptin 5 mg, taken orally in the morning. • Empagliflozin 10 mg/ linagliptin 5 mg, taken orally in the morning.
Number of participants	N = 677
Duration of follow-up	Treatment for 52 weeks and 4 weeks follow-up.
Indirectness	22 countries were included however they have not stated which countries were included.
Method of analysis	ACA
Additional comments	• Efficacy analyses were performed on the full analysis set which included subjects treated with ≥1 dose of study drug who had a baseline and ≥1 treatment HbA1c value. Safety was assessed in the treated set, which comprised subjects treated ≥1 dose of study drug. • Rescue medication was to be initiated if a subject had blood glucose >240 mg/dL after an overnight fast between weeks 1 and 12, blood glucose >200 mg/dL after an overnight fast between weeks 12 and 24, or blood glucose >180 mg/dL or HbA1c >8% (>63.9 mmol/mol) after an overnight fast between weeks 24 and 52. The initiation, choice, and dosage of rescue medication were at the discretion of the investigator, according to local prescribing information, but the use of DPP-4 inhibitors, GLP-1 analogues, and SGLT2 inhibitors was not permitted.

3.2. Study arms

3.2.1. Empagliflozin 25 mg once daily (N = 133)

Taken orally in the morning

3.2.2. Empagliflozin 10 mg once daily (N = 132)

Taken orally in the morning

3.2.3. Linagliptin 5 mg once daily (N = 133)

Taken orally in the morning

3.3. Characteristics

3.3.1. Arm-level characteristics

Characteristic	Empagliflozin 25 mg once daily (N = 133)	Empagliflozin 10 mg once daily (N = 132)	Linagliptin 5 mg once daily (N = 133)
% Male No of events	n = 77 ; % = 57.9	n = 64 ; % = 48.5	n = 75 ; % = 56.4
Mean age (SD) (years) Mean (SD)	56 (9.3)	53.9 (10.5)	53.8 (11.5)
White No of events	n = 93 ; % = 69.9	n = 99 ; % = 75	n = 103 ; % = 77.4
Asian No of events	n = 19 ; % = 14.3	n = 13 ; % = 9.8	n = 17 ; % = 12.8
Other No of events	n = 21 ; % = 15.8	n = 20 ; % = 15.2	n = 13 ; % = 9.8
Comorbidities Nominal	NR	NR	NR
Presence of frailty Nominal	NR	NR	NR

Characteristic	Empagliflozin 25 mg once daily (N = 133)	Empagliflozin 10 mg once daily (N = 132)	Linagliptin 5 mg once daily (N = 133)
≤1 years No of events	n = 48 ; % = 36.1	n = 43 ; % = 32.6	n = 50 ; % = 37.6
>1 to 5 years No of events	n = 48 ; % = 36.1	n = 60 ; % = 45.5	n = 57 ; % = 42.9
>5 to 10 years No of events	n = 25 ; % = 18.8	n = 15 ; % = 11.4	n = 22 ; % = 16.5
10 years No of events	n = 12 ; % = 9	n = 14 ; % = 10.6	n = 4 ; % = 3
HbA1c (%) Mean (SD)	7.99 (0.97)	8.05 (1.03)	8.05 (0.89)
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
Other antidiabetic medication used	NR	NR	NR

Characteristic	Empagliflozin 25 mg once daily (N = 133)	Empagliflozin 10 mg once daily (N = 132)	Linagliptin 5 mg once daily (N = 133)
Nominal			
Blood pressure-lowering medication used Nominal	NR	NR	NR
Other treatment being received Nominal	NR	NR	NR

4. Li, 2016

Bibliographic Reference	Li, Feng-Fei; Gao, Gu; Li, Qian; Zhu, Hong-Hong; Su, Xiao-Fei; Wu, Jin-Dan; Ye, Lei; Ma, Jian-Hua; Influence of Dapagliflozin on Glycemic Variations in Patients with Newly Diagnosed Type 2 Diabetes Mellitus.; Journal of diabetes research; 2016; vol. 2016; 5347262

4.1. Study details

Secondary publication of another included study- see primary study for details	Wang, L. Xu, L. Yuan et al., "Sodium-glucose co-transporter-2 inhibitors suppress atrial natriuretic peptide secretion in patients with newly diagnosed Type 2 diabetes," Diabetic Medicine, 2016
Other publications associated with this study included in review	None.
Trial name / registration number	Not reported
Study type	Randomised controlled trial (RCT)
Study location	China
Study setting	Hospital
Study dates	07/2010 to 03/2012
Sources of funding	Funded by Nanjing Public Health Bureau Project (no. YKK11110), Jiangsu Provincial Department of Science and Technology Project (no. BL2014010), and project funded by China Postdoctoral Science Foundation (2015M581829).
Inclusion criteria	• Patients with newly diagnosed or drug-naive T2DM • Patients receiving 8 weeks of lifestyle management counselling, those who continued to experience inadequate glycemic control, as defined by HbA1c levels of 7.5–10.5%, were recruited.
Exclusion criteria	• History of diabetes insipidus • Severe uncontrolled hypertension (systolic blood pressure ≥ 180 mmHg and/or diastolic blood pressure ≥ 110 mmHg) and use of any renin-angiotensin system blocker • Replacement or chronic systemic corticosteroid treatment • History or current diagnosis of significant comorbid diseases, such as cardiovascular, hepatic, and renal diseases

	• Positive test for islet cell autoantibodies (such as glutamic acid decarboxylase autoantibodies, islet cell autoantibodies, or insulinoma-like antigen 2), indicating the possibility of type 1 diabetes mellitus.
Recruitment / selection of participants	Subjects were randomised to receive one of the following blinded treatment regimens in a 1 : 1 : 1 ratio: dapagliflozin 5 mg, once daily; dapagliflozin 10 mg, once daily; dapagliflozin 5 mg/10 mg matching placebo, once daily (distributed by Bristol-Myers Squibb, Lawrenceville, NJ), for 24 weeks, and, after 4 weeks of treatment, patients lacking glycemic control (fasting blood glucose > 11.1 mmol/L) were eligible to receive another antihyperglycemic drug, such as metformin, based on their particular symptoms. Scheduled visits were at weeks 1 and 24.
Intervention(s)	Dapagliflozin 5 mg or dapagliflozin 10 mg or dapagliflozin 5 mg/10 mg once daily.
Comparator	Placebo
Number of participants	28
Duration of follow-up	24 weeks
Indirectness	
Additional comments	

4.2. Study arms

4.2.1. Dapagliflozin 5 mg or dapagliflozin 10 mg or dapagliflozin 5 mg/10 mg daily (N = 18)

Taken orally

4.2.2. Placebo daily (N = 10)

Taken orally

5. Li, 2019

Bibliographic Reference	Li, J; Zhang, P.; Fan, B; Guo, X; Zheng, Z; The efficacy of saxagliptin in T2DM patients with non-alcoholic fatty liver disease: preliminary data; Rev Assoc Med Bras; 2019; vol. 65 (no. 1); 33-37

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	Not reported
Study type	Randomised controlled trial (RCT)
Study location	Shandong, China
Study setting	Community
Study dates	07/204 to 12/2016
Sources of funding	Not reported
Inclusion criteria	• Aged ≥30 to ≤60 years • Diagnosis of type 2 diabetes (WHO 1999 classification) or • Newly diagnosed or diagnosed <2 years of enrolment • Naive to hypoglycaemic drug treatment • HbA1c level ≥7 to ≤9% • Diagnosis of non-alcoholic fatty liver disease (Guidelines for management of non-alcoholic fatty liver disease [2010 revised edition], Chinese Society of Hepatology, Chinese Medical Association) • No liver protection treatment
Exclusion criteria	• Acute complications and severe chronic complications of diabetes • Viral hepatitis, drug hepatitis, auto-immune liver disease, other liver diseases caused by clear damage factors, hepatolenticular degeneration, and total parenteral nutrition

	• Liver cirrhosis, severe liver and kidney insufficiency, cardio-cerebrovascular diseases, acute infection, and genetic diseases
Recruitment / selection of participants	Recruited from Department of Endocrinology, Qilu Hospital of Shandong University, Qingdao, China. Randomisation according to computer-generated random number table one of 3 arms. All participants received information on diet and exercise.
Intervention(s)	• Saxagliptin 5 mg once daily Oral saxagliptin tablets 5 mg once daily for 24 weeks.
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	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	5) All treatment naïve Inclusion criteria: did not receive hypoglycaemic drug treatment
Comparator	• Glimepiride 2mg once daily • Glimepiride 2mg once daily and Polyene phosphatidylcholine 456 mg thrice daily Oral glimepiride tablets 2 mg once daily in both of these groups for 24 weeks with glimepiride dose adjusted based on blood glucose measurements.
Number of participants	N=64 (two arms only, third arm N=31 excluded from data extraction)
Duration of follow-up	24 weeks
Method of analysis	Other Not explicitly reported but results reported for all randomised participants who completed trial (that is, excluding participants lost to follow up).

5.2. Study arms

5.2.1. Saxagliptin 5 mg once daily (N = 31)

Oral saxagliptin tablets 5 mg once daily for 24 weeks.

5.2.2. Glimepiride 2 mg once daily (N = 33)

Oral glimepiride tablets 2 mg once daily for 24 weeks.

5.2.3. Glimepiride 2 mg once daily + Polyene phosphatidylcholine 456 mg thrice daily (N = 31)

Oral glimepiride tablets 2 mg once daily + Polyene phosphatidylcholine 456 mg thrice daily for 24 weeks.

5.3. Characteristics

5.3.1. Arm-level characteristics

Characteristic	Saxagliptin 5 mg once daily (N = 31)	Glimepiride 2 mg once daily (N = 33)	Glimepiride 2 mg once daily + Polyene phosphatidylcholine 456 mg thrice daily (N = 31)
% Male Sample size	n = 15 ; % = 48.4	n = 17 ; % = 51.5	n = 16 ; % = 51.6
Mean age (SD) (years) Mean (SD)	46.6 (8.2)	47.4 (9.4)	49.3 (8.9)
Ethnicity Nominal	NR	NR	NR
Comorbidities Nominal	NR	NR	NR
Presence of frailty Nominal	NR	NR	NR
Time since type 2 diabetes diagnosis (years) Mean (SD)	11.3 (6.6)	10.2 (7.6)	9.6 (5.4)
HbA1c (%) Mean (SD)	7.79 (0.52)	7.82 (0.61)	7.85 (0.57)
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	NR	NR	NR

Characteristic	Saxagliptin 5 mg once daily (N = 31)	Glimepiride 2 mg once daily (N = 33)	Glimepiride 2 mg once daily + Polyene phosphatidylcholine 456 mg thrice daily (N = 31)
Nominal			
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)	27.2 (4.1)	26.5 (3.2)	26 (2.9)
Number of people with obesity Nominal	NR	NR	NR
Cholesterol and lipid levels (mmol/L) Mean (SD)	NA (NA)	NA (NA)	NA (NA)
Total cholesterol Mean (SD)	5.4 (0.9)	5.6 (0.8)	5.6 (1.2)
Triglycerides Mean (SD)	2 (1.1)	2.1 (0.8)	2.1 (1)
Albumin creatinine ratio Nominal	NR	NR	NR
eGFR (mL/min/1.73m2) Nominal	NR	NR	NR
Other antidiabetic medication used Nominal	NR	NR	NR

Characteristic	Saxagliptin 5 mg once daily (N = 31)	Glimepiride 2 mg once daily (N = 33)	Glimepiride 2 mg once daily + Polyene phosphatidylcholine 456 mg thrice daily (N = 31)
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

6. Liu, 2020

Bibliographic Reference	Liu, Lin; Yan, Hongmei; Xia, MingFeng; Zhao, Lin; Lv, Minzhi; Zhao, Naiqin; Rao, Shengxiang; Yao, Xiuzhong; Wu, Weiyun; Pan, Baishen; Bian, Hua; Gao, Xin; Efficacy of exenatide and insulin glargine on nonalcoholic fatty liver disease in patients with type 2 diabetes.; Diabetes/metabolism research and reviews; 2020; vol. 36 (no. 5); e3292

6.1. 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	NCT02303730
Study type	Randomised controlled trial (RCT) Open-label trial
Study location	China
Study setting	Community
Study dates	05/2017 to 11/2017
Sources of funding	Funded by: 3SBio Inc; AstraZeneca China; National Key R&D Program of China, Grant/Award Numbers: 2017YFC1309800,2017YFC1309801, 2017YFC1309804.
Inclusion criteria	• Aged ≥18 to ≤70 years • Newly diagnosed type 2 diabetes mellitus (WHO Diagnostic criteria 1999) • Patients with non-alcoholic fatty disease (NAFLD) with magnetic resonance spectroscopy measurement of liver fat content>10%. • HbA1c level ≥7% to ≤10% • No heavy drinking history≤5 years (alcohol intake: male<20 g/d; female<10 g/d) • HBsAg (-), hepatitis C virus antibody (HCV-Ab) (-) • BMI ≥24 kg/m2

Exclusion criteria	• Pregnancy, lactation, intended pregnancy, or failure to take adequate contraceptive measures (e.g. sterilization, intrauterine device, oral contraceptives, and persistent use of condoms) • Diagnosis of type 1 diabetes mellitus, gestational diabetes mellitus or other special types of diabetes • Liver and renal dysfunction (ALT or AST) 2.5 times higher than the upper limit of normal, or total bilirubin 1.5 times higher than the upper limit of normal, or Cr ≥ 115 μmol/L) • Increased amylase (blood amylase is 2.5 times higher than the upper limit of normal) or presence of gastrointestinal disease • Use of drugs that may affect liver fat content≤1 one month before or during the trial period, such as glucocorticoids, thyroid hormone, etc. • Use of GLP-1RA, DPP-4 inhibitors, or insulin ≤3 months before enrolment • Presence of serious dyslipidaemia or other endocrine diseases (hypothyroidism, hypothalamic-pituitary dysfunction, etc) • Fatty liver caused by viral hepatitis, drug, alcohol, Wilson disease or total parenteral nutrition • Presence of liver cancer, infection, biliary tract disease or recently increased liver enzyme due to medication • Participation in strenuous exercise or administration of any drugs that affect glucose metabolism • History of pancreatitis, alcohol abuse, metal disorders or history of allergy to investigational drug • Congestive heart failure defined as New York Heart Association (NYHA) class III or IV, unstable angina or myocardial infarction in recent 6 months • Any situation that may affect the implementation or results of the study
Recruitment / selection of participants	Participants recruited from 4 hospitals in China. After 2 week screening period, participants randomised 1:1 to exenatide or insulin glargine for 24 weeks. Central randomisation list used generated by Department of Biostatistics, School of Public Health, Fudan University. Visits at weeks 4, 8, 12, 16, 20 and 24 with telephone calls at weeks 1, 2 and 6.
Intervention(s)	• Exenatide 10 mcg twice daily Participants received 5 mcg twice daily for 4 weeks and then 10 mcg twice daily for 20 weeks.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Exclusion criteria: New York Heart Association (NYHA) class III or IV. May be some participants with NYHA class II congestive heart failure.
Strata 2: People with atherosclerotic cardiovascular diseases	Not stated/unclear Exclusion criteria: Unstable angina or myocardial infarction in recent 6 months. According to this, trial population may include participants with other types of atherosclerotic heart disease.

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 Inclusion criteria: Participants with non-alcoholic fatty disease with magnetic resonance spectroscopy measurement of liver fat content>10%
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 All participants had managed diabetes using diet and exercise only.
Population subgroups	
Comparator	• Insulin glargine Participants received subcutaneous insulin glargine once daily for 24 weeks, starting at dose of 0.1 to 0.3 IU/kg (0.1-0.2 IU/kg for HbA1c<8%; 0.2-0.3 IU/kg for HbA1c>8% and then dose up-titrated to achieve FPG<7.0 mmol/L.

Number of participants	N=76
Duration of follow-up	24 weeks
Method of analysis	Modified ITT Full analysis set for all efficacy outcomes included all randomised and treated patients with more than efficacy result. Safety set included all participants who received at least one dose of study drug
Additional comments	

6.2. Study arms

6.2.1. Exenatide 10 mcg twice daily (N = 38)

Subcutaneous injection of exenatide 5 mcg twice daily for 4 weeks then exenatide 10 mcg twice daily for 20 weeks.

6.2.2. Insulin glargine 0.1-0.3IU/kg once daily (N = 38)

Subcutaneous injection of insulin glargine once daily, gradually up-titrated to achieve FPG<7.0 mmol/L.

6.3. Characteristics

6.3.1. Arm-level characteristics

Characteristic	Exenatide 10 mcg twice daily (N = 38)	Insulin glargine 0.1-0.3IU/kg once daily (N = 38)
% Male Sample size	n = 19 ; % = 54.3	n = 19 ; % = 52.8
Mean age (SD) Mean (SD)	47.63 (10.14)	50.56 (11.78)
Ethnicity Custom value	NR	NR
Comorbidities Custom value	NR	NR
Presence of frailty	NR	NR

Characteristic	Exenatide 10 mcg twice daily (N = 38)	Insulin glargine 0.1-0.3IU/kg once daily (N = 38)
Custom value		
Time since type 2 diabetes diagnosis Mean (SD)	0.32 (0.79)	0.52 (1.25)
HbA1c (%) Mean (SD)	8.32 (0.94)	8.58 (0.91)
Blood pressure (mmHg) Mean (SD)	NA (NA)	NA (NA)
Systolic blood pressure Mean (SD)	129.6 (14.48)	127.97 (11.3)
Diastolic blood pressure Mean (SD)	80.46 (8.57)	78.64 (8.67)
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)	79.28 (9.64)	77.63 (13.7)
BMI (kg/m2) Mean (SD)	28.49 (3.02)	27.84 (3.1)

Characteristic	Exenatide 10 mcg twice daily (N = 38)	Insulin glargine 0.1-0.3IU/kg once daily (N = 38)
Number of people with obesity Custom value	NR	NR
Cholesterol and lipid levels (mmol/L) Mean (SD)	NA (NA)	NA (NA)
Total cholesterol Mean (SD)	4.96 (0.94)	4.92 (0.89)
HDL-cholesterol Mean (SD)	1.11 (0.19)	1.08 (0.22)
LDL-cholesterol Mean (SD)	3.01 (0.76)	2.81 (0.72)
Triglyceride Mean (SD)	2.01 (1.23)	2.41 (1.59)
Albumin creatinine ratio Custom value	NR	NR
eGFR (mL/min/1.73m2) Custom value	NR	NR
Other antidiabetic medication used Custom value	NR	NR
Blood pressure-lowering medication used Custom value	NR	NR
Statins/lipid-lowering medication used Custom value	NR	NR
Other treatment being received Custom value	NR	NR

Data for group baseline characteristics are for the following number of participants: Exenatide, n=35; Insulin glargine, n=36.

7. Mari, 2008

Bibliographic Reference	Mari, A.; Scherbaum, W. A.; Nilsson, P. M.; Lalanne, G.; Schweizer, A.; Dunning, B. E.; Jauffret, S.; Foley, J. E.; Characterization of the influence of vildagliptin on model-assessed -cell function in patients with type 2 diabetes and mild hyperglycaemia; J Clin Endocrinol Metab; 2008; vol. 93 (no. 1); 103-9

7.1. Study details

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	Additional outcomes reported in: • Scherbaum, W. A., Schweizer, A., Mari, A., Nilsson, P. M., Lalanne, G., Jauffret, S., & Foley, J. E. (2008). Efficacy and tolerability of vildagliptin in drug-naive patients with type 2 diabetes and mild hyperglycaemia. Diabetes, Obesity and Metabolism, 10(8), 675-682.
Trial name / registration number	NCT00101712
Study type	Randomised controlled trial (RCT)
Study location	International (69 sites in Finland, France, Germany, Romania, Spain and Sweden)
Study setting	Community
Study dates	10/2004 to 05/2006
Sources of funding	Funded by Novartis Pharmaceuticals Corporation
Inclusion criteria	• Aged ≥18 years • Diagnosis of type 2 diabetes≥8 weeks before enrolment • Naive to treatment with oral antidiabetic drug (defined as no such drug≥12 weeks before screening and no such drug≥3 consecutive months at any time • HbA1c level ≥6.2 to ≤7.5% at screening (≤7.0% for participating centres in Finland and Spain) • BMI ≥22 to ≤45 kg/m2 • If female then non-fertile or of childbearing potential using medically-approved birth control method

Exclusion criteria	• History of type 1 or secondary form of diabetes • Acute metabolic diabetic complications ≤6 months of enrolment • Evidence of significant diabetic complications • History of significant cardiac arrhythmia, congestive heart failure or New York Heart Association class III or IV • Liver disease (e.g. cirrhosis or chronic active hepatitis • Any significant laboratory abnormality
Recruitment / selection of participants	Recruited from 69 sites in 6 countries with 2 week screening period, 52 week treatment period followed by 4 week treatment-free washout period. All participants received individualized lifestyle counselling regarding weight loss, diet and physical activity.
Intervention(s)	• Vildagliptin 50 mg once daily Oral vildagliptin tablets 50 mg once daily, 30 min before breakfast, for 52 weeks.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Exclusion criteria: NYHA class 3 and 4. Trial may include participants with NYHA class 2.
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	Mixed population 46.2% of vildagliptin group and 46.7% of placebo group were obese (BMI>=30 kg/m2)
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 Inclusion criteria: participants who had not taken oral antidiabetic drug in previous 12 weeks and had not taken any such drug for than 3 consecutive months at any time.
Comparator	• Placebo Placebo for vildagliptin for 52 weeks
Number of participants	N= 306
Duration of follow-up	52 weeks + 4 week washout period
Method of analysis	Not stated/unclear Population used for analysis not reported; also reports results for completer population/

7.2. Study arms

7.2.1. Vildagliptin 50 mg once daily (N = 156)

Oral vildagliptin tablets 50 mg once daily for 52 weeks.

7.2.2. Placebo (N = 150)

Placebo to vildagliptin for 52 weeks.

7.3. Characteristics

7.3.1. Arm-level characteristics

Characteristic	Vildagliptin 50 mg once daily (N = 156)	Placebo (N = 150)
% Male Sample size	n = 93 ; % = 59.6	n = 89 ; % = 59.3
Mean age (SD) Mean (SD)	63.3 (10.2)	62.8 (11)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Caucasian Sample size	n = 155 ; % = 99.4	n = 149 ; % = 99.3
Other Sample size	n = 1 ; % = 0.6	n = 1 ; % = 0.7
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosis (years) Mean (SD)	2.5 (2.9)	2.7 (3.2)
HbA1c (%) Significant difference between groups, p=0.0403 Mean (SD)	6.7 (0.4)	6.8 (0.4)
Blood pressure Nominal	NR	NR
Heart rate Nominal	NR	NR
Smoking status Nominal	NR	NR
Alcohol consumption	NR	NR

Characteristic	Vildagliptin 50 mg once daily (N = 156)	Placebo (N = 150)
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 (kg/m2) Mean (SD)	30.4 (4.9)	30 (4.9)
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 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

8. Miyagawa, 2015

Bibliographic Reference	Miyagawa, J.; Odawara, M.; Takamura, T.; Iwamoto, N.; Takita, Y.; Imaoka, T.; Once-weekly glucagon-like peptide-1 receptor agonist dulaglutide is non-inferior to once-daily liraglutide and superior to placebo in Japanese patients with type 2 diabetes: a 26-week randomized phase III study; Diabetes Obes Metab; 2015; vol. 17 (no. 10); 974-83

8.1. Study details

Secondary publication of another included study- see primary study for details	No
Other publications associated with this study included in review	52-week efficacy results reported in: • Odawara, M., Miyagawa, J., Iwamoto, N., Takita, Y., Imaoka, T., & Takamura, T. (2016). Once-weekly glucagon-like peptide-1 receptor agonist dulaglutide significantly decreases glycated haemoglobin compared with once-daily liraglutide in Japanese patients with type 2 diabetes: 52 weeks of treatment in a randomized phase III study. *Diabetes, Obesity and Metabolism*, *18*(3), 249-257. 26-week health-related quality of life outcomes reported in: • Suzuki, S., Oura, T., Takeuchi, M., & Boye, K. S. (2017). Evaluation of the impact of once weekly dulaglutide on patient-reported outcomes in Japanese patients with type 2 diabetes: comparisons with liraglutide, insulin glargine, and placebo in two randomized studies. *Health and Quality of Life Outcomes*, *15*(1), 1-10.
Trial name / registration number	NCT01558271
Study type	Randomised controlled trial (RCT)
Study location	Japan (33 sites in 14 cities)
Study setting	Community
Study dates	04/2012 to 10/2013
Sources of funding	Eli Lilly Japan K.K., Kobe, Japan.
Inclusion criteria	• Diagnosis of type 2 diabetes before screening

	• Management with diet and exercise only or treatment with oral antidiabetic monotherapy (except for thiazolidinedione) and willing to discontinue medication with 8 week washout period before randomisation • HbA1c level 7.0-10.0% inclusive at screening and randomisation for those on diet and exercise only; or HbA1c level 6.5-9.0% inclusive at screening and HbA1c level 7.0-10.0% inclusive at randomisation for those on oral antidiabetic monotherapy • BMI ≥18.5 to ≥35.0 kg/m2
Exclusion criteria	• Diagnosis of type 1 diabetes. • Previous treatment with any other GLP-1 analogue. • Receiving more than half of maximum dose of sulfonylureas at screening • Currently taking insulin or thiazolidinediones (TZD), or previous insulin or TZD treatment ≤3 months screening. • Obvious clinical signs or symptoms of pancreatitis, history of chronic pancreatitis, or acute pancreatitis at screening, as determined by investigator • Serum amylase concentration ≥3 times upper limit of reference range and/or a serum lipase concentration ≥2 times upper limit of reference range, as determined by central laboratory at screening • History (personal or family) of medullary C-cell hyperplasia, focal hyperplasia, or medullary thyroid carcinoma
Recruitment / selection of participants	Participants recruited from 33 sites in Japan. Initial 2 week screening period, then 2 week lead-in period for treatment-naive participants and 8 week wash out period for participants on monotherapy. Eligible participants randomized to treatment in 4:2:1 ratio (dulaglutide; liraglutide; placebo) using computer-generated random sequence with interactive voice response system and stratified by pre-study oral antidiabetic medication status (yes/no), BMI group (<25; ≥25 kg/m2), and HbA1c (≤8.5; >8.5%). Participants and investigators masked to assignment to dulaglutide and placebo treatment but not masked to assignment to liraglutide treatment. At end of 26 weeks, participants in placebo group switched to dulaglutide 0.75 once weekly for remaining 26 weeks. Participants not tolerating study drugs discontinued them but remained in study to collect safety data.
Intervention(s)	• Dulaglutide 0.75 mg once weekly Subcutaneous injection of dulaglutide 0.75 mg once weekly for 26 weeks, provided in non-identifiable solution in prefilled syringe and initiated at full dose. Subsequent 26 weeks was open-label dulaglutide.
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	7) Mixed population Participants were treatment-naive (diabetes managed with diet and exercise only) or if on oral antidiabetic monotherapy had 8-week washout period
Comparator	• Liraglutide 0.9 mg once weekly • Placebo

	Open label subcutaneous liraglutide up-titrated from 0.3 mg/day during week 1 to 0.6 mg/day during week 2 and 0.9 mg/day at start of week 3 for remaining 49 weeks. Participants in placebo arm received placebo for 26 weeks then were switched over to dulaglutide 0.75 mg once weekly for remaining 26 weeks.
Number of participants	N=492
Duration of follow-up	26 weeks + 52 weeks Participants in dulaglutide and liraglutide arms received treatment for 52 weeks. Participants in placebo arm switched to dulaglutide 0.75 mg once daily at 26 weeks for 26 weeks.
Method of analysis	Modified ITT mITT analysis for efficacy analysis - all randomised participants who took at least one dose of study drug. Other Safety analysis conducted on as-treated population according to actual treatments received.
Additional comments	

8.2. Study arms

8.2.1. Dulaglutide 0.75 mg once weekly (N = 281)

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

8.2.2. Liraglutide 0.9 mg once daily (N = 141)

Subcutaneous injection of liraglutide 0.9 mg once daily for 52 weeks.

8.2.3. Placebo once weekly for 26 weeks then dulalgutide 0.75 mg once weekly for 26 weeks (N = 79)

Placebo injection once weekly using non-identifiable prefilled syringe (same as used for dulaglutide) for 26 weeks, then switched to dulaglutide 0.75 mg once weekly for 26 weeks.

8.3. Characteristics

8.3.1. Arm-level characteristics

Characteristic	Dulaglutide 0.75 mg once weekly (N = 281)	Liraglutide 0.9 mg once daily (N = 141)	Placebo once weekly for 26 weeks then dulaglutide 0.75 mg once weekly for 26 weeks (N = 79)
% Male Sample size	n = 228 ; % = 81	n = 113 ; % = 83	n = 55 ; % = 79
Mean age (SD) Mean (SD)	57.2 (9.6)	57.9 (10.4)	57.7 (8.3)
Ethnicity Nominal	NR	NR	NR
Comorbidities Nominal	NR	NR	NR
Presence of frailty Nominal	NR	NR	NR
Time since type 2 diabetes diagnosis (years) Mean (SD)	6.8 (5.6)	6.3 (6)	6.3 (5.1)
HbA1c (%) Mean (SD)	8.15 (0.77)	8.08 (0.89)	8.2 (0.83)
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	NR	NR	NR

Characteristic	Dulaglutide 0.75 mg once weekly (N = 281)	Liraglutide 0.9 mg once daily (N = 141)	Placebo once weekly for 26 weeks then dulaglutide 0.75 mg once weekly for 26 weeks (N = 79)
Nominal			
People with significant cognitive impairment Nominal	NR	NR	NR
People with a learning disability Nominal	NR	NR	NR
Weight (kg) Mean (SD)	71.3 (12.5)	70.2 (12.5)	69.3 (11.6)
BMI (kg/m2) Mean (SD)	25.6 (3.6)	25.5 (3.5)	25.2 (3.2)
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
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Naive to oral antihyperglycaemic medication Sample size	n = 186 ; % = 66	n = 89 ; % = 65	n = 48 ; % = 69
Pre-study oral antihyperglycaemic medication	n = 94 ; % = 34	n = 48 ; % = 35	n = 22 ; % = 31

Characteristic	Dulaglutide 0.75 mg once weekly (N = 281)	Liraglutide 0.9 mg once daily (N = 141)	Placebo once weekly for 26 weeks then dulaglutide 0.75 mg once weekly for 26 weeks (N = 79)
Sample size			
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

All baseline characteristics data are for the following number of participants: Dulaglutide, n=280; Liraglutide, n=137; Placebo, n=70.

9. Miyazaki, 2002

Bibliographic Reference	Miyazaki, Y.; Matsuda, M.; DeFronzo, R. A.; Dose-response effect of pioglitazone on insulin sensitivity and insulin secretion in type 2 diabetes; Diabetes Care; 2002; vol. 25 (no. 3); 517-23

9.1. 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	NR
Study type	Randomised controlled trial (RCT)
Study location	NR
Study setting	Multicentre
Study dates	NR
Sources of funding	Support for the multicentre trial was provided by Takeda
Inclusion criteria	- HbA1c >= 7% - fasting plasma glucose>= 140mg/dl - fasting c-peptide >1 ng/ml
Exclusion criteria	-Use of insulin -Unstable proliferative retinopathy - Impaired liver function (aspartate aminotransferase or alanine aminotransferase >2.5 * upper limit of normal

	- Impaired kidney function (serum creatinine >1.8 mg/dl) - Anemia
Recruitment / selection of participants	Patients taking previous antidiabetic therapy (sulfonylureas or metformin) underwent a 6- to 8-week single-blind washout period before the baseline OGTT was performed. After the washout period, only patients with HbA1c 7.0% were enrolled. Patients were randomized to one of five parallel treatment groups: pioglitazone 7.5, 15, 30, or 45 mg/day or placebo. During the double-blind period, patients were seen every 2 weeks for the first 6 weeks and every 4 weeks for the remaining 20 weeks. At 26 weeks, all subjects underwent repeat 75-g OGTT. To minimize the confounding effect of weight loss on metabolic changes, no specific dietary modifications were recommended during the study
Intervention(s)	Pioglitazone 7.5/15/30/45 mg/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	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	3) Selection of specific population Only people with >7.0% enrolled, excluded responders.
Number of participants	54
Duration of follow-up	26 weeks
Indirectness	Direct
Method of analysis	Not stated/unclear

9.2. Study arms

9.2.1. Pioglitazone 7.5mg/day (N = 13)

9.2.2. Pioglitazone 15mg/day (N = 12)

9.2.3. Pioglitazone 30mg/day (N = 11)

9.2.4. Pioglitazone 45mg/day (N = 11)

9.2.5. Placebo (N = 11)

9.3. Characteristics

9.3.1. Study-level characteristics

Characteristic	Study (N =)
% Male Sample size	n = 34 ; % = 58.6
Mean age (SD) Mean (SD)	54 (1)
BMI Mean (SD)	31.5 (0.6)

9.3.2. Arm-level characteristics

Characteristic	Pioglitazone 7.5mg/day (N = 13)	Pioglitazone 15mg/day (N = 12)	Pioglitazone 30mg/day (N = 11)	Pioglitazone 45mg/day (N = 11)	Placebo (N = 11)
Age Mean (SD)	51 (3)	57 (4)	51 (2)	51 (2)	58 (3)
Caucasian Nominal	10	10	6	7	9
African-American Nominal	1	1	0	1	1

Characteristic	Pioglitazone 7.5mg/day (N = 13)	Pioglitazone 15mg/day (N = 12)	Pioglitazone 30mg/day (N = 11)	Pioglitazone 45mg/day (N = 11)	Placebo (N = 11)
Mexican-American Nominal	0	1	4	2	1
Asian Nominal	2	0	0	0	0
Others Nominal	0	0	1	1	0
Male Sample size	n = 10 ; % = 76.9	n = 8 ; % = 66.6	n = 8 ; % = 72.7	n = 5 ; % = 45.5	n = 3 ; % = 27.2

10. Moretto, 2008

Bibliographic Reference	Moretto, T. J.; Milton, D. R.; Ridge, T. D.; Macconell, L. A.; Okerson, T.; Wolka, A. M.; Brodows, R. G.; Efficacy and tolerability of exenatide monotherapy over 24 weeks in antidiabetic drug-naive patients with type 2 diabetes: a randomized, double-blind, placebo-controlled, parallel-group study; Clin Ther; 2008; vol. 30 (no. 8); 1448-60

10.1. 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	NCT00381342
Study type	Randomised controlled trial (RCT)
Study location	International (23 centres in India, Puerto Rico, Romania, Russia, USA)
Study setting	Community
Study dates	09/2006 to 09/2007
Sources of funding	Funded by Amylin Pharmaceuticals, Inc, San Diego, CA, USA and Eli Lilly and Co. Indiana, IN, USA. Publication funded by Eli Lilly and Co.
Inclusion criteria	• Aged ≥18 years • If female, either using contraceptives for >12 weeks before screening and continuing throughout study, or postmenopausal or surgically sterile • Diagnosis of type 2 diabetes • BMI 25-45 kg/m2 inclusive • Managing their type 2 diabetes with diet and exercise consistent with the local standards of medical care in the opinion of the investigator • HbA1c 6.5-10.0% inclusive at screening
Exclusion criteria	• Previous treatment with antidiabetic agent • Blood pressure ≥160/≥110 mmHg

	• History or presence of clinically significant cardiac disease ≤1 year before participation in study • History of renal transplant or active renal or hepatic disease • Previous weight loss medication ≤12 weeks prior to screening
Recruitment / selection of participants	At screening, each patient received next consecutive patient number from block of patient numbers assigned to investigator. One week after screening, a 2-week, single-blind lead-in period in which participants received subcutaneous placebo injections twice per day (b.i.d.) to acclimatize them to self-administering injections. Participants were then randomly assigned 1:1:1 ratio, using computer-generated randomization sequence generated by interactive voice-response system to one of the 3 double-blind treatment arms, stratified by screening HbA1c (≤8%, >8%) within each site. Participants discontinued trial due to if (i) they had increase of 1% HbA1c level from baseline at any study visit, (ii) HbA1c>10.5% at or after week 12, or (iii) had ≥4 fasting serum glucose concentrations >260 mg/dL for 7 consecutive days according to self-monitored blood glucose tests.
Intervention(s)	• Exenatide 10 mcg twice daily • Exenatide 5 mcg twice daily Participants instructed to maintain individualised diet and exercise regimen during trial and self-administered exenatide in upper arm, thought or abdomen twice daily (15 min before both breakfast and dinner). Participants in exenatide 10 mcg arm received 5 mcg twice daily for 4 weeks then 10 mcg twice daily for 20 weeks. Participants in exenatide 5 mcg arm received 5 mcg twice daily for 24 weeks.
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: history or presence of clinically significant cardiac disease within 1 year prior to study
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	People without chronic kidney disease Exclusion criteria: history of renal transplant or active renal or hepatic disease
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	5) All treatment naïve All participants managed using only diet and exercise (exclusion criteria: previous treatment with anti-diabetic agent).
Population subgroups	
Comparator	• Placebo Participants in this arm received volume equivalent to 5 mcg exenatide twice daily for 4 weeks then volume equivalent to exenatide 5 mcg or 10 mcg twice daily for 20 weeks.
Number of participants	N=233
Duration of follow-up	24 weeks
Method of analysis	Modified ITT mTT - all randomised participants who received ≥1 dose of study drug - for all outcomes. Primary endpoint was HbA1c at week 24 or LOCF.

