National Institute for Health and Care Excellence

1

Final

Type 2 diabetes in adults: management (medicines update)

[F2.8] Evidence reviews for subsequent pharmacological management of type 2 diabetes – Appendix D7

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

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 All NICE guidance is subject to regular review and may be updated or withdrawn.

ISBN: 978-1-4731-9261-4

Appendices

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

437. Shankar, 2017

Bibliographic Reference	Shankar, R. R.; Bao, Y.; Han, P.; Hu, J.; Ma, J.; Peng, Y.; Wu, F.; Xu, L.; Engel, S. S.; Jia, W.; Sitagliptin added to stable insulin therapy with or without metformin in Chinese patients with type 2 diabetes; J Diabetes Invest; 2017; vol. 8 (no. 3); 321-329

437.1. 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	NCT01590797
Study type	Randomised controlled trial (RCT)
Study location	China
Study setting	Hospital
Study dates	07/2012 - 06/2014
Sources of funding	Merck & Co., Inc., Kenilworth, New Jersey, USA
Inclusion criteria	Aged 18–79 years with type 2 diabetes mellitus and were on a stable insulin (intermediate- or long-acting, or premixed insulin) regimen for ≥10 weeks with or without metformin ≥1,500 mg/day, and had inadequate glycemic control (screening HbA1c 7.5–11%).
Exclusion criteria	A site fasting fingerstick glucose of <130 mg/dL (7.2 mmol/L) or >260 mg/dL (14.4 mmol/L) at day 1, type 1 diabetes mellitus, New York Heart Association class III–IV congestive heart failure, unstable cardiac disease, marked renal impairment (estimated glomerular filtration rate <60 mL/min/1.73 m2 or, for patients taking metformin, creatinine ≥1.4 mg/dL [124 lmol/L] in men and ≥1.3 mg/dL [115 lmol/L] in women), triglycerides >600 mg/ dL, or elevated (>twofold upper limit of normal) aspartate

	aminotransferase or alanine aminotransferase. Treatment with any AHA other than the protocol-required insulin (alone or with metformin) within 12 weeks of study entry or having ever been treated with a DPP-4 inhibitor or a glucagon-like peptide 1 analogue were also excluded.
Recruitment / selection of participants	Patients with inadequately controlled type 2 diabetes mellitus and on stable insulin +/- metformin were recruited from 28 clinical sites in China and randomised 1:1 to receive sitagliptin 100 mg once daily or placebo once daily for 24 weeks. Patients were randomised based on their use of metformin (taking or not taking metformin) and the type of insulin (premixed vs intermediate-/long-acting) at screening.
Intervention(s)	Sitagliptin 100 mg daily Administered orally.
Cointervention	Insulin (intermediate- or long- acting or premixed insulin) +/- metformin
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure
Strata 2: People with atherosclerotic cardiovascular disease	People without atherosclerotic cardiovascular diseases
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	People without chronic kidney disease
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear

Subgroup 2: Onset of type 2 diabetes mellitus	Mixed population
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	eGFR ≥30mL/min/1.73m2
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Comparator	Placebo once daily Administered orally.
Number of participants	N=467
Duration of follow-up	24-week
Method of analysis	Modified ITT Not stated/unclear
Additional comments	Analysis is unclear but likely a mITT. Patients who received rescue medication were excluded and the last-observation-carried forward method was used to impute missing data.

437.2. Study arms

437.2.1. Sitagliptin 100 mg once daily (N = 234)

Administered orally

437.2.2. Placebo once daily (N = 233)

Administered orally

437.3. Characteristics

437.3.1. Arm-level characteristics

Characteristic	Sitagliptin 100 mg once daily (N = 234)	Placebo once daily (N = 233)
% Male No of events	n = 130 ; % = 55.6	n = 116 ; % = 49.8
Mean age (SD) (years) Mean (SD)	58.6 (8.4)	56.7 (9.1)
Chinese No of events	n = 234 ; % = 100	n = 233 ; % = 100
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	11 (5)	11.3 (5.8)
HbA1c (%) Mean (SD)	8.7 (0.9)	8.8 (0.9)
Smoking status Nominal	NR	NR
Alcohol consumption Nominal	NR	NR
People with a learning disability Nominal	NR	NR
Number of people with obesity Nominal	NR	NR
Albumin creatinine ratio Nominal	NR	NR
Premixed insulin No of events	n = 173 ; % = 73.9	n = 176 ; % = 75.5

Characteristic	Sitagliptin 100 mg once daily (N = 234)	Placebo once daily (N = 233)
Long- or intermediate-acting No of events	n = 61 ; % = 26.1	n = 57 ; % = 24.5
Metformin No of events	n = 115 ; % = 49.2	n = 116 ; % = 49.8
Statins/lipid-lowering medication used No of events	n = 43 ; % = 18.4	n = 27 ; % = 11.6
Other treatment being received Nominal	NR	NR

438. Sivalingam, 2023

Bibliographic Reference	Sivalingam, Suvanjaa; Wasehuus, Victor Soendergaard; Rotbain Curovic, Viktor; Blond, Martin Baek; Hansen, Tine W; Persson, Frederik; Rossing, Peter; Albuminuria-lowering effect of adding semaglutide on top of empagliflozin in individuals with type 2 diabetes: A randomized and placebo-controlled study.; Diabetes, obesity & metabolism; 2023

438.1. Study details

Secondary publication of another included study- see primary study for details	N/A
Other publications associated with this study included in review	N/A
Trial name / registration number	NCT04061200
Study type	Randomised controlled trial (RCT)
Study location	Copenhagen, Denmark
Study setting	Diabetes Centre
Study dates	Screening took place between October 2020 and February 2023.
Sources of funding	Novo Nordisk
Inclusion criteria	• Male or female patients ≥18 years with type 2 diabetes (according to WHO criteria) • UACR > 100 mg/g in the latest recorded measurement documented in medical files • eGFR ≥ 30 ml/min/1.73m2 within 3 months of informed consent documented in medical flies and at visit 1 • Female participants of child bearing potential were required to use contraception

	• Treatment with maximal tolerated dose of ACE inhibitor 4 weeks prior to randomisation
Exclusion criteria	• Type 1 diabetes • Known or suspected hypersensitivity to trial products or related products • Cancer (except basal cell skin cancer or squamous cell skin cancer) or any other clinically significant disorder, except for conditions associated with type 2 diabetes, which in the investigators opinion could interfere with the results of the trial • Cardiac disease defined as: decompensated heart failure (NHYA class III-IV) and /or diagnosis of unstable angina pectoris and /or myocardial infarction within the last 6 months • Previous bowel restriction • Body mass index <18.g kg/m2 • Females of childbearing potential who are pregnant, breastfeeding, planning to conceive or are not usign adequate conceptive methods • Known or suspected abuse of alcohol or narcotics • Participation in another intervention study
Recruitment / selection of participants	Participants were recruited from the Steno Diabetes Centre in Copenhagen, Denmark
Intervention(s)	Semaglutide 1 mg once weekly subcutaneous injection administered using a pen injector. Injection could be taken at any time of day during the same weekday. A fixed dose escalation regimen was used: 0.25 mg/week for 4 weeks, escalated to 0.5 mg/week for 4 weeks, and then 1 mg/ week thereafter until 26 weeks of treatment, if tolerated. If the 1 mg dose was not tolerated, 0.25 mg or 0.5mg/week could be continued. Semaglutide was added to empagliflozin 25mg capsules once daily, which was given during a 26 week open label run-in period.
Cointervention	Participants were given empagliflozin 25 mg capsules once daily for 26 weeks during an open label run-in period and continued during the 26 week treatment period. Participants treated with a GLP-1 receptor agonist prior to screening had this discontinued. Participants receiving another SGLT2 inhibitor prior to screening were switched to empagliflozin.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear People with decompensated heart failure (NHYA class III-IV) within past 6 months were excluded. No further information in baseline characteristics.

Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear People with unstable angina pectoris and /or myocardial infarction within the last 6 months were excluded. No further information.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Albuminuria is an inclusion criterion, study does not report whether participants had a diagnosis of CKD.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear Only mean duration reported in baseline characteristics.
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear Only mean BMI reported in baseline characteristics
Subgroup 5: eGFR category at baseline	eGFR ≥30mL/min/1.73m2
Subgroup 6: Albuminuria category at baseline	Mixed population At screening, 66.7% of participants in the placebo and 56.7% of participants in the semaglutide arms had UACR >=30 to 300 mg/g and 33.3% of participants in the placebo, and 43.3% of participants in the semaglutide arms had UACR >300 mg/g.