10.2. Study arms

10.2.1. Exenatide 10 mcg twice daily (N = 78)

Subcutaneous injection of exenatide 5mcg twice per day (15 min before morning and evening meals) for 4 weeks then 10 mcg twice per day for 20 weeks.

10.2.2. Exenatide 5 mcg twice daily (N = 77)

Subcutaneous injection of exenatide 5mcg twice per day (15 min before morning and evening meals) for 24 weeks.

10.2.3. Placebo (N = 78)

Volume-matched placebo injections equivalent to exenatide 5 mcg twice daily for 4 weeks, then volume equivalent to exenatide 5 mcg or 10 mcg twice daily for 20 weeks.

10.3. Characteristics

10.3.1. Arm-level characteristics

Characteristic	Exenatide 10 mcg twice daily (N = 78)	Exenatide 5 mcg twice daily (N = 77)	Placebo (N = 78)
% Male Sample size	n = 40 ; % = 52	n = 48 ; % = 62	n = 42 ; % = 55
Mean age (SD) (years) Mean (SD)	55 (10)	54 (10)	53 (9)
Asian Sample size	n = 18 ; % = 23	n = 22 ; % = 29	n = 21 ; % = 27
Black Sample size	n = 3 ; % = 4	n = 0 ; % = 0	n = 3 ; % = 4
Hispanic Sample size	n = 1 ; % = 1	n = 5 ; % = 6	n = 2 ; % = 3
White Sample size	n = 56 ; % = 72	n = 50 ; % = 65	n = 51 ; % = 66
Comorbidities Custom value	NR	NR	NR

Characteristic	Exenatide 10 mcg twice daily (N = 78)	Exenatide 5 mcg twice daily (N = 77)	Placebo (N = 78)
Presence of frailty Custom value	NR	NR	NR
Time since type 2 diabetes diagnosis (years) Mean (SD)	2 (3)	2 (3)	1 (2)
HbA1c (%) Mean (SD)	7.8 (1)	7.9 (1)	7.8 (0.9)
Systolic blood pressure Mean (SD)	130 (12)	129 (11)	129 (12)
Diastolic blood pressure Mean (SD)	79 (8)	78 (7)	78 (7)
Heart rate Custom value	NR	NR	NR
Smoking status Custom value	NR	NR	NR
Alcohol consumption Custom value	NR	NR	NR
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 (kg) Mean (SD)	86 (16)	85 (15)	86 (16)
BMI (kg/m2) Mean (SD)	31 (5)	32 (5)	32 (5)

Characteristic	Exenatide 10 mcg twice daily (N = 78)	Exenatide 5 mcg twice daily (N = 77)	Placebo (N = 78)
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 Custom value	None	None	None
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

11. Mu, 2017

Bibliographic Reference	Mu, Y.; Pan, C.; Fan, B.; Hehnke, U.; Zhang, X.; Zhang, X.; Wang, X.; Liu, J.; Zhang, Y.; Du, J.; Ma, J.; Gong, Y.; Efficacy and safety of linagliptin/metformin single-pill combination as initial therapy in drug-naive Asian patients with type 2 diabetes; Diabetes Res Clin Pract; 2017; vol. 124; 48-56

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	NCT01708902.
Study type	Randomised controlled trial (RCT)
Study location	Multicenter. China, Malaysia, Philippines and Vietnam.
Study setting	Outpatient follow-up.
Study dates	October 9th 2012 to April 8th 2014.
Sources of funding	Supported by Boehringer Ingelheim and Eli Lilly and Company.
Inclusion criteria	Age 18-80; diagnosis of T2DM; never received any antidiabetes drugs (or no more than 30 cumulative days of antidiabetes therapy 12 weeks prior to randomisation and no antidiabetes therapy within these 12 weeks); HbA1c 7.5%-11.0% at screening for the main group and >11.0% at screening for the additional parallel group.
Exclusion criteria	History of acute coronary syndrome, stroke or transient ischaemic attacks within 3 months of randomisation; impaired hepatic function (serum levels of alanine aminotransferase, aspartate aminotransferase or alkaline phosphatase >3x upper limit of normal or bilirubin >1.5 x upper limit of normal); renal failure or renal impairment (eGFR <60mL/min); known history of pancreatitis.
Recruitment / selection of participants	No additional information.

Intervention(s)	Linagliptin and metformin (study A) N=294 Two groups. Linagliptin 2.5mg once a day and metformin 500mg twice a day (n=147) and linagliptin 2.5mg once a day and metformin 1000mg twice a day (n=147). Concomitant therapy: People whose glycaemia was not adequately controlled received hypoglycaemic rescue therapy to ensure their safety. The use of rescue therapy (with sulfonylureas, thiazolidinediones or insulin), was permitted only during the randomised treatment period and was administered only if the person had hyperglycaemia on fasting plasma testing confirmed by a second glucose determination performed on a different day. If this could not be controlled then the person was to be discontinued from the trial.
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	People without non-alcoholic fatty liver disease

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	Metformin (study A) N=289 Two groups. Metformin 500mg twice a day (n=145) and metformin 1000mg twice a day (n=144). Concomitant therapy: People whose glycaemia was not adequately controlled received hypoglycaemic rescue therapy to ensure their safety. The use of rescue therapy (with sulfonylureas, thiazolidinediones or insulin), was permitted only during the randomised treatment period and was administered only if the person had hyperglycaemia on fasting plasma testing confirmed by a second glucose determination performed on a different day. If this could not be controlled then the person was to be discontinued from the trial. Linagliptin (study A) N=147 Linagliptin 5mg once a day. Concomitant therapy: People whose glycaemia was not adequately controlled received hypoglycaemic rescue therapy to ensure their safety. The use of rescue therapy (with sulfonylureas, thiazolidinediones or insulin), was permitted only during the randomised treatment period and was administered only if the person had hyperglycaemia on fasting plasma testing confirmed by a second glucose determination performed on a different day. If this could not be controlled then the person was to be discontinued from the trial.

Number of participants	730 in study 1 (the main trial), 163 in study 2 (the side trial) - only the main trial is included as the side trial was only followed up for 12 weeks for the continuous outcomes.
Duration of follow-up	26 weeks.
Indirectness	No additional information.
Method of analysis	Other Full case analysis with last observation carried forward
Additional comments	No additional information.

11.2. Study arms

11.2.1. Linagliptin + metformin (study A) (N = 294)

Two groups. Linagliptin 2.5mg once a day and metformin 500mg twice a day (n=147) and linagliptin 2.5mg once a day and metformin 1000mg twice a day (n=147). Concomitant therapy: People whose glycaemia was not adequately controlled received hypoglycaemic rescue therapy to ensure their safety. The use of rescue therapy (with sulfonylureas, thiazolidinediones or insulin), was permitted only during the randomised treatment period and was administered only if the person had hyperglycaemia on fasting plasma testing confirmed by a second glucose determination performed on a different day. If this could not be controlled then the person was to be discontinued from the trial.

11.2.2. Metformin (study A) (N = 289)

Two groups. Metformin 500mg twice a day (n=145) and metformin 1000mg twice a day (n=144). Concomitant therapy: People whose glycaemia was not adequately controlled received hypoglycaemic rescue therapy to ensure their safety. The use of rescue therapy (with sulfonylureas, thiazolidinediones or insulin), was permitted only during the randomised treatment period and was administered only if the person had hyperglycaemia on fasting plasma testing confirmed by a second glucose determination performed on a different day. If this could not be controlled then the person was to be discontinued from the trial.

11.2.3. Linagliptin (study A) (N = 147)

Linagliptin 5mg once a day. Concomitant therapy: People whose glycaemia was not adequately controlled received hypoglycaemic rescue therapy to ensure their safety. The use of rescue therapy (with sulfonylureas, thiazolidinediones or insulin), was permitted only during the randomised treatment period and was administered only if the person had hyperglycaemia on fasting plasma testing confirmed by a second glucose determination performed on a different day. If this could not be controlled then the person was to be discontinued from the trial.

11.3. Characteristics

11.3.1. Arm-level characteristics

Characteristic	Linagliptin + metformin (study A) (N = 294)	Metformin (study A) (N = 289)	Linagliptin (study A) (N = 147)
% Male Sample size	n = 179 ; % = 61	n = 182 ; % = 63	n = 76 ; % = 52
Mean age (SD) (years) Mean (SD)	51.1 (9.8)	51.8 (10)	50.8 (10.5)
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 Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Less than and equal to 1 year Sample size	n = 236 ; % = 80	n = 223 ; % = 77	n = 110 ; % = 78
Greater than 1 to less than and equal to 5 years Sample size	n = 35 ; % = 12	n = 37 ; % = 13	n = 23 ; % = 16
Greater than 5 and less than and equal to 10 years Sample size	n = 11 ; % = 4	n = 14 ; % = 5	n = 7 ; % = 5
Greater than 10 years Sample size	n = 1 ; % = 0.03	n = 3 ; % = 1	n = 1 ; % = 1
HbA1c (%) Mean (SD)	8.7 (1)	8.7 (1.1)	8.7 (0.9)
Blood pressure Mean (SD)	NR (NR)	NR (NR)	NR (NR)

Characteristic	Linagliptin + metformin (study A) (N = 294)	Metformin (study A) (N = 289)	Linagliptin (study A) (N = 147)
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)	70.7 (12)	70.1 (11.5)	70.2 (13.5)
BMI (kg/m2) Mean (SD)	26 (3.65)	26 (3.3)	26.2 (3.9)
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)
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	Linagliptin + metformin (study A) (N = 294)	Metformin (study A) (N = 289)	Linagliptin (study A) (N = 147)
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

12. Nauck, 2016

Bibliographic Reference	Nauck, M. A.; Di Domenico, M.; Patel, S.; Kobe, M.; Toorawa, R.; Woerle, H. J.; Linagliptin and pioglitazone combination therapy versus monotherapy with linagliptin or pioglitazone: A randomised, double-blind, parallel-group, multinational clinical trial; Diabetes Vasc Dis Res; 2016; vol. 13 (no. 4); 286-298

12.1. 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	NCT01183013
Study type	Randomised controlled trial (RCT)
Study location	International (132 sites in Estonia, Germany, Latvia, Spain, UK and USA)
Study setting	Community
Study dates	08/2010 to 02/2013
Sources of funding	Funded by Boehringer Ingelheim and Eli Lilly and Co.
Inclusion criteria	• Aged ≥18 to ≤80 years at screening • Diagnosis of type 2 diabetes insufficient glycaemic control on diet and exercise alone • No use of oral antidiabetic drug≤10 weeks of screening • BMI≤45 kg/m2 at screening
Exclusion criteria	• Pregnancy, nursing baby, or of child-bearing potential and not practicing effective birth control/not planning to practice such control for duration of study • Uncontrolled hyperglycaemia with confirmed glucose level > 240 mg/dl (> 13.3 mmol/l) after overnight fast during screening or placebo run-in period • Myocardial infarction ≤6 months, stroke or TIA ≤ 3 months prior to informed consent

	• Clinical evidence of active liver disease (e.g. jaundice) or the ALT level > 2.5 times the upper limit of normal (according to pioglitazone label) • Bariatric surgery, performed ≤2 years prior to informed consent or planned at the time of informed consent • Gastrointestinal surgeries prior to informed consent that induce chronic malabsorption • Known hypersensitivity or allergy to the investigational products (linagliptin and/or pioglitazone) or their excipients (including matching placebos) • Any contraindication or restriction for the use of pioglitazone according to local prescribing information, including diagnosis of heart failure or history of heart failure, and haemodialysis patients • Treatment with rosiglitazone, pioglitazone, GLP-1 analogues, or insulin ≤3 months prior to informed consent • Treatment with anti-obesity drugs (e.g. sibutramine, orlistat) ≤3 months prior to informed consent • Alcohol or drug abuse≤3 months prior to informed consent or history of alcoholism • Current treatment with systemic corticosteroids at time of informed consent or change in dosage of thyroid hormones within 6 weeks prior to informed consent • History of pancreatitis or bladder cancer
Recruitment / selection of participants	Participants recruited from 132 sites across the world for 2 part trial (part A and part B). Initial washout period of >10 weeks for participants on oral antidiabetic monotherapy, followed by 2 week placebo run-in period for all participants. Part A was 30 week treatment period with randomisation using equal allocation to one of 7 treatment groups: Fixed-dose combination linagliptin 5 mg/pioglitazone 15, 30 or 45 mg once daily; linagliptin 5 mg once daily; pioglitazone 15, 30 or 45 mg once daily. Randomisation by computer-generated random sequence using interactive voice response system or web response system. Treatments masked using double-blind and double-dummy design. Part B was a planned extension period up to 54 weeks with 5 treatment groups: participants in the 2 groups who received pioglitazone 15 mg in part A (as monotherapy or fixed-dose combination) and who continued to part B were to receive pioglitazone 30 mg (either as monotherapy or fixed-dose combination, according to assignment in part A). Participants in 5 other part A treatment groups were to remain same in part B. However, due to USFDA and EMA safety concerns about pioglitazone (increased risk of bladder cancer) trial was attenuated so that all participants ended trial participation at 30 weeks and no new participants were entered into part B. Participants already in part B concluded participation by completing final visit procedures.
Intervention(s)	• Linagliptin 5 mg/Pioglitazone 15 mg SPC once daily • Linagliptin 5 mg/Pioglitazone 30 mg SPC once daily • Linagliptin 5 mg/Pioglitazone 45 mg SPC once daily All participants in these groups received treatment drugs for 30 weeks (part A). Participants in Pioglitazone 45 mg single-pill combination group initially received pioglitazone 30 mg, up-titrated to 45 mg over 6-week

	forced titration period. Participants in all groups received daily placebo pills.
Cointervention	Placebo. Reports double-dummy design but no further details reported so assume that all arms received two pills (one active treatment, one placebo).
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Exclusion criteria: Any contraindication or restriction for the use of pioglitazone according to local prescribing information, including diagnosis of heart failure or history of heart failure, and haemodialysis patients
Strata 2: People with atherosclerotic cardiovascular diseases	People without other cardiovascular diseases Exclusion criteria: Myocardial infarction ≤6 months, stroke or TIA ≤ 3 months prior to informed consent
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	eGFR ≥30mL/min/1.73m2

	All but one participant in trial (assigned to Linagliptin 5 mg/Pioglitazone 30 mg FDC group) had eGFR≥30mL/min/1.73 m2. This participant had eGFR of 27.85 mL/min.
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Sensitivity analysis category: Enrichment trial status	7) Mixed population Inclusion criteria: No use of oral antidiabetic drug≤10 weeks of screening
Population subgroups	
Comparator	• Pioglitazone 15 mg once daily • Pioglitazone 30 mg once daily • Pioglitazone 45 mg once daily • Linagliptin 5 mg once daily All participants in these groups received treatment drugs for 30 weeks (part A). Participants randomised to pioglitazone 45 mg group initially received pioglitazone 30 mg, up-titrated to 45 mg during 6 week forced titration period. Participants in all groups received daily placebo pills.
Number of participants	N=936
Duration of follow-up	30 weeks
Indirectness	No concerns
Method of analysis	ACA Secondary efficacy analysis of change in HbA1c based on observed cases with those with missing data excluded. Modified ITT Primary efficacy analysis of mean change from baseline in HbA1c conducted on all randomised participants who received at least one dose of study drug and had baseline and at least one on-treatment HbA1c measurement (Full analysis set). Safety analysis conducted on all randomised participants who received at least one dose of study drug.

12.2. Study arms

12.2.1. Pioglitazone 45 mg + Linagliptin 5 mg SPC once daily (N = 133)

Pioglitazone 45 mg/Linagliptin 5 mg single-pill combination (SPC) oral tablets once daily for 6 weeks, followed by linagliptin 5 mg low dose/pioglitazone 45 mg fixed-dose combination tablets once daily for up to 87 weeks.

12.2.2. Pioglitazone 30 mg + Linagliptin 5 mg SPC once daily (N = 133)

Linagliptin 5 mg low dose/Pioglitazone 30 mg single-pill combination (SPC) oral tablets once daily for up to 84 weeks.

12.2.3. Pioglitazone 15 mg + Linagliptin 5 mg SPC once daily (N = 126)

Linagliptin 5 mg/Pioglitazone 15 mg single-pill combination (SPC) oral tablets once daily for 30 weeks, followed by linagliptin 5 mg low dose/pioglitazone 30 mg fixed dose combination once daily for up to 54 weeks.

12.2.4. Linagliptin 5 mg once daily (N = 135)

Linagliptin 5mg low dose oral tablets once daily for 30 weeks followed by linagliptin 5mg low dose/Pioglitazone 30 mg fixed dose combination oral tablets once daily for up to 54 weeks.

12.2.5. Pioglitazone 45 mg once daily (N = 138)

Pioglitazone 30 mg oral capsules once daily for 6 weeks followed by pioglitazone 45 mg once daily for up to 78 weeks.

12.2.6. Pioglitazone 30 mg once daily (N = 140)

Pioglitazone 30 mg oral capsules once daily for up to 84 weeks.

12.2.7. Pioglitazone 15 mg once daily (N = 131)

Pioglitazone 15 mg oral capsules once daily for 30 weeks followed by pioglitazone 30 mg once daily for up to 54 weeks.

12.3. Characteristics

12.3.1. Arm-level characteristics

Characteristic	Pioglitazone 45 mg + Linagliptin 5 mg SPC once daily (N = 133)	Pioglitazone 30 mg + Linagliptin 5 mg SPC once daily (N = 133)	Pioglitazone 15 mg + Linagliptin 5 mg SPC once daily (N = 126)	Linagliptin 5 mg once daily (N = 135)	Pioglitazone 45 mg once daily (N = 138)	Pioglitazone 30 mg once daily (N = 140)	Pioglitazone 15 mg once daily (N = 131)
% Male Sample size	n = 73 ; % = 54.9	n = 68 ; % = 51.1	n = 71 ; % = 56.3	n = 83 ; % = 61.5	n = 72 ; % = 52.2	n = 73 ; % = 52.1	n = 73 ; % = 55.7
Mean age (SD) (years) Mean (SD)	59.8 (10.2)	56.7 (10.1)	57.1 (10)	56 (10.4)	56.5 (11)	57 (11.5)	56.3 (10.4)
Black/African American Sample size	n = 16 ; % = 12	n = 11 ; % = 8.3	n = 15 ; % = 11.9	n = 20 ; % = 14.8	n = 17 ; % = 12.3	n = 17 ; % = 12.1	n = 20 ; % = 15.3
Other American Indian/Alaska Native, Asian or Hawaiian/Pacific Islander Sample size	n = 4 ; % = 3.1	n = 3 ; % = 2.3	n = 4 ; % = 3.2	n = 4 ; % = 3	n = 2 ; % = 1.4	n = 3 ; % = 2.1	n = 3 ; % = 2.3
White Sample size	n = 113 ; % = 85	n = 119 ; % = 89.5	n = 107 ; % = 84.9	n = 111 ; % = 82.2	n = 119 ; % = 86.2	n = 120 ; % = 85.7	n = 108 ; % = 82.4
Comorbidities Custom value	NR	NR	NR	NR	NR	NR	NR
Presence of frailty Custom value	NR	NR	NR	NR	NR	NR	NR
Time since type 2 diabetes diagnosis	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Pioglitazone 45 mg + Linagliptin 5 mg SPC once daily (N = 133)	Pioglitazone 30 mg + Linagliptin 5 mg SPC once daily (N = 133)	Pioglitazone 15 mg + Linagliptin 5 mg SPC once daily (N = 126)	Linagliptin 5 mg once daily (N = 135)	Pioglitazone 45 mg once daily (N = 138)	Pioglitazone 30 mg once daily (N = 140)	Pioglitazone 15 mg once daily (N = 131)
(years) Full analysis set: LINA/PIOG 45, n=126; LINA/PIOG 30, n=125; LINA/PIOG 5, n=120; LINA 5, n=130; PIOG 45, n=134; PIOG 30, n=134; PIOG 15 ,n=124 Sample size							
< or equal to 1 year Sample size	n = 37 ; % = 29.4	n = 35 ; % = 28	n = 32 ; % = 26.7	n = 41 ; % = 31.5	n = 39 ; % = 29.1	n = 38 ; % = 28.4	n = 35 ; % = 28.2
>1 to < or equal to 5 years Sample size	n = 42 ; % = 33.3	n = 48 ; % = 38.4	n = 42 ; % = 35	n = 48 ; % = 36.9	n = 63 ; % = 47	n = 55 ; % = 41	n = 53 ; % = 42.7
>5 years to < or equal to 10 years Sample size	n = 26 ; % = 20.6	n = 32 ; % = 25.6	n = 33 ; % = 27.5	n = 25 ; % = 19.2	n = 26 ; % = 19.4	n = 30 ; % = 22.4	n = 26 ; % = 21
10 years Sample size	n = 21 ; % = 16.7	n = 10 ; % = 8	n = 13 ; % = 10.8	n = 16 ; % = 12.3	n = 6 ; % = 4.5	n = 11 ; % = 8.2	n = 10 ; % = 8.1
HbA1c (%) Full analysis set: LINA/PIOG 45, n=126; LINA/PIOG 30, n=125;	8 (0.8)	8.2 (1.1)	8.1 (0.9)	9 (0.9)	8.1 (0.9)	9 (0.9)	8.3 (0.9)

Characteristic	Pioglitazone 45 mg + Linagliptin 5 mg SPC once daily (N = 133)	Pioglitazone 30 mg + Linagliptin 5 mg SPC once daily (N = 133)	Pioglitazone 15 mg + Linagliptin 5 mg SPC once daily (N = 126)	Linagliptin 5 mg once daily (N = 135)	Pioglitazone 45 mg once daily (N = 138)	Pioglitazone 30 mg once daily (N = 140)	Pioglitazone 15 mg once daily (N = 131)
LINA/PIOG 5, n=120; LINA 5, n=130; PIOG 45, n=134; PIOG 30, n=134; PIOG 15 ,n=124 Mean (SD)							
Blood pressure Custom value	NR	NR	NR	NR	NR	NR	NR
Heart rate Custom value	NR	NR	NR	NR	NR	NR	NR
Smoking status Custom value	NR	NR	NR	NR	NR	NR	NR
Alcohol consumption Custom value	NR	NR	NR	NR	NR	NR	NR
Presence of severe mental illness Custom value	NR	NR	NR	NR	NR	NR	NR
People with significant cognitive impairment Custom value	NR	NR	NR	NR	NR	NR	NR

Characteristic	Pioglitazone 45 mg + Linagliptin 5 mg SPC once daily (N = 133)	Pioglitazone 30 mg + Linagliptin 5 mg SPC once daily (N = 133)	Pioglitazone 15 mg + Linagliptin 5 mg SPC once daily (N = 126)	Linagliptin 5 mg once daily (N = 135)	Pioglitazone 45 mg once daily (N = 138)	Pioglitazone 30 mg once daily (N = 140)	Pioglitazone 15 mg once daily (N = 131)
People with a learning disability Custom value	NR	NR	NR	NR	NR	NR	NR
Weight (kg) Mean (SD)	91.8 (18.5)	91.8 (19.3)	93.6 (19)	94.7 (19.3)	96.9 (19)	91.5 (19.9)	91.5 (20.7)
BMI (kg/m2) Mean (SD)	32.4 (5.4)	32.6 (5.7)	32.4 (5.5)	32.7 (5.3)	33.9 (5.5)	32.2 (5.3)	32.3 (5.6)
Number of people with obesity Custom value	NR	NR	NR	NR	NR	NR	NR
Cholesterol and lipid levels Custom value	NR	NR	NR	NR	NR	NR	NR
Albumin creatinine ratio Custom value	NR	NR	NR	NR	NR	NR	NR
eGFR (mL/min/1.73 m2) Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Normal renal function (> or equal to 90) Sample size	n = 35 ; % = 26.3	n = 43 ; % = 32.3	n = 42 ; % = 33.3	n = 48 ; % = 35.6	n = 55 ; % = 39.9	n = 52 ; % = 37.1	n = 52 ; % = 39.7

Characteristic	Pioglitazone 45 mg + Linagliptin 5 mg SPC once daily (N = 133)	Pioglitazone 30 mg + Linagliptin 5 mg SPC once daily (N = 133)	Pioglitazone 15 mg + Linagliptin 5 mg SPC once daily (N = 126)	Linagliptin 5 mg once daily (N = 135)	Pioglitazone 45 mg once daily (N = 138)	Pioglitazone 30 mg once daily (N = 140)	Pioglitazone 15 mg once daily (N = 131)
Mild impairment (60 to <90) Sample size	n = 82 ; % = 61.7	n = 79 ; % = 59.4	n = 69 ; % = 54.8	n = 78 ; % = 57.8	n = 64 ; % = 46.4	n = 67 ; % = 47.9	n = 67 ; % = 51.1
Moderate impairment (30 to <60) Sample size	n = 16 ; % = 12	n = 10 ; % = 7.5	n = 15 ; % = 11.9	n = 9 ; % = 6.7	n = 19 ; % = 13.8	n = 20 ; % = 14.3	n = 12 ; % = 9.2
Severe impairment or end-stage renal disease (<30) Sample size	n = 0 ; % = 0	n = 1 ; % = 0.8	n = 0 ; % = 0	n = 0 ; % = 0	n = 0 ; % = 0	n = 0 ; % = 0	n = 0 ; % = 0
Other antidiabetic medication used Full analysis set: LINA/PIOG 45, n=126; LINA/PIOG 30, n=125; LINA/PIOG 5, n=120; LINA 5, n=130; PIOG 45, n=134; PIOG 30, n=134; PIOG 15 ,n=124 Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
No prior antidiabetic drug used	n = 82 ; % = 65.1	n = 82 ; % = 65.6	n = 84 ; % = 70	n = 82 ; % = 63.1	n = 92 ; % = 68.7	n = 82 ; % = 61.2	n = 86 ; % = 69.4

Characteristic	Pioglitazone 45 mg + Linagliptin 5 mg SPC once daily (N = 133)	Pioglitazone 30 mg + Linagliptin 5 mg SPC once daily (N = 133)	Pioglitazone 15 mg + Linagliptin 5 mg SPC once daily (N = 126)	Linagliptin 5 mg once daily (N = 135)	Pioglitazone 45 mg once daily (N = 138)	Pioglitazone 30 mg once daily (N = 140)	Pioglitazone 15 mg once daily (N = 131)
Sample size							
One prior antidiabetic drug used Sample size	n = 42 ; % = 34.1	n = 38 ; % = 30.4	n = 35 ; % = 29.2	n = 47 ; % = 36.2	n = 37 ; % = 27.6	n = 48 ; % = 35.8	n = 35 ; % = 28.2
Two prior antidiabetic drugs used Sample size	n = 1 ; % = 0.8	n = 5 ; % = 4	n = 1 ; % = 0.8	n = 1 ; % = 0.8	n = 5 ; % = 3.7	n = 4 ; % = 3	n = 3 ; % = 2.4
Blood pressure-lowering medication used Custom value	NR	NR	NR	NR	NR	NR	NR
Statins/lipid-lowering medication used Custom value	NR	NR	NR	NR	NR	NR	NR
Other treatment being received Custom value	NR	NR	NR	NR	NR	NR	NR

13. Odawara, 2016

Bibliographic Reference	Odawara, M; Miyagawa, J; Iwamoto, N; Takita, Y; Imaoka, T; Takamura, T; Once-weekly glucagon-like peptide-1 receptor agonist dulaglutide significantly decreases glycated haemoglobin compared with once-daily liraglutide in Japanese patients with type 2 diabetes: 52 weeks of treatment in a randomized phase III study.; Diabetes, obesity & metabolism; 2016; vol. 18 (no. 3); 249-57

13.1. Study details

Secondary publication of another included study- see primary study for details	Yes, see primary study (Miyagawa 2015) for details of trial: Miyagawa, J., Odawara, M., Takamura, T., Iwamoto, N., Takita, Y., & Imaoka, T. (2015). Once-weekly glucagon-like peptide-1 receptor agonist dulaglutide is non-inferior to once-daily liraglutide and superior to placebo in Japanese patients with type 2 diabetes: a 26-week randomized phase III study. *Diabetes, Obesity and Metabolism*, *17*(10), 974-983.
Other publications associated with this study included in review	Health-related quality of life outcomes reported in: Suzuki, S., Oura, T., Takeuchi, M., & Boye, K. S. (2017). Evaluation of the impact of once weekly dulaglutide on patient-reported outcomes in Japanese patients with type 2 diabetes: comparisons with liraglutide, insulin glargine, and placebo in two randomized studies. *Health and Quality of Life Outcomes*, *15*(1), 1-10.
Trial name / registration number	NCT01558271
Study type	Randomised controlled trial (RCT)
Study location	Japan (33 sites in 14 cities)
Study setting	Community
Study dates	04/2012 to 10/2013
Sources of funding	Eli Lilly Japan K.K., Kobe, Japan.
Inclusion criteria	• Diagnosis of type 2 diabetes before screening • Management with diet and exercise only or treatment with oral antidiabetic monotherapy (except for thiazolidinedione) and willing to discontinue medication with 8 week washout period before randomisation • HbA1c level 7.0-10.0% inclusive at screening and randomisation for those on diet and exercise only; or HbA1c level 6.5-9.0% inclusive at screening and HbA1c level 7.0-10.0% inclusive at randomisation for those on oral antidiabetic monotherapy • BMI ≥18.5 to ≥35.0 kg/m2
Exclusion criteria	• Diagnosis of type 1 diabetes. • Previous treatment with any other GLP-1 analogue.

	• Receiving more than half of maximum dose of sulfonylureas at screening • Currently taking insulin or thiazolidinediones (TZD), or previous insulin or TZD treatment ≤3 months screening. • Obvious clinical signs or symptoms of pancreatitis, history of chronic pancreatitis, or acute pancreatitis at screening, as determined by investigator • Serum amylase concentration ≥3 times upper limit of reference range and/or a serum lipase concentration ≥2 times upper limit of reference range, as determined by central laboratory at screening • History (personal or family) of medullary C-cell hyperplasia, focal hyperplasia, or medullary thyroid carcinoma
Recruitment / selection of participants	Participants recruited from 33 sites in Japan. Initial 2 week screening period, then 2 week lead-in period for treatment-naive participants and 8 week wash out period for participants on monotherapy. Eligible participants randomized to treatment in 4:2:1 ratio (dulaglutide; liraglutide; placebo) using computer-generated random sequence with interactive voice response system and stratified by pre-study oral antidiabetic medication status (yes/no), BMI group (<25; ≥25 kg/m2), and HbA1c (≤8.5; >8.5%). Participants and investigators masked to assignment to dulaglutide and placebo treatment but not masked to assignment to liraglutide treatment. At end of 26 weeks, participants in placebo group switched to dulaglutide 0.75 once weekly for remaining 26 weeks. Participants not tolerating study drugs discontinued them but remained in study to collect safety data.
Intervention(s)	• Dulaglutide 0.75 mg once weekly Subcutaneous injection of dulaglutide 0.75 mg once weekly for 52 weeks, provided in non-identifiable solution in prefilled syringe and initiated at full dose.
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

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	Inclusion criteria: treatment-naive (diabetes managed with diet and exercise only) or if on oral antidiabetic monotherapy had 8-week washout period
Comparator	• Liraglutide 0.9 mg once daily Open label subcutaneous liraglutide up-titrated from 0.3 mg/day during week 1 to 0.6 mg/day during week 2 and 0.9 mg/day at start of week 3 for remaining 49 weeks.
Number of participants	N=422 (Note that data in this article are only for the participants who were originally assigned to the dulaglutide or liraglutide; data does not include the participants who were assigned to placebo for 26 weeks and who subsequently switched to dulaglutide).
Duration of follow-up	52 weeks
Indirectness	Trial conducted in Japan, unlikely to be representative of UK population.
Method of analysis	Other Safety analysis conducted on as-treated population according to actual treatments received.

13.2. Study arms

13.2.1. Dulaglutide 0.75 mg once weekly (N = 281)

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

13.2.2. Liraglutide 0.9 mg once daily (N = 141)

Subcutaneous injection of liraglutide 0.9 mg once daily for 52 weeks.

14. Pan, 2012

Bibliographic Reference	Pan, C. Y.; Yang, W.; Tou, C.; Gause-Nilsson, I.; Zhao, J.; Efficacy and safety of saxagliptin in drug-naïve Asian patients with type 2 diabetes mellitus: a randomized controlled trial; Diabetes Metab Res Rev; 2012; vol. 28 (no. 3); 268-75

14.1. 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	NCT00698932
Study type	Randomised controlled trial (RCT)
Study location	International (40 sites in China, India, Philippines, and South Korea)
Study setting	Community
Study dates	06/2008 to 10/2009
Sources of funding	Funded by Astra-Zeneca and Bristol-Myers Squibb.
Inclusion criteria	• Men and non-pregnant, non-breastfeeding women aged≥18 years • Diagnosis of type 2 diabetes • Never received medication for type 2 diabetes (insulin or oral hypoglycaemic agents) or had received such for<6 months since diagnosis • No anti-hyperglycaemic therapy for >3 consecutive days or 7 non-consecutive days during the 8 weeks (12 weeks for thiazolidinediones) before trial enrolment • Fasting C-peptide level≥0.33 nmol/L and HbA1c 7.2–10.0% (55–86 mmol/mol) at lead-in and HbA1c 7.0–10.0% (53–86 mmol/mol) at randomization
Exclusion criteria	• Diagnosis of type 1 diabetes • History of diabetic ketoacidosis or hyperosmolar non-ketonic coma • Symptoms of poorly controlled diabetes

	• New York Heart Association class III or IV congestive heart failure or left ventricular ejection fraction of≤40% • Significant cardiovascular history within 6-mo of visit 1 • History of haemoglobinopathies • Unstable or rapidly progressing renal disease based on investigator's clinical judgement • Autoimmune skin disorder • Gastro-intestinal surgery that could alter drug absorption • Illegal drug or alcohol abuse in past year • Any clinically significant abnormality that would compromise study participation • Immunocompromised conditions (e.g. human immunodeficiency virus) • Serum creatinine of≥1.4 mg/dL for women and ≥1.5 mg/dL for men at randomization • Insulin therapy within 1 year of enrolment (with exception of its use during hospitalization or for gestational diabetes) • Previous treatment with any DPP-4 inhibitor • Currently receiving treatment with systemic glucocorticoids (other than replacement therapy or treatment with cytochrome P450 3A4 inducers)
Recruitment / selection of participants	Participants recruited from 40 centres (China, 19 sites; India, 8 sites; Philippines, 7 sites; South Korea, 6 sites). Initial enrolment period (visit 1), 4 week single-blind placebo-controlled lead-in period (during which laboratory measurements taken and diet/lifestyle counselling provided), and then, 24 week double-blind treatment period to visit 12. Diet/lifestyle modifications reinforced throughout trial period. Randomisation at visit 4 (week 0/baseline) by computer-generated allocation sequence, stratified by country.
Intervention(s)	• Saxagliptin 5 mg once daily Oral saxagliptin 5 ng tablets once daily for 24 weeks.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Exclusion criteria: NYHA class 3 or 4. Trial could include participants with NYHA class 2 but no data provided.
Strata 2: People with atherosclerotic cardiovascular diseases	People without other cardiovascular diseases Exclusion criteria: significant cardiovascular history within 6 months of visit 1.
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 Inclusion criteria: Never received medication for type 2 diabetes (insulin or oral hypoglycaemic agents) or had received such for<6 months since diagnosis; and no anti-hyperglycaemic therapy for >3 consecutive days or 7 non-consecutive days during the 8 weeks (12 weeks for thiazolidinediones) before trial enrolment.
Population subgroups	
Comparator	• Placebo Matching placebo for 24 weeks. Identical tablets and packaging to saxagliptin treatment used.
Number of participants	N=568
Duration of follow-up	24 weeks
Method of analysis	Modified ITT

	Efficacy analysis set included all randomised participants who received at least one dose of study drug, had baseline data, and data for at least one post-baseline efficacy endpoint, with data on or after rescue medication excluded. Safety analysis included all participants who received at least one dose of study drug and excluded data on or after rescue medication use.