Population subgroups	NA
Comparator	Placebo 1 mg once weekly subcutaneous injection administered using a pen injector. Injection could be taken at any time of day during the same weekday. A fixed dose escalation regimen was used: 0.25 mg/week for 4 weeks, escalated to 0.5 mg/week for 4 weeks, and then 1 mg/week thereafter until 26 weeks of treatment, if tolerated. Placebo was added to empagliflozin 25mg capsules once daily, which was given during a 26 week open label run-in period.
Number of participants	634 participants were assessed for eligibility, 73 were enrolled, and 60 were randomised. Of 30 participants allocated to placebo, 26 completed and were analysed. Of 30 participants allocated to semagluitde, 28 were analysed.
Duration of follow-up	26 weeks
Indirectness	Directly applicable
Method of analysis	ITT Corrected differences at randomization derived from a randomization constrained repeated measures regression model.
Additional comments	NA

438.2. Study arms

438.2.1. Semaglutide (N = 30)

Semaglutide 1 mg subcutaneous injection

438.2.2. Placebo (N = 30)

Placebo 1 mg subcutaneous injection

438.3. Characteristics

438.3.1. Arm-level characteristics

Characteristic	Semaglutide (N = 30)	Placebo (N = 30)
% Male Sample size	n = 24 ; % = 80	n = 23 ; % = 76.7
Mean age (SD) Mean (SD)	70.5 (6.8)	69.4 (9.1)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 29 ; % = 97	n = 30 ; % = 100
Other Sample size	n = 1 ; % = 3	n = 0 ; % = 0
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 diagnosed Mean (SD)	18 (10)	19 (11)
HbA1c (%) Mean (SD)	7.9 (3.2)	7.6 (3.2)
Cardiovascular risk factors Sample size	n = NA ; % = NA	n = NA ; % = NA
History of cardiovascular disease Sample size	n = 5 ; % = 16.7	n = 6 ; % = 20
Blood pressure (mmHg) Mean (SD)	NA (NA)	NA (NA)
Systolic blood pressure Mean (SD)	136 (16)	135 (15)
Diastolic blood pressure	72 (11)	74 (11)

Characteristic	Semaglutide (N = 30)	Placebo (N = 30)
Mean (SD)		
Heart rate (beats per minute) Mean (SD)	73 (14)	70 (12)
Smoking status Current smoker Sample size	n = 6 ; % = 20	n = 7 ; % = 23.3
Alcohol consumption Mean (SD)	NR (NR)	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)	93 (16.4)	92.9 (12.2)
BMI (kg/m²) Mean (SD)	31.1 (5.6)	30 (4.9)
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR
Cholesterol and lipid levels Mean (SD)	NA (NA)	NA (NA)
HDL cholesterol Mean (SD)	0.97 (0.21)	1.18 (0.61)
LDL cholesterol Mean (SD)	1.65 (0.68)	1.85 (0.78)
Albumin creatinine ratio (mg/g) UACR Sample size	n = NA ; % = NA	n = NA ; % = NA
<30 mg/g Sample size	n = 0 ; % = 0	n = 2 ; % = 6.7

Characteristic	Semaglutide (N = 30)	Placebo (N = 30)
30 to 300 mg/g Sample size	n = 19 ; % = 63.3	n = 24 ; % = 80
>300 mg/g Sample size	n = 11 ; % = 36.7	n = 4 ; % = 13.3
eGFR mL/min/1.73m2 (ml/min/1.73 m²) Sample size	n = NA ; % = NA	n = NA ; % = NA
≤30 mL/min/1.73m² Sample size	n = 1 ; % = 3.3	n = 5 ; % = 16.7
>30 to ≤45 mL/min/1.73m² Sample size	n = 6 ; % = 20	n = 8 ; % = 26.7
>45 to ≤60 mL/min/1.73m² Sample size	n = 8 ; % = 26.7	n = 5 ; % = 16.7
>60 mL/min/1.73m² Sample size	n = 15 ; % = 50	n = 12 ; % = 40
Metformin Sample size	n = NR ; % = NR	n = NR ; % = NR
Insulin Sample size	n = 0 ; % = 0	n = 0 ; % = 0
Sulfonylureas Sample size	n = 14 ; % = 46.7	n = 16 ; % = 53.3
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
Mean eGFR (ml/min/1.73 m²) Mean (SD)	64.7 (24.5)	55.7 (22.6)

439. Skov, 2014

Bibliographic Reference	Skov, Vibe; Cangemi, Claudia; Gram, Jeppe; Christensen, Mette M; Grodum, Ellen; Sorensen, Ditte; Argraves, W Scott; Henriksen, Jan E; Rasmussen, Lars M; Metformin, but not rosiglitazone, attenuates the increasing plasma levels of a new cardiovascular marker, fibulin-1, in patients with type 2 diabetes.; Diabetes care; 2014; vol. 37 (no. 3); 760-6

439.1. Study details

Secondary publication of another included study- see primary study for details	This is a subsidiary study of the following parent study: Gram, J.; Henriksen, J. E.; Grodum, E.; Juhl, H.; Hansen, T. B.; Christiansen, C.; Yderstræde, K.; Gjessing, H.; Hansen, H. M.; Vestergaard, V.; Hangaard, J.; Beck-Nielsen, H. Pharmacological treatment of the pathogenetic defects in type 2 diabetes: the randomized multicenter South Danish Diabetes Study. Diabetes Care; 2011; vol. 34 (no. 1); 27-33.
Other publications associated with this study included in review	No additional information.
Trial name / registration number	NCT00121966

440. Skrivanek, 2014

Bibliographic Reference	Skrivanek, Z; Gaydos, B L; Chien, J Y; Geiger, M J; Heathman, M A; Berry, S; Anderson, J H; Forst, T; Milicevic, Z; Berry, D; Dose-finding results in an adaptive, seamless, randomized trial of once-weekly dulaglutide combined with metformin in type 2 diabetes patients (AWARD-5).; Diabetes, obesity & metabolism; 2014; vol. 16 (no. 8); 748-56

440.1. Study details

Secondary publication of another included study- see primary study for details	Nauck, M.; Weinstock, R. S.; Umpierrez, G. E.; Guerci, B.; Skrivanek, Z.; Milicevic, Z. Efficacy and safety of dulaglutide versus sitagliptin after 52 weeks in type 2 diabetes in a randomized controlled trial (AWARD-5). Diabetes Care; 2014; vol. 37 (no. 8); 2149-2158. **(N.B. after the dose selection occurred (as reported in Skrivanek 2014), patients from the non-selected arms were discontinued and additional patients were assigned to the remaining arms: dulaglutide 1.5 mg, dulaglutide 0.75 mg, sitagliptin 100 mg, or placebo in a 2:2:2:1 ratio and entered the AWARD-5 trial so this study has been included as a separate study altogether because it included only a small subset of the total number of patients included in the AWARD-5 trial)**
Other publications associated with this study included in review	Weinstock, R S; Guerci, B; Umpierrez, G; Nauck, M A; Skrivanek, Z; Milicevic, Z. Safety and efficacy of once-weekly dulaglutide versus sitagliptin after 2 years in metformin-treated patients with type 2 diabetes (AWARD-5): a randomized, phase III study. Diabetes, obesity & metabolism; 2015; vol. 17 (no. 9); 849-58.
Trial name / registration number	AWARD-5/NCT00734474
Study type	Randomised controlled trial (RCT)
Study location	US
Study setting	No additional information.
Study dates	No additional information.
Sources of funding	Eli Lily and company

Inclusion criteria	Patients with type 2 diabetes were required to be treated with metformin (≥1500 mg/day) for ≥ 6 weeks prior to randomization; other oral antidiabetic medications were discontinued. After lead-in, patients were randomised to dulaglutide injection (seven doses during dose-finding; only selected dose(s) after dose selection occurred), sitagliptin 100 mg once daily or placebo (injectable and oral), all in combination with metformin.
Exclusion criteria	No additional information.
Recruitment / selection of participants	Patients with type 2 diabetes who were being treated with metformin≥ 6 weeks prior to randomisation were randomised 3:1:1 to seven dulaglutide doses, sitagliptin (100 mg) or placebo.
Intervention(s)	Dulaglutide 0.2 mg /Dulaglutide 0.5 mg /Dulaglutide 0.75 mg /Dulaglutide 1.0 mg /Dulaglutide 1.5 mg /Dulaglutide 2.0 mg /Dulaglutide 3.0 mg All administered once weekly and subcutaneously.
Cointervention	Metformin (≥ 1500 mg/day) Administered orally.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Copied from parent study (Nauck 2014)
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Copied from parent study (Nauck 2014)
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Copied from parent study (Nauck 2014).
Strata 4: People with	Not stated/unclear

type 2 diabetes mellitus and high cardiovascular risk	
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Mixed population
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	No additional information.
Comparator	Sitagliptin 100 mg daily Administered orally. Placebo daily Administered subcutaneously and orally
Number of participants	N=230

Duration of follow-up	26-week
Indirectness	No additional information.
Method of analysis	Not stated/unclear
Additional comments	

440.2. Study arms

440.2.1. Dulaglutide 0.25 mg once weekly (N = 24)

Administered subcutaneously

440.2.2. Dulaglutide 0.5 mg once weekly (N = 25)

Administered subcutaneously

440.2.3. Dulaglutide 0.75 mg once weekly (N = 21)

Administered subcutaneously

440.2.4. Dulaglutide 1.0 mg once weekly (N = 10)

Administered subcutaneously

440.2.5. Dulaglutide 1.5 mg once weekly (N = 25)

Administered subcutaneously

440.2.6. Dulaglutide 2.0 mg once weekly (N = 30)

Administered subcutaneously

440.2.7. Dulaglutide 3.0 mg once weekly (N = 15)

Administered subcutaneously

440.2.8. Sitagliptin 100 mg daily (N = 42)

Administered orally

440.2.9. Placebo daily/weekly (N = 38)

Administered orally and subcutaneously

440.3. Characteristics

440.3.1. Arm-level characteristics

Characteristic	Dulaglutide 0.25 mg once weekly (N = 24)	Dulaglutide 0.5 mg once weekly (N = 25)	Dulaglutide 0.75 mg once weekly (N = 21)	Dulaglutide 1.0 mg once weekly (N = 10)	Dulaglutide 1.5 mg once weekly (N = 25)	Dulaglutide 2.0 mg once weekly (N = 30)	Dulaglutide 3.0 mg once weekly (N = 15)	Sitagliptin 100 mg daily (N = 42)	Placebo daily/weekly (N = 38)
% Male No of events	n = 9 ; % = 38	n = 13 ; % = 52	n = 10 ; % = 48	n = 3 ; % = 30	n = 10 ; % = 40	n = 8 ; % = 27	n = 5 ; % = 33	n = 21 ; % = 50	n = 12 ; % = 32
Mean age (SD) (years) Mean (SD)	57 (7)	55 (10)	52 (11)	55 (9)	53 (11)	53 (11)	53 (11)	53 (12)	53 (10)
Black No of events	n = 0 ; % = 0	n = 2 ; % = 8	n = 0 ; % = 0	n = 0 ; % = 0	n = 2 ; % = 8	n = 3 ; % = 10	n = 1 ; % = 7	n = 2 ; % = 5	n = 2 ; % = 5
White No of events	n = 12 ; % = 50	n = 9 ; % = 36	n = 13 ; % = 62	n = 4 ; % = 40	n = 10 ; % = 40	n = 13 ; % = 43	n = 7 ; % = 47	n = 20 ; % = 48	n = 15 ; % = 40
East Asian No of events	n = 5 ; % = 21	n = 0 ; % = 0	n = 1 ; % = 5	n = 0 ; % = 0	n = 2 ; % = 8	n = 6 ; % = 20	n = 0 ; % = 0	n = 4 ; % = 10	n = 4 ; % = 11
Hispanic No of events	n = 6 ; % = 25	n = 14 ; % = 56	n = 7 ; % = 33	n = 6 ; % = 60	n = 11 ; % = 44	n = 8 ; % = 27	n = 7 ; % = 47	n = 16 ; % = 38	n = 17 ; % = 45