14.2. Study arms

14.2.1. Saxagliptin 5 mg once daily (N = 284)

Oral saxagliptin 5 mg tablets once daily for 24 weeks.

14.2.2. Placebo (N = 284)

Matching oral placebo tablet for 24 weeks.

14.3. Characteristics

14.3.1. Arm-level characteristics

Characteristic	Saxagliptin 5 mg once daily (N = 284)	Placebo (N = 284)
% Male Sample size	n = 160 ; % = 56.3	n = 155 ; % = 54.6
Mean age (SD) Mean (SD)	51.2 (10)	51.6 (10.3)
Ethnicity Ethnicity not reported, only country of participation Sample size	n = NA ; % = NA	n = NA ; % = NA
China Sample size	n = 169 ; % = 59.5	n = 166 ; % = 58.5
India Sample size	n = 62 ; % = 21.8	n = 60 ; % = 21.1
Philipines Sample size	n = 35 ; % = 12.3	n = 36 ; % = 12.7
South Korea Sample size	n = 18 ; % = 6.3	n = 22 ; % = 7.7

Characteristic	Saxagliptin 5 mg once daily (N = 284)	Placebo (N = 284)
Comorbidities Custom value	NR	NR
Presence of frailty Custom value	NR	NR
Time since type 2 diabetes diagnosis (years) Mean (SD)	0.8 (1.4)	1.2 (2.6)
HbA1c (%) Mean (SD)	8.1 (0.8)	8.2 (0.8)
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)	69.2 (11.4)	69.2 (12.4)
BMI (kg/m2) Mean (SD)	25.9 (3.4)	25.9 (3.7)
Number of people with obesity Custom value	NR	NR
Cholesterol and lipid levels (mmol/L) LDL-cholesterol data not represented in clinical	NA (NA)	NA (NA)

Characteristic	Saxagliptin 5 mg once daily (N = 284)	Placebo (N = 284)
database for participants with triglyceride levels>400 mg/dL Mean (SD)		
Total cholesterol Mean (SD)	5 (0.06)	5 (0.07)
HDL-cholesterol Mean (SD)	1.2 (0.02)	1.1 (0.02)
LDL-cholesterol Mean (SD)	3 (0.05)	2.9 (0.06)
Triglyceride Mean (SD)	1.9 (0.08)	2.1 (0.11)
Albumin creatinine ratio Custom value	NR	NR
eGFR (mL/min/1.73m2) Custom value	NR	NR
Other antidiabetic medication used Custom value	NR	NR
Blood pressure-lowering medication used Custom value	NR	NR
Statins/lipid-lowering medication used Custom value	NR	NR
Other treatment being received Custom value	NR	NR

15. Perez, 2009

Bibliographic Reference	Perez, A.; Zhao, Z.; Jacks, R.; Spanheimer, R.; Efficacy and safety of pioglitazone/metformin fixed-dose combination therapy compared with pioglitazone and metformin monotherapy in treating patients with T2DM; Curr Med Res Opin; 2009; vol. 25 (no. 12); 2915-23

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	Perez, Alfonso, Jacks, Randal, Arora, Vipin et al. (2010) Effects of pioglitazone and metformin fixed-dose combination therapy on cardiovascular risk markers of inflammation and lipid profile compared with pioglitazone and metformin monotherapy in patients with type 2 diabetes. Journal of clinical hypertension (Greenwich, Conn.) 12(12): 973-82
Trial name / registration number	NCT00727857.
Study type	Randomised controlled trial (RCT)
Study location	Multicentre trial (134 sites in 6 countries).
Study setting	Outpatient follow-up.
Study dates	No additional information.
Sources of funding	Funded by Takeda Global Research & Development Center, Inc.
Inclusion criteria	At least 18 years of age with type 2 diabetes; baseline HbA1c 7.5%-10.0%; treatment naïve (had not received treatment with antidiabetic medication in the 12 weeks prior to screening other than short-term use of up to 15 days); body mass index no more than 45 kg/m2; had to have received counselling on lifestyle modification including diet and exercise.
Exclusion criteria	Type 1 diabetes; NYHA class III or IV heart failure; history of myocardial infarction, cerebrovascular accident, percutaneous coronary intervention, coronary artery bypass graft or transient ischaemic attack in the 6 months prior to screening; serum creatinine level equal to or more than 1.5mg/dL in men or equal to or more than 1.4mg/dL in women; a triglyceride level >500mg/dL; an ALT level greater than 2.5 times the upper limit of normal, active liver disease or jaundice; discontinuation from a thiazolidinedione or metformin therapy due to lack of efficacy, or clinical or laboratory signs of intolerance; pregnancy, intent to become pregnant, or lactation during the study in women.

Recruitment / selection of participants	People were withdrawn from the study and completed an early termination visit if they voluntarily withdrew; had an adverse event their imposed an unnecessary risk; major protocol deviation; loss to follow-up; pregnancy; lack of efficacy with FPG elevated from baseline and >230mg/dL from week 8-16; or lack of efficacy with HbA1c decreased <0.5% from baseline or level >8.5% at week 16 or later.
Intervention(s)	Pioglitazone + Metformin N=201 Pioglitazone 15mg twice a day and metformin 850mg twice a day for 24 weeks. Concomitant therapy: Other antidiabetes medications were not allowed during the treatment 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, presence of diabetes, age and smoking status.
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	2) Excluding non-responders (but not exclusively including only responders)
Population subgroups	No additional information.
Comparator	Pioglitazone N=189 Pioglitazone 15mg twice a day for 24 weeks. Concomitant therapy: Other antidiabetes medications were not allowed during the treatment period. Metformin N=210 Metformin 850mg twice a day for 24 weeks. Concomitant therapy: Other antidiabetes medications were not allowed during the treatment period.
Number of participants	600
Duration of follow-up	24 weeks.
Indirectness	No additional information.
Method of analysis	Other Full case analysis - people had to receive at least one dose of the medication and have one analysis value. Last observation carried forward.
Additional comments	No additional information.

15.2. Study arms

15.2.1. Pioglitazone + Metformin (N = 201)

Pioglitazone 15mg twice a day and metformin 850mg twice a day for 24 weeks. Concomitant therapy: Other antidiabetes medications were not allowed during the treatment period.

15.2.2. Pioglitazone (N = 189)

Pioglitazone 15mg twice a day for 24 weeks. Concomitant therapy: Other antidiabetes medications were not allowed during the treatment period.

15.2.3. Metformin (N = 210)

Metformin 850mg twice a day for 24 weeks. Concomitant therapy: Other antidiabetes medications were not allowed during the treatment period.

15.3. Characteristics

15.3.1. Arm-level characteristics

Characteristic	Pioglitazone + Metformin (N = 201)	Pioglitazone (N = 189)	Metformin (N = 210)
% Male Sample size	n = 90 ; % = 45	n = 66 ; % = 35	n = 98 ; % = 57
Mean age (SD) (years) Mean (SD)	54.7 (12.2)	54 (12.1)	53.7 (12)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Hispanic or Latino Sample size	n = 49 ; % = 24.4	n = 49 ; % = 25.9	n = 55 ; % = 26.2
Non-Hispanic and Non-Latino Sample size	n = 42 ; % = 20.9	n = 36 ; % = 19	n = 46 ; % = 21.9
American Indian or Alaska Native Sample size	n = 63 ; % = 31.3	n = 62 ; % = 32.8	n = 67 ; % = 31.9

Characteristic	Pioglitazone + Metformin (N = 201)	Pioglitazone (N = 189)	Metformin (N = 210)
Asian Sample size	n = 3 ; % = 1.5	n = 5 ; % = 2.6	n = 5 ; % = 2.4
Black or African American Sample size	n = 12 ; % = 6	n = 13 ; % = 6.9	n = 14 ; % = 6.7
White Sample size	n = 184 ; % = 91.5	n = 165 ; % = 87.3	n = 185 ; % = 88.1
Multiracial Sample size	n = 61 ; % = 30.3	n = 56 ; % = 29.6	n = 61 ; % = 29
Comorbidities Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Hypertension Sample size	n = 91 ; % = 45.3	n = 95 ; % = 50	n = 94 ; % = 45
Hyperlipidaemia Sample size	n = 90 ; % = 44.8	n = 85 ; % = 44.7	n = 95 ; % = 45.5
Heart failure Sample size	n = 0 ; % = 0	n = 1 ; % = 0.5	n = 1 ; % = 0.5
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosis Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
HbA1c (%) Mean (SE)	8.89 (0.07)	8.69 (0.07)	8.65 (0.07)
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

Characteristic	Pioglitazone + Metformin (N = 201)	Pioglitazone (N = 189)	Metformin (N = 210)
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 Mean (SD)	NR (NR)	NR (NR)	NR (NR)
BMI (kg/m2) Mean (SD)	30.8 (5.7)	31.2 (5.5)	30.8 (5.7)
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Cholesterol and lipid levels (mg/dL) Mean (SE)	NA (NA)	NA (NA)	NA (NA)
Total cholesterol Mean (SE)	195.5 (2.85)	198.4 (2.95)	196 (2.79)
HDL cholesterol Mean (SE)	41.8 (0.76)	43.4 (0.79)	42.5 (0.75)
LDL cholesterol Mean (SE)	118.3 (2.38)	118.9 (2.47)	117.1 (2.34)
Triglycerides Mean (SE)	202.3 (10.17)	204.2 (10.49)	213.7 (9.95)
Albumin creatinine ratio Mean (SD)	NR (NR)	NR (NR)	NR (NR)

Characteristic	Pioglitazone + Metformin (N = 201)	Pioglitazone (N = 189)	Metformin (N = 210)
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 = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
ACEIs/ARBs Sample size	n = 57 ; % = 28.4	n = 69 ; % = 36.3	n = 68 ; % = 32.5
Diuretics Sample size	n = 27 ; % = 13.4	n = 28 ; % = 14.7	n = 28 ; % = 13.4
Beta blockers Sample size	n = 19 ; % = 9.5	n = 20 ; % = 10.5	n = 18 ; % = 8.6
Calcium channel blockers Sample size	n = 17 ; % = 8.5	n = 16 ; % = 8.4	n = 22 ; % = 10.5
Statins/lipid-lowering medication used Sample size	n = 30 ; % = 14.9	n = 26 ; % = 13.7	n = 39 ; % = 18.7
Other treatment being received Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Antiplatelets Sample size	n = 33 ; % = 16.4	n = 29 ; % = 15.3	n = 34 ; % = 16.3
NSAIDs Sample size	n = 23 ; % = 11.4	n = 23 ; % = 12.1	n = 25 ; % = 12

16. Perez, 2010

Bibliographic Reference	Perez, Alfonso; Jacks, Randal; Arora, Vipin; Spanheimer, Robert; Effects of pioglitazone and metformin fixed-dose combination therapy on cardiovascular risk markers of inflammation and lipid profile compared with pioglitazone and metformin monotherapy in patients with type 2 diabetes.; Journal of clinical hypertension (Greenwich, Conn.); 2010; vol. 12 (no. 12); 973-82

16.1. Study details

Secondary publication of another included study- see primary study for details	Perez, A., Zhao, Z., Jacks, R. et al. (2009) Efficacy and safety of pioglitazone/metformin fixed-dose combination therapy compared with pioglitazone and metformin monotherapy in treating patients with T2DM. Curr Med Res Opin 25(12): 2915-23
Other publications associated with this study included in review	No additional information.

17. Pfützner, 2011

Bibliographic Reference	Pfützner, A.; Paz-Pacheco, E.; Allen, E.; Frederich, R.; Chen, R.; Initial combination therapy with saxagliptin and metformin provides sustained glycaemic control and is well tolerated for up to 76 weeks; Diabetes Obes Metab; 2011; vol. 13 (no. 6); 567-76

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	Jadzinsky, M, Pfutzner, A, Paz-Pacheco, E et al. (2009) 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 11(6): 611-22
Trial name / registration number	CV181-039. NCT00327015.
Study type	Randomised controlled trial (RCT)
Study location	Multicentre trial.
Study setting	Outpatient follow-up.
Study dates	No additional information.
Sources of funding	Funded, designed and supervised by Bristol-Myers Squibb and AstraZeneca.
Inclusion criteria	People who were treatment-naïve (people who have never received treatment for diabetes or who had received medical treatment for less than 1 month since original diagnosis and who had not received therapy for more than three consecutive days or seven non-consecutive days during the 8 weeks before screening) with type 2 diabetes; 18-77 years of age; inadequate glycaemic control (HbA1c 8.0-12.0%); BMI no more than 40kg/m2; fasting C-peptide concentration at least 1.0ng/mL.
Exclusion criteria	Symptoms of poorly controlled diabetes; history of diabetic ketoacidosis or hyperosmolar nonketotic coma; insulin therapy within 1 year of screening; cardiovascular event within the prior 6 months or NYHA stage III/IV congestive heart failure and/or known LVEF less than or equal to 40%; significant history of renal or hepatic disease or a psychiatric disorder; 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	People who completed all visits during the 24-week period or who met progressively strict glycaemic rescue criteria (FPG >240mg/dL at week 6, >220mg/dL at week 8, >200mg/dL at week 12 onwards) entered the long-term period. People who were rescued in the 24 week phase were advanced directly to the 52 week extension period and received open label pioglitazone 15mg once daily (titratable to 45mg once daily) added to their blinded study medication. No changes in metformin dose was permitted. People with HbA1c >8.0% at week 30, 37 or 50 or >7.5% at week 63 were similarly rescued with pioglitazone. People who did not have a reduction in FPG of at least 30mg/dL within 8 weeks of starting rescue therapy were discontinued from the study and referred for additional antihyperglycaemic intervention.
Intervention(s)	Saxagliptin + Metformin N=643 Two groups: Saxagliptin 10mg + metformin initially 500mg daily (n=323) and saxagliptin 5mg + metformin initially 500mg daily (n=320). Metformin was titrated to 1000mg/day at week 1, if FPG was >110mg/day and it was tolerated then it was increased in 500mg/day increments during weeks 2-5 to a maximum of 2000mg/day. Saxagliptin was taken once daily before the morning meal, metformin was taken in divided doses with the morning and evening meals. Concomitant therapy: Pioglitazone 15mg once daily (titratable to 45mg once daily) was provided as rescue therapy to anyone who required it.
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 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	7) Mixed population
Population subgroups	No additional information.
Comparator	Saxagliptin N=335 Saxagliptin 10mg daily with placebo. Saxagliptin was taken once daily before the morning meal. Concomitant therapy: Pioglitazone 15mg once daily (titratable to 45mg once daily) was provided as rescue therapy to anyone who required it. Metformin N=328 Metformin initially 500mg daily with placebo. Metformin was titrated to 1000mg/day at week 1, if FPG was >110mg/day and it was tolerated then it was increased in 500mg/day increments during weeks 2-5 to a maximum of 2000mg/day. Metformin was taken in divided doses with the morning and evening meals.

	Concomitant therapy: Pioglitazone 15mg once daily (titratable to 45mg once daily) was provided as rescue therapy to anyone who required it.
Number of participants	1306
Duration of follow-up	72 weeks.
Indirectness	No additional information.
Method of analysis	Other Full case analysis - people who received at least one dose of treatment and had at least one efficacy measurement taken before rescue medication was used. Last observation carried forward.
Additional comments	No additional information.

17.2. Study arms

17.2.1. Saxagliptin + Metformin (N = 643)

Two groups: Saxagliptin 10mg + metformin initially 500mg daily (n=323) and saxagliptin 5mg + metformin initially 500mg daily (n=320). Metformin was titrated to 1000mg/day at week 1, if FPG was >110mg/day and it was tolerated then it was increased in 500mg/day increments during weeks 2-5 to a maximum of 2000mg/day. Saxagliptin was taken once daily before the morning meal, metformin was taken in divided doses with the morning and evening meals. Concomitant therapy: Pioglitazone 15mg once daily (titratable to 45mg once daily) was provided as rescue therapy to anyone who required it.

17.2.2. Saxagliptin (N = 335)

Saxagliptin 10mg daily with placebo. Saxagliptin was taken once daily before the morning meal. Concomitant therapy: Pioglitazone 15mg once daily (titratable to 45mg once daily) was provided as rescue therapy to anyone who required it.

17.2.3. Metformin (N = 328)

Metformin initially 500mg daily with placebo. Metformin was titrated to 1000mg/day at week 1, if FPG was >110mg/day and it was tolerated then it was increased in 500mg/day increments during weeks 2-5 to a maximum of 2000mg/day. Metformin was taken in divided doses with the morning and evening meals. Concomitant therapy: Pioglitazone 15mg once daily (titratable to 45mg once daily) was provided as rescue therapy to anyone who required it.

17.3. Characteristics

17.3.1. Arm-level characteristics

Characteristic	Saxagliptin + Metformin (N = 643)	Saxagliptin (N = 335)	Metformin (N = 328)
% Male Sample size	n = 311 ; % = 48	n = 169 ; % = 50	n = 163 ; % = 50
Mean age (SD) (years) Mean (SD)	52.1 (11)	52.1 (10.2)	51.8 (10.7)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 489 ; % = 76	n = 255 ; % = 76	n = 251 ; % = 77
Asian Sample size	n = 105 ; % = 16	n = 56 ; % = 17	n = 52 ; % = 16
Black/African American Sample size	n = 14 ; % = 2	n = 6 ; % = 2	n = 4 ; % = 1
Other Sample size	n = 35 ; % = 5	n = 18 ; % = 5	n = 21 ; % = 6
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)	1.7 (3.1)	1.7 (2.8)	1.7 (3.1)
HbA1c (%) Mean (SD)	9.5 (1.2)	9.6 (1.3)	9.4 (1.3)
Blood pressure Mean (SD)	NR (NR)	NR (NR)	NR (NR)
Heart rate Mean (SD)	NR (NR)	NR (NR)	NR (NR)

Characteristic	Saxagliptin + Metformin (N = 643)	Saxagliptin (N = 335)	Metformin (N = 328)
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 Mean (SD)	NR (NR)	NR (NR)	NR (NR)
BMI (kg/m2) Mean (SD)	30.2 (4.7)	30.2 (4.9)	30.2 (4.9)
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)
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

Characteristic	Saxagliptin + Metformin (N = 643)	Saxagliptin (N = 335)	Metformin (N = 328)
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

18. Pistrosch, 2013

Bibliographic Reference	Pistrosch, F.; Köhler, C.; Schaper, F.; Landgraf, W.; Forst, T.; Hanefeld, M.; Effects of insulin glargine versus metformin on glycemic variability, microvascular and beta-cell function in early type 2 diabetes; Acta Diabetol; 2013; vol. 50 (no. 4); 587-95

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	NCT00857870.
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 Sanofi-Aventis, Germany.
Inclusion criteria	Drug naïve type 2 diabetes mellitus with <5 years after diagnosis and a HbA1c between 6.5 and 8%.
Exclusion criteria	Renal dysfunction with a calculated glomerular filtration rate below 60mL/min; acute or chronic diseases which could lead to tissue hypoxia; the use of intravascular contrast agents throughout the study; increase in serum transaminases more than 2.5 times the upper limit of normal; systemic corticosteroid treatment.
Recruitment / selection of participants	No additional information.
Intervention(s)	Metformin N=36 Metformin 1000mg twice a day.

	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, systolic blood pressure, age and presence of type 2 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	5) All treatment naïve
Population subgroups	No additional information.
Comparator	Insulin N=39 Insulin glargine at bedtime for 36 weeks. Insulin dose was titrated stepwise to a target fasting glucose of no more than 5.6 mmol/L according to a standardized titrated schedule. Concomitant therapy: No additional information.
Number of participants	75
Duration of follow-up	36 weeks.
Indirectness	No additional information.
Method of analysis	Per protocol
Additional comments	No additional information.

18.2. Study arms

18.2.1. Metformin (N = 36)

Metformin 1000mg twice a day. Concomitant therapy: No additional information.

18.2.2. Insulin (N = 39)

Insulin glargine at bedtime for 36 weeks. Insulin dose was titrated stepwise to a target fasting glucose of no more than 5.6 mmol/L according to a standardized titrated schedule. Concomitant therapy: No additional information.

18.3. Characteristics

18.3.1. Arm-level characteristics

Characteristic	Metformin (N = 36)	Insulin (N = 39)
% Male Sample size	n = 18 ; % = 50	n = 26 ; % = 66.7
Mean age (SD) (years) Mean (SD)	62.03 (9.4)	60 (9.3)
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 (1.6)	2.8 (1.4)
HbA1c (%) Mean (SD)	6.9 (0.4)	6.36 (0.4)
Blood pressure (mmHg) Mean (SD)	NA (NA)	NA (NA)
Systolic blood pressure Mean (SD)	141.5 (14.8)	141 (15.7)
Diastolic blood pressure Mean (SD)	81.2 (10.4)	85.3 (9.8)
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 = 36)	Insulin (N = 39)
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)	87.6 (17.9)	87.6 (15.1)
BMI (kg/m2) Mean (SD)	29.9 (5.3)	29.2 (4.6)
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

19. Pi-Sunyer, 2007

Bibliographic Reference	Pi-Sunyer, F. X.; Schweizer, A.; Mills, D.; Dejager, S.; Efficacy and tolerability of vildagliptin monotherapy in drug-naïve patients with type 2 diabetes; Diabetes Res Clin Pract; 2007; vol. 76 (no. 1); 132-8

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	NCT00120536, CLAF237A2384
Study type	Randomised controlled trial (RCT)
Study location	International (98 centres in US, India, and Slovakia)
Study setting	Community
Study dates	06/2005 to 07/2006
Sources of funding	Funded by Novartis Pharmaceuticals Corporation.
Inclusion criteria	• Aged 18-80 years • If female, non-fertile or of childbearing potential using medically-approved birth control method • Oral antidiabetic drug-naive (Not receiving oral antidiabetic drugs≥12 weeks prior to screening and not received oral antidiabetic drug>3 consecutive months at any time in the past) • HbA1c level 7.5-10% inclusive • BMI 22–45 kg/m2 inclusive • FPG<15 mmol/L
Exclusion criteria	• History of type 1 or secondary forms of diabetes • Acute metabolic diabetic complications • Serious cardiovascular events in previous 6 months (e.g. Myocardial infarction, unstable angina, or coronary artery bypass surgery) • Congestive heart failure, NYHA Class III or IV • Liver disease (e.g. cirrhosis or chronic active hepatitis)

	• ALT or AST >3 times the upper limit of normal (ULN) • Direct bilirubin>1.3 times the ULN • Serum creatinine levels>220mmol/L • Clinically significant abnormal thyroid stimulating hormone • Fasting triglycerides>7.9 mmol/L
Recruitment / selection of participants	Participants recruited from 98 centres in USA (88 centres), India (4 centres) and Slovakia (6 centres). Two-week screening period, and 24-week treatment period. No information about randomisation method provided. Efficacy and tolerability assessed at weeks 4, 8, 12, 16 and 24.
Intervention(s)	• Vildagliptin 50 mg once daily • Vildagliptin 50 mg twice daily • Vildagliptin 100 mg once daily Oral vildagliptin for 24 weeks.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Exclusion criteria: NYHA class 3 or 4. Trial may have included some participants who were NYHA class 2.
Strata 2: People with atherosclerotic cardiovascular diseases	People without other cardiovascular diseases Exclusion criteria: Serious cardiovascular events in previous 6 months (e.g. Myocardial infarction, unstable angina, or coronary artery bypass surgery)
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 Inclusion criteria: as no oral antidiabetic drug for at least 12-mo prior to screening and no OAD for >3 consecutive months at any time in past.
Comparator	• Placebo No details reported but double-blind trial so presumably matching placebo for 24 weeks.
Number of participants	N=354
Duration of follow-up	24 weeks
Indirectness	None
Method of analysis	Modified ITT Primary and secondary efficacy analysis conducted on all randomised participants who received at least one dose of study drug and had baseline and at least one post-baseline HbA1c assessment.

19.2. Study arms

19.2.1. Vildagliptin 100 mg once daily (N = 91)

Oral vildagliptin tablet 100 mg once daily for 24 weeks.

19.2.2. Vildagliptin 50 mg twice daily (N = 83)

Oral vildagliptin tablet 50 mg once twice daily for 24 weeks.

19.2.3. Vildagliptin 50 mg once daily (N = 88)

Oral vildagliptin tablet 50 mg once daily for 24 weeks.

19.2.4. Placebo (N = 92)

Matching placebo for 24 weeks.

19.3. Characteristics

19.3.1. Arm-level characteristics

Characteristic	Vildagliptin 100 mg once daily (N = 91)	Vildagliptin 50 mg twice daily (N = 83)	Vildagliptin 50 mg once daily (N = 88)	Placebo (N = 92)
% Male Sample size	n = 49 ; % = 53.8	n = 47 ; % = 56.6	n = 49 ; % = 55.7	n = 50 ; % = 54.3
Mean age (SD) (year) Mean (SD)	52 (11.7)	50.2 (12.7)	50.6 (10.4)	52 (12)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Asian (Indian subcontinent) Sample size	n = 15 ; % = 16.5	n = 15 ; % = 18.1	n = 14 ; % = 15.9	n = 15 ; % = 16.3
Asian (non-Indian subcontinent) Sample size	n = 1 ; % = 1.1	n = 1 ; % = 1.2	n = 3 ; % = 3.4	n = 1 ; % = 1.1
Black Sample size	n = 11 ; % = 12.1	n = 5 ; % = 6	n = 7 ; % = 8	n = 12 ; % = 13
Caucasian Sample size	n = 53 ; % = 58.2	n = 44 ; % = 53	n = 48 ; % = 54.5	n = 47 ; % = 51.1
Hispanic or Latino Sample size	n = 11 ; % = 12.1	n = 18 ; % = 21.7	n = 16 ; % = 18.2	n = 17 ; % = 18.5
Comorbidities Custom value	NR	NR	NR	NR
Presence of frailty	NR	NR	NR	NR

Characteristic	Vildagliptin 100 mg once daily (N = 91)	Vildagliptin 50 mg twice daily (N = 83)	Vildagliptin 50 mg once daily (N = 88)	Placebo (N = 92)
Custom value				
Time since type 2 diabetes diagnosis (years) Mean (SD)	2.1 (2.9)	2.4 (3.2)	1.8 (2.7)	2.5 (3.7)
HbA1c (%) Mean (SD)	8.3 (0.8)	8.4 (0.9)	8.4 (0.9)	8.5 (0.8)
Blood pressure Custom value	NR	NR	NR	NR
Heart rate Custom value	NR	NR	NR	NR
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
People with significant cognitive impairment Custom value	NR	NR	NR	NR
People with a learning disability Custom value	NR	NR	NR	NR
Weight (kg) Mean (SD)	90.8 (19.9)	89.9 (18.5)	90.5 (22.3)	93 (23.2)
BMI (kg/m2) Mean (SD)	31.9 (5)	32.3 (6)	31.9 (5.4)	32.7 (6.4)
Number of people with obesity Custom value	NR	NR	NR	NR

Characteristic	Vildagliptin 100 mg once daily (N = 91)	Vildagliptin 50 mg twice daily (N = 83)	Vildagliptin 50 mg once daily (N = 88)	Placebo (N = 92)
Cholesterol and lipid levels Custom value	NR	NR	NR	NR
Albumin creatinine ratio Custom value	NR	NR	NR	NR
eGFR (mL/min/1.73m2) Custom value	NR	NR	NR	NR
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
Other treatment being received Custom value	NR	NR	NR	NR

20. Pratley, 2014

Bibliographic Reference	Pratley, R. E.; Fleck, P.; Wilson, C.; Efficacy and safety of initial combination therapy with alogliptin plus metformin versus either as monotherapy in drug-naive patients with type 2 diabetes: A randomized, double-blind, 6-month study; Diabetes Obes Metab; 2014; vol. 16 (no. 7); 613-621

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	NCT01023581.
Study type	Randomised controlled trial (RCT)
Study location	Multisite trial (198 sites worldwide).
Study setting	Outpatient follow-up.
Study dates	No additional information.
Sources of funding	Sponsored by Takeda Development Center Americas, Inc., Deerfield, IL, USA, and Takeda Development Centre Europe Ltd., London, UK.
Inclusion criteria	Aged 18-80 years with inadequately controlled T2DM (HbA1c 7.5-10%) following diet/exercise therapy alone for at least 2 months prior to screening; had taken fewer than 7 days of any antidiabetic medication within 2 months of screening; had a body mass index of 23-45 kg/m2 (20-35 kg/m2 for Asian participants) and a minimum fasting C-peptide of 0.8ng/mL. Just prior to randomisation (week -1 of the placebo run-in/stabilisation period), additional requirements were: HbA1c 7.5-10%, inclusive (weekly repeat tests permitted up to 2 weeks); 75-125% study drug compliance during run-in/stabilisation; no use of oral or systemically injected corticosteroids or weight-loss drugs.
Exclusion criteria	Low haemoglobin; elevated blood pressure; heart failure (NYHA class III-IV); coronary angioplasty, stent placement, bypass surgery or myocardial infarction within 3 months of screening; elevated ALT or serum creatinine or low creatinine clearance.

Recruitment / selection of participants	No additional information.
Intervention(s)	Alogliptin + Metformin N=225 Two groups: Alogliptin 12.5mg twice a day and metformin 1000mg twice a day (n=114) and alogliptin 12.5mg twice a day and metformin 500mg twice a day (n=111). Concomitant therapy: Rescue medication was a sulfonylurea (specific type/dose to be chosen by the investigator), which was added to the double-blind study medication regimen, or another medication if it was contraindicated or inappropriate.
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, 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	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=225 Two groups: Metformin 1000mg twice a day (n=111) and metformin 500mg twice a day (n=114). Concomitant therapy: Rescue medication was a sulfonylurea (specific type/dose to be chosen by the investigator), which was added to the double-blind study medication regimen, or another medication if it was contraindicated or inappropriate. Alogliptin N=225 Two groups: Alogliptin 25mg once a day (n=112) and alogliptin 12.5mg twice a day (n=113). Concomitant therapy: Rescue medication was a sulfonylurea (specific type/dose to be chosen by the investigator), which was added to the double-blind study medication regimen, or another medication if it was contraindicated or inappropriate. Placebo N=109 Matching placebo. Concomitant therapy: Rescue medication was a sulfonylurea (specific type/dose to be chosen by the investigator), which was added to the double-blind study medication regimen, or another medication if it was contraindicated or inappropriate.

Number of participants	784
Duration of follow-up	26 weeks.
Indirectness	No additional information.
Method of analysis	Other Full analysis set - only people who received at least one dose of the intervention and were followed up with at least one measurement.
Additional comments	No additional information.

20.2. Study arms

20.2.1. Alogliptin + Metformin (N = 225)

Two groups: Alogliptin 12.5mg twice a day and metformin 1000mg twice a day (n=114) and alogliptin 12.5mg twice a day and metformin 500mg twice a day (n=111). Concomitant therapy: Rescue medication was a sulfonylurea (specific type/dose to be chosen by the investigator), which was added to the double-blind study medication regimen, or another medication if it was contraindicated or inappropriate.

20.2.2. Metformin (N = 225)

Two groups: Metformin 1000mg twice a day (n=111) and metformin 500mg twice a day (n=114). Concomitant therapy: Rescue medication was a sulfonylurea (specific type/dose to be chosen by the investigator), which was added to the double-blind study medication regimen, or another medication if it was contraindicated or inappropriate.

20.2.3. Alogliptin (N = 225)

Two groups: Alogliptin 25mg once a day (n=112) and alogliptin 12.5mg twice a day (n=113). Concomitant therapy: Rescue medication was a sulfonylurea (specific type/dose to be chosen by the investigator), which was added to the double-blind study medication regimen, or another medication if it was contraindicated or inappropriate.

20.2.4. Placebo (N = 109)

Matching placebo. Concomitant therapy: Rescue medication was a sulfonylurea (specific type/dose to be chosen by the investigator), which was added to the double-blind study medication regimen, or another medication if it was contraindicated or inappropriate.

20.3. Characteristics

20.3.1. Arm-level characteristics

Characteristic	Alogliptin + Metformin (N = 225)	Metformin (N = 225)	Alogliptin (N = 225)	Placebo (N = 109)
% Male Sample size	n = 110 ; % = 49	n = 98 ; % = 44	n = 111 ; % = 49	n = 55 ; % = 51
Mean age (SD) (years) Mean (SD)	54.1 (11)	53.6 (10.8)	53.2 (9.6)	53.1 (9.6)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Asian Sample size	n = 46 ; % = 20	n = 39 ; % = 17	n = 38 ; % = 17	n = 20 ; % = 18
Black or African American Sample size	n = 11 ; % = 5	n = 12 ; % = 5	n = 6 ; % = 3	n = 8 ; % = 7
White Sample size	n = 154 ; % = 68	n = 164 ; % = 73	n = 167 ; % = 74	n = 76 ; % = 70
Other Sample size	n = 14 ; % = 6	n = 10 ; % = 4	n = 14 ; % = 6	n = 5 ; % = 5
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)	4.2 (4.9)	3.6 (4.3)	3.7 (4)	4.3 (4.78)
HbA1c (%) Mean (SD)	NR (NR)	NR (NR)	NR (NR)	NR (NR)
Blood pressure (mmHg) Mean (SD)	NA (NA)	NA (NA)	NA (NA)	NA (NA)
Systolic blood pressure Mean (SD)	126.2 (12.85)	126.6 (12.08)	126.4 (12.82)	127.6 (12.7)

Characteristic	Alogliptin + Metformin (N = 225)	Metformin (N = 225)	Alogliptin (N = 225)	Placebo (N = 109)
Diastolic blood pressure Mean (SD)	77 (7.7)	75.2 (7.94)	77.6 (7.8)	79.1 (7.36)
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 Mean (SD)	NR (NR)	NR (NR)	NR (NR)	NR (NR)
BMI (kg/m2) Mean (SD)	31 (5.4)	30.4 (4.9)	30.6 (5.2)	31.2 (5.3)
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Cholesterol and lipid levels (mg/dL) Mean (SD)	NA (NA)	NA (NA)	NA (NA)	NA (NA)
Total cholesterol Mean (SD)	195.3 (45)	198.8 (42.3)	197.9 (46.5)	196.5 (39.7)
HDL cholesterol Mean (SD)	44.7 (10.4)	46.2 (11.2)	45.3 (11.5)	44.2 (9.2)

Characteristic	Alogliptin + Metformin (N = 225)	Metformin (N = 225)	Alogliptin (N = 225)	Placebo (N = 109)
LDL cholesterol Mean (SD)	112.5 (31.2)	116.9 (35.8)	112.8 (36.9)	115 (35)
Triglycerides Mean (SD)	193.9 (148)	186.1 (115.2)	207.6 (164.9)	197.8 (148.4)
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

21. Roden, 2005

Bibliographic Reference	Roden, M; Laakso, M; Johns, D; Widel, M; Urquhart, R; Richardson, C; Mariz, S; Tan, M H; Long-term effects of pioglitazone and metformin on insulin sensitivity in patients with Type 2 diabetes mellitus.; Diabetic medicine : a journal of the British Diabetic Association; 2005; vol. 22 (no. 8); 1101-6

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	Europe (study A and B) and Canada (study B only).
Study setting	Outpatient follow-up.
Study dates	No additional information.
Sources of funding	Sponsored by Eli Lilly and Company and Takeda Europe R & D.
Inclusion criteria	Male and females with type 2 diabetes; aged 35-75 years; HbA1c between 7.5-11%.
Exclusion criteria	Previous treatment with metformin, pioglitazone or other thiazolidinediones.
Recruitment / selection of participants	No additional information.
Intervention(s)	Study A intervention: Pioglitazone N=597 Pioglitazone initially 30mg once a day titrated up to a maximum of 45mg per day for 52 weeks. Concomitant therapy: No additional information.