Characteristic	Dulaglutide 0.25 mg once weekly (N = 24)	Dulaglutide 0.5 mg once weekly (N = 25)	Dulaglutide 0.75 mg once weekly (N = 21)	Dulaglutide 1.0 mg once weekly (N = 10)	Dulaglutide 1.5 mg once weekly (N = 25)	Dulaglutide 2.0 mg once weekly (N = 30)	Dulaglutide 3.0 mg once weekly (N = 15)	Sitagliptin 100 mg daily (N = 42)	Placebo daily/weekly (N = 38)
Others No of events	n = 1 ; % = 4	n = 0 ; % = 0	n = 0 ; % = 0	n = 0 ; % = 0	n = 0 ; % = 0	n = 0 ; % = 0	n = 0 ; % = 0	n = 0 ; % = 0	n = 0 ; % = 0
Time since type 2 diabetes diagnosed (years) Mean (SD)	7 (4)	7 (4)	7 (5)	7 (5)	9 (7)	7 (5)	7 (6)	9 (5)	7 (6)
Smoking status Nominal	NR	NR	NR	NR	NR	NR	NR	NR	NR
Alcohol consumption Nominal	NR	NR	NR	NR	NR	NR	NR	NR	NR
Presence of severe mental illness Nominal	NR	NR	NR	NR	NR	NR	NR	NR	NR
People with significant cognitive impairment Nominal	NR	NR	NR	NR	NR	NR	NR	NR	NR
People with a learning disability	NR	NR	NR	NR	NR	NR	NR	NR	NR

Characteristic	Dulaglutide 0.25 mg once weekly (N = 24)	Dulaglutide 0.5 mg once weekly (N = 25)	Dulaglutide 0.75 mg once weekly (N = 21)	Dulaglutide 1.0 mg once weekly (N = 10)	Dulaglutide 1.5 mg once weekly (N = 25)	Dulaglutide 2.0 mg once weekly (N = 30)	Dulaglutide 3.0 mg once weekly (N = 15)	Sitagliptin 100 mg daily (N = 42)	Placebo daily/weekly (N = 38)
Nominal									
Number of people with obesity Nominal	NR	NR	NR	NR	NR	NR	NR	NR	NR
Metformin No of events	n = 24 ; % = 100	n = 25 ; % = 100	n = 21 ; % = 100	n = 10 ; % = 100	n = 25 ; % = 100	n = 30 ; % = 100	n = 15 ; % = 100	n = 42 ; % = 100	n = 38 ; % = 100
Statins/lipid-lowering medication used Nominal	NR	NR	NR	NR	NR	NR	NR	NR	NR
Other treatment being received Nominal	NR	NR	NR	NR	NR	NR	NR	NR	NR

441. Softeland, 2017

Bibliographic Reference	Softeland, E.; Meier, J. J.; Vangen, B.; Toorawa, R.; Maldonado-Lutomirsky, M.; Broedl, U. C.; Empagliflozin as add-on therapy in patients with type 2 diabetes inadequately controlled with linagliptin and metformin: A 24-week randomized, double-blind, parallel-group trial; Diabetes Care; 2017; vol. 40 (no. 2); 201-209

441.1. Study details

Secondary publication of another included study- see primary study for details	No
Other publications associated with this study included in review	None
Trial name / registration number	NCT01734785
Study type	Randomised controlled trial (RCT) Double-blind, double-dummy, parallel group RCT
Study location	International (90 sites in 10 countries: Australia, Brazil, Canada, France, Korea, New Zealand, Norway, Spain, Taiwan, U.S.A)
Study setting	Outpatient
Study dates	03/2013 to 03/2015
Sources of funding	Funded by Boehringer Ingelheim and Eli Lilly and Company Diabetes Alliance
Inclusion criteria	• Aged≥18 years • Type 2 diabetes diagnosis • HbA1c 8-10.5% inclusive • On diet and exercise regimen • Stable dose of immediate-release metformin either ≥1500 mg/day or maximum tolerated dose, or maximum dose according to local label

	• BMI≤45 kg/m2
Exclusion criteria	• Uncontrolled hyperglycemia (glucose level>15.0 mmol/L after an overnight fast during the open-label or placebo add-on periods, confirmed by a second measurement) • Treatment with any anti-diabetes agent except metformin within12 weeks prior to start of open-label treatment • Treatment with any anti-diabetes agent except study drug and metformin prior to randomization to double-blind treatment • eGFR<60 mL/min/1.73 m2 • Hereditary galactose intolerance • Acute coronary syndrome, stroke, or transient ischemic attack within 3 months prior to consent • Any previous (within the past 2 years) or planned bariatric surgery • Treatment with anti-obesity drugs within 3 months prior to consent
Recruitment / selection of participants	Participants recruited from 90 sites in 10 countries and all were initially treated with open-label linagliptin 5 mg for 16 weeks in addition to background metformin at unchanged dose, followed in addition by 1 week of open-label placebo. Participants who had HbA1c 7-10,5% inclusive and satisfied other inclusion criteria then randomised 1:1:1 to one of the three arms. Randomisation used third-party interactive voice/web-response system, stratified by HbA1c (<8.5%; ≥8.5%) and eGFR (≥90 mL/min/1.73 m2; 60-89; MDRD equation) at end of initial 16-wk open label period. Rescue therapy, chosen at discretion of investigator (excluding DPP-4 inhibitors,GLP-1 RAs and SGLT2 inhibitors), permitted during double-blind treatment phase though not in open-label periods.
Intervention(s)	• Empagliflozin 10 mg daily • Empagliflozin 25 mg daily Single-pill combinations of empagliflozin and linagliptin 5 mg daily in morning for 24 weeks.
Cointervention	• Metformin • Linagliptin 5 mg All participants received stable dose of immediate-release metformin either ≥1500 mg, maximum tolerated dose, or maximum dose according to local label. In addition, all participants received oral linagliptin 5 mg either as a single-pill combination with empagliflozin or in addition to placebo. Tablets taken in morning.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 2: People with atherosclerotic	Not stated/unclear

cardiovascular disease	Exclusion criteria state: "acute coronary syndrome, stroke, or transient ischemic attack within 3 months prior to consent." No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear CKD not an inclusion/exclusion criteria. Exclusion criteria state: "eGFR <60mL/min/1.73m2." No information about CKD in the baseline characteristics table.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe 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<60 mL/min/1.73 m2
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Comparator	• Placebo

	Placebo in addition to oral linagliptin 5 mg once daily in morning for 24 weeks.
Number of participants	N=333
Duration of follow-up	24 weeks
Indirectness	None
Method of analysis	Modified ITT mITT analysis for efficacy outcomes (all randomised participants who received at least one study drug dose during double-blind period and who had baseline and at least one post-baseline HbA1c measurement during double-blind period) using observed data only and data after use of rescue medication set to missing. Safety analysis included all participants receiving at least one dose of double-blind treatment. Sensitivity analysis for HbA1c and weight with LOCF for missing data.
Additional comments	

441.2. Study arms

441.2.1. Empagliflozin 10 mg once daily (N = 112)

Single pill combination of empagliflozin 10 mg and linagliptin 5 mg once daily for 24 weeks, in addition to maximum tolerated dose of metformin.

441.2.2. Empagliflozin 25 mg once daily (N = 111)

Single pill combination of empagliflozin 25 mg and linagliptin 5 mg once daily for 24 weeks, in addition to maximum tolerated dose of metformin.

441.2.3. Placebo (N = 110)

Placebo + linagliptin 5 mg once daily for 24 weeks, in addition to maximum tolerated dose of metformin.

441.3. Characteristics

441.3.1. Arm-level characteristics

Characteristic	Empagliflozin 10 mg once daily (N = 112)	Empagliflozin 25 mg once daily (N = 111)	Placebo (N = 110)
% Male Sample size	n = 66 ; % = 60.6	n = 71 ; % = 64.5	n = 60 ; % = 55.6
Mean age (SD) (years) Mean (SD)	54.3 (9.6)	55.4 (9.9)	55.9 (9.7)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Asian Sample size	n = 26 ; % = 23.9	n = 30 ; % = 27.3	n = 32 ; % = 29.6
Other Sample size	n = 16 ; % = 14.7	n = 15 ; % = 13.6	n = 17 ; % = 15.7
White Sample size	n = 67 ; % = 61.5	n = 65 ; % = 59.1	n = 59 ; % = 54.6
Comorbidities Nominal	NR	NR	NR
Presence of frailty Nominal	NR	NR	NR
Time since type 2 diabetes diagnosed Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Less than 1 year Sample size	n = 6 ; % = 5.5	n = 7 ; % = 6.4	n = 9 ; % = 8.3
more than 1 year-5 years Sample size	n = 30 ; % = 27.5	n = 41 ; % = 37.3	n = 31 ; % = 28.7
more than 5 years-10 years Sample size	n = 42 ; % = 38.5	n = 35 ; % = 31.8	n = 38 ; % = 35.2
More than 10 years Sample size	n = 31 ; % = 28.4	n = 27 ; % = 24.5	n = 30 ; % = 27.8

Characteristic	Empagliflozin 10 mg once daily (N = 112)	Empagliflozin 25 mg once daily (N = 111)	Placebo (N = 110)
Cardiovascular risk factors 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 Nominal	NR	NR	NR
Blood pressure-lowering medication used Nominal	NR	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR	NR
Other treatment being received Nominal	NR	NR	NR

Baseline characteristics data is for Empagliflozin 10 mg, N=109; Empagliflozin 25 mg, N=110; and placebo, N=108.

442. Sone, 2019

Bibliographic Reference	Sone, H.; Kaneko, T.; Shiki, K.; Tachibana, Y.; Pfarr, E.; Lee, J.; Tajima, N.; Efficacy and safety of empagliflozin as add-on to insulin in Japanese patients with type 2 diabetes: a randomised, double-blind, placebo-controlled trial; Diabetes Obes Metab; 2019

442.1. Study details

Secondary publication of another included study- see primary study for details	No
Other publications associated with this study included in review	None
Trial name / registration number	NCT02589639
Study type	Randomised controlled trial (RCT) Double-blind parallel-group RCT
Study location	Japan (51 sites)
Study setting	Outpatient
Study dates	11/2015 to 01/2018
Sources of funding	Supported by Nippon Boehringer Ingelheim Co. Ltd.
Inclusion criteria	• Aged≥20 to <75 years • Diagnosis of type 2 diabetes • Insufficient glycaemic control despite receiving insulin with or without oral antidiabetic≥12 weeks prior to screening • HbA1c of≥7.5% to≤10.0% (for participants pre-treated with insulin only) or an HbA1c of≥7.0% to≤9.5% at screening and≥7.5% to≤10.0% after the 10-week wash-out period (for participants pre-treated with insulin and an OAD) • Fasting C-peptide >0.5 ng/mL

	• BMI>22 kg/m2 and ≤40 kg/m2
Exclusion criteria	• Receiving a sulphonylurea at dose more than half of maximum approved daily dose, GLP-1 RA, a thiazolidinedione or SGLT2 inhibitor • eGFR<45 mL/min/1.73m2 during screening or run-in period • Experienced a cardiovascular and/or stroke event in the last 12 weeks
Recruitment / selection of participants	Participants from 51 sites in Japan attended screening, then underwent 10-week wash-out period of oral antidiabetics, a 2-week open-label placebo period, and then 52 week treatment period (first 16 weeks, no change to background insulin dose; subsequent 36 weeks, amendment of insulin dose permitted at investigator discretion. Random assignment using computer-generated sequence, stratified by baseline HbA1c (<8.5%, ≥8.5%), renal function (eGFR<60mL/min/1.73m2) and type of pretreatment insulin (basal; other). In first 16 weeks, insulin could be used as rescue therapy if overnight fast>270 mg/dL in weeks 1-12) or >240 mg/dL in weeks 12-16.
Intervention(s)	• Empagliflozin 10 mg daily • Empagliflozin 25 mg daily Oral empagliflozin 10 or 25 mg daily for 52 weeks, in addition to background insulin.
Cointervention	• Insulin All participants continued on their background insulin dose for 52 weeks.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Exclusion criteria state: "Acute coronary syndrome, stroke or TIA within 12 weeks prior to informed consent." No further information / no information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear CKD not an inclusion/exclusion criteria. Exclusion criteria state: "Impaired renal function, defined as eGFR<45 mL/min/1.73m2 (Japanese equation) as determined during screening and/or run-in phase." Baseline characteristics reports 37.2% overall had diabetic nephropathy.

Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe 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: Participants with eGFR<45 mL/min/1.73m2
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	
Comparator	• Placebo Matching placebo for 52 weeks in addition to insulin.
Number of participants	N=269
Duration of follow-up	52 weeks
Indirectness	None

Method of analysis	Modified ITT mITT LOCF analysis (all randomised participants who received at least one dose of study drug and had baseline HbA1c assessment) conducted for efficacy outcomes; safety analysis conducted on all randomised participants who received at least one dose of study drug

442.2. Study arms

442.2.1. Empagliflozin 10 mg daily (N = 89)

Oral empagliflozin 10 mg daily for 52 weeks, in addition to insulin.

442.2.2. Empagliflozin 25 mg daily (N = 90)

Oral empagliflozin 25 mg daily for 52 weeks, in addition to insulin.

442.2.3. Placebo (N = 90)

Matching placebo for 52 weeks, in addition to insulin.

442.3. Characteristics

442.3.1. Arm-level characteristics

Characteristic	Empagliflozin 10 mg daily (N = 89)	Empagliflozin 25 mg daily (N = 90)	Placebo (N = 90)
% Male Sample size	n = 63 ; % = 73.3	n = 61 ; % = 67.8	n = 69 ; % = 76.7
Mean age (SD) (years) Mean (SD)	58.3 (10)	58.6 (9.5)	59.1 (10.7)
Ethnicity All participants reported as Japanese Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Japanese Sample size	n = 89 ; % = 100	n = 90 ; % = 100	n = 90 ; % = 100
Comorbidities	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Empagliflozin 10 mg daily (N = 89)	Empagliflozin 25 mg daily (N = 90)	Placebo (N = 90)
Sample size			
Diabetic retinopathy Sample size	n = 33 ; % = 38.4	n = 43 ; % = 47.8	n = 31 ; % = 34.4
Diabetic nephropathy Sample size	n = 31 ; % = 36	n = 34 ; % = 37.8	n = 34 ; % = 37.8
Diabetic neuropathy Sample size	n = 16 ; % = 18.6	n = 27 ; % = 30	n = 16 ; % = 17.8
Hypertension Sample size	n = 52 ; % = 60.5	n = 56 ; % = 62.2	n = 62 ; % = 68.9
Presence of frailty Nominal	NR	NR	NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	14.4 (8.5)	14.6 (8.2)	12.4 (7.3)
Cardiovascular risk factors 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 Includes number of participants	n = 65 ; % = 75.5	n = 62 ; % = 68.9	n = 59 ; % = 65.5

Characteristic	Empagliflozin 10 mg daily (N = 89)	Empagliflozin 25 mg daily (N = 90)	Placebo (N = 90)
with BMI>=25 kg/m2 (Japanese definition) Sample size			
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Insulin monotherapy Sample size	n = 54 ; % = 62.8	n = 62 ; % = 68.9	n = 77 ; % = 85.6
Insulin + one oral antidiabetic agent Sample size	n = 32 ; % = 37.2	n = 28 ; % = 31.1	n = 13 ; % = 14.4
Basal insulin Sample size	n = 41 ; % = 47.7	n = 39 ; % = 43.3	n = 41 ; % = 45.6
Prandial insulin Sample size	n = 0 ; % = 0	n = 1 ; % = 1.1	n = 0 ; % = 0
Premixed insulin Sample size	n = 16 ; % = 18.6	n = 19 ; % = 21.1	n = 22 ; % = 24.4
Other Sample size	n = 1 ; % = 1.2	n = 0 ; % = 0	n = 0 ; % = 0
Basal + prandial insulin Sample size	n = 28 ; % = 32.6	n = 31 ; % = 34.4	n = 27 ; % = 30
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

Baseline characteristics for empagliflozin 10 mg arm is for N=86 because 3 participants in that arm did not receive study drug.

443. Sridhar, 2013

Bibliographic Reference	Sridhar, S.; Walia, R.; Sachdeva, N.; Bhansali, A.; Effect of pioglitazone on testosterone in eugonadal men with type 2 diabetes mellitus: a randomized double-blind placebo-controlled study; Clin Endocrinol; 2013; vol. 78 (no. 3); 454-9

443.1. Study details

Secondary publication of another included study- see primary study for details	No
Other publications associated with this study included in review	None
Trial name / registration number	NCT01206400
Study type	Randomised controlled trial (RCT) Double-blind parallel-group RCT.
Study location	India
Study setting	Outpatient
Study dates	09/2010 to 12/2011
Sources of funding	Drug and placebo tablets provided by Sun Pharmaceutical Industries Ltd, Mumbai, India.
Inclusion criteria	• Eugonadal men (well virilized with total testosterone level ≥12 nM on two occasions) • Aged 30–55 years • Type 2 diabetes<5 years • BMI of 20–30 kg/m2 • HbA1c level of≤7.5% • Receiving glimepiride (1–4 mg) and metformin (1–2 g)

Exclusion criteria	• Previous use of pioglitazone • Current smoking • Serum albumin<3 g/dl • Hepatic dysfunction • Heart failure • Renal failure • Presence of macular oedema • Any acute illnesses
Recruitment / selection of participants	One-hundred and 160 Indian patients screened. Participants who satisfied inclusion criteria randomly assigned to groups. Both participants and physicians blinded to assignment. Compliance determined by pill count. Participants received disease education and dietary/exercise advice throughout trial. All other medications continued without dose modification. Glimepiride could be reduced if hypoglycaemia occurred.
Intervention(s)	• Pioglitazone 30 mg daily Oral pioglitazone 30 mg daily, for 6 months, in addition to glimepiride and metformin.
Cointervention	• Glimepiride • Metformin All participants continued to receive pre-trial glimepiride and metformin.
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Heart failure is an exclusion criterion.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear CKD not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and high	Not stated/unclear

cardiovascular risk	
Subgroup 1: People with moderate or severe 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: hepatic dysfunction
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
Comparator	• Placebo Matching placebo for 6 months, in addition to glimepiride and metformin.
Number of participants	N=54 randomised (4 participants were excluded from analysis)
Duration of follow-up	6 months
Indirectness	All participants were eugonadal men.
Method of analysis	Modified ITT Appears to be mITT completer analysis (excludes 4 randomised participants, 3 lost to follow up and 1 discontinued medication)

443.2. Study arms

443.2.1. Pioglitazone 30 mg daily (N = 25)

Oral pioglitazone 30 mg daily, for 6 months, in addition to glimepiride and metformin.