	Study B intervention: Pioglitazone (background sulfonylurea) N=316 Pioglitazone initially 30mg once a day titrated up to a maximum of 45mg per day for 52 weeks. In addition people in this arm received a regular sulfonylurea that remained unchanged throughout the study. Concomitant therapy: No additional information.
Cointervention	For people in study A - none. For people in study B - all people received a sulfonylurea throughout 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	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	5) All treatment naïve
Population subgroups	No additional information.
Comparator	Study A comparator: Metformin N=597 Metformin initially 850mg once a day titrated up to a maximum of 2550mg per day for 52 weeks. Concomitant therapy: No additional information. Study B comparator: Metformin N=597 Metformin initially 850mg once a day titrated up to a maximum of 2550mg per day for 52 weeks. Concomitant therapy: No additional information.
Number of participants	1830
Duration of follow-up	52 weeks.
Indirectness	No additional information.
Method of analysis	Not stated/unclear
Additional comments	No additional information.

21.2. Study arms

21.2.1. Pioglitazone (N = 597)

Pioglitazone initially 30mg once a day titrated up to a maximum of 45mg per day for 52 weeks. Concomitant therapy: No additional information.

21.2.2. Metformin (N = 597)

Metformin initially 850mg once a day titrated up to a maximum of 2550mg per day for 52 weeks. Concomitant therapy: No additional information.

21.2.3. Pioglitazone (background sulfonylurea) (N = 316)

Pioglitazone initially 30mg once a day titrated up to a maximum of 45mg per day for 52 weeks. In addition people in this arm received a regular sulfonylurea that remained unchanged throughout the study. Concomitant therapy: No additional information.

21.2.4. Metformin (background sulfonylurea) (N = 320)

Metformin initially 850mg once a day titrated up to a maximum of 2550mg per day for 52 weeks. In addition people in this arm received a regular sulfonylurea that remained unchanged throughout the study. Concomitant therapy: No additional information.

21.3. Characteristics

21.3.1. Arm-level characteristics

Characteristic	Pioglitazone (N = 597)	Metformin (N = 597)	Pioglitazone (background sulfonylurea) (N = 316)	Metformin (background sulfonylurea) (N = 320)
% Male Sample size	n = NR ; % = 52.6	n = NR ; % = 57.8	n = NR ; % = 53.6	n = NR ; % = 54.7
Mean age (SD) (years) Mean (SD)	57 (9.4)	56 (9.3)	60 (8.8)	60 (8)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Pioglitazone (N = 597)	Metformin (N = 597)	Pioglitazone (background sulfonylurea) (N = 316)	Metformin (background sulfonylurea) (N = 320)
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)	3.4 (4.3)	3.1 (3.8)	7 (5.6)	7.1 (5.6)
HbA1c (%) Mean (SD)	8.7 (1)	8.7 (1)	8.8 (0.98)	8.8 (0.97)
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
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Other antidiabetic medication used Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Pioglitazone (N = 597)	Metformin (N = 597)	Pioglitazone (background sulfonylurea) (N = 316)	Metformin (background sulfonylurea) (N = 320)
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

22. Roden, 2015

Bibliographic Reference	Roden, Michael; Merker, Ludwig; Christiansen, Anita Vedel; Roux, Flavien; Salsali, Afshin; Kim, Gabriel; Stella, Peter; Woerle, Hans J; Broedl, Uli C; Safety, tolerability and effects on cardiometabolic risk factors of empagliflozin monotherapy in drug-naive patients with type 2 diabetes: a double-blind extension of a Phase III randomized controlled trial.; Cardiovascular diabetology; 2015; vol. 14; 154

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	Roden, M.; Weng, J.; Eilbracht, J.; Delafont, B.; Kim, G.; Woerle, H. J.; Broedl, U. C.; Empagliflozin monotherapy with sitagliptin as an active comparator in patients with type 2 diabetes: A randomised, double-blind, placebo-controlled, phase 3 trial; Lancet Diabetes Endocrinol; 2013; vol. 1 (no. 3); 208-219
Trial name / registration number	EMPA-REG EXTEND MONO/NCT01289990
Study type	Randomised controlled trial (RCT)
Study location	International (124 academic medical centres, hospitals, or private practices in 9 countries: Belgium, Canada, China, Germany, India, Ireland, Japan, Switzerland, and USA).
Study setting	Community
Study dates	02/2011 to 05/2013
Sources of funding	Funded by Boehringer Ingelheim and Eli Lilly & Co.
Inclusion criteria	• Aged≥18 years (≥20 years in Japan) • Diagnosis of type 2 diabetes • Drug-naive (no oral or injectable anti-diabetes therapy for ≥12 weeks prior to randomisation) • Insufficient glycaemic control on diet and exercise • HbA1c 7-10% inclusive (7-9% inclusive in Germany) • BMI≤45 kg/m2
Exclusion criteria	• Uncontrolled hyperglycaemia (glucose concentration >13.3 mmol/l following overnight fast, confirmed by second measurement)

	• Acute coronary syndrome (non-STEMI, STEMI and unstable angina pectoris), stroke or transient ischaemic attach within 3 months prior to informed consent • Indication of liver disease, either ALT, AST, or alkaline phosphatase above 3 x upper normal limit • Impaired renal function (eGFR<50 ml/min) • Bariatric surgery within the past two years or other gastrointestinal surgeries • Medical history of cancer • Contraindications to sitagliptin • Blood dyscrasias or any disorders causing haemolysis or unstable red blood cell • Treatment with any anti-diabetes drug within 12 weeks prior to randomisation • Treatment with anti-obesity drugs or any other treatment leading to unstable body weight • Current treatment with systemic steroids or change in dosage of thyroid hormones within 6 weeks prior to informed consent or any other uncontrolled endocrine disorder except T2DM • Pre-menopausal women who are nursing or pregnant or are of child-bearing potential and not practicing an acceptable method of birth control • Alcohol or drug abuse • Intake of an investigational drug in another trial within 30 days prior to intake of study medication in this trial • Any other clinical condition that would jeopardize patients safety while participating in this clinical trial
Recruitment / selection of participants	899 participants were originally recruited for 24 week RCT (NCT01177813) examining interventions. Participants in this extension trial were included if they had completed the original 24 week trial, were still eligible according to original criteria, and consented to continue for a further 52 weeks (total 76 weeks treatment). Participants remained in groups assigned in original trial, continued to receive diet and exercise counselling based on local recommendations. Participants who received rescue medication in original 24 week trial and were still on it continued on it for duration of this extension trial. Rescue medication (choice at investigator's discretion but GLP-1 RA and DPP-4 inhibitor not allowed) could be initiated in extension period if there was confirmed plasma glucose level >10 mmol/L after overnight fast or HbA1c>8%. Participants with uncontrolled hyper- or hypo-glycaemia discontinued trial. Note that original trial also included a non-randomised open-label empagliflozin 25 mg arm (n=87; data not extracted).
Intervention(s)	• Empagliflozin 25 mg once daily • Empagliflozin 10 mg once daily All participants received 3 tablets for 76 weeks: Empagliflozin 25 mg or 10 mg once daily plus matching placebo tablets for the other active arms (placebo for sitagliptin, placebo for other empagliflozin dose).
Cointervention	Placebo in triple-dummy design with matching placebo tables for other active arms.

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: Acute coronary syndrome (non-STEMI, STEMI and unstable angina pectoris), stroke or transient ischaemic attach within 3 months prior to informed consent.
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	eGFR ≥30mL/min/1.73m2 Exclusion criteria: Impaired renal function (eGFR<50 ml/min)
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Sensitivity analysis	7) Mixed population

category: Enrichment trial status	Inclusion criteria: Drug-naive (no oral or injectable anti-diabetes therapy for ≥12 weeks prior to randomisation)
Population subgroups	
Comparator	• Sitagliptin 100 mg once daily • Placebo All participants received 3 tablets for 76 weeks. For sitagliptin, sitagliptin 100 mg tablet, placebo for empagliflozin 25 mg and placebo for empagliflozin 10 mg. For placebo arm, participants received 3 placebo tablets (one for each of the 3 active arms: empagliflozin 25 mg, empagliflozin 10 mg, sitagliptin 100 mg).
Number of participants	N=899 in original 24 week trial N=615 in 52 week extension trial (completers of original trial, still meets original eligibility criteria, and consented to participate in extension period)
Duration of follow-up	76 weeks
Indirectness	None
Method of analysis	Modified ITT Full analysis set used for HbA1c, FPG, weight, and blood pressure included all randomised participants who received one or more study drug dose and had baseline HbA1c measurement in initial 24 week study. Safety analysis used all randomised participants who received one or more study drug dose.
Additional comments	

22.2. Study arms

22.2.1. Empagliflozin 25 mg once daily (N = 224)

Oral empagliflozin tablets 25 mg once daily for 24 weeks. Those consented to extension period continued for a further 52 weeks

22.2.2. Empagliflozin 10 mg once daily (N = 224)

Oral empagliflozin tablets 10 mg once daily for 24 weeks. Those consented to extension period continued for a further 52 weeks

22.2.3. Sitagliptin 100 mg once daily (N = 223)

Oral sitagliptin tablets 100 mg once daily for 24 weeks. Those consented to extension period continued for a further 52 weeks

22.2.4. Placebo (N = 228)

Matching placebo for 24 weeks. Those consented to extension period continued for a further 52 weeks

22.3. Characteristics

22.3.1. Arm-level characteristics

Characteristic	Empagliflozin 25 mg once daily (N = 224)	Empagliflozin 10 mg once daily (N = 224)	Sitagliptin 100 mg once daily (N = 223)	Placebo (N = 228)
% Male Sample size	n = 145 ; % = 64.7	n = 142 ; % = 63.4	n = 141 ; % = 63.2	n = 123 ; % = 53.9
Mean age (SD) Mean (SD)	53.8 (11.6)	56.2 (11.6)	55.1 (9.9)	54.9 (10.9)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Asian Sample size	n = 144 ; % = 64.3	n = 143 ; % = 63.8	n = 143 ; % = 64.1	n = 146 ; % = 64
Black/African-American Sample size	n = 7 ; % = 3.1	n = 3 ; % = 1.3	n = 3 ; % = 1.3	n = 6 ; % = 2.6
Other Sample size	n = 0 ; % = 0	n = 1 ; % = 0.1	n = 1 ; % = 0.4	n = 0 ; % = 0
White Sample size	n = 73 ; % = 32.6	n = 77 ; % = 34.4	n = 76 ; % = 34.1	n = 76 ; % = 33.3
Comorbidities Custom value	NR	NR	NR	NR
Presence of frailty Custom value	NR	NR	NR	NR
Time since type 2 diabetes diagnosis (years) Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Empagliflozin 25 mg once daily (N = 224)	Empagliflozin 10 mg once daily (N = 224)	Sitagliptin 100 mg once daily (N = 223)	Placebo (N = 228)
< or equal to 1 year Sample size	n = 91 ; % = 40.6	n = 87 ; % = 38.8	n = 93 ; % = 41.7	n = 72 ; % = 31.6
>1 to 5 years Sample size	n = 83 ; % = 37.1	n = 92 ; % = 41.1	n = 86 ; % = 38.6	n = 104 ; % = 45.6
>5 to 10 years Sample size	n = 37 ; % = 16.5	n = 29 ; % = 12.9	n = 32 ; % = 14.3	n = 33 ; % = 14.5
More than 10 years Sample size	n = 13 ; % = 5.8	n = 16 ; % = 7.1	n = 12 ; % = 5.4	n = 19 ; % = 8.3
HbA1c (%) Mean (SD)	7.86 (0.85)	7.87 (0.88)	7.85 (0.79)	7.91 (0.78)
Blood pressure (mmHg) Mean (SD)	NA (NA)	NA (NA)	NA (NA)	NA (NA)
Systolic blood pressure Mean (SD)	129.9 (17.5)	133 (16.6)	132.5 (15.8)	130.4 (16.3)
Diastolic blood pressure Mean (SD)	78.3 (9.4)	79.2 (9.6)	80.1 (10)	78.9 (9.6)
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
People with significant cognitive impairment Custom value	NR	NR	*empty data*	NR

Characteristic	Empagliflozin 25 mg once daily (N = 224)	Empagliflozin 10 mg once daily (N = 224)	Sitagliptin 100 mg once daily (N = 223)	Placebo (N = 228)
People with a learning disability Custom value	NR	NR	NR	NR
Weight (kg) Mean (SD)	77.8 (18)	78.4 (18.7)	79.3 (20.4)	78.2 (19.9)
BMI Nominal	28.2 (5.5)	28.3 (5.5)	28.2 (5.2)	28.7 (6.2)
Number of people with obesity Custom value	NR	NR	NR	NR
Cholesterol and lipid levels (mmol/L) Mean (SE)	NA (NA)	NA (NA)	NA (NA)	NA (NA)
Total cholesterol Mean (SE)	5 (0.08)	5 (0.08)	4.95 (0.07)	5.03 (0.08)
HDL-cholesterol Mean (SE)	1.25 (0.02)	1.24 (0.02)	1.26 (0.02)	1.26 (0.02)
LDL-cholesterol Mean (SE)	2.75 (0.07)	2.86 (0.07)	2.74 (0.05)	2.9 (0.06)
Triglycerides Mean (SE)	2.37 (0.2)	2.08 (0.12)	2.2 (0.13)	2.01 (0.09)
eGFR (mL/min/1.73m2) Mean (SD)	87.6 (18.3)	87.7 (19.2)	87.6 (17.3)	86.8 (17.9)
Other antidiabetic medication used Nominal	NR	NR	NR	NR
Blood pressure-lowering medication used Nominal	NR	NR	NR	NR

Characteristic	Empagliflozin 25 mg once daily (N = 224)	Empagliflozin 10 mg once daily (N = 224)	Sitagliptin 100 mg once daily (N = 223)	Placebo (N = 228)
Statins/lipid-lowering medication used Custom value	NR	NR	NR	NR
Other treatment being received Custom value	NR	NR	NR	NR

All data are reported for the participants in the original 24 week trial. Article reports baseline characteristics for participants who continued trial were comparable with overall 24 week trial population.

23. Rosenstock, 2009

Bibliographic Reference	Rosenstock, J.; Aguilar-Salinas, C.; Klein, E.; Nepal, S.; List, J.; Chen, R.; Effect of saxagliptin monotherapy in treatment-naïve patients with type 2 diabetes; Curr Med Res Opin; 2009; vol. 25 (no. 10); 2401-11

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	CV181-011
Study type	Randomised controlled trial (RCT)
Study location	International
Study setting	No additional information
Study dates	No additional information
Sources of funding	Funded by Bristol Myers-Squibb and AstraZeneca
Inclusion criteria	Aged 18-77 years Type 2 diabetes inadequately controlled (HbA1c >7-10%) with exercise and diet alone Treatment naïve (defined as never receiving medical treatment for diabetes, insulin or other oral antihyperglycemic medication for >6 months since diagnosis, or antihyperglycemic medication for >3 consecutive, or >7 non-consecutive days in the past 2 months Fasting C-peptide ≥1 ng/mL BMI ≤40 kg/m2

Exclusion criteria	Symptoms of poorly controlled diabetes History of diabetic ketoacidosis or hyperosmolar nonketoic coma Cardiovascular event within 6 months 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 drug or alcohol abuse within the past year Those who were immunocompromised Active liver disease or clinically significant comorbidities on screening tests of hepatic, renal, endocrine, metabolic or haematologic function
Recruitment / selection of participants	No additional information
Intervention(s)	Participants were randomised to one of three saxagliptin doses - 2.5, 5 or 10 mg per day. Participants who demonstrated a lack of adequate glucose control during the 24-week treatment period were eligible for the addition of open-label metformin as rescue therapy. The glycemic rescue criteria were fasting plasma glucose >240 mg/dL (13.3 mmol/L) at weeks 4 and 6, >220 mg/dL (12.2 mmol/L) at week 8, or >200 mg/dL (11.1 mmol/L) at weeks 12, 16, 20, and 24 *three study arms containing different doses of saxagliptin were combined for this review*
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Exclusion criteria: NYHA class III/IV or ejection fraction <40%
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	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	6) No response criteria
Population subgroups	No additional information
Comparator	Participants randomised to the placebo arm received a placebo tablet once daily. Participants who demonstrated a lack of adequate glucose control during the 24-week treatment period were eligible for the addition of open-label metformin as rescue therapy. The glycemic rescue criteria were fasting plasma glucose >240 mg/dL (13.3 mmol/L) at weeks 4 and 6, >220 mg/dL (12.2 mmol/L) at week 8, or >200 mg/dL (11.1 mmol/L) at weeks 12, 16, 20, and 24
Number of participants	403 randomised

	306 received saxagliptin, 210 completed 102 received 2.5 mg saxagliptin 106 received 5 mg saxagliptin 98 received 10 mg saxagliptin 95 received placebo, 55 completed *Study also includes a group of 66 participants who received non-randomised, open-label 10 mg saxagliptin - not included in this analysis*
Duration of follow-up	24 weeks
Indirectness	None
Method of analysis	ITT
Additional comments	No additional information

23.2. Study arms

23.2.1. Saxagliptin (N = 306)

2.5, 5 or 10 mg saxagliptin per day *three study arms combined for this review*

23.2.2. Placebo (N = 95)

Placebo once daily

23.3. Characteristics

23.3.1. Arm-level characteristics

Characteristic	Saxagliptin (N = 306)	Placebo (N = 95)
% Male Sample size	n = 157 ; % = 51	n = 47 ; % = 50
Mean age (SD) Mean (SD)	53 (*empty data*)	53.91 (11.27)
Ethnicity	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Saxagliptin (N = 306)	Placebo (N = 95)
Sample size		
White Sample size	n = 262 ; % = 86	n = 79 ; % = 83
Black/African American Sample size	n = 16 ; % = 5	n = 6 ; % = 6
Asian Sample size	n = 15 ; % = 5	n = 3 ; % = 3
Other Sample size	n = 13 ; % = 4	n = 7 ; % = 7
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosis (years) Mean (SD)	2.6 (3.3)	2.3 (2.7)
HbA1c (%) Mean (SD)	7.9 (1)	7.9 (0.9)
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	Saxagliptin (N = 306)	Placebo (N = 95)
People with a learning disability Nominal	NR	NR
Weight (kg) Mean (SD)	90.78 (18.11)	86.56 (16.9)
BMI (kg/m²) Mean (SD)	31.99 (4.68)	30.93 (4.26)
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

24. Rosenstock, 2016

Bibliographic Reference	Rosenstock, J.; Chuck, L.; Gonzalez-Ortiz, M.; Merton, K.; Craig, J.; Capuano, G.; Qiu, R.; Initial combination therapy with canagliflozin plus metformin versus each component as monotherapy for drug-naive type 2 diabetes; Diabetes Care; 2016; vol. 39 (no. 3); 353-362

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	NCT01809327.
Study type	Randomised controlled trial (RCT)
Study location	Multicentre trial (12 countries).
Study setting	Outpatient follow-up.
Study dates	16th May 2013 to 1st December 2014.
Sources of funding	Supported by Janssen Research & Development LLC. Researchers received grants from multiple pharmacological companies.
Inclusion criteria	18-75 years of age; drug naïve type 2 diabetes (not on antihyperglycaemic therapy or off for at least 12 weeks before screening) that was inadequately controlled with diet and exercise (HbA1c 7.5-12.0% at screening).
Exclusion criteria	History of type 1 diabetes; repeated fasting self-monitored blood glucose >300mg/dL; myocardial infarction, unstable angina, revascularisation procedure or cerebrovascular accident no less than 12 weeks before screening; NYHA III-IV cardiac disease; uncontrolled hypertension; eGFR <60mL/min/1.73m2 or serum creatinine more than or equal to 1.4mg/dL for men and more than or equal to 1.3mg/dL for women; were taking any antihyperglycaemic therapy within 12 weeks before screening or during the placebo run-in period.
Recruitment / selection of participants	People were discontinued from the study if they had fasting plasma glucose values meeting prespecified glycaemic withdrawal criteria (FPG >270mg/dL after day 1 through week 6; >240mg/dL after week 6 through week 12; >200mg/dL after week 12 through week 26), serum creatinine

	greater than or equal to 1.5mg/dL for men or greater than or equal to 1.4mg/dL for women or eGFR <50mL/min/1.73m2.
Intervention(s)	Canagliflozin + metformin N=474 Two groups: Canagliflozin 300mg once a day and metformin extended release initially 500mg increased up to 2000mg once a day or the maximum tolerated dose over 9 weeks (n=237) or canagliflozin 100mg once a day and metformin extended release initially 500mg increased up to 2000mg once a day or the maximum tolerated dose over 9 weeks (n=237). 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	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 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	Not stated/unclear

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	7) Mixed population
Population subgroups	No additional information.
Comparator	Canagliflozin N=475 Two groups: Canagliflozin 300mg once a day and matching placebo (n=238) or canagliflozin 100mg once a day and matching placebo (n=237). Concomitant therapy: No additional information. Metformin N=237 Metformin extended release initially 500mg increased up to 2000mg once a day or the maximum tolerated dose over 9 weeks and matching placebo. Concomitant therapy: No additional information.
Number of participants	1186
Duration of follow-up	26 weeks.
Indirectness	No additional information.
Method of analysis	Modified ITT All people who were randomised and received at least one dose of the double-blind study drug.

Additional comments	No additional information.

24.2. Study arms

24.2.1. Canagliflozin + metformin (N = 474)

Two groups: Canagliflozin 300mg once a day and metformin extended release initially 500mg increased up to 2000mg once a day or the maximum tolerated dose over 9 weeks (n=237) or canagliflozin 100mg once a day and metformin extended release initially 500mg increased up to 2000mg once a day or the maximum tolerated dose over 9 weeks (n=237). Concomitant therapy: No additional information.

24.2.2. Canagliflozin (N = 475)

Two groups: Canagliflozin 300mg once a day and matching placebo (n=238) or canagliflozin 100mg once a day and matching placebo (n=237). Concomitant therapy: No additional information.

24.2.3. Metformin (N = 237)

Metformin extended release initially 500mg increased up to 2000mg once a day or the maximum tolerated dose over 9 weeks and matching placebo. Concomitant therapy: No additional information.

24.3. Characteristics

24.3.1. Arm-level characteristics

Characteristic	Canagliflozin + metformin (N = 474)	Canagliflozin (N = 475)	Metformin (N = 237)
% Male Sample size	n = 263 ; % = 56	n = 230 ; % = 48	n = 116 ; % = 49
Mean age (SD) (years) Mean (SD)	54.8 (9.7)	54.9 (10.2)	55.2 (9.8)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 376 ; % = 79	n = 400 ; % = 84	n = 192 ; % = 81
Black/African American	n = 14 ; % = 3	n = 20 ; % = 4	n = 9 ; % = 4

Characteristic	Canagliflozin + metformin (N = 474)	Canagliflozin (N = 475)	Metformin (N = 237)
Sample size			
Asian Sample size	n = 11 ; % = 2	n = 8 ; % = 2	n = 9 ; % = 4
Other Sample size	n = 73 ; % = 15	n = 47 ; % = 10	n = 27 ; % = 11
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)	3.1 (3.6)	3.4 (4.4)	3.3 (4.5)
HbA1c (%) Mean (SD)	8.9 (1.2)	8.8 (1.2)	8.8 (1.2)
Blood pressure (mmHg) Mean (SD)	NA (NA)	NA (NA)	NA (NA)
Systolic blood pressure Mean (SD)	127.8 (11.9)	129.5 (11.6)	129.4 (12)
Diastolic blood pressure Mean (SD)	78.3 (8)	78.8 (7.8)	78.3 (7.8)
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

Characteristic	Canagliflozin + metformin (N = 474)	Canagliflozin (N = 475)	Metformin (N = 237)
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)	89.9 (19.7)	91.6 (19.3)	92.1 (20.1)
BMI (kg/m2) Mean (SD)	32.4 (6)	32.5 (5.6)	33 (6)
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Cholesterol and lipid levels (mg/dL) Mean (SD)	NA (NA)	NA (NA)	NA (NA)
HDL cholesterol Mean (SD)	44 (10.6)	43.6 (10.6)	43.7 (10.6)
LDL cholesterol Mean (SD)	118.7 (39.4)	119.3 (38.2)	115.5 (36.3)
Triglycerides Mean (SD)	172.7 (95.3)	180.2 (114)	188.6 (126.6)
Albumin creatinine ratio Mean (SD)	NR (NR)	NR (NR)	NR (NR)
eGFR (mL/min/1.73m2) (ml/min/1.73 m2) Mean (SD)	88 (19)	87.5 (18.7)	87 (19)
Other antidiabetic medication used Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Blood pressure-lowering medication used	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Canagliflozin + metformin (N = 474)	Canagliflozin (N = 475)	Metformin (N = 237)
Sample size			
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

25. Rosenstock, 2007

Bibliographic Reference	Rosenstock, J.; Kim, S. W.; Baron, M. A.; Camisasca, R. P.; Cressier, F.; Couturier, A.; Dejager, S.; Efficacy and tolerability of initial combination therapy with vildagliptin and pioglitazone compared with component monotherapy in patients with type 2 diabetes; Diabetes Obes Metab; 2007; vol. 9 (no. 2); 175-85

25.1. 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	NCT00101803
Study type	Randomised controlled trial (RCT)
Study location	International (145 sites in 8 countries: Czech Republic, India, Italy, Slovakia, South Korea, Taiwan, UK, USA)
Study setting	Community
Study dates	01/2005 to 01/2006
Sources of funding	Funded by Novartis Pharmaceuticals Corporation.
Inclusion criteria	• Aged 18-80 years • Diagnosis of type 2 diabetes mellitus • HbA1c level 7.5-11% inclusive at screening • No pharmacological treatment ≥12-mo before screening • No oral antidiabetic medication≥3 consecutive months at any time • BMI 22-45 kg/m2 inclusive • Fasting plasma glucose <15 mmol/l
Exclusion criteria	• History of type 1 or secondary forms of diabetes • Acute metabolic diabetic complications • Myocardial infarction, unstable angina or coronary artery bypass surgery within the previous 6 months • Congestive heart failure • Liver disease (e.g. cirrhosis or chronic active hepatitis)

	• Any contraindications and warnings according to the country-specific label for pioglitazone • Alanine aminotransferase or aspartate aminotransferase>2.5 times upper limit of normal (ULN) • Direct bilirubin>1.3 times the ULN • Serum creatinine levels>220mmol/l • Clinically significant abnormal TSH or fasting triglycerides>7.9 mmol/l
Recruitment / selection of participants	Participants recruited from 145 centres in 8 countries. Treatment blinding maintained using double-dummy technique. All participants given glucose monitoring devices/supplies and instructed how to use them. All lab assessments conducted by central laboratory with standardised/validated procedures.
Intervention(s)	• Vildagliptin 100 mg + Pioglitazone 30 mg once daily • Vildagliptin 50 mg + Pioglitazone 15mg once daily All drugs were oral and taken for 24 weeks. Pioglitazone doses based on recommended doses in prescribing information. Reports double dummy design but no further information reported, so assumed that participants in these arms received two active treatment pills only.
Cointervention	Placebo pills for comparator arms only (vildagliptin 100 mg once daily, pioglitazone 30 mg once daily)
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Exclusion criteria: Congestive heart failure
Strata 2: People with atherosclerotic cardiovascular diseases	People without other cardiovascular diseases Exclusion criteria: Myocardial infarction, unstable angina or coronary artery bypass surgery within the previous 6 months
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 Inclusion criteria: no pharmacological treatment for at least 12 weeks prior to screening and no OAD for more than three consecutive months at any time in the past
Population subgroups	
Comparator	• Vildagliptin 100 mg once daily • Pioglitazone 130 mg once daily Oral vildagliptin or oral pioglitazone 30 mg once daily for 24 weeks. Participants in both groups received placebo pills.
Number of participants	N=607
Duration of follow-up	24 weeks
Indirectness	None
Method of analysis	Modified ITT Primary efficacy analysis (HbA1c) and secondary efficacy analysis conducted on all randomised participants who received at least one study drug and had baseline and at least one post--baseline efficacy assessment (HbA1c).

25.2. Study arms

25.2.1. Pioglitazone 30 mg once daily (N = 161)

Oral pioglitazone 30 mg once daily for 24 weeks.

25.2.2. Pioglitazone 15 mg + Vildagliptin 50 mg once daily (N = 144)

Oral vildagliptin 50 mg + oral pioglitazone 15 mg once daily for 24 weeks.

25.2.3. Pioglitazone 30 mg + Vildagliptin 100 mg once daily (N = 148)

Oral vildagliptin 100 mg + oral pioglitazone 30 mg once daily for 24 weeks.

25.2.4. Vildagliptin 100 mg once daily (N = 154)

Oral vildagliptin 100 mg once daily for 24 weeks.

25.3. Characteristics

25.3.1. Arm-level characteristics

Characteristic	Pioglitazone 30 mg once daily (N = 161)	Pioglitazone 15 mg + Vildagliptin 50 mg once daily (N = 144)	Pioglitazone 30 mg + Vildagliptin 100 mg once daily (N = 148)	Vildagliptin 100 mg once daily (N = 154)
% Male Sample size	n = 103 ; % = 64	n = 84 ; % = 58.3	n = 86 ; % = 58.1	n = 98 ; % = 63.6
Mean age (SD) (years) Mean (SD)	52.4 (10.3)	51 (11)	51 (11.3)	51.4 (10.8)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Asian Sample size	n = 69 ; % = 42.9	n = 68 ; % = 47.2	n = 66 ; % = 44.7	n = 70 ; % = 45.5
Caucasian Sample size	n = 71 ; % = 44.1	n = 52 ; % = 36.1	n = 56 ; % = 37.8	n = 60 ; % = 39
Hispanic or Latino Sample size	n = 14 ; % = 8.7	n = 15 ; % = 10.4	n = 23 ; % = 15.5	n = 17 ; % = 11

Characteristic	Pioglitazone 30 mg once daily (N = 161)	Pioglitazone 15 mg + Vildagliptin 50 mg once daily (N = 144)	Pioglitazone 30 mg + Vildagliptin 100 mg once daily (N = 148)	Vildagliptin 100 mg once daily (N = 154)
Other Sample size	n = 7 ; % = 4.3	n = 9 ; % = 6.3	n = 3 ; % = 2	n = 7 ; % = 4.5
Comorbidities Custom value	NR	NR	NR	NR
Presence of frailty Custom value	NR	NR	NR	NR
Time since type 2 diabetes diagnosis (years) Mean (SD)	2.2 (3.3)	2 (3.2)	2 (3.1)	1.9 (3.1)
HbA1c (%) Mean (SD)	8.7 (1)	8.8 (0.9)	8.8 (1.1)	8.6 (1)
Blood pressure Custom value	NR	NR	NR	NR
Heart rate Custom value	NR	NR	NR	NR
Smoking status Custom value	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	NR	NR	NR	NR

Characteristic	Pioglitazone 30 mg once daily (N = 161)	Pioglitazone 15 mg + Vildagliptin 50 mg once daily (N = 144)	Pioglitazone 30 mg + Vildagliptin 100 mg once daily (N = 148)	Vildagliptin 100 mg once daily (N = 154)
Nominal				
Weight Nominal	NR	NR	NR	NR
BMI (kg/m2) Mean (SD)	28.9 (5.5)	29 (5.4)	29.6 (5.8)	29.4 (5.8)
Number of people with obesity Nominal	NR	NR	NR	NR
Cholesterol and lipid levels (mmol/L) Mean (SD)	NA (NA)	NA (NA)	NA (NA)	NA (NA)
Total cholesterol Mean (SD)	5.3 (0.1)	5.2 (0.1)	5.2 (0.1)	5.4 (0.1)
HDL-cholesterol Mean (SD)	1.13 (0.03)	1.1 (0.03)	1.09 (0.02)	1.09 (0.03)
LDL-cholesterol Mean (SD)	3.2 (0.1)	3.1 (0.1)	3.1 (0.1)	3.2 (0.1)
Non-HDL-cholesterol Mean (SD)	4.1 (0.1)	4.1 (0.1)	4.1 (0.1)	4.3 (0.1)
Triglycerides Mean (SD)	2.3 (0.1)	2.5 (0.2)	2.4 (0.1)	2.5 (0.1)
Albumin creatinine ratio Nominal	NR	NR	NR	NR
eGFR (mL/min/1.73m2) Nominal	NR	NR	NR	NR
Other antidiabetic medication used	NR	NR	NR	NR

Characteristic	Pioglitazone 30 mg once daily (N = 161)	Pioglitazone 15 mg + Vildagliptin 50 mg once daily (N = 144)	Pioglitazone 30 mg + Vildagliptin 100 mg once daily (N = 148)	Vildagliptin 100 mg once daily (N = 154)
Nominal				
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

26. Ross, 2015

Bibliographic Reference	Ross, S. A.; Caballero, A. E.; Del Prato, S.; Gallwitz, B.; Lewis-D'Agostino, D.; Bailes, Z.; Thiemann, S.; Patel, S.; Woerle, H. J.; von Eynatten, M.; Initial combination of linagliptin and metformin compared with linagliptin monotherapy in patients with newly diagnosed type 2 diabetes and marked hyperglycaemia: A randomized, double-blind, active-controlled, parallel group, multinational clinical trial; Diabetes Obes Metab; 2015; vol. 17 (no. 2); 136-144

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	NCT01512979.
Study location	Multicentre trial (Canada, India, Israel, Malaysia, Mexico, the Philippines, Russia, Sri Lanka, Thailand, Ukraine and the USA).
Study setting	Outpatient follow-up.
Study dates	24th January 2012 to 15th April 2013.
Sources of funding	Sponsored by Boehringer Ingelheim.
Inclusion criteria	Aged at least 18 years; newly diagnosed with type 2 diabetes (<12 months before the first visit); HbA1c 8.5-12.0%; no glucose-lowering drug in the previous 12 weeks; body mass index no more than 45kg/m2.
Exclusion criteria	Acute coronary syndrome, stroke or TIA within the previous 3 months; hepatic disease (serum level of ALT, AST and/or ALP >3 times the upper limit of normal); kidney disease (creatinine clearance of <60mL/min as calculated by the Cockcroft-Gault equation); contraindication to metformin or linagliptin; premenopausal women who were nursing, pregnant or not practicing birth control; bariatric surgery within the previous 2 years; history of cancer or pancreatitis; treatment with anti-obesity drugs or systemic steroids.

Recruitment / selection of participants	No additional information.
Intervention(s)	Linagliptin + Metformin N=159 Linagliptin 5mg once daily and metformin 1500-2000mg daily (delivered split over two daily administrations). Metformin was initiated at 1000mg daily for the first week, then increased to 1500mg for the second week, then increased to 200mg daily over weeks 3-6 if tolerated and if fasting plasma glucose was >6.1mmol/L. Concomitant therapy: People received diet and exercise counselling before the open-label placebo run in phase (for 1 week) and were reminded at each subsequent visit to follow the diet and exercise plan. Rescue medication (with any glucose-lowering therapy apart from a DPP-4 inhibitor, metformin or a GLP-1 receptor agonist) was available if FPG >15mmol/L during weeks 1-6, >13.3mmol/L during weeks 7-12, >11.1mmol/L during weeks 13-24, confirmed by at least 2 measurements on 2 different days.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear
Strata 2: People with atherosclerotic cardiovascular diseases	Mixed population
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, number of people with previous macro- or microvascular disease, number of people requiring antihypertensives and with a mild renal impairment 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	eGFR ≥30mL/min/1.73m2
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	Linagliptin N=157 Linagliptin 5mg once daily. Concomitant therapy: People received diet and exercise counselling before the open-label placebo run in phase (for 1 week) and were reminded at each subsequent visit to follow the diet and exercise plan. Rescue medication (with any glucose-lowering therapy apart from a DPP-4 inhibitor, metformin or a GLP-1 receptor agonist) was available if FPG >15mmol/L during weeks 1-6, >13.3mmol/L during weeks 7-12, >11.1mmol/L during weeks 13-24, confirmed by at least 2 measurements on 2 different days.
Number of participants	316
Duration of follow-up	24 weeks.
Indirectness	No additional information.
Method of analysis	Per protocol Per protocol completers cohort - all people who received at least 1 dose of the study drug

Additional comments	No additional information.

26.2. Study arms

26.2.1. Linagliptin + Metformin (N = 159)

Linagliptin 5mg once daily and metformin 1500-2000mg daily (delivered split over two daily administrations). Metformin was initiated at 1000mg daily for the first week, then increased to 1500mg for the second week, then increased to 200mg daily over weeks 3-6 if tolerated and if fasting plasma glucose was >6.1mmol/L. Concomitant therapy: People received diet and exercise counselling before the open-label placebo run in phase (for 1 week) and were reminded at each subsequent visit to follow the diet and exercise plan. Rescue medication (with any glucose-lowering therapy apart from a DPP-4 inhibitor, metformin or a GLP-1 receptor agonist) was available if FPG >15mmol/L during weeks 1-6, >13.3mmol/L during weeks 7-12, >11.1mmol/L during weeks 13-24, confirmed by at least 2 measurements on 2 different days.

26.2.2. Linagliptin (N = 157)

Linagliptin 5mg once daily. Concomitant therapy: People received diet and exercise counselling before the open-label placebo run in phase (for 1 week) and were reminded at each subsequent visit to follow the diet and exercise plan. Rescue medication (with any glucose-lowering therapy apart from a DPP-4 inhibitor, metformin or a GLP-1 receptor agonist) was available if FPG >15mmol/L during weeks 1-6, >13.3mmol/L during weeks 7-12, >11.1mmol/L during weeks 13-24, confirmed by at least 2 measurements on 2 different days.

26.3. Characteristics

26.3.1. Arm-level characteristics

Characteristic	Linagliptin + Metformin (N = 159)	Linagliptin (N = 157)
% Male Sample size	n = 69 ; % = 43	n = 77 ; % = 49
Mean age (SD) (years) Mean (SD)	49 (10.9)	48.6 (11.2)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 97 ; % = 61	n = 85 ; % = 54.1

Characteristic	Linagliptin + Metformin (N = 159)	Linagliptin (N = 157)
Asian Sample size	n = 57 ; % = 35.8	n = 64 ; % = 40.8
Black Sample size	n = 5 ; % = 3.1	n = 6 ; % = 3.8
Native American/Alaskan Sample size	n = 0 ; % = 0	n = 2 ; % = 1.3
Comorbidities Sample size	n = NA ; % = NA	n = NA ; % = NA
Retinopathy Sample size	n = 7 ; % = 4.4	n = 6 ; % = 3.8
Neuropathy Sample size	n = 14 ; % = 8.8	n = 13 ; % = 8.3
Nephropathy Sample size	n = 2 ; % = 1.3	n = 2 ; % = 1.3
Coronary artery disease Sample size	n = 10 ; % = 6.3	n = 13 ; % = 8.3
Peripheral artery disease Sample size	n = 7 ; % = 4.4	n = 1 ; % = 0.6
Cerebrovascular disease Sample size	n = 7 ; % = 4.4	n = 9 ; % = 5.7
Hypertension Sample size	n = 65 ; % = 40.9	n = 69 ; % = 43.9
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosis Sample size	n = NA ; % = NA	n = NA ; % = NA
<1 year Sample size	n = 159 ; % = 100	n = 155 ; % = 98.7
HbA1c (%)	9.79 (1.19)	9.88 (1.1)

Characteristic	Linagliptin + Metformin (N = 159)	Linagliptin (N = 157)
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 Sample size	n = NR ; % = NR	n = NR ; % = NR
BMI (kg/m2) Mean (SD)	29.84 (5.82)	29.63 (5.43)
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) Sample size	n = NA ; % = NA	n = NA ; % = NA
Normal (≥90 ml/min/1.73 m2) Sample size	n = 87 ; % = 54.7	n = 90 ; % = 57.3

Characteristic	Linagliptin + Metformin (N = 159)	Linagliptin (N = 157)
Mild impairment (60 to <90 ml/min/1.73 m2) Sample size	n = 69 ; % = 43.4	n = 64 ; % = 40.8
Moderate impairment (30 to <60 ml/min/1.73 m2) Sample size	n = 3 ; % = 1.9	n = 3 ; % = 1.9
Severe impairment (<30 ml/min/1.73 m2) Sample size	n = 0 ; % = 0	n = 0 ; % = 0
Other antidiabetic medication used Sample size	n = 0 ; % = 0	n = 0 ; % = 0
Blood pressure-lowering medication used Sample size	n = 65 ; % = 40.9	n = 65 ; % = 41.4
Statins/lipid-lowering medication used Sample size	n = 30 ; % = 18.9	n = 33 ; % = 21
Other treatment being received Sample size	n = NA ; % = NA	n = NA ; % = NA
Aspirin Sample size	n = 22 ; % = 13.8	n = 20 ; % = 12.7

27. Russell-Jones, 2012

Bibliographic Reference	Russell-Jones, D.; Cuddihy, R. M.; Hanefeld, M.; Kumar, A.; González, J. G.; Chan, M.; Wolka, A. M.; Boardman, M. K.; Efficacy and safety of exenatide once weekly versus metformin, pioglitazone, and sitagliptin used as monotherapy in drug-naive patients with type 2 diabetes (DURATION-4): a 26-week double-blind study; Diabetes Care; 2012; vol. 35 (no. 2); 252-8

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	NCT00676338. DURATION-4 trial.
Study type	Randomised controlled trial (RCT)
Study location	Multicentre trial (including Argentina, Belgium, Brazil, Canada, France, Germany, Hungary, India, Israel, Italy, South Korea, Mexico, Poland, Romania, the Russian Federation, Slovakia, South Africa, Spain, Taiwan, Turkey, the United Kingdom and the United States).
Study setting	Outpatient follow-up.
Study dates	November 2008 to June 2010.
Sources of funding	Funded by Amylin Pharmaceuticals and Eli Lilly. Authors received grants from various pharmaceutical companies.
Inclusion criteria	Adults with type 2 diabetes; HbA1c 7.1-11.0%; BMI 23-45 kg/m2; history of stable weight.
Exclusion criteria	Treated with any antihyperglycaemic drug for >7 days within 3 months of screening.
Recruitment / selection of participants	No additional information.
Intervention(s)	Exenatide N=248

	Exenatide 2.0mg once a week subcutaneously plus daily placebo oral tablet for 26 weeks. Additional safety data was obtained 10 weeks after this. Concomitant therapy: Standard diet and exercise counselling was provided in each treatment group.
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 category at baseline	Not stated/unclear
Sensitivity analysis category: Enrichment trial status	6) No response criteria
Population subgroups	No additional information.
Comparator	Metformin N=246 Metformin increased in weekly increments up to target doses of 2000mg/day (or up to 2500mg/day based on glycaemic control) and subcutaneous placebo once a week for 26 weeks. Additional safety data was obtained 10 weeks after this. Concomitant therapy: Standard diet and exercise counselling was provided in each treatment group. Pioglitazone N=163 Pioglitazone increased in weekly increments up to target doses of 45mg/day and subcutaneous placebo once a week for 26 weeks. Additional safety data was obtained 10 weeks after this. Concomitant therapy: Standard diet and exercise counselling was provided in each treatment group. Sitagliptin N=163 Sitagliptin 100mg/day and subcutaneous placebo once a week for 26 weeks. Additional safety data was obtained 10 weeks after this. Concomitant therapy: Standard diet and exercise counselling was provided in each treatment group.
Number of participants	820
Duration of follow-up	26 weeks.
Indirectness	No additional information.

Method of analysis	ITT
Additional comments	No additional information.

27.2. Study arms

27.2.1. Exenatide (N = 248)

Exenatide 2.0mg once a week subcutaneously plus daily placebo oral tablet for 26 weeks. Additional safety data was obtained 10 weeks after this. Concomitant therapy: Standard diet and exercise counselling was provided in each treatment group.

27.2.2. Metformin (N = 246)

Metformin increased in weekly increments up to target doses of 2000mg/day (or up to 2500mg/day based on glycaemic control) and subcutaneous placebo once a week for 26 weeks. Additional safety data was obtained 10 weeks after this. Concomitant therapy: Standard diet and exercise counselling was provided in each treatment group.

27.2.3. Pioglitazone (N = 163)

Pioglitazone increased in weekly increments up to target doses of 45mg/day and subcutaneous placebo once a week for 26 weeks. Additional safety data was obtained 10 weeks after this. Concomitant therapy: Standard diet and exercise counselling was provided in each treatment group.

27.2.4. Sitagliptin (N = 163)

Sitagliptin 100mg/day and subcutaneous placebo once a week for 26 weeks. Additional safety data was obtained 10 weeks after this. Concomitant therapy: Standard diet and exercise counselling was provided in each treatment group.

27.3. Characteristics

27.3.1. Arm-level characteristics

Characteristic	Exenatide (N = 248)	Metformin (N = 246)	Pioglitazone (N = 163)	Sitagliptin (N = 163)
% Male Sample size	n = 139 ; % = 56	n = 154 ; % = 62.6	n = 97 ; % = 59.5	n = 94 ; % = 57.7

Characteristic	Exenatide (N = 248)	Metformin (N = 246)	Pioglitazone (N = 163)	Sitagliptin (N = 163)
Mean age (SD) (years) Mean (SD)	54 (11)	54 (11)	55 (11)	52 (11)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Caucasian Sample size	n = 169 ; % = 68.1	n = 160 ; % = 65	n = 110 ; % = 67.5	n = 113 ; % = 69.3
East Asian Sample size	n = 34 ; % = 13.7	n = 31 ; % = 12.6	n = 19 ; % = 11.7	n = 18 ; % = 11
West Asian Sample size	n = 21 ; % = 8.5	n = 20 ; % = 8.1	n = 15 ; % = 9.2	n = 15 ; % = 9.2
Hispanic Sample size	n = 16 ; % = 6.5	n = 21 ; % = 8.5	n = 15 ; % = 9.2	n = 13 ; % = 8
African Sample size	n = 7 ; % = 2.8	n = 11 ; % = 4.5	n = 4 ; % = 2.5	n = 3 ; % = 1.8
Other Sample size	n = 1 ; % = 0.4	n = 3 ; % = 1.2	n = 0 ; % = 0	n = 1 ; % = 0.6
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)	2.7 (3.2)	2.6 (3.6)	2.7 (3.7)	2.7 (3.7)
HbA1c (%) Mean (SD)	8.5 (1.2)	8.6 (1.2)	8.5 (1.2)	8.5 (1.3)
Blood pressure Mean (SD)	NR (NR)	NR (NR)	NR (NR)	NR (NR)
Heart rate Mean (SD)	NR (NR)	NR (NR)	NR (NR)	NR (NR)

Characteristic	Exenatide (N = 248)	Metformin (N = 246)	Pioglitazone (N = 163)	Sitagliptin (N = 163)
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)	87.5 (18.9)	85.9 (19.6)	86.1 (17.8)	88.7 (18.7)
BMI (kg/m2) Mean (SD)	31.4 (5.3)	30.7 (5.5)	31.1 (5.3)	31.8 (5.4)
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)
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	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Exenatide (N = 248)	Metformin (N = 246)	Pioglitazone (N = 163)	Sitagliptin (N = 163)
Sample size				
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

28. Scherbaum, 2002

Bibliographic Reference	Scherbaum, W. A.; Göke, B.; Metabolic efficacy and safety of once-daily pioglitazone monotherapy in patients with type 2 diabetes: a double-blind, placebo-controlled study; Horm Metab Res; 2002; vol. 34 (no. 10); 589-95

28.1. 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	NR
Study type	Randomised controlled trial (RCT)
Study location	Germany
Study setting	Multicentre
Study dates	NR
Sources of funding	This study was supported by Takeda Pharmaceuticals, Europe
Inclusion criteria	- Female participants in the study had to be postmenopausal, surgically sterilised, or using appropriate contraceptive methods to avoid pregnancy
Exclusion criteria	-Type 1 diabetes - Secondary failure to treatment with sulphonylureas - Requirement for other antidiabetic treatment - History of ketoacidosis, malabsorption, acute or chronic pancreatitis, liver disease, significant ventricular hypertrophy, complex cardiac arrhythmias, angina pectoris, heart failure, myocardial infarction, hypertension (diastolic pressure > 100 mmHg), stroke, or hypothyroidism - History of transient ischaemic attack or stroke

	- significant anaemia of any aetiology - clinically relevant haematological or malignant disease in the last 10 years - HIV infection - alcohol or drug abuse - participation in a clinical trial in the 3 months prior to study
Recruitment / selection of participants	Following enrolment in the study, patients were required to discontinue their previous oral antidiabetic therapy and to enter a 10-week placebo washout period. During this time, patients underwent a complete medical history and physical examination, including vital signs, laboratory tests, and an electrocardiogram to determine eligibility for the double-blind phase of the study. At the end of the washout period, HbA1C had to remain between 7.5% and 12 %, and FBG had to be between 140 mg/dl and 250 mg/ dl.
Intervention(s)	Eligible patients were randomised to one of three treatment regimens for 26 weeks: pioglitazone 15 mg once-daily + dietary controls, pioglitazone 30 mg once-daily + diet
Cointervention	Patients were required to follow a disease- and bodyweight-oriented diet throughout the study period. They were taught the nutritional recommendations of the Diabetes and Nutrition Study Group (DNSG) of the European Association for the Study of Diabetes (EASD). The recommended diet included a protein intake of 10% – 20% of total daily calories. The carbohydrate : fat ratio was individualised, based on patients' eating habits as well as on glucose and lipid goals. For patients with normal lipid profiles, 30 % of the total daily caloric consumption was to be derived from fat, with an equal distribution among saturated, polyunsaturated, and monounsaturated fats. These recommendations were made prior to the start of the study. Diet was monitored at each visit to the clinic, and dietary advice was continuously available on request. However, compliance to diet was not monitored (such as in a diary). Also, bodyweight was recorded at the clinic at each visit, as well as each week by the patient at home.
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 Myocardial infarction and stroke excluded, others not stated
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	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	2) Excluding non-responders (but not exclusively including only responders) HbA1C had to remain between 7.5% and 12%, and FBG had to be between 140 mg/dl and 250 mg/ dl.
Population subgroups	
Comparator	diet + matching placebo (identical in colour, shape, taste, size, and odour to active treatment).
Number of participants	252
Duration of follow-up	26 weeks
Indirectness	Direct

Method of analysis	Per protocol ITT

28.2. Study arms

28.2.1. Placebo + diet (N = 84)

28.2.2. Placebo 15mg / day + diet (N = 89)

28.2.3. Placebo 30mg / day + diet (N = 78)

28.3. Characteristics

28.3.1. Arm-level characteristics

Characteristic	Placebo + diet (N = 84)	Placebo 15mg / day + diet (N = 89)	Placebo 30mg / day + diet (N = 78)
Male (n (%)) Sample size	n = 47 ; % = 55.9	n = 56 ; % = 62.9	n = 32 ; % = 41
Aged >= 65 years Sample size	n = 27 ; % = 32.1	n = 24 ; % = 26.9	n = 26 ; % = 33.3
Diabetes duration (yrs) Nominal	5.6	5.4	4.6

29. Scherbaum, 2008

Bibliographic Reference	Scherbaum, W. A.; Schweizer, A.; Mari, A.; Nilsson, P. M.; Lalanne, G.; Jauffret, S.; Foley, J.; Efficacy and tolerability of vildagliptin in drug-naive patients with type 2 diabetes and mild hyperglycaemia; Diabetes Obes Metab; 2008; vol. 10 (no. 8); 675-682

29.1. Study details

Secondary publication of another included study- see primary study for details	Yes, see: • Mari, A., Scherbaum, W. A., Nilsson, P. M., Lalanne, G., Schweizer, A., Dunning, B. E., ... & Foley, J. E. (2008). Characterization of the influence of vildagliptin on model-assessed β-cell function in patients with type 2 diabetes and mild hyperglycaemia. *The Journal of Clinical Endocrinology & Metabolism*, *93*(1), 103-109.
Other publications associated with this study included in review	Original article reported in: • Mari, A., Scherbaum, W. A., Nilsson, P. M., Lalanne, G., Schweizer, A., Dunning, B. E., ... & Foley, J. E. (2008). Characterization of the influence of vildagliptin on model-assessed β-cell function in patients with type 2 diabetes and mild hyperglycaemia. The Journal of Clinical Endocrinology & Metabolism, 93(1), 103-109.
Trial name / registration number	NCT00101712
Study type	Randomised controlled trial (RCT)
Study location	International (69 sites in 6 countries: in Finland (3 sites), France (4 sites), Germany (42 sites), Romania (5 sites), Spain (7 sites), Sweden (8 sites))
Study setting	Community
Study dates	10/2004 to 05/2006
Sources of funding	Funded by Novartis Pharmaceuticals Corporation.
Inclusion criteria	• Male or female (non-fertile or of childbearing potential using medically approved birth control method) • Aged≥18 years • Diagnosis of type 2 diabetes mellitus for at least 8 weeks previously • HbA1c level 6.2-7.5% inclusive at screening (upper limit of 7% in Finland and Spain) • BMI 22-45 kg/m2 inclusive

	• Drug-naive (no oral antidiabetic drug [OAD] for at least 12 weeks prior to screening and no OAD for more than 3 consecutive months at any time in past)
Exclusion criteria	• History of type 1 or secondary forms of diabetes • Acute metabolic diabetic complications within the past 6 months or evidence of significant diabetic complications • History of significant cardiac arrhythmia, congestive heart failure, or New York Heart Association Class III or IV • Liver diseases (e.g. cirrhosis or chronic active hepatitis) • Significant laboratory abnormalities
Recruitment / selection of participants	Participants recruited from 69 sites in 6 countries. Assessment at screening visit (week 2) for eligibility and randomisation at visit 2 to arms. All participants received individualized lifestyle counselling (weight management, diet, exercise) at each visit. Assessments at weeks 4, 12, 16, 24, 32, 40 and 52, followed by 4 week treatment-free period and final assessment at week 56. All lab assessments conducted by same laboratory according to standardised/validated procedures.
Intervention(s)	• Vildagliptin 50 mg once daily Oral vildagliptin 50 mg once daily for 52 weeks.
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Exclusion criteria: congestive heart failure, NYHA class 3 and 4
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 Exclusion criteria: History of 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 Inclusion criteria: no oral anti-diabetic drug (OAD) for at least 12 weeks prior to screening and no OAD for more than three consecutive months at any time in the past
Population subgroups	Results also reported for these subgroups: • Obesity • Non-obesity
Comparator	• Placebo Oral matching placebo for 52 weeks.
Number of participants	N=306
Duration of follow-up	52 weeks + 4 week washout period
Method of analysis	ACA Not reported but appears to be available case analysis (different number of participants for each reported outcome)

29.2. Study arms

29.2.1. Vildagliptin 50 mg once daily (N = 156)

Oral vildagliptin 50 mg once daily for 52 weeks.

29.2.2. Placebo (N = 150)

Matching placebo for 52 weeks.

29.3. Characteristics

29.3.1. Arm-level characteristics

Characteristic	Vildagliptin 50 mg once daily (N = 156)	Placebo (N = 150)
HbA1c (%) Significant difference between groups, p=0.0403 Mean (SD)	6.7 (0.4)	6.8 (0.4)

See Mari 2008 for baseline characteristics

30. Schernthaner, 2004

Bibliographic Reference	Schernthaner, G.; Matthews, D. R.; Charbonnel, B.; Hanefeld, M.; Brunetti, P.; Efficacy and safety of pioglitazone versus metformin in patients with type 2 diabetes mellitus: a double-blind, randomized trial; J Clin Endocrinol Metab; 2004; vol. 89 (no. 12); 6068-76

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	QUARTET study.
Study type	Randomised controlled trial (RCT)
Study location	Multicentre trial (12 European countries).
Study setting	Outpatient follow-up.
Study dates	No additional information.
Sources of funding	No additional information.
Inclusion criteria	People with HbA1c between 7.5% and 11% with stable or worsening glycaemic control for at least 3 months.
Exclusion criteria	Prior use of glucose-lowering pharmacotherapy and specific contraindications to either drug (corticosteroids and beta blockers were permitted if commenced at least 4 weeks before screening, antihypertensives [except thiazides] were allowed dependent on clinical need, lipid lowering agents were allowed).
Recruitment / selection of participants	No additional information.
Intervention(s)	Pioglitazone N=597

	Initially 30mg pioglitazone, increased to up to 45mg of pioglitazone once a day with metformin placebo three times a day for a 12 week forced titration period followed by a 40 week maintenance period. 52 weeks in total. Concomitant therapy: Dietary advice was given at baseline and if body weight increased by more than 5% at any stage of HbA1c increased to greater than 9% after complete dose titrated, people were given additional intensive dietary counselling.
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	5) All treatment naïve
Population subgroups	No additional information.
Comparator	Metformin N=597 Initially 850mg metformin once a day, increased up to a maximum of 850mg three times a day with pioglitazone placebo once a day for a 12 week forced titration period followed by a 40 week maintenance period. 52 weeks in total. Concomitant therapy: Dietary advice was given at baseline and if body weight increased by more than 5% at any stage of HbA1c increased to greater than 9% after complete dose titrated, people were given additional intensive dietary counselling.
Number of participants	1194
Duration of follow-up	12 months.
Indirectness	No additional information.
Method of analysis	ITT
Additional comments	No additional information.

30.2. Study arms

30.2.1. Pioglitazone (N = 597)

Initially 30mg pioglitazone, increased to up to 45mg of pioglitazone once a day with metformin placebo three times a day for a 12 week forced titration period followed by a 40 week maintenance period. 52 weeks in total. Concomitant therapy: Dietary advice was given at baseline and if body weight increased by more than 5% at any stage of HbA1c increased to greater than 9% after complete dose titrated, people were given additional intensive dietary counselling.

30.2.2. Metformin (N = 597)

Initially 850mg metformin once a day, increased up to a maximum of 850mg three times a day with pioglitazone placebo once a day for a 12 week forced titration period followed by a 40 week maintenance period. 52 weeks in total. Concomitant therapy: Dietary advice was given at baseline and if body weight increased by more than 5% at any stage of HbA1c increased to greater than 9% after complete dose titrated, people were given additional intensive dietary counselling.

30.3. Characteristics

30.3.1. Arm-level characteristics

Characteristic	Pioglitazone (N = 597)	Metformin (N = 597)
% Male Sample size	n = 314 ; % = 53	n = 345 ; % = 58
Mean age (SD) (years) Mean (SD)	57 (9.4)	56 (9.3)
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)	3.4 (4.3)	3.1 (3.8)
HbA1c (%) Mean (SD)	8.7 (1)	8.7 (1)
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

Characteristic	Pioglitazone (N = 597)	Metformin (N = 597)
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)	88.2 (15.5)	89.7 (16.6)
BMI (kg/m2) Mean (SD)	31.2 (4.9)	31.4 (5.2)
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

31. Schwartz, 2006

Bibliographic Reference	Schwartz, Sherwyn; Fonseca, Vivian; Berner, Bret; Cramer, Marilou; Chiang, Yu-Kun; Lewin, Andrew; Efficacy, tolerability, and safety of a novel once-daily extended-release metformin in patients with type 2 diabetes.; Diabetes care; 2006; vol. 29 (no. 4); 759-64

31.1. Study details

Trial name / registration number	NR
Study type	Randomised controlled trial (RCT)
Study location	USA
Study setting	85 centres
Study dates	August 2001 - October 2003
Sources of funding	Financial support for this study was provided by Depomed
Inclusion criteria	- 18-79 years of age - Type 2 diabetes - Patients were either drug naive (with newly diagnosed diabetes or treated with diet and exercise only) or had received prior drug therapy (monotherapy with oral hypoglycaemic agents other than metformin up to the maximum dose allowed, metformin monotherapy up to 2,000 mg/day, or metformin up to 1,500 mg/day with sulfonylurea up to one-half the maximum allowed dose) - HbA1c levels 7-12% (drug-naive patients) or 6.5 - 10% (prior drug therapy patients) - FPG levels 120-400mg/dl (drug-naive patients) or 120-250 mg/dl (prior drug therapy patients), C-peptide levels >1.0 ng/ml, BMI 22-50kg/m2 - Negative pregnancy test for female patients
Exclusion criteria	-receiving insulin, systemic corticosteroids, nicotinic acid, or isoniazid -History of had a history of background retinopathy, symptomatic autonomic neuropathy, or unstable angina - Chronic gastroparesis or chronic severe gastrointestinal symptoms, a history of gastric or duodenal ulcers, abdominal surgery within 1 year, or active gastrointestinal disease within 2 years - Any uncontrolled or untreated cardiovascular, hepatic, pulmonary, renal, or neurological system conditions

Recruitment / selection of participants	The trial enrolled male and female outpatients, 18–79 years of age, with type 2 diabetes. Patients were either drug naïve (with newly diagnosed diabetes or treated with diet and exercise only) or had received prior drug therapy (monotherapy with oral hypoglycaemic agents other than metformin up to the maximum dose allowed, metformin monotherapy up to 2,000 mg/day, or metformin up to 1,500 mg/day with sulfonylurea up to one-half the maximum allowed dose). Patients underwent a full physical examination. After a 6-week washout of current antihyperglycemic agents (for prior drug therapy patients), all patients began metformin dosing at 1,000 mg q.d., which was titrated to their assigned dose over 2–3 weeks and continued at that dose for a total treatment duration of 24 weeks. All study drugs and placebos were taken after a meal. Patients were evaluated every 1–2 weeks during the screening and washout periods, weekly for the first 4 weeks of treatment and then every 4 weeks until the end of study.
Intervention(s)	
Cointervention	appropriate placebo tablets to maintain the study blind
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear
Strata 2: People with atherosclerotic cardiovascular diseases	Mixed population Angina only mentioned
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
Number of participants	750
Duration of follow-up	24 weeks
Indirectness	direct
Method of analysis	Per protocol ITT

31.2. Study arms

31.2.1. ER metformin 1,500mg /day (N = 178)

Extended-release metformin (Glumetza; Depomed, Menlo Park, CA),

31.2.2. ER metformin 1,500mg (AM/PM) (N = 182)

500 mg in the morning and 1,000 mg in the evening

31.2.3. ER metformin 2,000 mg / day (N = 172)

31.2.4. 1,500 mg immediate-release metformin (N = 174)

(Glucophage; Bristol-Myers Squibb, Princeton, NJ) (500 mg in the morning and 1,000 mg in the evening),

31.3. Characteristics

31.3.1. Arm-level characteristics

Characteristic	ER metformin 1,500mg /day (N = 178)	ER metformin 1,500mg (AM/PM) (N = 182)	ER metformin 2,000 mg / day (N = 172)	1,500 mg immediate-release metformin (N = 174)
Age (yrs) Mean (SD)	54 (11.4)	54 (11.8)	55 (11.7)	54 (12.5)
≥65 Sample size	n = 138 ; % = 77.5	n = 142 ; % = 78	n = 129 ; % = 75	n = 135 ; % = 77.6
>= 65 Sample size	n = 40 ; % = 22.5	n = 40 ; % = 22	n = 43 ; % = 25	n = 39 ; % = 22.4
Male Sample size	n = 83 ; % = 46.6	n = 111 ; % = 61	n = 91 ; % = 52.9	n = 95 ; % = 54.6
Female Sample size	n = 95 ; % = 53.4	n = 71 ; % = 39	n = 81 ; % = 47.1	n = 79 ; % = 45.4
Caucasian Sample size	n = 107 ; % = 60.1	n = 116 ; % = 63.7	n = 107 ; % = 62.2	n = 111 ; % = 63.8
Black Sample size	n = 30 ; % = 16.9	n = 18 ; % = 9.9	n = 23 ; % = 13.4	n = 22 ; % = 12.6
Asian Sample size	n = 5 ; % = 2.8	n = 5 ; % = 2.7	n = 3 ; % = 1.7	n = 3 ; % = 1.7
Hispanic Sample size	n = 32 ; % = 18	n = 38 ; % = 20.9	n = 36 ; % = 20.9	n = 37 ; % = 21.3
Native American Sample size	n = 1 ; % = 0.6	n = 3 ; % = 1.6	n = 1 ; % = 0.6	n = 0 ; % = 0
Other Sample size	n = 3 ; % = 1.7	n = 2 ; % = 1.1	n = 2 ; % = 1.2	n = 1 ; % = 0.6
≤30 less than 30	n = 60 ; % = 33.9	n = 67 ; % = 37	n = 53 ; % = 30.8	n = 58 ; % = 33.3

Characteristic	ER metformin 1,500mg /day (N = 178)	ER metformin 1,500mg (AM/PM) (N = 182)	ER metformin 2,000 mg / day (N = 172)	1,500 mg immediate-release metformin (N = 174)
Sample size				
≤30 greater than or equal too eppi error Sample size	n = 117 ; % = 66.1	n = 114 ; % = 63	n = 119 ; % = 69.2	n = 116 ; % = 66.7
Duration of diabetes Mean (SD)	3.9 (4.5)	4.5 (4.9)	3.9 (4.3)	4.4 (5.4)
Drug naive Sample size	n = 81 ; % = 45.5	n = 86 ; % = 47.3	n = 84 ; % = 48.8	n = 87 ; % = 50
Metformin only Sample size	n = 43 ; % = 24.2	n = 44 ; % = 24.2	n = 45 ; % = 26.2	n = 43 ; % = 24.7
Sulfonylurea only Sample size	n = 29 ; % = 16.3	n = 30 ; % = 16.5	n = 22 ; % = 12.8	n = 30 ; % = 17.2
Metformin and sulfonylurea Sample size	n = 20 ; % = 11.2	n = 12 ; % = 6.6	n = 17 ; % = 9.9	n = 10 ; % = 5.7

32. Schweizer, 2007

Bibliographic Reference	Schweizer, A.; Couturier, A.; Foley, J. E.; Dejager, S.; Comparison between vildagliptin and metformin to sustain reductions in HbA1c over 1 year in drug-naive patients with Type 2 diabetes; Diabet Med; 2007; vol. 24 (no. 9); 955-61

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	NCT00099866.
Study type	Randomised controlled trial (RCT)
Study location	Multicentre trial (10 countries in the Americas and Europe).
Study setting	Outpatient follow-up.
Study dates	No additional information.
Sources of funding	Funded by Novartis Pharmaceuticals Corporation.
Inclusion criteria	People with type 2 diabetes mellitus who had an HbA1c of 7.5-11.0% while receiving no drug treatment; people who had previously taken no oral glucose lowering agents for more than three consecutive months at any time (considered drug naïve); male and female patients (non-fertile or of childbearing potential and using a medically approved birth control method); aged 18-78 years; fasting plasma glucose <15mmol/L.
Exclusion criteria	History of type 1 diabetes or secondary forms of diabetes; acute metabolic diabetic complications within the past 6 months; congestive heart failure requiring pharmacological treatment, myocardial infarction, unstable angina or coronary artery bypass surgery within the previous 6 months; liver disease such as cirrhosis or chronic active hepatitis; renal disease or renal dysfunction suggested by elevated serum creatinine levels; ALT or AST greater than three times the upper limit of normal; direct bilirubin greater than 1.3 times the upper limit of normal; clinically significant abnormal TSH or fasting triglycerides >7.9 mmol/L.

Recruitment / selection of participants	During the study, people were discontinued due to 'unsatisfactory therapeutic effect' if FPG >15mmol/L (or 13.3 mmol/L in Argentina) confirmed by a repeated measurement in the absence of intercurrent illness, or if they had symptoms of worsening hyperglycaemia in the absence of intercurrent illness or other incidental circumstances potentially causing deterioration of glucose control. People could also be withdrawn as a result of unsatisfactory therapeutic effect on the investigator's judgement alone.
Intervention(s)	Vildagliptin N=526 Vildagliptin 100mg daily (given as equally divided doses). 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	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, systolic blood pressure, 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	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=254 Metformin titrated to 2000mg daily (given as divided doses). Concomitant therapy: No additional information.
Number of participants	780
Duration of follow-up	52 weeks.
Indirectness	No additional information.
Method of analysis	ACA Other People who received at least one dose of the medication and had at least one post-baseline safety assessment
Additional comments	No additional information.

32.2. Study arms

32.2.1. Vildagliptin (N = 526)

Vildagliptin 100mg daily (given as equally divided doses). Concomitant therapy: No additional information.

32.2.2. Metformin (N = 254)

Metformin titrated to 2000mg daily (given as divided doses). Concomitant therapy: No additional information.

32.3. Characteristics

32.3.1. Arm-level characteristics

Characteristic	Vildagliptin (N = 526)	Metformin (N = 254)
% Male Sample size	n = 278 ; % = 52.9	n = 146 ; % = 57.5
Mean age (SD) (years) Mean (SD)	52.8 (11.7)	53.6 (10.2)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Caucasian Sample size	n = 357 ; % = 67.9	n = 177 ; % = 69.7
Hispanic or Latino Sample size	n = 104 ; % = 19.8	n = 55 ; % = 21.7
Black Sample size	n = 42 ; % = 8	n = 13 ; % = 5.1
All Other Sample size	n = 23 ; % = 4.3	n = 9 ; % = 3.5
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) IQR	3.54	3.28
Time since type 2 diabetes diagnosis (years) Median (IQR)	1.05 (NA to NA)	1.03 (NA to NA)

Characteristic	Vildagliptin (N = 526)	Metformin (N = 254)
HbA1c (%) Mean (SD)	8.7 (1.1)	8.7 (1.1)
Blood pressure (mmHg) Mean (SD)	NA (NA)	NA (NA)
Systolic blood pressure Mean (SD)	133 (14)	133 (16)
Diastolic blood pressure Mean (SD)	82 (8)	82 (9)
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)	32.4 (5.7)	32.5 (5.7)
Number of people with obesity Sample size	n = NA ; % = NA	n = NA ; % = NA
Cholesterol and lipid levels Mean (SD)	NA (NA)	NA (NA)

Characteristic	Vildagliptin (N = 526)	Metformin (N = 254)
Total cholesterol Mean (SD)	5.3 (1.1)	5.2 (1.1)
HDL cholesterol Mean (SD)	1.2 (0.2)	1.2 (0.3)
LDL cholesterol Mean (SD)	3.1 (0.9)	3.1 (0.9)
Triglycerides Mean (SD)	2.4 (1.8)	2.4 (1.6)
Albumin creatinine ratio Mean (SD)	NR (NR)	NR (NR)
eGFR (mL/min/1.73m2) Mean (SD)	NR (NR)	NR (NR)
Other antidiabetic medication used Mean (SD)	NR (NR)	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

33. Schweizer, 2009

Bibliographic Reference	Schweizer, A.; Dejager, S.; Bosi, E.; Comparison of vildagliptin and metformin monotherapy in elderly patients with type 2 diabetes: a 24-week, double-blind, randomized trial; Diabetes Obes Metab; 2009; vol. 11 (no. 8); 804-12

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	NCT00246619.
Study type	Randomised controlled trial (RCT)
Study location	Multicentre trial.
Study setting	Outpatient follow-up.
Study dates	14th September 2006 to 29th May 2008.
Sources of funding	Funded by Novartis Pharmaceutical Corporation.
Inclusion criteria	People with type 2 diabetes aged at least 65 years; HbA1c 7-9% at screening; people who were drug naïve (had taken no oral glucose-lowering agents for at least 12 weeks prior to screening and no oral glucose-lowering agents for more than three consecutive months at any time in the past); FPG <15mmol/L; BMI 22-40kg/m2.
Exclusion criteria	History of type 1 or secondary forms of diabetes; acute metabolic diabetic complications within the past 6 months; congestive heart failure requiring pharmacological treatment or myocardial infarction, unstable angina or stroke or coronary artery bypass surgery within the past 6 months; liver disease such as cirrhosis or chronic active hepatitis; renal disease or renal dysfunction suggested by elevated serum creatinine levels.
Recruitment / selection of participants	No additional information.

Intervention(s)	Vildagliptin N=169 Vildagliptin 100mg daily (as a once-daily dose) for 24 weeks of active treatment. 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	Mixed population 33% of people had previous cardiac disorders
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Mixed population Some with mild renal insufficiency defined by the study (60%)
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	People at higher risk of developing cardiovascular disease Based on age, BMI, previous cardiac disease/CKD, dyslipidaemia (in 40%) 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	6) No response criteria
Population subgroups	No additional information.
Comparator	Metformin N=166 Metformin starting at 500mg/day titrated up, with weekly increases of 500mg to a maximum of 1500mg daily (as divided doses, 1000mg in the morning, 500mg in the evening) for 24 weeks of active treatment. Concomitant therapy: No additional information.
Number of participants	335
Duration of follow-up	24 weeks.
Indirectness	Outcome indirectness - the study reports acute coronary syndrome. This was included as a non-fatal myocardial infarction, but downgraded for indirectness.
Method of analysis	Other People who received at least one dose of the medication and had at least one post-baseline assessment
Additional comments	No additional information.