443.2.2. Placebo (N = 25)

Matching placebo for 6 months, in addition to glimepiride and metformin.

443.3. Characteristics

443.3.1. Arm-level characteristics

Characteristic	Pioglitazone 30 mg daily (N = 25)	Placebo (N = 25)
% Male Sample size	n = 25 ; % = 100	n = 25 ; % = 100
Mean age (SD) (years) Mean (SD)	47.9 (5.8)	44 (7.2)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Asian Sample size	n = 25 ; % = 100	n = 25 ; % = 100
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	2.2 (1.7)	2.9 (2.1)
Cardiovascular risk factors Nominal	NR	NR
Smoking status Nominal	NR	NR

Characteristic	Pioglitazone 30 mg daily (N = 25)	Placebo (N = 25)
Alcohol consumption Nominal	NR	NR
Presence of severe mental illness Nominal	NR	NR
People with significant cognitive impairment Nominal	NR	NR
People with a learning disability Nominal	NR	NR
Number of people with obesity Nominal	NR	NR
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

444. Strain, 2013

Bibliographic Reference	Strain, W. D.; Lukashevich, V.; Kothny, W.; Hoellinger, M. J.; Paldánius, P. M.; Individualised treatment targets for elderly patients with type 2 diabetes using vildagliptin add-on or lone therapy (INTERVAL): a 24 week, randomised, double-blind, placebo-controlled study; Lancet; 2013; vol. 382 (no. 9890); 409-16

444.1. 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	INTERVAL trial. NCT01257451.
Study type	Randomised controlled trial (RCT)
Study location	Multicentre (Belgium, Bulgaria, Germany, Finland, Slovakia, Spain and the UK).
Study setting	Outpatient follow-up.
Study dates	December 22nd 2010 to March 14th 2012.
Sources of funding	Funded by Novartis Pharma AG.
Inclusion criteria	People aged 70 years or older with type 2 diabetes who were drug-naive or inadequately controlled with HbA1c levels of 7.0% or greater and 10.0% or less; fasting plasma glucose of less than 15 mmol/L and BMI of 19-45 kg/m2 at screening.
Exclusion criteria	Use of insulin treatment (>7 consecutive days) or incretin-based therapies in the preceding 12 weeks; use of corticosteroids within 8 weeks; use of growth hormone within 6 months of the screening visit; people with acute metabolic diabetic disorders, myocardial infarction, coronary artery bypass surgery, or stroke within 6 months; unstable angina within 3 months; congestive heart failure (NYHA III or IV); malignancy within 5 years; liver

	disease such as cirrhosis or hepatitis; substantial laboratory abnormalities including liver function tests, renal dysfunction as suggested by reduced glomerular filtration rate (<30mL/min/1.73m2) or positive hepatitis B or C tests.
Recruitment / selection of participants	No additional information.
Intervention(s)	Vildagliptin N=139 Vildagliptin 50 mg twice daily (unless they received sulfonylurea monotherapy where they receive vildagliptin 50mg once daily instead).
Cointervention	People continued stable doses of their oral antidiabetic medication throughout the study.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear People with congestive heart failure (New York Heart Association classification of III or IV) were excluded. Class II not an exclusion criteria. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear The study excluded people with myocardial infarction, coronary artery bypass surgery, or stroke within 6 months, and people with unstable angina within 3 months. No information about CVD preceding the 6 / 3 months or other types of CVD. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear CKD not an inclusion/exclusion criteria. Exclusion criteria sate: "substantial laboratory abnormalities including liver function tests, renal dysfunction as suggested by reduced glomerular filtration rate (<30 mL/min per 1·73 m²)." No information in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	People without frailty

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
Population subgroups	No additional information.
Comparator	Placebo N=139 Placebo twice daily (unless they received sulfonylurea monotherapy where they receive placebo once daily instead).
Number of participants	278.
Duration of follow-up	24 weeks.
Indirectness	Population indirectness - Unclear how many people were taking antidiabetic medications before the trial. The trial allowed people in who were drug naive. However, it states "almost all patients were using concomitant medications...". Therefore, it is likely this study is relevant for this review. Given the uncertainty this study is being downgraded for population indirectness.
Method of analysis	Per protocol ITT Primary analysis
Additional comments	No additional information.

444.2. Study arms

444.2.1. Vildagliptin (N = 139)

Vildagliptin 50 mg twice daily (unless they received sulfonylurea monotherapy where they receive vildagliptin 50mg once daily instead). Concomitant therapy: People continued stable doses of their oral antidiabetic medication throughout the study.

444.2.2. Placebo (N = 139)

Placebo twice daily (unless they received sulfonylurea monotherapy where they receive placebo once daily instead). Concomitant therapy: People continued stable doses of their oral antidiabetic medication throughout the study.

444.3. Characteristics

444.3.1. Arm-level characteristics

Characteristic	Vildagliptin (N = 139)	Placebo (N = 139)
% Male Sample size	n = 73 ; % = 52.5	n = 53 ; % = 38.1
Mean age (SD) (years) Mean (SD)	75.1 (4.3)	74.4 (4)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 135 ; % = 97.1	n = 134 ; % = 96.4
Other Sample size	n = 4 ; % = 2.9	n = 5 ; % = 3.6
Comorbidities Sample size	n = NA ; % = NA	n = NA ; % = NA
Hypertension Sample size	n = 117 ; % = 84.2	n = 115 ; % = 82.7
Dyslipidaemia Sample size	n = 37 ; % = 26.6	n = 29 ; % = 20.9

Characteristic	Vildagliptin (N = 139)	Placebo (N = 139)
Hypercholesterolaemia Sample size	n = 22 ; % = 15.8	n = 22 ; % = 15.8
Hyperlipidaemia Sample size	n = 36 ; % = 25.9	n = 28 ; % = 20.1
Myocardial ischaemia Sample size	n = 22 ; % = 15.8	n = 24 ; % = 17.3
Peripheral neuropathy Sample size	n = 30 ; % = 21.6	n = 36 ; % = 25.9
Osteoarthritis Sample size	n = 27 ; % = 19.4	n = 28 ; % = 20.1
Presence of frailty Sample size	n = NA ; % = NA	n = NA ; % = NA
Yes Sample size	n = 12 ; % = 8.6	n = 14 ; % = 10.1
No Sample size	n = 126 ; % = 90.6	n = 123 ; % = 88.5
Missing Sample size	n = 1 ; % = 0.7	n = 2 ; % = 1.4
Time since type 2 diabetes diagnosed (years) Mean (SD)	12.2 (7.9)	10.6 (6.9)
Cardiovascular risk factors Sample size	n = NR ; % = NR	n = 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

Characteristic	Vildagliptin (N = 139)	Placebo (N = 139)
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR
Other antidiabetic medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Blood pressure-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Statins/lipid-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR

445. Strojek, 2011

Bibliographic Reference	Strojek, K.; Yoon, K. H.; Hruba, V.; Elze, M.; Langkilde, A. M.; Parikh, S.; Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with glimepiride: a randomized, 24-week, double-blind, placebo-controlled trial; Diabetes Obes Metab; 2011; vol. 13 (no. 10); 928-38

445.1. Study details

Secondary publication of another included study- see primary study for details	No
Other publications associated with this study included in review	For 48-week results, see: • Strojek, K., Yoon, K. H., Hruba, V., Sugg, J., Langkilde, A. M., & Parikh, S. (2014). Dapagliflozin added to glimepiride in patients with type 2 diabetes mellitus sustains glycemic control and weight loss over 48 weeks: a randomized, double-blind, parallel-group, placebo-controlled trial. *Diabetes Therapy*, *5*, 267-283.
Trial name / registration number	NCT00680745
Study type	Randomised controlled trial (RCT) Double-blind, double-dummy. parallel-group RCT
Study location	International (84 sites in 7 countries: Czech Republic, Hungary, Republic of Korea, Philippines, Poland, Thailand, Ukraine)
Study setting	Outpatient
Study dates	04/2008 to 11/2009
Sources of funding	Astra Zeneca and Bristol-Myers Squib funded medical writing and editorial assistance.
Inclusion criteria	• Aged ≥18 years • Type 2 diabetes • HbA1c 7-10% inclusive • Stable dose of sulphonylurea monotherapy (at least half maximum recommended dose) ≥8 weeks prior to enrolment • FPG≤15 mmol/L

	• Fasting C-peptide≥0.33 nmol/l
Exclusion criteria	• Type 1 or other types of diabetes • History of diabetic ketoacidosis or hyperosmolar non-ketotic coma • Poorly controlled diabetes characterised by polyuria/polydipsia with >10% weight loss • Use of insulin for >7 consecutive days during the 24 weeks prior to enrolment • Use of glimepiride >4mg/day during the 8 weeks up to and including enrolment. • BMI>45.0kg/m2 • Calculated creatinine clearance <50mL/min or serum creatinine >177µmol/L • Urine albumin/creatinine ratio >203.4mg/mmol • Aspartate aminotransferase and/or alanine aminotransferase and/or creatine kinase ≥3 times upper limit of normal range • Serum total bilirubin >34µmol/L • Hb ≤10g/dL for men and ≤9.5g/dL for women • Systolic blood pressure ≥180mmHg and/or diastolic blood pressure ≥110mmHg; • Cardiovascular event within 6 months of enrolment • Congenital renal glycosuria • Significant renal, hepatic, haematological, oncological, endocrine, immunological (including hypersensitivity to study medications), or psychiatric disease (including alcohol and substance misuse) • Pregnancy or lactation • Use of systemic corticosteroids for >4weeks within 3months of enrolment • Use of weight loss medication within 30 days of enrolment
Recruitment / selection of participants	Participants recruited from 84 sites in 7 countries. Eligible participants continued with or were switched to open-label glimepiride 4 mg/day for 8-wk lead-in period. After one-week period in which eligibility of participants of those switched to glimepiride confirmed, participants block randomised sequentially by centre 1:1:1:1 using computer-generated schedule. Treatment assignment to arms double-blind and double-dummy due to different size of dapagliflozin tablets. Participants with inadequate glycaemic control remained in trial but received open-label rescue therapy (metformin, pioglitazone or rosiglitazone). Criteria for inadequate control progressively stricter throughout trial. Participants with HbA1c>8% for continuous 12-wk period were discontinued.
Intervention(s)	• Dapagliflozin 2.5 mg daily • Dapagliflozin 5 mg daily • Dapagliflozin 10 mg daily Oral dapagliflozin 2.5 mg, 5 mg or 10 mg daily and placebo dummy for 48 weeks, in addition to background glimepiride.
Cointervention	• Glimepiride 4 mg daily