33.2. Study arms

33.2.1. Vildagliptin (N = 169)

Vildagliptin 100mg daily (as a once-daily dose) for 24 weeks of active treatment. Concomitant therapy: No additional information.

33.2.2. Metformin (N = 166)

Metformin starting at 500mg/day titrated up, with weekly increases of 500mg to a maximum of 1500mg daily (as divided doses, 1000mg in the morning, 500mg in the

evening) for 24 weeks of active treatment. Concomitant therapy: No additional information.

33.3. Characteristics

33.3.1. Arm-level characteristics

Characteristic	Vildagliptin (N = 169)	Metformin (N = 166)
% Male Sample size	n = 75 ; % = 44.4	n = 88 ; % = 53
Mean age (SD) (years) Mean (SD)	71.6 (5.2)	70.2 (5.1)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Caucasian Sample size	n = 123 ; % = 72.8	n = 117 ; % = 70.5
Asian Sample size	n = 32 ; % = 18.9	n = 36 ; % = 21.7
Hispanics Sample size	n = 13 ; % = 7.7	n = 10 ; % = 6
All others Sample size	n = 1 ; % = 0.6	n = 3 ; % = 1.8
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)	2.9 (4.2)	3 (4.7)
HbA1c (%) Mean (SD)	7.8 (0.6)	7.7 (0.6)
Blood pressure	NR (NR)	NR (NR)

Characteristic	Vildagliptin (N = 169)	Metformin (N = 166)
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 ; % = 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)	29.8 (4.4)	29.4 (4.6)
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) Sample size	n = NA ; % = NA	n = NA ; % = NA
>80 mL/min/1.73m2 Sample size	n = 65 ; % = 38.5	n = 72 ; % = 43.4
50-80 mL/min/1.73m2 Sample size	n = 102 ; % = 60.4	n = 90 ; % = 54.2

Characteristic	Vildagliptin (N = 169)	Metformin (N = 166)
30-49 mL/min/1.73m2 Sample size	n = 2 ; % = 1.2	n = 4 ; % = 2.4
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

34. Seino, 2018

Bibliographic Reference	Seino, Y.; Terauchi, Y.; Osonoi, T.; Yabe, D.; Abe, N.; Nishida, T.; Zacho, J.; Kaneko, S.; Safety and efficacy of semaglutide once weekly vs sitagliptin once daily, both as monotherapy in Japanese people with type 2 diabetes; Diabetes Obes Metab; 2018; vol. 20 (no. 2); 378-388

34.1. 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	NCT002254291
Study type	Randomised controlled trial (RCT)
Study location	Japan
Study setting	NR
Study dates	NR
Sources of funding	Novo Nordisk
Inclusion criteria	1. Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial 2. Male or female, age ≥20 years at the time of signing informed consent 3. HbA1c 6.5–9.5% (48–80 mmol/mol) (both inclusive) for subjects treated with oral antidiabetic drug (OAD) monotherapy and 7.0–10.5% (53–91 mmol/mol) (both inclusive) for subjects treated with diet and exercise at screening 4. Japanese subjects with type 2 diabetes mellitus (diagnosed clinically) and on:

	a) stable OAD monotherapy* in addition to diet and exercise therapy for at least 30 days prior to screening OR b) stable diet and exercise therapy for at least 30 days prior to screening *Stable OAD monotherapy was defined as receiving half-maximum or below dose according to Japanese labelling for 30 days prior to screening. For metformin only, the maximum dose of 750 mg/day was allowed except for METGLUCO®. For METGLUCO®, the allowable half-maximum dose of 1125 mg/day was applied.
Exclusion criteria	1. Known or suspected hypersensitivity to trial product(s) or related products 2. Previous participation in this trial. Participation is defined as informed consent 3. Female who is pregnant, breast-feeding or intends to become pregnant or is of child-bearing potential and not using an adequate contraceptive method (e.g. abstinence [not having sex], diaphragm, condom [by the partner], intrauterine device, sponge, spermicide or oral contraceptives) throughout the trial including the 5-week follow-up period 4. Receipt of any investigational medicinal product within 90 days before screening 5. Treatment with glucose-lowering agent(s) other than stated in the inclusion criteria within 60 days before Visit 1 (week −2) and treatment with once-weekly glucagon-like peptide-1 (GLP-1) receptor agonists within 90 days before Visit 1 (week −2). An exception is short-term treatment (≤7 days in total) with insulin in connection with inter-current illness 6. Any disorder which, in the opinion of the investigator, might jeopardise subject’s safety or compliance with the protocol 7. History of chronic or idiopathic acute pancreatitis 8. Screening calcitonin value ≥50 ng/L 9. Personal or family history of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia syndrome type 2 (MEN2) 10. Impaired renal function defined as estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m2 per Modification of Diet in Renal Disease (MDRD) formula (4 variable version) 11. Acute coronary or cerebrovascular event within 90 days before randomisation (Visit 2 [week 0]) 12. Heart failure, New York Heart Association (NYHA) class IV

	13. Known proliferative retinopathy or maculopathy requiring acute treatment according to the opinion of the investigator 14. Diagnosis of malignant neoplasm in the previous 5 years (except basal cell skin cancer or squamous cell skin cancer) 15. Mental inability, unwillingness or language barrier precluding adequate understanding of or compliance with trial procedures
Recruitment / selection of participants	NR
Intervention(s)	S.C. Semaglutide 0.5 mg (n=103) Participants received 0.5 mg S.C. semaglutide once weekly for 30 weeks. Participants followed a fixed dose-escalation regimen of semaglutide 0.5 mg (maintenance dose reached after 4 weeks of 0.25 mg semaglutide once weekly) S.C. Semaglutide 1.0 mg (n=102) Participants received 1.0 mg S.C. semaglutide once weekly for 30 weeks. Participants followed a fixed dose-escalation regimen of semaglutide 1.0 mg (maintenance dose reached after 4 weeks of 0.25 mg semaglutide once weekly, followed by 4 weeks of 0.5mg semaglutide)
Cointervention	None
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	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	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	NR
Comparator	Sitaglitpin 100mg (n=103) Participants received 100mg once daily for 30 weeks
Number of participants	308
Duration of follow-up	35 weeks
Indirectness	NA
Method of analysis	ACA
Additional comments	All data analysed using all case analyses

34.2. Study arms

34.2.1. Semaglutide 0.5 mg (N = 103)

Participants received 0.5mg S.C. semaglutide once weekly for 30 weeks

34.2.2. Semaglutide 1.0 mg (N = 102)

Participants received 1.0mg S.C. semaglutide once weekly for 30 weeks

34.2.3. Sitagliptin (N = 103)

Participants received once daily 100mg sitagliptin for 30 weeks

34.3. Characteristics

34.3.1. Arm-level characteristics

Characteristic	Semaglutide 0.5 mg (N = 103)	Semaglutide 1.0 mg (N = 102)	Sitagliptin (N = 103)
% Male Sample size	n = 79 ; % = 76.7	n = 75 ; % = 73.5	n = 81 ; % = 78.6
Mean age (SD) Mean (SD)	58.8 (10.4)	58.1 (11.6)	57.9 (10.1)
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)) Mean (SD)	8 (5.2)	7.8 (6.9)	8.1 (6.7)
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	Semaglutide 0.5 mg (N = 103)	Semaglutide 1.0 mg (N = 102)	Sitagliptin (N = 103)
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
People with significant congitive 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 treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR

35. Shihara, 2011

Bibliographic Reference	Shihara, Nobuyuki; Kitaoka, Masafumi; Inagaki, Nobuya; Kadowaki, Takashi; Koumoto, Seisuke; Satoh, Jo; Terauchi, Yasuo; Nunoi, Kiyohide; Yamada, Yuichiro; Sakamaki, Hiroyuki; Seino, Yutaka; Randomized controlled trial of single-agent glimepiride and pioglitazone in Japanese patients with type 2 diabetes: A comparative study.; Journal of diabetes investigation; 2011; vol. 2 (no. 5); 391-8

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	University Hospital Medical Information Network: UMIN000004582
Study type	Randomised controlled trial (RCT)
Study location	Japan
Study setting	No additional information
Study dates	August 2007 - February 2010
Sources of funding	Funded by Sanofi Aventis
Inclusion criteria	Outpatients of either sex with type 2 diabetes mellitus Aged 30–75 years Committed to a stable dietary and exercise regimen for >1 month before randomization HbA1c 6.9-10.4% 1 month before and at randomization, with a difference <1% between measurements
Exclusion criteria	Type 1 diabetes mellitus Use of insulin or any oral hypoglycaemic agent (including an alpha-glucosidase inhibitor) in the month before randomization

	Heart failure or history of heart failure Any serious intercurrent complication involving the heart, kidney, liver, pancreas or other organs, or hematological condition
Recruitment / selection of participants	No additional information
Intervention(s)	Participants allocated to the intervention initially received 0.5 mg glimepiride if their HbA1c was 6.9-7.4%, or 1.0 mg per day if their HbA1c was 7.4-10.4%. The dose could be increased to a maximum of 6 mg/day in order to achieve morning fasting blood glucose of<120 mg/dL. The dosage could be decreased according to the supervising physician's judgment if morning fasting blood glucose was <80 mg/dL. Drug doses were titrated according to morning fasting blood glucose measured at scheduled clinic visits.
Cointervention	
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	8) Not reported
Population subgroups	No additional information
Comparator	Participants allocated to the comparator initially received 15 mg pioglitazone per day, which could be increased to a maximum of 45 and 30 mg/day in men and women, respectively, in order to achieve morning blood glucose of <120 mg/dL. The dosage could be decreased according to the supervising physician's judgment if morning fasting blood glucose was <80 mg/dL. Drug doses were titrated according to morning fasting blood glucose measured at scheduled clinic visits.
Number of participants	191 randomised 95 received glimepiride, 86 completed 96 received pioglitazone, 91 completed
Duration of follow-up	6 months
Indirectness	None
Method of analysis	ITT
Additional comments	None

35.2. Study arms

35.2.1. Glimepiride (N = 95)

Initially 0.5 (HbA1c 6.9-7.4%) or 1.0 mg (7.4-10.4%) per day up to a maximum of 6 mg per day

35.2.2. Pioglitazone (N = 96)

Initially 15 mg per day, up to a maximum of 45 (men) and 30 mg (women) per day

35.3. Characteristics

35.3.1. Arm-level characteristics

Characteristic	Glimepiride (N = 95)	Pioglitazone (N = 96)
% Male Sample size	n = 62 ; % = 65	n = 65 ; % = 68
Mean age (SD) (years) Mean (SD)	57.7 (10.4)	56.8 (10.3)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosis (years) Data for 41 and 52 participants Mean (SD)	6 (8.2)	4.1 (4.3)
HbA1c (%) Data for 95 and 95 participants Mean (SD)	7.8 (0.9)	7.8 (0.9)
Blood pressure Nominal	NR	NR
Heart rate Nominal	NR	NR
Smoking status Nominal	NR	NR
Alcohol consumption	NR	NR

Characteristic	Glimepiride (N = 95)	Pioglitazone (N = 96)
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 (kg) Data for 93 and 92 participants Mean (SD)	65.6 (12.5)	65.5 (14.6)
BMI (kg/m²) Data for 93 and 92 participants Mean (SD)	24.6 (3.8)	24.5 (4.3)
Number of people with obesity Nominal	NR	NR
Cholesterol and lipid levels Mean (SD)	NA (NA)	NA (NA)
TC Mean (SD)	207.5 (39.1)	205.5 (38.2)
LDL Mean (SD)	126.5 (36.5)	123.2 (32.6)
HDL Mean (SD)	59.3 (23)	52.8 (13.7)
TG Mean (SD)	129.8 (68.4)	164 (112.4)
Albumin creatinine ratio Nominal	NR	NR
eGFR (mL/min/1.73m2) Nominal	NR	NR

Characteristic	Glimepiride (N = 95)	Pioglitazone (N = 96)
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

36. Sorli, 2017

Bibliographic Reference	Sorli, C.; Harashima, S. I.; Tsoukas, G. M.; Unger, J.; Karsbol, J. D.; Hansen, T.; Bain, S. C.; Efficacy and safety of once-weekly semaglutide monotherapy versus placebo in patients with type 2 diabetes (SUSTAIN 1): a double-blind, randomised, placebo-controlled, parallel-group, multinational, multicentre phase 3a trial; Lancet Diabetes Endocrinol; 2017; vol. 5 (no. 4); 251-260

36.1. 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	SUSTAIN 1/NCT02054897
Study type	Randomised controlled trial (RCT)
Study location	International (72 sites in Canada, Italy, Japan, Mexico, Russia, South Africa, UK and USA)
Study setting	Community
Study dates	02/2014 to 08/2014
Sources of funding	Funded directly by Novo Nordisk A/S, Denmark.
Inclusion criteria	• Aged ≥18 years (≥20 years for Japan) • Diagnosis of type 2 diabetes • Management with diet and exercise only ≥30 days before screening when enrolled • HbA1c level 7·0-10·0% inclusive.
Exclusion criteria	• Female that is pregnant, breastfeeding, or intends to get pregnant, or is of child-bearing potential and not using adequate contraception as required by local practice, both during trial and 5-week FU period • Use of glucose-lowering drugs ≤90 days before screening (except for ≤7 days treatment with insulin) • History of chronic or idiopathic acute pancreatitis

	• Personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2 • Impaired renal function (eGFR <30 mL/min per 1·73 m²) • Screening calcitonin values of at least 50 ng/L (pg/mL) • Heart failure (New York Heart Association class IV) • Any acute coronary or cerebrovascular events in the 90 days before randomisation
Recruitment / selection of participants	Participants recruited from 33 sites across 6 countries with some recruited using advertisements at some sites. Random assignment 2:2:1:1 to semaglutide 1mg, semaglutide 0.5 mg, placebo for semaglutide 1mg, or placebo for semaglutide 0.5 mg, using automated voice/web recognition system with no human involvement.
Intervention(s)	• Semaglutide 1.0 mg once weekly • Semaglutide 0.5 mg once weekly Subcutaneous injection of semaglutide in prefilled 1.5 mL PDS290 pen-injector. Participants administered own injections and encourage to administer them on same day each week in same body area (thigh, abdomen or upper arm). Time of day and proximity of meal times not specified. Participants in semaglutide 0.5 mg group reached maintenance dose after 4 weeks of 0.25 mg once weekly. Participants in semaglutide 1.0 mg group, maintenance dose reached after 4 weeks of 0.25 mg, followed by 4 weeks of 0.5 mg. Participants with unacceptable hyperglycaemia (assessed by FPG) could be offered rescue medication at discretion of investigator (ADA and EASD guidelines), either metformin as first choice or other antidiabetic drugs (except GLP-1RA and DPP-4 inhibitors) as add-ons to study treatment.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Exclusion criteria: heart failure (NYHA class IV). Trial may therefore include participants with NYHA class II and III.
Strata 2: People with atherosclerotic cardiovascular diseases	Not stated/unclear Exclusion criteria: Any acute coronary or cerebrovascular events in the 90 days before randomisation. Treial may therefore include participants with other CV 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	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 Inclusion criteria: Management with diet and exercise only ≥30 days before screening when enrolled
Population subgroups	
Comparator	• Placebo to semaglutide 1.0 mg once weekly • Placebo to semaglutide 0.5 mg once weekly Volume-matched placebo injection provided in prefilled 1.5 mL PDS290 pen-injector identical in appearance, taste and smell to those used for semaglutide arms. See intervention details for dose-matching escalation. Participants with unacceptable hyperglycaemia could be offered rescue medication at discretion of investigator (ADA and EASD guidelines), either metformin as first choice or other antidiabetic drugs (except GLP-1RA and DPP-4 inhibitors) as add-ons to study treatment.
Number of participants	N=388
Duration of follow-up	30 weeks
Method of analysis	Modified ITT

	Efficacy and safety analysis with all randomised participants who took at least one dose of study drug or placebo. Efficacy analysis used data before initiation of any rescue medication or before premature treatment discontinuation. Safety analysis used data before premature treatment discontinuation with window of 42 days to identify treatment-emergent AEs. Sensitivity analysis used all data regardless of whether data obtained while participants discontinued treatment or whether participant given rescue medication.

36.2. Study arms

36.2.1. Semaglutide 1 mg once weekly (N = 130)

Subcutaneous injection of semaglutide 1 mg once weekly for 30 weeks.

36.2.2. Semaglutide 0.5 mg once weekly (N = 129)

Subcutaneous injection of semaglutide 0.5 mg once weekly for 30 weeks.

36.2.3. Placebo once weekly (N = 129)

Subcutaneous volume-matched placebo injection (1 mg or 0.5 mg) once weekly for 30 weeks.

36.3. Characteristics

36.3.1. Arm-level characteristics

Characteristic	Semaglutide 1 mg once weekly (N = 130)	Semaglutide 0.5 mg once weekly (N = 129)	Placebo once weekly (N = 129)
% Male Sample size	n = 80 ; % = 62	n = 60 ; % = 47	n = 70 ; % = 54
Mean age (SD) (years) Mean (SD)	52.7 (11.9)	54.6 (11.1)	53.9 (11)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Asian Sample size	n = 25 ; % = 19	n = 26 ; % = 20	n = 32 ; % = 25
Black/African American	n = 11 ; % = 8	n = 11 ; % = 9	n = 9 ; % = 7

Characteristic	Semaglutide 1 mg once weekly (N = 130)	Semaglutide 0.5 mg once weekly (N = 129)	Placebo once weekly (N = 129)
Sample size			
Hispanic or Latino Sample size	n = 45 ; % = 35	n = 34 ; % = 27	n = 36 ; % = 28
Not hispanic or latino Sample size	n = 85 ; % = 65	n = 94 ; % = 73	n = 93 ; % = 72
White Sample size	n = 88 ; % = 68	n = 83 ; % = 65	n = 78 ; % = 60
Time since type 2 diabetes diagnosis (years) Mean (SD)	3.62 (4.88)	4.81 (6.1)	4.06 (5.48)
HbA1c (%) Mean (SD)	8.12 (0.81)	8.09 (0.89)	7.95 (0.85)
Weight (kg) Mean (SD)	96.87 (25.59)	89.81 (22.96)	89.05 (22.16)
BMI (kg/m2) Mean (SD)	33.92 (8.43)	32.46 (7.62)	32.4 (6.86)
eGFR (mL/min/1.73m2) Mean (SD)	100.9 (27.74)	95.91 (26.23)	100.2 (24.97)

37. Stenlöf, 2013

Bibliographic Reference	Stenlöf, K.; Cefalu, W. T.; Kim, K. A.; Alba, M.; Usiskin, K.; Tong, C.; Canovatchel, W.; Meininger, G.; Efficacy and safety of canagliflozin monotherapy in subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise; Diabetes Obes Metab; 2013; vol. 15 (no. 4); 372-82

37.1. 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	NCT01081834
Study type	Randomised controlled trial (RCT)
Study location	17 countries including: US Sweden South Korea
Study setting	Hospital
Study dates	03/2010 to 03/2012
Sources of funding	Janssen Global Services, LLC. Canagliflozin is being developed by Janssen Research & Development, LLC, in collaboration with Mitsubishi Tanabe Pharma Corporation.
Inclusion criteria	• Men and women 18–80 years of age with T2DM who met one of the two following criteria: (i) not on an antihyperglycaemic agent at screening with HbA1c ≥7.0 and ≤10.0% or (ii) on

	antihyperglycaemic agent monotherapy [except peroxisome proliferator-activated receptor-γ (PPARγ) agonist] or metformin plus sulfonylurea combination therapy (at ≤50% of maximally or near-maximally effective doses) with HbA1c ≥6.5 and ≤9.5% at screening and HbA1c ≥7.0 and ≤10.0% and fasting plasma glucose <15.0 mmol/l at week −2.
Exclusion criteria	• Subjects were excluded if they had repeated Fasting Plasma Glucose measurements >15.0 mmol/l during the pre-treatment phase (or >19.4 mmol/l for the high glycaemic sub study) • A history of type 1 diabetes, hereditary glucose-galactose malabsorption, primary renal glucosuria or cardiovascular (CV) disease (including myocardial infarction, unstable angina, revascularisation procedure or cerebrovascular accident) • Treatment with a PPARγ agonist, insulin, another SGLT2 inhibitor or any other antihyperglycaemic agents except as specified in the inclusion criteria within 12 weeks before screening • Estimated glomerular filtration rate (eGFR) <50 ml/min/1.73 m2 at screening.
Recruitment / selection of participants	Men and women aged 18 - 80 years were recruited from 17 countries. The study included both subjects with inadequate control on diet and exercise and subjects on anantihyperglycaemic agent , who underwent a washout of the agent. Subjects not on an antihyperglycaemic directly entered a 2-week, single-blind, placebo run-in period (week −2 to day 1), while subjects on an antihyperglycaemic underwent an 8-week, antihyperglycaemic washout/diet and exercise period followed by the placebo run-in period.
Intervention(s)	Canagliflozin 300 mg daily, taken orally Canagliflozin 100 mg daily, taken orally During the double-blind treatment period, glycaemic rescue therapy with metformin was initiated if Fasting Plasma Glucose >15.0 mmol/l after day 1 to week 6, >13.3 mmol/l after week 6 to week 12 and >11.1 mmol/l after week 12 to week 26.
Cointervention	None.
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	Mixed population
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	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 daily, taken orally During the double-blind treatment period, glycaemic rescue therapy with metformin was initiated if FPG >15.0 mmol/l after day 1 to week 6, >13.3

	mmol/l after week 6 to week 12 and >11.1 mmol/l after week 12 to week 26.
Number of participants	N=584
Duration of follow-up	26-week treatment period, no follow-up reported.
Indirectness	The study reports that 17 countries were included in this study, but the countries are not listed. The White, Black and Asian populations included in the study may provide some generalisability to a UK population but this could be limited due to the settings and countries.
Method of analysis	Modified ITT

37.2. Study arms

37.2.1. Placebo once daily (N = 192)

37.2.2. Canagliflozin 100 mg (N = 195)

37.2.3. Canagliflozin 300 mg (N = 197)

37.3. Characteristics

37.3.1. Arm-level characteristics

Characteristic	Placebo once daily (N = 192)	Canagliflozin 100 mg (N = 195)	Canagliflozin 300 mg (N = 197)
% Male No of events	n = 88 ; % = 45.8	n = 81 ; % = 41.5	n = 89 ; % = 45.2
Mean age (SD) Mean (SD)	55.7 (10.9)	55.1 (10.8)	55.3 (10.2)
White No of events	n = 20 ; % = 10.4	n = 26 ; % = 13.3	n = 17 ; % = 8.6
Black or African American No of events	n = 9 ; % = 4.7	n = 18 ; % = 9.2	n = 14 ; % = 7.1

Characteristic	Placebo once daily (N = 192)	Canagliflozin 100 mg (N = 195)	Canagliflozin 300 mg (N = 197)
Asian No of events	n = 29 ; % = 15.1	n = 27 ; % = 13.8	n = 29 ; % = 14.7
Other No of events	n = 20 ; % = 10.4	n = 26 ; % = 13.3	n = 17 ; % = 8.6
Comorbidities Nominal	NR	NR	NR
Presence of frailty Nominal	NR	NR	NR
Time since type 2 diabetes diagnosis Mean (SD)	4.2 (4.1)	4.5 (4.4)	4.3 (4.7)
Smoking status Nominal	NR	NR	NR
Alcohol consumption Nominal	NR	NR	NR
Number of people with obesity Nominal	NR	NR	NR
Albumin creatinine ratio Nominal	NR	NR	NR
Other antidiabetic medication used No of events	n = 92 ; % = 47.9	n = 94 ; % = 48.2	n = 95 ; % = 48.2
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

38. Suzuki, 2017

Bibliographic Reference	Suzuki, Shuichi; Oura, Tomonori; Takeuchi, Masakazu; Boye, Kristina S; Evaluation of the impact of once weekly dulaglutide on patient-reported outcomes in Japanese patients with type 2 diabetes: comparisons with liraglutide, insulin glargine, and placebo in two randomized studies.; Health and quality of life outcomes; 2017; vol. 15 (no. 1); 123

38.1. Study details

Secondary publication of another included study- see primary study for details	26 week efficacy results, including placebo: • Miyagawa, J., Odawara, M., Takamura, T., Iwamoto, N., Takita, Y., & Imaoka, T. (2015). Once-weekly glucagon-like peptide-1 receptor agonist dulaglutide is non-inferior to once-daily liraglutide and superior to placebo in Japanese patients with type 2 diabetes: a 26-week randomized phase III study. *Diabetes, Obesity and Metabolism*, *17*(10), 974-983.
Other publications associated with this study included in review	52 week efficacy results: • Odawara, M., Miyagawa, J., Iwamoto, N., Takita, Y., Imaoka, T., & Takamura, T. (2016). Once-weekly glucagon-like peptide-1 receptor agonist dulaglutide significantly decreases glycated haemoglobin compared with once-daily liraglutide in J apanese patients with type 2 diabetes: 52 weeks of treatment in a randomized phase III study. *Diabetes, Obesity and Metabolism*, *18*(3), 249-257.
Trial name / registration number	Secondary article reporting on NCT01558271 and NCT01584232
Study type	Randomised controlled trial (RCT)
Study location	Japan (33 sites in 14 cities)
Study setting	Community
Study dates	04/2012 to 10/2013
Sources of funding	Eli Lilly Japan K.K., Kobe, Japan.
Inclusion criteria	• Diagnosis of type 2 diabetes before screening • Management with diet and exercise only or treatment with oral antidiabetic monotherapy (except for thiazolidinedione) and willing to discontinue medication with 8 week washout period before randomisation • HbA1c level 7.0-10.0% inclusive at screening and randomisation for those on diet and exercise only; or HbA1c level 6.5-9.0% inclusive at screening and HbA1c level 7.0-10.0% inclusive at randomisation for those on oral antidiabetic monotherapy

	• BMI ≥18.5 to ≥35.0 kg/m2
Exclusion criteria	• Diagnosis of type 1 diabetes. • Previous treatment with any other GLP-1 analogue. • Receiving more than half of maximum dose of sulfonylureas at screening • Currently taking insulin or thiazolidinediones (TZD), or previous insulin or TZD treatment ≤3 months screening. • Obvious clinical signs or symptoms of pancreatitis, history of chronic pancreatitis, or acute pancreatitis at screening, as determined by investigator • Serum amylase concentration ≥3 times upper limit of reference range and/or a serum lipase concentration ≥2 times upper limit of reference range, as determined by central laboratory at screening • History (personal or family) of medullary C-cell hyperplasia, focal hyperplasia, or medullary thyroid carcinoma
Recruitment / selection of participants	Participants recruited from 33 sites in Japan. Initial 2 week screening period, then 2 week lead-in period for treatment-naive participants and 8 week wash out period for participants on monotherapy. Eligible participants randomized to treatment in 4:2:1 ratio (dulaglutide; liraglutide; placebo) using computer-generated random sequence with interactive voice response system and stratified by pre-study oral antidiabetic medication status (yes/no), BMI group (<25; ≥25 kg/m2), and HbA1c (≤8.5; >8.5%). Participants and investigators masked to assignment to dulaglutide and placebo treatment but not masked to assignment to liraglutide treatment. At end of 26 weeks, participants in placebo group switched to dulaglutide 0.75 once weekly for remaining 26 weeks. Participants not tolerating study drugs discontinued them but remained in study to collect safety data.
Intervention(s)	• Dulaglutide 0.75 mg once weekly Subcutaneous injection of dulaglutide 0.75 mg once weekly for 52 weeks, provided in non-identifiable solution in prefilled syringe and initiated at full dose.
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	Not stated/unclear

diabetes mellitus and chronic kidney 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 6: Albuminuria category at baseline	Not stated/unclear
Sensitivity analysis category: Enrichment trial status	5) All treatment naïve Participants were treatment-naive (diabetes managed with diet and exercise only) or if on oral antidiabetic monotherapy had 8-week washout period
Comparator	• Liraglutide 0.9 mg once weekly • Placebo Open label subcutaneous liraglutide uptitrated from 0.3 mg/day during week 1 to 0.6 mg/day during week 2 and 0.9 mg/day at start of week 3 for remaining 49 weeks. Participants in placebo arm received placebo for 26 weeks then were switched over to dulaglutide 0.75 mg once weekly for remaining 26 weeks.
Number of participants	N=492
Duration of follow-up	26 weeks
Indirectness	All participants are Japanese so unlikely to be representative of UK population. Participants who were already on oral antidiabetic medication had 8-week washout period before randomisation.
Method of analysis	Modified ITT mITT analysis for efficacy analysis - all randomised participants who took at least one dose of study drug.

	Other Safety analysis conducted on as-treated population according to actual treatments received.

38.2. Study arms

38.2.1. Dulaglutide 0.75 mg once weekly (N = 281)

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

38.2.2. Liraglutide 0.9 mg once daily (N = 141)

Subcutaneous injection of liraglutide 0.9 mg once daily for 52 weeks.

38.2.3. Placebo once weekly for 26 weeks then dulalgutide 0.75 mg once weekly for 26 weeks N=79 (N = 79)

Placebo injection once weekly using non-identifiable prefilled syringe (same as used for dulaglutide) for 26 weeks, then switched to dulaglutide 0.75 mg once weekly for 26 weeks.

39. Tan, 2005

Bibliographic Reference	Tan, M. H.; Baksi, A.; Krahulec, B.; Kubalski, P.; Stankiewicz, A.; Urquhart, R.; Edwards, G.; Johns, D.; Comparison of pioglitazone and gliclazide in sustaining glycemic control over 2 years in patients with type 2 diabetes; Diabetes Care; 2005; vol. 28 (no. 3); 544-50

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	Links to Charbonnel 2005 - different population numbers but states in the paper that the continuous outcomes were reported here previously.
Trial name / registration number	GLAL study.
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 Takeda Europe Research and Development Centre.
Inclusion criteria	People with type 2 diabetes inadequate controlled (HbA1c 7.5-11.0%) with diet alone; male and females aged 35-75 years; no prior use of any oral antidiabetic medication.
Exclusion criteria	No additional information.
Recruitment / selection of participants	No additional information.
Intervention(s)	Gliclazide N=297 Gliclazide starting at 80mg daily for 4 weeks, increased to 160mg daily for 4 weeks, increased to 240mg daily for 4 weeks then 320mg daily for 4 weeks. This was then continued for up to 2 years.
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	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	No additional information.
Comparator	Pioglitazone N=270 Pioglitazone starting at 15mg daily for 4 weeks, increased to 30mg daily for 4 weeks, increased to 45mg daily for 8 weeks. This was then continued for up to 2 years.
Number of participants	567
Duration of follow-up	24 months, but reporting follow up for an additional 12 months, so will count as 12 months in the results spreadsheet.
Indirectness	No additional information.
Method of analysis	Not stated/unclear Appears to be completers only.
Additional comments	No additional information.

39.2. Study arms

39.2.1. Gliclazide (N = 297)

Gliclazide starting at 80mg daily for 4 weeks, increased to 160mg daily for 4 weeks, increased to 240mg daily for 4 weeks then 320mg daily for 4 weeks. This was then continued for up to 2 years. Concomitant therapy: No additional information.

39.2.2. Pioglitazone (N = 270)

Pioglitazone starting at 15mg daily for 4 weeks, increased to 30mg daily for 4 weeks, increased to 45mg daily for 8 weeks. This was then continued for up to 2 years. Concomitant therapy: No additional information.

39.3. Characteristics

39.3.1. Arm-level characteristics

Characteristic	Gliclazide (N = 297)	Pioglitazone (N = 270)
% Male Sample size	n = 182 ; % = 61.3	n = 171 ; % = 63.3

Characteristic	Gliclazide (N = 297)	Pioglitazone (N = 270)
Mean age (SD) (years) Mean (SD)	56 (9.9)	57 (9.8)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 275 ; % = 92.6	n = 253 ; % = 93.7
Others Sample size	n = 22 ; % = 7.4	n = 17 ; % = 6.3
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)	2.9 (3.8)	2.7 (3.5)
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

Characteristic	Gliclazide (N = 297)	Pioglitazone (N = 270)
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

40. Tao, 2018

Bibliographic Reference	Tao, T.; Wu, P.; Wang, Y.; Liu, W.; Comparison of glycemic control and beta-cell function in new onset T2DM patients with PCOS of metformin and saxagliptin monotherapy or combination treatment; BMC Endocrine Disorders; 2018; vol. 18 (no. 1); 14

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	ChiCTR-IPR-17011120.
Study type	Randomised controlled trial (RCT)
Study location	China.
Study setting	Outpatient follow-up.
Study dates	No additional information.
Sources of funding	Supported by the National Natural Science Foundation of China (grant number 81200628), the Chinese Medical Association Clinical Research and Special Funds - Squibb Endocrinology Diabetes Research projects [2012]; the Natural Science Foundation of Shanghai, China [grant number 12ZR1417800]l and the Shanghai Science and Technology Development Fund [grant number 08411953000].
Inclusion criteria	Newly diagnosed people with type 2 diabetes mellitus and polycystic ovarian syndrome.
Exclusion criteria	People with coronary atherosclerotic heart disease; abnormal liver and renal function; diabetic ketoacidosis; chronic inflammatory disease; severe gastrointestinal disease.
Recruitment / selection of participants	People were recruited from the Outpatient Department of Endocrinology and Metabolism at Shanghai Renji Hospital.
Intervention(s)	Saxagliptin + Metformin N=25

	Saxagliptin 5mg/day and metformin 2000mg/day for 24 weeks at a fixed dose. Concomitant therapy: All people were given a control diet for 2 weeks before the program. All people were given advice on diet and exercise and were asked to follow a behaviour modification program.
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 Based on 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 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	Saxagliptin N=25 Saxagliptin 5mg/day for 24 weeks at a fixed dose. Concomitant therapy: All people were given a control diet for 2 weeks before the program. All people were given advice on diet and exercise and were asked to follow a behaviour modification program. Metformin N=25 Metformin 2000mg/day for 24 weeks at a fixed dose. Concomitant therapy: All people were given a control diet for 2 weeks before the program. All people were given advice on diet and exercise and were asked to follow a behaviour modification program.
Number of participants	75
Duration of follow-up	24 weeks.
Indirectness	Population indirectness - People with polycystic ovary syndrome and type 2 diabetes.
Method of analysis	Per protocol
Additional comments	No additional information.

40.2. Study arms

40.2.1. Saxagliptin + Metformin (N = 25)

Saxagliptin 5mg/day and metformin 2000mg/day for 24 weeks at a fixed dose. Concomitant therapy: All people were given a control diet for 2 weeks before the program. All people were given advice on diet and exercise and were asked to follow a behaviour modification program.

40.2.2. Saxagliptin (N = 25)

Saxagliptin 5mg/day for 24 weeks at a fixed dose. Concomitant therapy: All people were given a control diet for 2 weeks before the program. All people were given advice on diet and exercise and were asked to follow a behaviour modification program.

40.2.3. Metformin (N = 25)

Metformin 2000mg/day for 24 weeks at a fixed dose. Concomitant therapy: All people were given a control diet for 2 weeks before the program. All people were given advice on diet and exercise and were asked to follow a behaviour modification program.