	All participants received open-label oral glimepiride 4 mg daily for 48 weeks. Could be down-titrated to 2 mg or discontinued in case of hypoglycaemia at investigator discretion. No up-titration allowed.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Heart failure not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Mixed population "Cardiovascular event within 6 months of enrolment" in the exclusion criteria (see supplement. Baseline characteristics reports ~36% of participants with prior history of cardiovascular disease.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear CKD not an inclusion/exclusion criteria. Exclusion criteria included: significant renal disease; creatinine clearance <50 mL/min or serum creatinine >177 µmol/L; urine albumin/creatinine ratio >203.4 mg/mmol. No information in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe 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: people with significant hepatic disease

Subgroup 4: People with obesity	Mixed population ~45% participants were obese
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Comparator	• Placebo Placebo + placebo (double-dummy trial) for 48 weeks, in addition to glimepiride.
Number of participants	N=596 (507 randomised, 1 participant excluded as did not receive study drug)
Duration of follow-up	24 and 48 weeks
Indirectness	None
Method of analysis	Modified ITT mITT (full analysis) set used for HbA1c and weight (all randomised participants who took dose of study drug and at least baseline and one post-baseline efficacy measurement) using observed data only and excluding data gathered after rescue medication for 48 week data; safety set was all randomised participants who took one dose of study drug and included data gathered after rescue medication.

445.2. Study arms

445.2.1. Dapagliflozin 2.5 mg daily (N = 154)

Oral dapagliflozin 2.5 mg daily for 48 weeks, in addition to open-label glimepiride 4 mg daily.

445.2.2. Dapagliflozin 5 mg daily (N = 142)

Oral dapagliflozin 5 mg daily for 48 weeks, in addition to open-label glimepiride 4 mg daily.

445.2.3. Dapagliflozin 10 mg daily (N = 151)

Oral dapagliflozin 10 mg daily for 48 weeks, in addition to open-label glimepiride 4 mg daily.

445.2.4. Placebo (N = 145)

Matching placebo daily for 48 weeks, in addition to open-label glimepiride 4 mg daily.

445.3. Characteristics

445.3.1. Arm-level characteristics

Characteristic	Dapagliflozin 2.5 mg daily (N = 154)	Dapagliflozin 5 mg daily (N = 142)	Dapagliflozin 10 mg daily (N = 151)	Placebo (N = 145)
% Male Sample size	n = 77 ; % = 50	n = 71 ; % = 50	n = 66 ; % = 43.7	n = 71 ; % = 49
Mean age (SD) (years) Mean (SD)	59.9 (10.1)	60.2 (9.7)	58.9 (8.3)	60.3 (10.2)
Ethnicity Data for number of participants by region of participating site Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Europe Sample size	n = 108 ; % = 70.1	n = 96 ; % = 67.6	n = 106 ; % = 70.2	n = 101 ; % = 69.7
Asia/Pacific Sample size	n = 46 ; % = 29.9	n = 46 ; % = 32.4	n = 45 ; % = 29.8	n = 44 ; % = 30.3
Comorbidities Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Hypertension Sample size	n = 108 ; % = 70.1	n = 100 ; % = 70.4	n = 113 ; % = 74.8	n = 116 ; % = 80
Presence of frailty Nominal	NR	NR	NR	NR
Time since type 2 diabetes diagnosed Mean (SD)	7.7 (6)	7.4 (5.7)	7.2 (5.5)	7.4 (5.7)

Characteristic	Dapagliflozin 2.5 mg daily (N = 154)	Dapagliflozin 5 mg daily (N = 142)	Dapagliflozin 10 mg daily (N = 151)	Placebo (N = 145)
Cardiovascular risk factors Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
History of cardiovascular disease Sample size	n = 56 ; % = 38.4	n = 55 ; % = 38.7	n = 46 ; % = 30.5	n = 55 ; % = 37.9
Smoking status Nominal	NR	NR	NR	NR
Alcohol consumption Nominal	NR	NR	NR	NR
Presence of severe mental illness Nominal	NR	NR	NR	NR
People with significant cognitive impairment Nominal	NR	NR	NR	NR
People with a learning disability Nominal	NR	NR	NR	NR
Number of people with obesity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
BMI 25 kg/m2 or more Sample size	n = 130 ; % = 84.4	n = 114 ; % = 80.3	n = 120 ; % = 79.5	n = 125 ; % = 86.2
BMI 30 kg/m2 or more Sample size	n = 74 ; % = 48.1	n = 73 ; % = 51.4	n = 68 ; % = 45	n = 66 ; % = 45.5
Other antidiabetic medication used Nominal	NR	NR	NR	NR

Characteristic	Dapagliflozin 2.5 mg daily (N = 154)	Dapagliflozin 5 mg daily (N = 142)	Dapagliflozin 10 mg daily (N = 151)	Placebo (N = 145)
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

446. Strojek, 2014

Bibliographic Reference	Strojek, Krzysztof; Yoon, Kun-Ho; Hruba, Veronika; Sugg, Jennifer; Langkilde, Anna Maria; Parikh, Shamik; Dapagliflozin added to glimepiride in patients with type 2 diabetes mellitus sustains glycemic control and weight loss over 48 weeks: a randomized, double-blind, parallel-group, placebo-controlled trial.; Diabetes therapy : research, treatment and education of diabetes and related disorders; 2014; vol. 5 (no. 1); 267-83

446.1. Study details

Secondary publication of another included study- see primary study for details	Yes, original 24-week data reported in: • Strojek, K., Yoon, K. H., Hruba, V., Elze, M., Langkilde, A. M., & Parikh, S. (2011). Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with glimepiride: a randomized, 24-week, double-blind, placebo-controlled trial. *Diabetes, Obesity and Metabolism*, *13*(10), 928-938.
Other publications associated with this study included in review	See above
Trial name / registration number	NCT00680745

446.2. Study arms

446.2.1. Dapagliflozin 2.5 mg daily (N = 154)

Oral dapagliflozin 2.5 mg daily for 48 weeks, in addition to open-label glimepiride 4 mg daily.

446.2.2. Dapagliflozin 5 mg daily (N = 142)

Oral dapagliflozin 5 mg daily for 48 weeks, in addition to open-label glimepiride 4 mg daily.

446.2.3. Dapagliflozin 10 mg daily (N = 151)

Oral dapagliflozin 10 mg daily for 48 weeks, in addition to open-label glimepiride 4 mg daily.

446.2.4. Placebo (N = 145)

Matching placebo daily for 48 weeks, in addition to open-label glimepiride 4 mg daily.

447. Su, 2014

Bibliographic Reference	Su, Y.; Su, Y. L.; Lv, L. F.; Wang, L. M.; Li, Q. Z.; Zhao, Z. G.; A randomized controlled clinical trial of vildagliptin plus metformin combination therapy in patients with type II diabetes mellitus; Exp Ther Med; 2014; vol. 7 (no. 4); 799-803

447.1. 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	Hospital
Study dates	No additional information.
Sources of funding	No additional information.
Inclusion criteria	Patients diagnosed with type II diabetes with a 75-g oral glucose tolerance test that were aged between 18 and 70 years-old were included in the study. In addition, the included patients had been treated with metformin and A-glycosidase inhibitors for longer than three months, had HbA1c levels >6.5%, FBG levels >7.0 mmol/l and normal hepatorenal function.
Exclusion criteria	Patients excluded from the study had type I or other specific forms of diabetes, were younger than 18 or older than 70 years-old or had used hypoglycemic agents other than metformin and A-glycosidase inhibitors. Patients with diabetic ketoacidosis, hyperglycemic nonketotic hyperosmolar syndrome, chronic complications that required insulin treatment or patients that required insulin treatment under stress were also

	excluded. Patients with evident liver or kidney disease (ALT or AST levels >3 times the normal upper limit, total bilirubin levels >1.5 times the normal upper limit or CREA levels >115 µmol/l], pregnant or lactating women and patients with poor compliance were also excluded from the study.
Recruitment / selection of participants	Patients with type 2 diabetes mellitus on metformin therapy were recruited and randomised 1:1 to vildagliptin or placebo.
Intervention(s)	Vildagliptin 100 mg orally in two equal doses, daily.
Cointervention	Metformin
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear CKD not an inclusion/exclusion criteria. Inclusion criteria state: "Patients had normal hepatorenal function". Exclusion criteria state: "Patients with evident liver or kidney disease [alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels >3 times the normal upper limit, total bilirubin levels >1.5 times the normal upper limit or creatinine (CREA) levels >115 µmol/l] were excluded." No information in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe 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
Comparator	Placebo
Number of participants	N=600
Duration of follow-up	24-week
Indirectness	
Method of analysis	Not stated/unclear

447.2. Study arms

447.2.1. Vildagliptin 100 mg daily (N = 300)

Administered orally as two equal doses

447.2.2. Placebo daily (N = 300)

Administered orally

447.3. Characteristics

447.3.1. Study-level characteristics

Characteristic	Study (N = 600)
% Male No of events	n = 324 ; % = 54

447.3.2. Arm-level characteristics

Characteristic	Vildagliptin 100 mg daily (N = 300)	Placebo daily (N = 300)
Mean age (SD) (years) Mean (SD)	47.61 (14.41)	48.67 (11.56)
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed Nominal	NR	NR
Smoking status Nominal	NR	NR
No alcohol consumption No of events	n = 300 ; % = 100	n = 300 ; % = 100
Presence of severe mental illness Nominal	NR	NR
People with significant cognitive impairment Nominal	NR	NR
People with a learning disability Nominal	NR	NR

448. Takahashi, 2023

Bibliographic Reference	Takahashi, Yuka; Nomoto, Hiroshi; Yokoyama, Hiroki; Takano, Yoshinari; Nagai, So; Tsuzuki, Atsushi; Cho, Kyu Yong; Miya, Aika; Kameda, Hiraku; Takeuchi, Jun; Taneda, Shinji; Kurihara, Yoshio; Atsumi, Tatsuya; Nakamura, Akinobu; Miyoshi, Hideaki; Improvement of glycaemic control and treatment satisfaction by switching from liraglutide or dulaglutide to subcutaneous semaglutide in patients with type 2 diabetes: A multicentre, prospective, randomized, open-label, parallel-group comparison study (SWITCH-SEMA 1 study).; Diabetes, obesity & metabolism; 2023

448.1. Study details

Secondary publication of another included study- see primary study for details	No
Other publications associated with this study included in review	None
Trial name / registration number	SWITCH-SEMA 1/jRCTs1011200008 (Japan Registry of Clinical Trials)
Study type	Randomised controlled trial (RCT) Open-label parallel-group RCT
Study location	Japan (8 hospital sites)
Study setting	Community
Study dates	11/2020 to 11/2021
Sources of funding	Research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.
Inclusion criteria	• Age 20-90 years inclusive • HbA1c level 6.0-10.0% inclusive • BMI ≥22 kg/m2

	• Received ≥12 weeks of either liraglutide 0.9-1.8 mg/day (referred to as plan A in article) or dulaglutide 0.75 mg/week (referred to as plan B in article) treatment before randomisation
Exclusion criteria	• Treatment with GLP-1RA other than liraglutide and dulaglutide • Allergy to semaglutide • Unstable diabetic retinopathy • Severe hepatopathy or nephropathy • Severe ketosis, diabetic coma, or precoma • Severe infection, trauma, and/or recent or planned surgery • Definite or suspected pregnancy • Incompatibility with the trial for other reasons as determined by the physician
Recruitment / selection of participants	Eligible participants were patients who visited 1 of 8 participating hospital sites in Japan. Randomisation performed using computer-based dynamic allocation method by independent specialist centre, stratified by age, BMI and HbA1c level. Plan A and Plan B were separate RCTs and randomisation was 1:1 to: (Plan A) continue liraglutide or switch to semaglutide, or (Plan B) continue dulaglutide or switch to semaglutide. Insulin dose not adjusted for trial. Dose of sulphonylureas and insulin could be reduced if there was hypoglycaemia risk.
Intervention(s)	• Semaglutide 0.25-1.0 mg weekly In Plan A trial, participants who were on subcutaneous injection of liraglutide 0.9-1.8 mg daily switched to subcutaneous injection of semaglutide 0.25-1.0 mg weekly for 24 weeks. In Plan B, participants who were on subcutaneous injection of dulaglutide 0.75 mg weekly switched to subcutaneous injection of semaglutide 0.25-1.0 mg weekly for 24 weeks. Maintenance dose of semaglutide was 0.5-1.0 mg/week with final dose decided by physicians in charge based on the condition of each participant.
Cointervention	Other concurrent antihyperglycaemic drug treatment was permitted except for GLP-1 receptor agonists other than liraglutide and dulaglutide.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear
Strata 3: People with type 2 diabetes	People with chronic kidney disease

mellitus and chronic kidney disease	Severe nephropathy is an exclusion criterion. CKD not an inclusion criterion. Baseline characteristics table reports that all participants had diabetic nephropathy (on the basis of macroalbuminuria and microalbuminuria). Allocated to CKD strata as the study has classified the population as people with diabetic nephropathy.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe 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
Comparator	• Liraglutide 0.9-1.8 mg daily (Plan A trial)

	• Dulaglutide 0.75 mg weekly (Plan B trial) In Plan A, participants continued subcutaneous injection of liraglutide 0.9-1.8 mg daily for 24 weeks. In Plan B trial, participants continued subcutaneous injection of dulaglutide 0.75 mg weekly for 24 weeks.
Number of participants	N=40 (Plan A trial - Liraglutide v Semaglutide) N=70 (Plan B trial - Dulaglutide v Semaglutide)
Duration of follow-up	24 weeks
Indirectness	None
Method of analysis	Modified ITT mITT analysis (all randomised participants who meet inclusion criteria, have sufficient endpoint data, and who did not deviate from protocol) for all outcomes

448.2. Study arms

448.2.1. Liraglutide 0.9-1.8 mg daily (N = 20)

Participants who were already receiving subcutaneous injection of liraglutide 0.9-1.8mg daily continued this for 24 weeks (referred to as Plan A in article).

448.2.2. Semaglutide 0.25-1.0 mg weekly (N = 20)

Participants who were receiving subcutaneous injection of liraglutide 0.9-1.8 mg daily switched to subcutaneous injection of semaglutide 0.25-1.0 mg weekly (referred to as Plan A in article).

448.2.3. Dulaglutide 0.75 mg weekly (N = 35)

Participants who were already receiving subcutaneous injection of dulaglutide 0.75 mg weekly continued this for 24 weeks (referred to as Plan B in article).

448.2.4. Semaglutide 0.25-1.0 mg weekly (N = 35)

Participants who were receiving subcutaneous injection of dulaglutide 0.75 mg weekly switched to subcutaneous injection of semaglutide 0.25-1.0 mg weekly (referred to as Plan B in article).

448.3. Characteristics

448.3.1. Arm-level characteristics

Characteristic	Liraglutide 0.9-1.8 mg daily (N = 20)	Semaglutide 0.25-1.0 mg weekly (N = 20)	Dulaglutide 0.75 mg weekly (N = 35)	Semaglutide 0.25-1.0 mg weekly (N = 35)
% Male Sample size	n = 12 ; % = 66.6	n = 12 ; % = 63.2	n = 13 ; % = 40.6	n = 20 ; % = 74.5
Mean age (SD) Median (IQR)	60.9 (49.5 to 72.3)	59.6 (49 to 72)	60.8 (49 to 71.8)	64.6 (54 to 75)
Ethnicity Nominal	NR	NR	NR	NR
Comorbidities Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Diabetic retinopathy Sample size	n = 6 ; % = 33.3	n = 5 ; % = 26.3	n = 12 ; % = 37.5	n = 9 ; % = 29
Diabetic nephropathy - microalbuminuria Sample size	n = 16 ; % = 88.9	n = 16 ; % = 84.2	n = 29 ; % = 90.6	n = 28 ; % = 90.3
Diabetic nephropathy - macroalbuminuria Sample size	n = 2 ; % = 11.1	n = 3 ; % = 15.8	n = 3 ; % = 9.4	n = 3 ; % = 9.7
Presence of frailty Nominal	NR	NR	NR	NR
Time since type 2 diabetes diagnosed (years) Significant difference (p=0.04) in duration of diabetes for Plan B trial (Dulaglutide v Semaglutide) Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Less than 5 years Sample size	n = 0 ; % = 0	n = 1 ; % = 5.3	n = 3 ; % = 9.4	n = 0 ; % = 0

Characteristic	Liraglutide 0.9-1.8 mg daily (N = 20)	Semaglutide 0.25-1.0 mg weekly (N = 20)	Dulaglutide 0.75 mg weekly (N = 35)	Semaglutide 0.25-1.0 mg weekly (N = 35)
5-15 years Sample size	n = 7 ; % = 38.9	n = 3 ; % = 15.8	n = 14 ; % = 43.8	n = 8 ; % = 25.8
More than 15 years Sample size	n = 11 ; % = 61.1	n = 15 ; % = 79	n = 15 ; % = 46.9	n = 23 ; % = 74.2
Cardiovascular risk factors Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Dyslipidaemia Sample size	n = 14 ; % = 77.8	n = 16 ; % = 84.2	n = 24 ; % = 75	n = 24 ; % = 74.4
Hypertension Sample size	n = 12 ; % = 66.7	n = 13 ; % = 68.4	n = 20 ; % = 62.5	n = 22 ; % = 71
Smoking status Nominal	NR	NR	NR	NR
Alcohol consumption Nominal	NR	NR	NR	NR
Presence of severe mental illness Nominal	NR	NR	NR	NR
People with significant cognitive impairment Nominal	NR	NR	NR	NR
People with a learning disability Nominal	NR	NR	NR	NR
Number of people with obesity Nominal	NR	NR	NR	NR
Other antidiabetic medication used Significant difference in use of SGLT2 inhibitors in	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Liraglutide 0.9-1.8 mg daily (N = 20)	Semaglutide 0.25-1.0 mg weekly (N = 20)	Dulaglutide 0.75 mg weekly (N = 35)	Semaglutide 0.25-1.0 mg weekly (N = 35)
Liraglutide v Semaglutide (Plan A) trial Sample size				
Liraglutide 0.9 mg/day Sample size	n = 7 ; % = 38.9	n = 8 ; % = 42.1	n = NA ; % = NA	n = NA ; % = NA
Liraglutide 1.2 mg/day Sample size	n = 8 ; % = 44.4	n = 4 ; % = 21.1	n = NA ; % = NA	n = NA ; % = NA
Liraglutide 1.5 mg/day Sample size	n = 2 ; % = 11.1	n = 2 ; % = 10.5	n = NA ; % = NA	n = NA ; % = NA
Liraglutide 1.8 mg/day Sample size	n = 1 ; % = 5.6	n = 5 ; % = 26.3	n = NA ; % = NA	n = NA ; % = NA
Metformin Sample size	n = 15 ; % = 83.3	n = 17 ; % = 89.3	n = 27 ; % = 84.4	n = 29 ; % = 93.6
SGLT2 inhibitors Sample size	n = 11 ; % = 61.1	n = 18 ; % = 94.7	n = 26 ; % = 81.3	n = 23 ; % = 74.2
Sulphonylureas Sample size	n = 2 ; % = 11.1	n = 3 ; % = 17.8	n = 8 ; % = 25	n = 12 ; % = 38.7
Glinides Sample size	n = 3 ; % = 16.7	n = 1 ; % = 5.3	n = 3 ; % = 9.4	n = 2 ; % = 6.4
Alpha-glucosidase inhibitors Sample size	n = 5 ; % = 27.8	n = 3 ; % = 15.8	n = 3 ; % = 9.4	n = 3 ; % = 9.7
Thiazolidinediones Sample size	n = 0 ; % = 0	n = 3 ; % = 15.8	n = 4 ; % = 12.5	n = 5 ; % = 16.1
Insulin Sample size	n = 13 ; % = 72.2	n = 12 ; % = 63.6	n = 10 ; % = 31.3	n = 12 ; % = 38.7
Blood pressure-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Liraglutide 0.9-1.8 mg daily (N = 20)	Semaglutide 0.25-1.0 mg weekly (N = 20)	Dulaglutide 0.75 mg weekly (N = 35)	Semaglutide 0.25-1.0 mg weekly (N = 35)
Angiotensin converting enzyme inhibitor/Angiotensin II receptor blockers Sample size	n = 7 ; % = 38.9	n = 13 ; % = 68.4	n = 14 ; % = 43.8	n = 18 ; % = 58.1
Beta-blockers Sample size	n = 3 ; % = 16.7	n = 1 ; % = 5.3	n = 5 ; % = 15.6	n = 2 ; % = 6.5
Calcium channel blockers Sample size	n = 8 ; % = 44.4	n = 13 ; % = 68.4	n = 17 ; % = 53.1	n = 17 ; % = 54.8
Statins/lipid-lowering medication used Significant difference in use of statins for Liraglutide v Semaglutide (Plan A) trial Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Ezetimibe Sample size	n = 2 ; % = 11.1	n = 3 ; % = 15.8	n = 4 ; % = 12.5	n = 2 ; % = 6.5
Fibrates Sample size	n = 6 ; % = 33.3	n = 3 ; % = 15.8	n = 3 ; % = 9.4	n = 2 ; % = 6.5
Statins Sample size	n = 9 ; % = 50	n = 16 ; % = 84.2	n = 24 ; % = 75	n = 20 ; % = 64.5
Other treatment being received Nominal	NR	NR	NR	NR

Data is for two separate trials: Plan A trial is liraglutide v semaglutide. Data for baseline characteristics for this trial is liraglutide, N=18 and semaglutide N=19. Plan B trial is dulaglutide v semaglutide. Data for baseline characteristics for this trial is dulaglutide, N=32 and semaglutide, N=31.

449. Takihata, 2013

Bibliographic Reference	Takihata, M.; Nakamura, A.; Tajima, K.; Inazumi, T.; Komatsu, Y.; Tamura, H.; Yamazaki, S.; Kondo, Y.; Yamada, M.; Kimura, M.; Terauchi, Y.; Comparative study of sitagliptin with pioglitazone in Japanese type 2 diabetic patients: the COMPASS randomized controlled trial; Diabetes Obes Metab; 2013; vol. 15 (no. 5); 455-62

449.1. Study details

Trial name / registration number	COMPASS/UMIN 000004716
Study type	Randomised controlled trial (RCT)
Study location	Japan
Study setting	Hospital
Study dates	01/2011 - 12/2011
Sources of funding	Grants-in-Aid for Scientific Research (B) 21390282 and (B) 24390235 from the Ministry of Education, Culture, Sports, Science and Technology (MEXT) of Japan, a Grant for the Strategic Japanese-Danish Cooperative Program on Molecular Diabetology from the Japan Science and Technology Agency, a Grant-in-Aid from the Uehara Memorial Foundation to one author, and a Grant-in-Aid from the Joint Research Association for Japanese Diabetes to another author.
Inclusion criteria	• Patients with type 2 diabetes mellitus • Men and women between the ages of 20–75 years whose diabetes had been inadequately controlled (HbA1c, 6.9–9.5%) with metformin and/or sulphonylurea.
Exclusion criteria	• Patients with a history of diabetic ketoacidosis or diabetic coma within 6 months prior to study entry • Patients with a history of cardiac failure • Patients who underwent a surgical operation during the observation period of this study • Patients with severe infection or severe trauma • Patients who were pregnant or lactating, (vi) patients with renal insufficiency [serum creatinine > 132.6 μmol/l, estimated glomerular filtration rate (e-GFR) < 30 ml/min] • Patients with severe liver dysfunction • Patients who had received insulin therapy • Patients with a history of a hypersensitive reaction to sitagliptin or pioglitazone

	• Patients who were judged as being inappropriate by the physicians in charge
Recruitment / selection of participants	Patients with type 2 diabetes whose diabetes was inadequately controlled with metformin and/or sulphonylurea were
Intervention(s)	Pioglitazone 15 mg daily Administered orally
Cointervention	No additional information.
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Cardiac failure stated in exclusion criteria.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear CKD not an inclusion/exclusion criteria. Exclusion criteria state: "patients with renal insufficiency [serum creatinine>132.6μmol/l, estimated glomerular filtration rate(e-GFR)<30ml/min]". No information in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type	Not stated/unclear

2 diabetes mellitus	
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	eGFR ≥30mL/min/1.73m2
Subgroup 6: Albuminuria category at baseline	Mixed population
Population subgroups	
Comparator	Sitagliptin 50 mg daily Administered orally
Number of participants	N=130
Duration of follow-up	24-week
Indirectness	No additional information.
Method of analysis	ITT
Additional comments	

449.2. Study arms

449.2.1. Pioglitazone 15 mg daily (N = 65)

Administered orally

449.2.2. Sitagliptin 50 mg daily (N = 65)

Administered orally

449.3. Characteristics

449.3.1. Arm-level characteristics

Characteristic	Pioglitazone 15 mg daily (N = 65)	Sitagliptin 50 mg daily (N = 65)
% Male No of events	n = 32 ; % = 49	n = 36 ; % = 55
Mean age (SD) (years) Mean (SD)	60.7 (9.5)	60.3 (7.5)
Ethnicity Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed Nominal	NR	NR
Smoking status Nominal	NR	NR
Alcohol consumption Nominal	NR	NR
Presence of severe mental illness Nominal	NR	NR
People with significant cognitive impairment Nominal	NR	NR
People with a learning disability Nominal	NR	NR
Number of people with obesity	NR	NR

Characteristic	Pioglitazone 15 mg daily (N = 65)	Sitagliptin 50 mg daily (N = 65)
Nominal		
Metformin and/or sulphonylurea No of events	n = 65 ; % = 100	n = 65 ; % = 100
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

450. Tan, 2004

Bibliographic Reference	Tan, M.; Johns, D.; González Gálvez, G.; Antúnez, O.; Fabián, G.; Flores-Lozano, F.; Zúñiga Guajardo, S.; Garza, E.; Morales, H.; Konkoy, C.; Herz, M.; Effects of pioglitazone and glimepiride on glycemic control and insulin sensitivity in Mexican patients with type 2 diabetes mellitus: A multicenter, randomized, double-blind, parallel-group trial; Clin Ther; 2004; vol. 26 (no. 5); 680-93

450.1. Study details

Secondary publication of another included study- see primary study for details	
Trial name / registration number	GLAD
Study type	Randomised controlled trial (RCT)
Study location	16 centres in Mexico
Study setting	No additional information
Study dates	NR
Sources of funding	This work relates to Eli Lilly and Company protocol H6E-MC-GLAD. The main author is an employee of Eli Lilly and Company
Inclusion criteria	HbA1c values >7.5% to ≤11% in patients who were not receiving oral antihyperglycemic medications (OAMs), and >7.5% to ≤9.5% in patients who were receiving OAM monotherapy. Patients must have undergone an adequate trial of dietary and lifestyle interventions before enrolment, as determined by the investigator
Exclusion criteria	Treatment with a TZD or insulin within the previous 3 months; current prescription for a maximum dose of an oral antihyperglycemic medication (OAM) or for combination OAM therapy; treatment with systemic glucocorticoids (excluding topical and inhaled preparations) within the previous 30 days; cardiac disease with substantial limitation of functional capacity (New York Heart Association Class III or IV); serum triglycerides >400 mg/dL (>4.5 mmol/L); serum creatinine >2.0 mg/dL (>177 µmol/L); renal transplantation or current renal dialysis; alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels >2.5 times the upper limit of normal of the central laboratory; clinical signs or symptoms of liver disease; hemoglobin <105 g/L for women and 115 g/L for men; previous

	HIV infection; body mass index <25 kg/m2 or >35 kg/m2; and signs or symptoms of substance abuse
Recruitment / selection of participants	No additional information
Intervention(s)	Pioglitazone (n=121) Patients received pioglitazone titrated to achieve a FBG concentration ≤7 mmol/L and a 1-hour postprandial blood glucose concentration ≤10 mmol/L. The initial dose was 15 mg per day administered as a single capsule. Doses were adjusted in 15-mg increments to a maximum of 45 mg per day and patients received therapy for 52 weeks
Cointervention	None
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Exclusion criteria state: "Cardiac disease with substantial limitation of functional capacity (New York Heart Association Class III or IV." No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear CKD not an inclusion/exclusion criteria. Exclusion criteria state: "serum creatinine >2.0 mg/dL (>177 µmol/L); renal transplantation or current renal dialysis." No information in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe 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
Population subgroups	NA
Comparator	Glimepiride (n=123) Patients received glimepiride titrated to achieve a FBG concentration ≤7 mmol/L and a 1-hour postprandial blood glucose concentration ≤10 mmol/L. The