40.3. Characteristics

40.3.1. Arm-level characteristics

Characteristic	Saxagliptin + Metformin (N = 25)	Saxagliptin (N = 25)	Metformin (N = 25)
% Male Sample size	n = 0 ; % = 0	n = 0 ; % = 0	n = 0 ; % = 0
Mean age (SD) (years) Mean (SD)	29 (5)	30 (5)	28 (3)
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

Characteristic	Saxagliptin + Metformin (N = 25)	Saxagliptin (N = 25)	Metformin (N = 25)
Time since type 2 diabetes diagnosis Mean (SD)	NR (NR)	NR (NR)	NR (NR)
HbA1c (%) Mean (SD)	7.4 (0.3)	7.4 (0.3)	7.3 (0.2)
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 (95% CI)	69.3 (64.6 to 74.1)	70.4 (63.7 to 77.1)	67.9 (63.6 to 72.2)
BMI (kg/m2) Mean (95% CI)	26.38 (24.66 to 28.1)	27.2 (24.94 to 29.46)	26.4 (24.63 to 28.18)
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

Characteristic	Saxagliptin + Metformin (N = 25)	Saxagliptin (N = 25)	Metformin (N = 25)
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

41. Wainstein, 2012

Bibliographic Reference	Wainstein, J; Katz, L; Engel, S S; Xu, L; Golm, G T; Hussain, S; O'Neill, E A; Kaufman, K D; Goldstein, B J; Initial therapy with the fixed-dose combination of sitagliptin and metformin results in greater improvement in glycaemic control compared with pioglitazone monotherapy in patients with type 2 diabetes.; Diabetes, obesity & metabolism; 2012; vol. 14 (no. 5); 409-18

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	NCT00532935.
Study type	Randomised controlled trial (RCT)
Study location	Multicentre trial.
Study setting	Outpatient follow-up.
Study dates	No additional information.
Sources of funding	All authors except one were employees of Merck Sharp and Dohme Corporation, with the other author receiving honoraria for lecturing with the organisation.
Inclusion criteria	At least 18 to no more than 78 years of age with a diagnosis of type 2 diabetes and inadequate glycaemic control (defined as HbA1c no less than 7.5% and no more than 12.0% while on a diet/exercise regimen); not on an antihyperglycaemic agent in the 3 months prior to the screening visit and were to have had less than 4 weeks of cumulative duration of treatment and an antihyperglycaemic over the 3 years prior to the screening visit.
Exclusion criteria	History of type 1 diabetes; contraindication to biguanide or thiazolidinedione medications; previous treatment with any DPP-4 inhibitor or incretin mimetic; required treatment with CYP2C8 inhibitors or inducers; had impaired renal function (creatinine clearance <60mL/min); alanine aminotransferase or aspartate aminotransferase levels more than twofold the upper limit of normal, or a fasting glucose value <130 mg/dL or >320 mg/dL prior to randomisation.

Recruitment / selection of participants	No additional information.
Intervention(s)	Sitagliptin + Metformin N=261 Sitagliptin 50mg + Metformin 500mg twice daily in a fixed dose combination. The dose was increased to 50/500mg in the morning and 50/1000mg in the evening at week 2, then to 50/1000mg twice daily at week 4. Given for a total of 32 weeks.
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	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	Pioglitazone N=256 Pioglitazone 30mg per day, increased to 45mg per day at week 4. Given for a total of 32 weeks.
Number of participants	521 (includes 2 people who were randomised twice at two different sites but who were not included in any analyses).
Duration of follow-up	32 weeks.
Indirectness	No additional information.
Method of analysis	ACA Efficacy outcomes = People who took at least one dose of the medication and had both a baseline measurement and at least one post-randomisation measurement of the respective endpoint. Safety = People who took at least one dose of the medication.
Additional comments	No additional information.

41.2. Study arms

41.2.1. Sitagliptin + Metformin (N = 261)

Sitagliptin 50mg + Metformin 500mg twice daily in a fixed dose combination. The dose was increased to 50/500mg in the morning and 50/1000mg in the evening at week 2, then to 50/1000mg twice daily at week 4. Given for a total of 32 weeks. Concomitant therapy: No additional information.

41.2.2. Pioglitazone (N = 256)

Pioglitazone 30mg per day, increased to 45mg per day at week 4. Given for a total of 32 weeks. Concomitant therapy: No additional information.

41.3. Characteristics

41.3.1. Arm-level characteristics

Characteristic	Sitagliptin + Metformin (N = 261)	Pioglitazone (N = 256)
% Male Sample size	n = 143 ; % = 54.8	n = 134 ; % = 52.3
Mean age (SD) (years) Mean (SD)	52.4 (10.7)	52.2 (11)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 168 ; % = 64.4	n = 167 ; % = 65.2
Asian Sample size	n = 58 ; % = 22.2	n = 55 ; % = 21.5
Multiracial Sample size	n = 27 ; % = 10.3	n = 29 ; % = 11.3
Black or African Sample size	n = 6 ; % = 2.3	n = 5 ; % = 2
American Indian Sample size	n = 2 ; % = 0.8	n = 0 ; % = 0
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of frailty Sample size	n = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosis (years) Mean (SD)	3.2 (4)	3.3 (3.5)

Characteristic	Sitagliptin + Metformin (N = 261)	Pioglitazone (N = 256)
Smoking status Sample size	n = NA ; % = NA	n = NA ; % = NA
Alcohol consumption Sample size	n = NA ; % = NA	n = NA ; % = NA
Presence of severe mental illness Sample size	n = NA ; % = NA	n = NA ; % = NA
People with significant cognitive impairment Sample size	n = NA ; % = NA	n = NA
People with a learning disability Sample size	n = NA ; % = NA	n = NA ; % = NA
Number of people with obesity Sample size	n = NA ; % = NA	n = 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

42. Wang, 2013

Bibliographic Reference	Wang, H.; Ni, Y.; Yang, S.; Li, H.; Li, X.; Feng, B.; The effects of gliclazide, metformin, and acarbose on body composition in patients with newly diagnosed type 2 diabetes mellitus; Curr Ther Res Clin Exp; 2013; vol. 75; 88-92

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	China.
Study setting	Outpatient follow-up.
Study dates	No additional information.
Sources of funding	Supported by a Young Medical Talents Training Program Grant of Pudong Health Bureau of Shanghai (No. PWRq2012-08) and the Key Disciplines Group Construction Project of Pudong Health Bureau of Shanghai (No. PWZxkq2010-04).
Inclusion criteria	People newly diagnosed with type 2 diabetes according to the results of oral glucose tolerance test; hyperglycaemia (HbA1c 7-10%); drug naïve.
Exclusion criteria	Severe congestive heart failure (NYHA III-IV); liver dysfunction (AST/ALT >1.5 x upper limit of normal); renal dysfunction (creatinine clearance <90mL/min; creatinine clearance calculated using the Cockcroft-Gault formula); extraordinary body weight (body mass index <18.5 or >35kg/m2); dyslipidaemia (total cholesterol >6.21mmol/L; triglycerides >2.25mmol/L, LDL cholesterol >4.13mmol/L); people receiving antidiabetes treatment before the study; taking pharmacologic agents known to affect carbohydrate homeostasis or influence lipid levels; type 1 diabetes mellitus.
Recruitment / selection of participants	No additional information.

Intervention(s)	Gliclazide N=30 Gliclazide 120mg/day for 6 months. Concomitant therapy: All people received diet therapy.
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 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, 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	5) All treatment naïve
Population subgroups	No additional information.
Comparator	Metformin N=30 Metformin 1700mg/day for 6 months. Concomitant therapy: All people received diet therapy. A third arm (n=30) was reported where people received acarbose. This arm is not extracted as it is not relevant to the protocol.
Number of participants	90 (including the acarbose arm, 60 without).
Duration of follow-up	6 months.
Indirectness	Outcome indirectness - only withdrawal due to adverse events was reported in a manner where it could be attributed to study arms and so this was extracted instead of withdrawal due to any reason.
Method of analysis	Not stated/unclear
Additional comments	No additional information.

42.2. Study arms

42.2.1. Gliclazide (N = 30)

Gliclazide 120mg/day for 6 months. Concomitant therapy: All people received diet therapy.

42.2.2. Metformin (N = 30)

Metformin 1700mg/day for 6 months. Concomitant therapy: All people received diet therapy.

42.3. Characteristics

42.3.1. Arm-level characteristics

Characteristic	Gliclazide (N = 30)	Metformin (N = 30)
% Male Sample size	n = 21 ; % = 70	n = 18 ; % = 60
Mean age (SD) (years) Mean (SD)	55.89 (10.5)	54 (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 Mean (SD)	NR (NR)	NR (NR)
HbA1c (%) Mean (SD)	8.4 (0.93)	8.07 (0.77)
Blood pressure (mmHg) Mean (SD)	NA (NA)	NA (NA)
Systolic blood pressure Mean (SD)	125.1 (9.4)	126.4 (9)
Diastolic blood pressure Mean (SD)	76.3 (7.4)	74.9 (7)
Heart rate Mean (SD)	NR (NR)	NR (NR)
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Gliclazide (N = 30)	Metformin (N = 30)
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)	70.4 (11.7)	71.6 (12.7)
BMI Mean (SD)	NR (NR)	NR (NR)
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)	5.23 (1.02)	5.02 (0.85)
HDL cholesterol Mean (SD)	1.05 (0.33)	1.09 (0.32)
LDL cholesterol Mean (SD)	2.6 (0.68)	2.72 (0.67)
Triglycerides Mean (SD)	2.12 (1.25)	1.93 (0.53)
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	Gliclazide (N = 30)	Metformin (N = 30)
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

43. Wang, 2022

Bibliographic Reference	Wang, X.; Zhao, B.; Sun, H.; You, H.; Qu, S.; Effects of sitagliptin on intrahepatic lipid content in patients with non-alcoholic fatty liver disease; Frontiers in endocrinology; 2022; vol. 13; 866189

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	NCT05480007.
Study type	Randomised controlled trial (RCT)
Study location	China.
Study setting	Outpatient follow-up.
Study dates	No additional information.
Sources of funding	Supported by the Climbing Talent Program of Shanghai Tenth People's Hospital (2021SYPDRC047) and National Nature Science Foundation of China (NO.81900781).
Inclusion criteria	Age 30-70 years; fulfilment of the diagnostic criteria for T2DM by WHO in 1999 (HbA1c ranged from 7% to 10%, FPG <11 mol/L, 2-hour blood glucose postprandial <20mmol/L); fulfilment of the diagnostic criteria for NAFLD according to the guidelines of the Chinese Medical Association in 2010.
Exclusion criteria	T2DM complicated with ketoacidosis hyperosmolarity, acute and chronic infection; serious heart, liver, kidney, lung disease and liver damage; alcoholic fatty liver; drug use that influences glucose metabolism such as thiazide diuretics and hormones within three months; hypertension of more than or equal to 180/110 mmHg; gastrointestinal disease or absorption dysfunction; recent trauma, surgery or other conditions resulting in an increased stress response within the past three months.
Recruitment / selection of participants	Recruited from the outpatient department of Shanghai Tenth People's Hospital.

Intervention(s)	Sitagliptin + Metformin N=20 Sitagliptin 100mg per day and metformin 500mg three times a day for 24 weeks. Concomitant therapy: Health education regarding eating a diabetic diet and performing routine exercise during the treatment 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 NAFLD and T2DM
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	8) Not reported
Population subgroups	No additional information.
Comparator	Sitagliptin N=17 Sitagliptin 100mg per day for 24 weeks. Concomitant therapy: Health education regarding eating a diabetic diet and performing routine exercise during the treatment period. Metformin N=17 Metformin 500mg three times a day for 24 weeks. Concomitant therapy: Health education regarding eating a diabetic diet and performing routine exercise during the treatment period.
Number of participants	54
Duration of follow-up	24 weeks.
Indirectness	No additional information.
Method of analysis	Not stated/unclear
Additional comments	No additional information.

43.2. Study arms

43.2.1. Sitagliptin + Metformin (N = 20)

Sitagliptin 100mg per day and metformin 500mg three times a day for 24 weeks. Concomitant therapy: Health education regarding eating a diabetic diet and performing routine exercise during the treatment period.

43.2.2. Sitagliptin (N = 17)

Sitagliptin 100mg per day for 24 weeks. Concomitant therapy: Health education regarding eating a diabetic diet and performing routine exercise during the treatment period.

43.2.3. Metformin (N = 17)

Metformin 500mg three times a day for 24 weeks. Concomitant therapy: Health education regarding eating a diabetic diet and performing routine exercise during the treatment period.

43.3. Characteristics

43.3.1. Arm-level characteristics

Characteristic	Sitagliptin + Metformin (N = 20)	Sitagliptin (N = 17)	Metformin (N = 17)
% Male Sample size	n = 9 ; % = 45	n = 10 ; % = 59	n = 9 ; % = 53
Mean age (SD) (years) Mean (SD)	54.55 (6.6)	54.4 (9)	55.63 (10.9)
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 Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
HbA1c (%) Mean (SD)	7.83 (0.58)	7.93 (0.91)	8.6 (1.17)
Blood pressure Mean (SD)	NR (NR)	NR (NR)	NR (NR)
Heart rate Mean (SD)	NR (NR)	NR (NR)	NR (NR)

Characteristic	Sitagliptin + Metformin (N = 20)	Sitagliptin (N = 17)	Metformin (N = 17)
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 Mean (SD)	NR (NR)	NR (NR)	NR (NR)
BMI (kg/m2) Mean (SD)	26.07 (3.24)	25.41 (3.45)	26.46 (2.86)
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)
HDL cholesterol Mean (SD)	1.34 (0.27)	1.31 (0.38)	1.18 (0.31)
LDL cholesterol Mean (SD)	2.54 (1.01)	3.02 (0.97)	2.83 (0.65)
Triglycerides Mean (SD)	1.26 (0.62)	1.7 (0.82)	1.94 (0.97)
Total cholesterol Mean (SD)	4.46 (1.03)	5.22 (0.92)	4.88 (0.64)
Albumin creatinine ratio	NR (NR)	NR (NR)	NR (NR)

Characteristic	Sitagliptin + Metformin (N = 20)	Sitagliptin (N = 17)	Metformin (N = 17)
Mean (SD)			
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

44. Wang, 2016

Bibliographic Reference	Wang, Y.; Xu, L.; Yuan, L.; Li, D.; Zhang, Y.; Zheng, R.; Liu, C.; Feng, X.; Li, Q.; Ma, J.; Sodium-glucose co-transporter-2 inhibitors suppress atrial natriuretic peptide secretion in patients with newly diagnosed Type 2 diabetes; Diabetic Med; 2016; vol. 33 (no. 12); 1732-1736

44.1. 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	Li FF, Gao G, Li Q, Zhu HH, Su XF, Wu JD, Ye L, Ma JH. Influence of Dapagliflozin on Glycemic Variations in Patients with Newly Diagnosed Type 2 Diabetes Mellitus. J Diabetes Res. 2016;2016:5347262.
Trial name / registration number	No information available.
Study type	Randomised controlled trial (RCT)
Study location	China
Study setting	Hospital
Study dates	07/2010 to 03/2012
Sources of funding	Grants from the National Natural Science Foundation of China, Jiangsu Planned Projects of Postdoctoral Research Funds, the Peak of Six Personnel in Jiangsu, and the Nanjing Medical Science and Technique Development Foundation.
Inclusion criteria	Newly diagnosed or drug-naive Type 2 diabetes
Exclusion criteria	• History of diabetes • Severe uncontrolled hypertension (systolic blood pressure ≥ 180 mmHg and/or diastolic blood pressure ≥ 110 mmHg) and use of any renin angiotensin system blocker. • Replacement of chronic system corticosteroid treatment • History or current diagnosis of significant comorbid diseases, such as cardiovascular, hepatic and renal diseases and/or • Positive test for islet cell autoantibodies (such as glutamic acid decarboxylase autoantibodies, islet-cell antibodies or insulinoma-like antigen 2 indicating the possibility of type 2 diabetes

Recruitment / selection of participants	After receiving 8 weeks of lifestyle management counselling, those who continued to experience inadequate glycaemic control, as defined by HbA1c levels of 58 - 80 mmol/mol (7.5-10.5%) were recruited.
Intervention(s)	Dapagliflozin After 4 weeks of treatment, patients lacking glycaemic control (fasting blood glucose >11.1 mmol/l) were eligible to receive another antihyperglycaemic drug such as metformin.
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
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	5) All treatment naïve
Population subgroups	No information reported.
Comparator	Placebo
Number of participants	N=28
Duration of follow-up	24-week treatment period + no follow-up.
Indirectness	Study was conducted in a hospital in China, the results may not be as generalisable to a UK population.
Method of analysis	Not stated/unclear
Additional comments	Unpaired Student's t-tests were used to compare all the variables measured for each treatment group and to determine significant differences between groups. Analyses of continuous outcomes were based on a ANCOVA model, with treatment as a fixed effect and baseline as the covariate, and were also used to estimate differences between placebo and treatment groups.

44.2. Study arms

44.2.1. Dapagliflozin (N = 18)

44.2.2. Placebo (N = 10)

44.3. Characteristics

44.3.1. Arm-level characteristics

Characteristic	Dapagliflozin (N = 18)	Placebo (N = 10)
% Male No of events	n = 11 ; % = 61	n = 2 ; % = 20
Mean age (SD) Mean (SD)	60.7 (10.1)	59.3 (9)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
Presence of frailty 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
BMI Nominal	NR	NR
Number of people with obesity Nominal	NR	NR
Albumin creatinine ratio Nominal	NR	NR
eGFR (mL/min/1.73m2)	NR	NR

Characteristic	Dapagliflozin (N = 18)	Placebo (N = 10)
Nominal		
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

45. Wolever, 2000

Bibliographic Reference	Wolever, T. M. S.; Assiff, L.; Basu, T.; Chiasson, J. L.; Boctor, M.; Gerstein, H. C.; Hunt, J. A.; Josse, R. G.; Lau, D.; Leiter, L. A.; Maheux, P.; Murphy, L.; Rodger, N. W.; Ross, S. A.; Ryan, E.; Tildesley, H. D.; Yale, J. F.; Miglitol, an alpha-glucosidase inhibitor, prevents the metformin-induced fall in serum folate and vitamin B12 in subjects with type 2 diabetes; Nutr Res; 2000; vol. 20 (no. 10); 1447-56

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	No additional information.
Study type	Randomised controlled trial (RCT)
Study location	Canada.
Study setting	Outpatient follow-up.
Study dates	No additional information.
Sources of funding	Supported by Bayer Canada Inc which also provided the study medications.
Inclusion criteria	Euthyroid male and non-pregnant females >40 years of age; BMI no more than 40 kg/m2; oral glucose lowering drugs had to be withdrawn and people had to undergo an 8 week placebo baseline period.
Exclusion criteria	Type 1 diabetes; insulin treatment; unwillingness to perform the self-blood glucose monitoring specified in the protocol; major debilitating diseases; recent cardiovascular events or surgery; presence of gastrointestinal diseases or use of drugs associated with abnormal intestinal motility or altered absorption; raised serum creatinine or aspartate transaminase; use of steroids; the presence of emotional disorders or substance abuse.
Recruitment / selection of participants	No additional information.

Intervention(s)	Metformin N=83 Metformin 500mg three times daily plus miglitol placebo with meals for 36 weeks. 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 category at baseline	Not stated/unclear
Sensitivity analysis category: Enrichment trial status	6) No response criteria
Population subgroups	No additional information.
Comparator	Placebo N=83 Placebo metformin and placebo miglitol tablets three times a day for 36 weeks. Concomitant therapy: No additional information. Two additional arms were reported, one received a combination of miglitol and metformin (n=76) while the other received miglitol only (n=82). Neither of these arms were extracted as they were not relevant to the protocol.
Number of participants	324
Duration of follow-up	9 months
Indirectness	No additional information.
Method of analysis	Other Appears to be completers only included in the analysis
Additional comments	No additional information.

45.2. Study arms

45.2.1. Metformin (N = 62)

Metformin 500mg three times daily plus miglitol placebo with meals for 36 weeks.
Concomitant therapy: No additional information.

45.2.2. Placebo (N = 45)

Placebo metformin and placebo miglitol tablets three times a day for 36 weeks. Concomitant therapy: No additional information.

45.3. Characteristics

45.3.1. Arm-level characteristics

Characteristic	Metformin (N = 62)	Placebo (N = 45)
% Male Sample size	n = 45 ; % = 73	n = 27 ; % = 60
Mean age (SD) (years) Mean (SE)	58.7 (1.1)	58.5 (1.6)
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)	7.3 (0.9)	4.5 (0.6)
HbA1c (%) Mean (SE)	8.2 (0.1)	7.8 (0.1)
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

Characteristic	Metformin (N = 62)	Placebo (N = 45)
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 (SE)	30.5 (0.6)	30.8 (0.6)
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

46. Wu, 2015

Bibliographic Reference	Wu, W.; Li, Y.; Chen, X.; Lin, D.; Xiang, S.; Shen, F.; Gu, X.; Effect of linagliptin on glycemic control in Chinese patients with newly-diagnosed, drug-naive type 2 diabetes mellitus: A randomized controlled trial; Med Sci Monit; 2015; vol. 21; 2678-2684

46.1. 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	Not reported
Study type	Randomised controlled trial (RCT)
Study location	Zhejiang, China
Study setting	Community
Study dates	09/2013 to 01/2014
Sources of funding	Supported by the National Science Foundation for Young Scholars of China (Grant No.81000356)
Inclusion criteria	• Aged 18-80 years, inclusive • Diagnosis of type 2 diabetes mellitus (WHO classification) • Fasting plasma glucose≤13.3 mmol/L • HbA1c level 7-10% inclusive at baseline • BMI 20-35 kg/m2 inclusive • Drug-naive (diet and exercise only)
Exclusion criteria	• Type 1 diabetes or secondary diabetes • Acute complications of diabetes • Myocardial infarction, stroke, unstable angina, or coronary artery bypass graft (CABG) in the past 6 months • Congestive heart failure • Impaired hepatic function (serum alanine aminotransferase, aspartate aminotransferase or alkaline phosphatase level exceeding twice the upper limit of normal) • Thyroid disorders

	• Chronic intestinal tract disorders • History of acute pancreatitis or pancreatic tumor • Fertile women not using contraceptives
Recruitment / selection of participants	Participants recruited from outpatient department of First Affiliated Hospital of Wenzhou Medical University, Zhejiang, China. Randomisation using computer-generated random sequence and sealed envelopes. Double blinded to treatment with assigned medication number enter in case report form and corresponding drug kit given to participant. Kit prepared by pharmacist who had not contact with participants.. All participants received health education before trial. Visits at weeks 6, 12, 18 and 24 with lab assessments conducted by same lab. Medication adherence was also assessed.
Intervention(s)	• Linagliptin 5 mg once daily Oral linagliptin 5 mg once daily for 24 weeks.
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Exclusion criteria: congestive heart failure
Strata 2: People with atherosclerotic cardiovascular diseases	People without other cardiovascular diseases Exclusion criteria: Myocardial infarction, stroke, unstable angina, or coronary artery bypass graft (CABG) in the past 6 months
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 Inclusion criteria: drug naive (diabetes treated only with diet and exercise)
Population subgroups	
Comparator	• Placebo Matching placebo once daily for 24 weeks.
Number of participants	N=57
Duration of follow-up	24 weeks
Method of analysis	Other Not explicitly reported by appears to be completer analysis for efficacy and safety analyses

46.2. Study arms

46.2.1. Linagliptin 5 mg once daily (N = 34)

Oral linagliptin tablet 5 mg once daily for 24 weeks.

46.2.2. Placebo (N = 23)

Matching placebo for 24 weeks.

46.3. Characteristics

46.3.1. Arm-level characteristics

Characteristic	Linagliptin 5 mg once daily (N = 34)	Placebo (N = 23)
% Male Reported % of males is not consistent with reported number of participants Sample size	n = 17 ; % = 50	n = 15 ; % = 65.7
Mean age (SD) (years) Mean (SD)	51.2 (7.5)	52.5 (11)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosis Nominal	NR	NR
HbA1c (%) Mean (SD)	8 (0.69)	7.97 (0.68)
Blood pressure (mmHg) Mean (SD)	NA (NA)	NA (NA)
Systolic blood pressure Mean (SD)	133.65 (11.91)	136.6 (13.55)
Diastolic blood pressure Mean (SD)	81.39 (6.96)	81 (5.69)
Heart rate Nominal	NR	NR
Smoking status Nominal	NR	NR
Alcohol consumption Nominal	NR	NR

Characteristic	Linagliptin 5 mg once daily (N = 34)	Placebo (N = 23)
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)	65.24 (8.45)	67.05 (8.12)
BMI (kg/m2) Mean (SD)	24.11 (2.28)	24.37 (2.09)
Number of people with obesity Nominal	NR	NR
Cholesterol and lipid levels (mmol/L) Mean (SD)	NA (NA)	NA (NA)
Total cholesterol Mean (SD)	4.41 (0.72)	4.67 (0.79)
HDL-cholesterol Mean (SD)	1.07 (0.12)	1.09 (0.15)
LDL-cholesterol Mean (SD)	2.46 (0.56)	2.63 (0.6)
Triglycerides Mean (SD)	1.71 (0.59)	1.75 (0.43)
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	NR	NR

Characteristic	Linagliptin 5 mg once daily (N = 34)	Placebo (N = 23)
Nominal		
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

47. Xu, 2015

Bibliographic Reference	Xu, W.; Bi, Y.; Sun, Z.; Li, J.; Guo, L.; Yang, T.; Wu, G.; Shi, L.; Feng, Z.; Qiu, L.; Li, Q.; Guo, X.; Luo, Z.; Lu, J.; Shan, Z.; Yang, W.; Ji, Q.; Yan, L.; Li, H.; Yu, X.; Li, S.; Zhou, Z.; Lv, X.; Liang, Z.; Lin, S.; Zeng, L.; Yan, J.; Ji, L.; Weng, J.; Comparison of the effects on glycaemic control and beta-cell function in newly diagnosed type 2 diabetes patients of treatment with exenatide, insulin or pioglitazone: a multicentre randomized parallel-group trial (the CONFIDENCE study); J Intern Med; 2015; vol. 277 (no. 1); 137-50

47.1. 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	CONFIDENCE/NCT01147627
Study type	Randomised controlled trial (RCT)
Study location	China (25 university-affiliated hospitals in 13 provinces)
Study setting	Community
Study dates	08/2010 to 08/2012
Sources of funding	Funded by Key Projects of Clinical Disciplines of Hospitals Affiliated to Ministry of Health from Ministry of Health of the People's Republic of China, the National Science Fund for Distinguished Young Scholars (81025005), investigator-initiated trial research funds from Eli Lilly and Co. and Amylin Pharmaceuticals, Inc., and the 5010 Project of Sun Yat-sen University.
Inclusion criteria	• Aged ≥30 to ≤70 years • Newly-diagnosed type 2 diabetic patients • Treatment-naive to glucose-lowering drugs • HbA1c ≥7.0 to ≤10.0% • BMI ≥20 to ≤35 kg/m2 • Stable body weight (≤10% variation)≥3 months prior to screening • Female patients of reproductive age should practice a reliable method of birth control throughout study

Exclusion criteria	• Pregnancy • Acute or severe chronic diabetic complications • Congestive heart failure (NYHA grade 3-4) • Severe gastrointestinal disease • Severe osteoporosis or history of pathological fracture, or use of bisphosphonates preparation • Other severe intercurrent illness • Serum aminotransferase (ALT and AST) level higher than 2 times of the upper normal limits and/or serum creatinine≥133μmol/L (1.5mg/dL) • Tested positive for glutamic acid decarboxylase antibody • Use of weight loss drugs, corticosteroids, drugs known to affect gastrointestinal motility, transplantation medications, or any investigational drug • History of pancreatitis • Serum triglyceride ≥ 5.0 mmol/L
Recruitment / selection of participants	Participants recruited from 25 university-affiliated hospitals in 13 Chinese provinces. Participants randomised 1:1:1 to groups using randomisation list generated by SAS software with allocation by secure Oracle-based interactive web-based response system in accordance with list. Participants followed up every 4 weeks for 12 weeks, then every 12 weeks until week 48. At each visit, anthropomorphic data, adverse events and hypoglycaemia episodes recorded and HbA1c, FPG and 2-h postprandialglucose (PPG) after mixed-meal test measured. Telephone calls scheduled at weeks 16, 20, 28, 32, 40 and 44 to collect information and provide guidance. All participants received diabetes information and lifestyle counselling at enrolment, reinforced during study. Baseline assessments repeated at week 48, with participants instructed to stop all antihyperglycaemic therapy 2 days beforehand to avoid acute drug effects on collected data. HbA1c assessed centrally at the Diabetes Centre of the Third Affiliated Hospital of Sun Yat-sen University, and insulin and proinsulin levels were measured centrally at the Beijing North Institute of Biological Technology. Remaining biochemical variables assessed locally at participating centres.
Intervention(s)	• Exenatide 10 mcg twice daily Subcutaneous injection of exenatide 5 mcg twice daily for 4 weeks then exenatide 10 mcg twice daily for remaining 44 weeks. Participants instructed to reduce dose to 5 mcg twice daily if experiencing frequent hypoglycaemia or could not tolerate adverse events.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Exclusion criteria: NYHA grade III and IV. Trial may include participants with NYHA grade 2.
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 Inclusion criteria: treatment-naive to glucose lowering drugs and newly diagnosed type 2 diabetes
Population subgroups	
Comparator	• Premixed biphasic insulin lispro 25%/insulin lispro protamine 75% twice daily • Pioglitazone 45 mg once daily Insulin injected twice daily at initial dose of 0.4 IU/kg, 50% 15 min before breakfast and 50% 15 min before dinner. Doses self-titrated after this

	based on self-monitored blood glucose levels. Pioglitazone administered at 30 mg once daily for 4 weeks, increasing to 45 mg once daily for remaining 44 weeks.
Number of participants	N=416
Duration of follow-up	48 weeks
Method of analysis	Per protocol Per protocol population conducted for efficacy analysis. Reports conducting analysis on ITT population but data not reported because results were similar to analysis on PP population. Modified ITT Safety analysis conducted on ITT population - all participants randomised who received at least one dose of study drug.

47.2. Study arms

47.2.1. Exenatide 10 mcg twice daily (N = 142)

Subcutaneous injection of exenatide 5 mcg twice daily for 4 weeks, increased to 10 mcg twice daily for remaining 44 weeks.

47.2.2. Biphasic insulin lispro 25%/insulin lispro protamine 75% twice daily (N = 138)

Subcutaneous injection of premixed biphasic insulin lispro 25%/insulin lispro protamine 75% twice daily titrated based on self-monitored blood glucose levels for 48 weeks.

47.2.3. Pioglitazone 45 mg once daily (N = 136)

Oral pioglitazone tablets 30 mg once daily for 4 weeks, increased to 45 mg once daily for remaining 44 weeks.

47.3. Characteristics

47.3.1. Arm-level characteristics

Characteristic	Exenatide 10 mcg twice daily (N = 142)	Biphasic insulin lispro 25%/insulin lispro protamine 75% twice daily (N = 138)	Pioglitazone 45 mg once daily (N = 136)
% Male Sample size	n = 98 ; % = 69	n = 85 ; % = 61.6	n = 83 ; % = 61
Mean age (SD) (years) Mean (SD)	50 (0.8)	51 (0.8)	50 (0.8)
HbA1c (%) Mean (SE)	8 (0.1)	8.1 (0.1)	8 (0.1)
Blood pressure Mean (SE)	NA (NA)	NA (NA)	NA (NA)
Systolic blood pressure Mean (SE)	126 (1)	124 (1)	125 (1)
Diastolic blood pressure Mean (SE)	80 (1)	79 (1)	80 (1)
Weight (kg) Mean (SE)	72.6 (1)	70.3 (1)	71.2 (1)
BMI (kg/m2) Mean (SE)	26.1 (0.3)	25.6 (0.3)	25.8 (0.3)
Cholesterol and lipid levels (mmol/L) Mean (SE)	NA (NA)	NA (NA)	NA (NA)
Total cholesterol Mean (SE)	5.1 (0.1)	5.2 (0.1)	5.3 (0.1)
HDL-cholesterol Mean (SE)	1.14 (0.02)	1.21 (0.03)	1.18 (0.02)

Characteristic	Exenatide 10 mcg twice daily (N = 142)	Biphasic insulin lispro 25%/insulin lispro protamine 75% twice daily (N = 138)	Pioglitazone 45 mg once daily (N = 136)
LDL-cholesterol Mean (SE)	3.2 (0.1)	3.2 (0.1)	3.2 (0.1)
Triglycerides Mean (SE)	1.9 (0.1)	1.9 (0.1)	2 (0.1)

48. Yamada, 2020

Bibliographic Reference	Yamada, Y.; Katagiri, H.; Deenadayalan, S.; Navarria, A.; Nishijima, K.; Seino, Y.; Fukushima, Y.; Hamamoto, Y.; Hisatomi, A.; Ide, Y.; Inoue, S.; Kawada, T.; Kim, H.; Kiyosue, A.; Matoba, K.; Matsuoka, O.; Nishimura, H.; Noguchi, M.; Osonoi, T.; Sawada, S.; Shibasaki, Y.; Shin, K.; Dose-response, efficacy, and safety of oral semaglutide monotherapy in Japanese patients with type 2 diabetes (PIONEER 9): a 52-week, phase 2/3a, randomised, controlled trial; Lancet Diabetes Endocrinol; 2020; vol. 8 (no. 5); 377-391

48.1. 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	PIONEER 9/NCT03018028
Study type	Randomised controlled trial (RCT)
Study location	Japan (16 sites)
Study setting	Community
Study dates	01/2017 to 07/2017
Sources of funding	Funded by Novo Nordisk.
Inclusion criteria	• Japanese adults aged ≥20 years or older • Diagnosis of type 2 diabetes ≥30 days before screening • Managed with diet and exercise only or received oral glucose-lowering drug monotherapy (at stable daily dose less than or equal to a half of the maximum approved dose in Japan) ≥30 days before screening • HbA1c level 7·0-10·0% inclusive for diet and exercise only or 6·5-9·5% inclusive for those on oral glucose-lowering drug monotherapy
Exclusion criteria	• Female who was pregnant, breast-feeding or had intention to become pregnant, or not using adequate contraception

	• Any disorder that might affect safety of participant or compliance with trial protocol • Treatment ≤90 before screening with once-weekly GLP-1 receptor agonist, once-weekly DPP-4 inhibitor, or thiazolidinedione • Severe renal impairment (eGFR <30 mL/min per 1·73 m²) • Proliferative retinopathy or maculopathy requiring acute treatment • Family or personal history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma • History of pancreatitis (acute or chronic) • History of major surgical procedures involving stomach potentially affecting absorption of trial product (e.g. subtotal and total gastrectomy, sleeve gastrectomy, gastric bypass surgery). • Any of: myocardial infarction, stroke or hospitalisation for unstable angina, or transient ischaemic attack within the past 180 days prior to the day of screening and randomisation • Subjects classified as being in New York Heart Association Class IV • Planned coronary, carotid or peripheral artery revascularisation known on the day of screening • Alanine aminotransferase >2·5 x upper limit of normal • Renal impairment (eGFR<30 mL/min/1·73 m2) as per Chronic Kidney Disease Epidemiology collaboration • Treatment with once-weekly glucagon-like peptide-1 receptor agonist, once-weekly DPP-4 inhibitor or thiazolidinedione in a period of 90 days before the day of screening • Treatment with any medication for the indication of diabetes or obesity other than stated in inclusion criteria in a period of 60 days before the day of screening (with exception of short-term insulin treatment for acute illness for a total of ≤14 days) • Proliferative retinopathy or maculopathy requiring acute treatment. Verified by fundus photography or dilated fundoscopy performed within 90 days prior to randomisation • History or presence of malignant neoplasms within the last 5 years (except basal and squamous cell skin cancer and in situ carcinomas) • Initiation of glucose-lowering medication between the day of screening and the day of randomisation
Recruitment / selection of participants	Participants recruited from 16 sites (clinics and university hospitals) in Japan. They were randomly assigned 1:1:1:1:1 to one of 5 arms using trial-specific interactive web response system that assigned treatment codes, stratified by pre-trial treatment at screening (without oral glucose lowering drug monotherapy; with monotherapy). Participants receiving diet and exercise only screened over 2 week period; those receiving monotherapy had 8 week screening/washout period.
Intervention(s)	• Semaglutide 14 mg once daily • Semaglutide 7 mg once daily • Semaglutide 3 mg once daily

	Participants received treatment for 52 weeks with a 5 week post-treatment follow up visit. Oral semaglutide initiated with 3 mg once daily tablet dose, escalated after 4 weeks to 7 mg for 7 mg and 14 mg arms, and an additional 7 mg 4 weeks after this for 14 mg arm. Tablets taken with ≤120 ml water in morning, in fasting state, and minimum of 30 min before first meal of day or other oral medication. Rescue medication could be offered at week 8+ for participants with persistent hypoglycaemia (>240 mg/dL from weeks 8-13, or >200 mg/dL week 14+, or if HbA1c>8.5% at week 26+). Rescue medication (excluding use of GLP-1RA, DPP-4 inhibitors, and amylin analogues) offered at investigator's discretion and participants could continue in trial.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Exclusion criteria: NYHA Class IV
Strata 2: People with atherosclerotic cardiovascular diseases	People without other cardiovascular diseases Exclusion criteria: myocardial infarction, stroke or hospitalisation for unstable angina,or transient ischaemic attack within the past 180 days prior to the day of screening and randomisation;
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	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 drug-naive (diet and exercise only) or if on oral glucose-lowering monotherapy (for more than 30 days before screening) then had 8 week screening and washout period.
Comparator	• Placebo for semaglutide • Liraglutide 0.9 mg once daily Placebo for semaglutide was visually identical tablets and packaging as used for semaglutide arms. Placebo tablets taken with ≤120 ml water in morning, in fasting state, and minimum of 30 min before first meal of day or other oral medication. Liraglutide initiated with 0.3 mg daily subcutaneous injection, escalated 0.3 mg after 1 and 2 weeks until 0.9 mg once daily dose achieved, and administered at fixed time in morning or evening irrespective of meal times. Rescue medication strategy same as for interventions.
Number of participants	N=243
Duration of follow-up	52 weeks
Method of analysis	ITT All randomised participants regardless of discontinuation or use of rescue medication with imputation of missing data for 6 groups (one group of those who discontinued treatment or initiated rescue medication; 5 groups (1 for each randomised treatment arm including all those in each group who had not initiated rescue medication). Missing data addressed using multiple imputation using assumption that participants at week 26 or week 52 were similar in terms of treatment arm and adherence, or rescue medication status.
Additional comments	Trial specifies 2 estimands: trial product and treatment policy. Trial product estimand is evaluation of treatment effect for all randomly assigned participants under assumption that all remained on trial product for entire length of trial and didn't use rescue medication. Model includes all post-baseline measurements collected at scheduled visits to week 26 or week 52 excluding those who took rescue medication. Treatment policy estimand is evaluation of treatment effect for all randomly assigned participants regardless of whether they discontinued or used rescue medication (that is, it is an ITT analysis).

48.2. Study arms

48.2.1. Semaglutide 14 mg once daily (N = 48)

Oral semaglutide tablet 14 mg once daily for 52 weeks.

48.2.2. Semaglutide 7 mg once daily (N = 49)

Oral semaglutide tablet 7 mg once daily for 52 weeks.

48.2.3. Semaglutide 3 mg once daily (N = 49)

Oral semaglutide tablet 3 mg once daily for 52 weeks.

48.2.4. Liraglutide 0.9 mg once daily (N = 48)

Subcutaneous injection of liraglutide 0.9 mg once daily for 52 weeks.

48.2.5. Placebo (N = 49)

Placebo tablet once daily for 52 weeks, using visually identical tablet and packaging as used for oral semaglutide.

48.3. Characteristics

48.3.1. Arm-level characteristics

Characteristic	Semaglutide 14 mg once daily (N = 48)	Semaglutide 7 mg once daily (N = 49)	Semaglutide 3 mg once daily (N = 49)	Liraglutide 0.9 mg once daily (N = 48)	Placebo (N = 49)
% Male Sample size	n = 40 ; % = 83	n = 36 ; % = 73	n = 36 ; % = 73	n = 39 ; % = 81	n = 40 ; % = 82
Mean age (SD) (years) Mean (SD)	61 (9)	60 (10)	58 (9)	59 (10)	59 (9)
Ethnicity Nominal	NR	NR	NR	NR	NR
Comorbidities Nominal	NR	NR	NR	NR	NR

Characteristic	Semaglutide 14 mg once daily (N = 48)	Semaglutide 7 mg once daily (N = 49)	Semaglutide 3 mg once daily (N = 49)	Liraglutide 0.9 mg once daily (N = 48)	Placebo (N = 49)
Presence of frailty Nominal	NR	NR	NR	NR	NR
Time since type 2 diabetes diagnosis (years) Mean (SD)	7.9 (5.9)	7.4 (5.6)	7.4 (5.5)	6.7 (5.2)	8.4 (6)
HbA1c (%) Mean (SD)	8 (0.9)	8.3 (1)	8.1 (0.8)	8.3 (0.8)	8.3 (1.1)
Blood pressure (mmHg) Mean (SD)	NA (NA)	NA (NA)	NA (NA)	NA (NA)	NA (NA)
Systolic blood pressure Mean (SD)	127 (13)	129 (12)	127 (14)	128 (13)	128 (13)
Diastolic blood pressure Mean (SD)	76 (9)	80 (10)	76 (8)	81 (11)	78 (12)
Heart rate Nominal	NR	NR	NR	NR	NR
Smoking status Nominal	NR	NR	NR	NR	NR
Alcohol consumption Nominal	NR	NR	NR	NR	NR
Presence of severe mental illness Nominal	NR	NR	NR	NR	NR
People with significant cognitive impairment Nominal	NR	NR	NR	NR	NR

Characteristic	Semaglutide 14 mg once daily (N = 48)	Semaglutide 7 mg once daily (N = 49)	Semaglutide 3 mg once daily (N = 49)	Liraglutide 0.9 mg once daily (N = 48)	Placebo (N = 49)
People with a learning disability Nominal	NR	NR	NR	NR	NR
Weight (kg) Mean (SD)	68 (13)	71.3 (10.8)	71.4 (14.3)	74.7 (15.4)	70.3 (12.4)
BMI (kg/m2) Mean (SD)	24.7 (4.1)	26.3 (3.5)	26.5 (4.6)	26.9 (4.8)	25.1 (3.9)
Number of people with obesity Nominal	NR	NR	NR	NR	NR
Cholesterol and lipid levels Nominal	NR	NR	NR	NR	NR
Albumin creatinine ratio Nominal	NR	NR	NR	NR	NR
eGFR (mL/min/1.73m2) Mean (SD)	94 (13)	96 (14)	99 (12)	99 (9)	96 (12)
Other antidiabetic medication used Pre-trial glucose-lowering therapy Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Metformin Sample size	n = 8 ; % = 17	n = 4 ; % = 8	n = 7 ; % = 14	n = 8 ; % = 17	n = 9 ; % = 18
DPP-4 inhibitor Sample size	n = 6 ; % = 13	n = 10 ; % = 20	n = 5 ; % = 10	n = 2 ; % = 4	n = 7 ; % = 14
SGLT2 inhibitor Sample size	n = 1 ; % = 2	n = 3 ; % = 6	n = 5 ; % = 10	n = 4 ; % = 8	n = 2 ; % = 4

Characteristic	Semaglutide 14 mg once daily (N = 48)	Semaglutide 7 mg once daily (N = 49)	Semaglutide 3 mg once daily (N = 49)	Liraglutide 0.9 mg once daily (N = 48)	Placebo (N = 49)
Alpha-glucosidase inhibitor Sample size	n = 3 ; % = 6	n = 2 ; % = 4	n = 1 ; % = 2	n = 3 ; % = 6	n = 1 ; % = 2
Sulfonylurea Sample size	n = 0 ; % = 0	n = 0 ; % = 0	n = 1 ; % = 2	n = 1 ; % = 2	n = 0 ; % = 0
Blood pressure-lowering medication used Nominal	NR	NR	NR	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR	NR	NR	NR
Other treatment being received Nominal	NR	NR	NR	NR	NR

49. Yamanouchi, 2005

Bibliographic Reference	Yamanouchi, T.; Sakai, T.; Igarashi, K.; Ichiyanagi, K.; Watanabe, H.; Kawasaki, T.; Comparison of metabolic effects of pioglitazone, metformin, and glimepiride over 1 year in Japanese patients with newly diagnosed Type 2 diabetes; Diabet Med; 2005; vol. 22 (no. 8); 980-5

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	No additional information.
Study location	Japan.
Study setting	Outpatient follow-up.
Study dates	No additional information.
Sources of funding	No additional information.
Inclusion criteria	People with a short duration of Type 2 diabetes; had not received an oral hypoglycaemic agent or a lipid drug; treated with diet and exercise alone for at least 3 months, including the 1 month for baseline measurements before the study (observation period) after which they had an HbA1c at least 7.0% and a fasting plasma glucose at least 7.78 mmol/L; BMI 22-35kg/m2.
Exclusion criteria	People who had unstable or rapidly progressive diabetic retinopathy, nephropathy or neuropathy; people with liver dysfunction (AST and ALT >1.5 x the upper limit of normal); impaired kidney function (serum creatinine >133 micromol/L); anaemia; myocardial infarction, angina, congestive heart failure or a documented cerebrovascular accident.
Recruitment / selection of participants	No additional information.
Intervention(s)	Pioglitazone N=38

	Pioglitazone 30-45mg/day. Concomitant therapy: Antihypertensive drugs or other concurrent treatments, including dietary regimens, remained unchanged throughout 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 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 systolic blood pressure, 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	5) All treatment naïve
Population subgroups	No additional information.
Comparator	Metformin N=39 Metformin 750mg/day. Concomitant therapy: Antihypertensive drugs or other concurrent treatments, including dietary regimens, remained unchanged throughout the study. Glimepiride N=37 Glimepiride 1.0-2.0mg/day. Concomitant therapy: Antihypertensive drugs or other concurrent treatments, including dietary regimens, remained unchanged throughout the study.
Number of participants	114
Duration of follow-up	12 months.
Indirectness	No additional information.
Method of analysis	Not stated/unclear
Additional comments	No additional information.

49.2. Study arms

49.2.1. Pioglitazone (N = 38)

Pioglitazone 30-45mg/day. Concomitant therapy: Antihypertensive drugs or other concurrent treatments, including dietary regimens, remained unchanged throughout the study.

49.2.2. Metformin (N = 39)

Metformin 750mg/day. Concomitant therapy: Antihypertensive drugs or other concurrent treatments, including dietary regimens, remained unchanged throughout the study.

49.2.3. Glimepiride (N = 37)

Glimepiride 1.0-2.0mg/day. Concomitant therapy: Antihypertensive drugs or other concurrent treatments, including dietary regimens, remained unchanged throughout the study.

49.3. Characteristics

49.3.1. Arm-level characteristics

Characteristic	Pioglitazone (N = 38)	Metformin (N = 39)	Glimepiride (N = 37)
% Male Sample size	n = 20 ; % = 53	n = 19 ; % = 49	n = 18 ; % = 49
Mean age (SD) (years) Mean (SD)	55.2 (9.2)	54.7 (9.8)	55.6 (9.3)
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) Mean (SD)	3.2 (2.1)	3 (2.5)	3.3 (2.6)

Characteristic	Pioglitazone (N = 38)	Metformin (N = 39)	Glimepiride (N = 37)
HbA1c (%) Mean (SD)	10.2 (0.8)	9.9 (0.7)	9.8 (0.7)
Blood pressure (mmHg) Mean (SD)	NA (NA)	NA (NA)	NA (NA)
Systolic blood pressure Mean (SD)	142.8 (17.1)	143.3 (18.8)	141.3 (21.3)
Diastolic blood pressure Mean (SD)	85.3 (9.8)	86.3 (10.1)	84.9 (7.7)
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 = 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 Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
People with a learning disability Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Weight Mean (SD)	NA (NA)	NA (NA)	NA (NA)
BMI (kg/m2) Mean (SD)	10.2 (0.8)	9.9 (0.7)	9.8 (0.7)
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Cholesterol and lipid levels Mean (SD)	NA (NA)	NA (NA)	NA (NA)

Characteristic	Pioglitazone (N = 38)	Metformin (N = 39)	Glimepiride (N = 37)
Total cholesterol Mean (SD)	5.77 (0.57)	5.7 (0.36)	5.89 (0.49)
HDL cholesterol Mean (SD)	1.38 (0.12)	1.33 (0.09)	1.35 (0.11)
Triglycerides Mean (SD)	2.47 (1.26)	2.31 (1.14)	2.63 (1.37)
Albumin creatinine ratio Mean (SD)	NA (NA)	NA (NA)	NA (NA)
eGFR (mL/min/1.73m2) Mean (SD)	NA (NA)	NA (NA)	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

50. Yoon, 2012

Bibliographic Reference	Yoon, K H; Steinberg, H; Teng, R; Golm, G T; Lee, M; O'Neill, E A; Kaufman, K D; Goldstein, B J; Efficacy and safety of initial combination therapy with sitagliptin and pioglitazone in patients with type 2 diabetes: a 54-week study.; Diabetes, obesity & metabolism; 2012; vol. 14 (no. 8); 745-52

50.1. 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	NCT00397631
Study type	Randomised controlled trial (RCT) Double-blind single-dummy placebo RCT with open-label pioglitazone.
Study location	International (sites in 14 countries: Brazil, Columbia, Costa Rica, Czech Republic, India, Lithuania, Malaysia, Peru, Philippines, Poland, Puerto Rico, Russian Federation, South Korea, USA)
Study setting	Community
Study dates	09/2007 to 01/2009
Sources of funding	Funded by Merck Sharp & Dohme LLC
Inclusion criteria	• Aged≥18 years • Diagnosis of type 2 diabetes mellitus • Not receiving oral antihyperglycaeic agents prior to screening • Not received anti-hyperglycaemic agent for ≥4 cumulative weeks in prior 2 years and none within 4-mo screening • HbA1c level 8-12% inclusive
Exclusion criteria	• Fasting fingerstick glucose level <7.2 mmol/l or >17.8 mmol./l at randomisation • Diagnosis of type 2 diabetes • Unstable cardiac disease

	• Significant renal impairment (estimated creatinine clearance <60 ml/min) or elevated ALT or AST levels (>2 times upper limit of normal)
Recruitment / selection of participants	Recruited from sites in 14 countries. Participants received diet and exercise counselling and then started 2 week single-blind placebo run-in period. Participants with adequate compliance (≥85% via tablet counts) during run-in period randomised 1:1 ratio to arms. Lab assessments conducted at central laboratory by technicians blinded to treatment. Thirty-week Extension study to original 24-week study (Yoon KH, Shockey GR, Teng R, Golm GT, Thakkar PR, Meehan AG, Williams-Herman DE, Kaufman KD, Amatruda JM, Steinberg H. Effect of initial combination therapy with sitagliptin, a dipeptidyl peptidase-4 inhibitor, and pioglitazone on glycemic control and measures of β-cell function in patients with type 2 diabetes. International journal of clinical practice. 2011 Feb;65(2):154-64.).
Intervention(s)	• Sitagliptin 100 mg once daily + Pioglitazone 30 mg once daily Participants in this arm took one oral sitagliptin tablet, double blinded, and one open-label pioglitazone tablet, both once daily for 24 weeks.
Cointervention	Placebo for sitagliptin in comparator arm only
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	7) Mixed population Inclusion criteria: no oral anti-hyperglycaemic agent prior to screening, with less than 4 weeks cumulative prior treatment in prior 2 years and none within 4-mo of screening visit.
Comparator	• Pioglitazone 30 mg once daily Oral pioglitazone tablet 30 mg once daily with matching placebo (for sitagliptin) for 24 weeks. Pioglitazone tablet was open-label.
Number of participants	N=520 in original trial; N=317 in extension trial
Duration of follow-up	54 weeks
Indirectness	None
Method of analysis	Modified ITT Efficacy analyses conducted on all randomised participants who received at least one study drug dose, and had both baseline and at least one post-baseline assessment. Safety analysis conducted on all randomised participants. Missing data not imputed.
Additional comments	

50.2. Study arms

50.2.1. Pioglitazone 30 mg + Sitagliptin 100 mg once daily (N = 261)

Oral sitagliptin 100 mg + Oral pioglitazone 30 mg once daily for 24 weeks.

50.2.2. Pioglitazone 30 mg once daily (N = 259)

Oral pioglitazone 30 mg once daily with matching placebo for 24 weeks.

50.3. Characteristics

50.3.1. Arm-level characteristics

Characteristic	Pioglitazone 30 mg + Sitagliptin 100 mg once daily (N = 261)	Pioglitazone 30 mg once daily (N = 259)
% Male Sample size	n = 86 ; % = 52.4	n = 90 ; % = 58.8
Mean age (SD) (years) Mean (SD)	51.4 (10)	52.3 (11.5)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Asian Sample size	n = 42 ; % = 25.6	n = 41 ; % = 26.8
Black Sample size	n = 7 ; % = 4.3	n = 3 ; % = 2
Hispanic or Latino Sample size	n = 64 ; % = 39	n = 58 ; % = 37.9
Not hispanic or latino Sample size	n = 100 ; % = 61	n = 95 ; % = 62.1
Other Sample size	n = 22 ; % = 13.4	n = 24 ; % = 15.7
White Sample size	n = 93 ; % = 56.7	n = 85 ; % = 55.6
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR

Characteristic	Pioglitazone 30 mg + Sitagliptin 100 mg once daily (N = 261)	Pioglitazone 30 mg once daily (N = 259)
Time since type 2 diabetes diagnosis (years) Mean (SD)	2.6 (4)	1.6 (3.7)
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
Number of people with obesity Nominal	NR	NR
Albumin creatinine ratio 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

51. Yoon, 2011

Bibliographic Reference	Yoon, K. H.; Shin, J. A.; Kwon, H. S.; Lee, S. H.; Min, K. W.; Ahn, Y. B.; Yoo, S. J.; Ahn, K. J.; Park, S. W.; Lee, K. W.; Sung, Y. A.; Park, T. S.; Kim, M. S.; Kim, Y. K.; Nam, M. S.; Kim, H. S.; Park Ie, B.; Park, J. S.; Woo, J. T.; Son, H. Y.; Comparison of the efficacy of glimepiride, metformin, and rosiglitazone monotherapy in korean drug-naïve type 2 diabetic patients: the practical evidence of antidiabetic monotherapy study; Diabetes Metab J; 2011; vol. 35 (no. 1); 26-33

51.1. 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	South Korea.
Study setting	Outpatient follow-up.
Study dates	February 2007 to December 2008.
Sources of funding	Grants from the Korean Diabetes Association. The investigators received drugs from Handok Pharmaceuticals Co. Ltd., GlaxoSmithKline Ltd. Korea, and Merck Ltd. Korea.
Inclusion criteria	Ages 30-65; HbA1c 6.5-9.5%; never taken an oral hypoglycaemic agent.
Exclusion criteria	Glucocorticoid users; pregnant women; people who had clinically significant liver disease (AST, ALT >2.5 x upper limit of normal); significant renal disease (serum creatinine >1.5 mg/dL in men, >1.4 mg/dL in women); a history of lactic acidosis; a history of unstable angina or severe angina pectoris; a history or treatment for congestive heart failure; contraindications to metformin or sulfonylurea treatment.
Recruitment / selection of participants	No additional information.

Intervention(s)	Glimepiride N=118 Glimepiride initially 2mg once a day, up to 4mg twice a day for 48 weeks. Concomitant therapy: All people received a lifestyle intervention including individualised education according to current, recommended guidelines for medical nutritional treatment. People were recommended to perform at least 150 minutes per week of moderate-intensity aerobic physical activity, provided exercise was not contraindicated.
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	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	Metformin N=114 Metformin initially 500mg once a day, up to 1000mg twice a day for 48 weeks. Concomitant therapy: All people received a lifestyle intervention including individualised education according to current, recommended guidelines for medical nutritional treatment. People were recommended to perform at least 150 minutes per week of moderate-intensity aerobic physical activity, provided exercise was not contraindicated. A third arm (n=117) received rosiglitazone. This arm was not included in this data extraction as it was not relevant to the review protocol.
Number of participants	349 (including rosiglitazone, 232 if excluding rosiglitazone).
Duration of follow-up	48 weeks.
Indirectness	No additional information.
Method of analysis	ITT
Additional comments	No additional information.

51.2. Study arms

51.2.1. Glimepiride (N = 118)

Glimepiride initially 2mg once a day, up to 4mg twice a day for 48 weeks. Concomitant therapy: All people received a lifestyle intervention including

individualised education according to current, recommended guidelines for medical nutritional treatment. People were recommended to perform at least 150 minutes per week of moderate-intensity aerobic physical activity, provided exercise was not contraindicated.

51.2.2. Metformin (N = 114)

Metformin initially 500mg once a day, up to 1000mg twice a day for 48 weeks. Concomitant therapy: All people received a lifestyle intervention including individualised education according to current, recommended guidelines for medical nutritional treatment. People were recommended to perform at least 150 minutes per week of moderate-intensity aerobic physical activity, provided exercise was not contraindicated.

51.3. Characteristics

51.3.1. Arm-level characteristics

Characteristic	Glimepiride (N = 118)	Metformin (N = 114)
% Male Sample size	n = 66 ; % = 55.93	n = 66 ; % = 57.89
Mean age (SD) (years) Mean (SD)	50.8 (8.9)	51.8 (8.5)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of frailty Mean (SD)	NR (NR)	NR (NR)
Time since type 2 diabetes diagnosis Mean (SD)	NR (NR)	NR (NR)
HbA1c (%) Mean (SD)	7.8 (0.8)	7.9 (0.8)
Blood pressure (mmHg) Mean (SD)	NA (NA)	NA (NA)

Characteristic	Glimepiride (N = 118)	Metformin (N = 114)
Systolic blood pressure Mean (SD)	126.3 (12.8)	128.2 (12.4)
Diastolic blood pressure Mean (SD)	78.4 (8.7)	79.8 (8.6)
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)	67.9 (10.9)	68.9 (11.1)
BMI (kg/m2) Mean (SD)	25.5 (3.1)	25.7 (3.2)
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR
Cholesterol and lipid levels (mg/dL) Mean (SD)	NA (NA)	NA (NA)
Total cholesterol Mean (SD)	190.2 (41.3)	186.8 (34.3)
HDL cholesterol Mean (SD)	45 (12)	43 (13)

Characteristic	Glimepiride (N = 118)	Metformin (N = 114)
LDL cholesterol Mean (SD)	110.9 (42)	106 (33.7)
Triglyceride Mean (SD)	127 (114)	144 (99)
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	n = NR ; % = NR
Blood pressure-lowering medication used Sample size	n = 34 ; % = 28.81	n = 33 ; % = 28.95
Statins/lipid-lowering medication used Sample size	n = 35 ; % = 29.66	n = 33 ; % = 28.95
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR

52. Yuan, 2012

Bibliographic Reference	Yuan, G. H.; Song, W. L.; Huang, Y. Y.; Guo, X. H.; Gao, Y.; Efficacy and tolerability of exenatide monotherapy in obese patients with newly diagnosed type 2 diabetes: a randomized, 26 weeks metformin-controlled, parallel-group study; Chin Med J (Engl); 2012; vol. 125 (no. 15); 2677-81

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	No additional information.
Study type	Randomised controlled trial (RCT)
Study location	China.
Study setting	Outpatient follow-up.
Study dates	No additional information.
Sources of funding	No additional information.
Inclusion criteria	Greater than 18 years of age; new type 2 diabetes (<1 month); HbA1c 7-10%; BMI 28-40kg/m2 or waist circumference >90cm (male) or 85cm (female); managing type 2 diabetes with diet and exercise prior to the study.
Exclusion criteria	Ever been treated with antidiabetic or lipid lowering agents; had blood pressure >150/100mmHg; had a history or presence of clinically significant cardiac disease within the year prior to inclusion in the study; had renal or hepatic dysfunction; had a history or clinically suspected hyper- or hypothyroid disease; Cushing syndrome.
Recruitment / selection of participants	No additional information.
Intervention(s)	Exenatide N=33

	Exenatide 5 micrograms injected subcutaneously twice daily before morning and evening meals for 4 weeks, then increased to 10 micrograms twice daily thereafter. Given for a total of 26 weeks. Concomitant therapy: On confirmed hypoglycaemic event (documented blood glucose <3.3 mmol/L) and 2 unconfirmed events allowed the dose of either drug to be decreased by 50% (additional episodes allowed further decrease or discontinuation).
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 Based on BMI, hypertension and presence of type 2 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

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=26 Metformin 500mg twice daily for 4 weeks, then increased to 500mg three times a day for 4-12 weeks. If fasting plasma glucose >6.1 mmol/L at week 12, metformin administrations was increased to 1000mg twice daily. Concomitant therapy: On confirmed hypoglycaemic event (documented blood glucose <3.3 mmol/L) and 2 unconfirmed events allowed the dose of either drug to be decreased by 50% (additional episodes allowed further decrease or discontinuation).
Number of participants	59
Duration of follow-up	26 weeks.
Indirectness	No additional information.
Method of analysis	ITT
Additional comments	No additional information.

52.2. Study arms

52.2.1. Exenatide (N = 33)

Exenatide 5 micrograms injected subcutaneously twice daily before morning and evening meals for 4 weeks, then increased to 10 micrograms twice daily thereafter. Given for a total of 26 weeks. Concomitant therapy: On confirmed hypoglycaemic event (documented blood glucose <3.3 mmol/L) and 2 unconfirmed events allowed the dose of either drug to be decreased by 50% (additional episodes allowed further decrease or discontinuation).

52.2.2. Metformin (N = 26)

Metformin 500mg twice daily for 4 weeks, then increased to 500mg three times a day for 4-12 weeks. If fasting plasma glucose >6.1 mmol/L at week 12, metformin administrations was increased to 1000mg twice daily. Concomitant therapy: On confirmed hypoglycaemic event (documented blood glucose <3.3 mmol/L) and 2 unconfirmed events allowed the dose of either drug to be decreased by 50% (additional episodes allowed further decrease or discontinuation).

52.3. Characteristics

52.3.1. Arm-level characteristics

Characteristic	Exenatide (N = 33)	Metformin (N = 26)
% Male Sample size	n = 17 ; % = 51	n = 12 ; % = 46
Mean age (SD) (years) Mean (SD)	58.5 (10.6)	56.8 (7.6)
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)	8.27 (1.58)	8.11 (1.92)
Blood pressure (mmHg) Mean (SD)	NA (NA)	NA (NA)
Systolic blood pressure Mean (SD)	138 (12)	130 (10)
Diastolic blood pressure Mean (SD)	87 (11)	85 (10)
Heart rate	NR (NR)	NR (NR)

Characteristic	Exenatide (N = 33)	Metformin (N = 26)
Mean (SD)		
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)	82.2 (12.8)	83.7 (10.7)
BMI (kg/m2) Mean (SD)	30.6 (2.8)	29.3 (2.6)
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

Characteristic	Exenatide (N = 33)	Metformin (N = 26)
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR

53. Zhang, 2020

Bibliographic Reference	Zhang, L. Y.; Qu, X. N.; Sun, Z. Y.; Zhang, Y.; Effect of liraglutide therapy on serum fetuin A in patients with type 2 diabetes and non-alcoholic fatty liver disease; Clinics & Research in Hepatology & Gastroenterology; 2020; vol. 44 (no. 5); 674-680

53.1. 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	Not reported
Study type	Randomised controlled trial (RCT)
Study location	Shandong, China
Study setting	Community/Hospital
Study dates	Not reported
Sources of funding	Funded by Yantai Affiliated Hospital of Binzhou Medical University
Inclusion criteria	• Aged ≥18 to ≤70 years • Treatment naive to hypoglycaemic drugs≥3 months before trial inclusion • HbA1c level ≥7.0 to ≤14% • BMI ≥20 to ≤35 kg/m2 • Weight fluctuation<10% ≤3 months before trial inclusion • Non-alcoholic fatty liver disease (as defined by Chinese Association for the Study of Liver Disease [2010]: i. no history of alcohol-drinking habits or alcohol intake <140g/week for men or <70g/week for women, in past 12 months; ii. liver imaging results meet diagnostic criteria of diffuse fatty liver and could not be explained by other reasons, and/or participants with metabolic syndrome-related components showing persistent elevation of ALT or AST, and gamma-GT of unknown cause >6 months; iii. specific diseases that could lead to steatosis have been excluded (e.g. viral

	hepatitis, drug-induced liver disease, total parenteral nutrition, Wilson's disease, and autoimmune liver disease.)
Exclusion criteria	• Diagnosis of type 1 diabetes or secondary diabetes • Presence of hypertension, kidney, cardiovascular, hyperthyroidism, hypothyroidism, acute stress state or any active inflammatory diseases • Receiving insulin
Recruitment / selection of participants	Participants recruited from Yantai Affiliated Hospital of Binzhou Medical University, China. All participants had previous metformin therapy (500 mg thrice daily) three times per day but maintained HbA1c>7%. Randomisation 1:1 to groups using computer-generated sequence. All participants given information about diet and exercise.
Intervention(s)	• Liraglutide 1.2 mg once daily Participants started on subcutaneous injections of liraglutide 0.6 mg once daily for 1 week, increased to 1.2 mg once daily for 23 weeks.
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	Not stated/unclear

2 diabetes mellitus	
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 All participants had previously taken metformin but maintained HbA1c % level >7% on it. Washout period of ≥3-mo inclusion criteria.
Population subgroups	
Comparator	• Pioglitazone 30 mg once daily Oral pioglitazone tablets 15 mg once daily for 1 week, increased to 30 mg once daily for remaining 23 weeks.
Number of participants	N=60
Duration of follow-up	24 weeks
Method of analysis	Not stated/unclear

53.2. Study arms

53.2.1. Liraglutide 1.2 mg once daily (N = 30)

Subcutaneous injection of liraglutide 0.6 mg once daily for 1 week and then 1.2 mg once daily for remaining 23 weeks.

53.2.2. Pioglitazone 30 mg once daily (N = 30)

Oral pioglitazone tablets 15 mg once daily for 1 week and then 30 mg once daily for remaining 23 weeks.

53.3. Characteristics

53.3.1. Arm-level characteristics

Characteristic	Liraglutide 1.2 mg once daily (N = 30)	Pioglitazone 30 mg once daily (N = 30)
% Male Sample size	n = 13 ; % = 43.3	n = 15 ; % = 50
Mean age (SD) (years) Mean (SD)	50.2 (11.5)	51.5 (12.1)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosis Nominal	NR	NR
HbA1c (%) Mean (SD)	8.1 (2)	8.1 (1.7)
Blood pressure (mmHg) Mean (SD)	NA (NA)	NA (NA)
Systolic blood pressure Mean (SD)	133.3 (17.1)	135.9 (12.6)
Diastolic blood pressure Mean (SD)	81.5 (13.4)	81.2 (12.1)
Heart rate Nominal	NR	NR
Smoking status Nominal	NR	NR
Alcohol consumption Nominal	NR	NR

Characteristic	Liraglutide 1.2 mg once daily (N = 30)	Pioglitazone 30 mg once daily (N = 30)
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)	79.3 (8.8)	78 (9.2)
BMI (kg/m2) Mean (SD)	27.6 (5.2)	27.1 (3.8)
Number of people with obesity Nominal	NR	NR
Cholesterol and lipid levels (mmol/L) Mean (SD)	NA (NA)	NA (NA)
Total cholesterol Mean (SD)	5.2 (1.1)	5.1 (1.5)
HDL-cholesterol Mean (SD)	1.1 (0.2)	1.1 (0.4)
LDL-cholesterol Mean (SD)	3.3 (1)	3.3 (1.3)
Triglycerides Mean (SD)	0.9 (0.5)	0.9 (0.6)
Albumin creatinine ratio Nominal	NR	NR
eGFR (mL/min/1.73m2) Mean (SD)	NR (NR)	NR (NR)

Characteristic	Liraglutide 1.2 mg once daily (N = 30)	Pioglitazone 30 mg once daily (N = 30)
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

54. Zhou, 2022

Bibliographic Reference	Zhou, H.; Ding, J.; Mohammad, O. H.; Wu, L.; Yang, S.; Effects of Metformin Combined with Dapagliflozin on Homocysteine, Cystatin C and Beta-2 Microglobulin Levels in Patients with Diabetes Mellitus; Indian journal of pharmaceutical sciences; 2022; vol. 84; 153-157

54.1. 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.
Study setting	Outpatient follow-up.
Study dates	No additional information.
Sources of funding	No additional information.
Inclusion criteria	Meeting the diagnostic criteria of T2DM; course of disease at least 12 months; people and their families know about the situations and give their informed consent.
Exclusion criteria	Combined with acute and chronic infectious diseases of various tissues and organs; combined with malignant tumours; combined with immune system diseases; have allergic reactions to the drugs adopted in our study.
Recruitment / selection of participants	No additional information.
Intervention(s)	Dapagliflozin + Metformin N=75 Dapagliflozin 10mg once a day and metformin 250mg twice daily for 24 weeks. 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	Metformin N=75 Metformin 250mg twice daily for 24 weeks. Concomitant therapy: No additional information.
Number of participants	150
Duration of follow-up	24 weeks.
Indirectness	No additional information.
Method of analysis	Not stated/unclear
Additional comments	No additional information.

54.2. Study arms

54.2.1. Dapagliflozin + Metformin (N = 75)

Dapagliflozin 10mg once a day and metformin 250mg twice daily for 24 weeks. Concomitant therapy: No additional information.

54.2.2. Metformin (N = 75)

Metformin 250mg twice daily for 24 weeks. Concomitant therapy: No additional information.

54.3. Characteristics

54.3.1. Arm-level characteristics

Characteristic	Dapagliflozin + Metformin (N = 75)	Metformin (N = 75)
% Male Sample size	n = 39 ; % = 52	n = 40 ; % = 53
Mean age (SD) (years) Mean (SD)	47.69 (5.32)	47.72 (5.26)

Characteristic	Dapagliflozin + Metformin (N = 75)	Metformin (N = 75)
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 Mean (SD)	NR (NR)	NR (NR)
BMI (kg/m2) Mean (SD)	27.69 (1.45)	27.61 (1.49)

Characteristic	Dapagliflozin + Metformin (N = 75)	Metformin (N = 75)
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)	6.17 (0.33)	6.15 (0.34)
HDL cholesterol Mean (SD)	1.15 (0.85)	1.16 (0.83)
LDL cholesterol Mean (SD)	1.16 (0.35)	1.14 (0.36)
Triglycerides Mean (SD)	3.03 (0.28)	3.05 (0.21)
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

55. Zografou, 2015

Bibliographic Reference	Zografou, Ioanna; Sampanis, Christos; Gkaliagkousi, Eugenia; Iliadis, Fotios; Papageorgiou, Athanasios; Doukelis, Panagiotis; Vogiatzis, Konstantinos; Douma, Stella; Effect of vildagliptin on hsCRP and arterial stiffness in patients with type 2 diabetes mellitus.; Hormones (Athens, Greece); 2015; vol. 14 (no. 1); 118-25

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	No additional information.
Study type	Randomised controlled trial (RCT)
Study location	Greece.
Study setting	Outpatient follow-up.
Study dates	No additional information.
Sources of funding	None declared.
Inclusion criteria	People age at least 18 to no more than 70 years old; inadequate glycaemic control (HbA1c 7-9%) despite diet and exercise for 3 months.
Exclusion criteria	People with any macrovascular or microvascular diabetic complications; history of heart disease; uncontrolled hypertension (systolic blood pressure more than 180 mmHg and/or diastolic blood pressure more than 110 mmHg); excessive dyslipidaemic (total cholesterol more than 110 mmHg, triglycerides more than 400 mg/dL); elevated liver enzymes three times above the upper normal range and any other comorbidity that could interfere with the study; pregnant women and those who were breastfeeding or planning for pregnancy; women of childbearing age were advised to use contraception if they were sexually active.
Recruitment / selection of participants	No additional information.

Intervention(s)	Vildagliptin + Metformin N=32 Vildagliptin 50mg twice daily plus metformin 850mg twice daily.
Cointervention	Concomitant therapy: Antihypertensive and lipid-lowering drugs were unchanged during the study period. People were instructed to maintain dietary habits and daily activities.
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	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=32 Metformin 850mg twice daily.
Number of participants	64
Duration of follow-up	6 months.
Indirectness	No additional information.
Method of analysis	Not stated/unclear
Additional comments	No additional information.

55.2. Study arms

55.2.1. Vildagliptin + Metformin (N = 32)

Vildagliptin 50mg twice daily plus metformin 850mg twice daily. Concomitant therapy: Antihypertensive and lipid-lowering drugs were unchanged during the study period. People were instructed to maintain dietary habits and daily activities.

55.2.2. Metformin (N = 32)

Metformin 850mg twice daily. Concomitant therapy: Antihypertensive and lipid-lowering drugs were unchanged during the study period. People were instructed to maintain dietary habits and daily activities.

55.3. Characteristics

55.3.1. Arm-level characteristics

Characteristic	Vildagliptin + Metformin (N = 32)	Metformin (N = 32)
% Male Sample size	n = 18 ; % = 56	n = 20 ; % = 63
Mean age (SD) (years) Mean (SD)	52 (11.2)	56 (10.5)
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 ; % = 12.5	n = NR ; % = 25
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

Characteristic	Vildagliptin + Metformin (N = 32)	Metformin (N = 32)
Blood pressure-lowering medication used Sample size	n = NR ; % = 40.6	n = NR ; % = 43.8
Statins/lipid-lowering medication used Sample size	n = NR ; % = 40.6	n = NR ; % = 53.1
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR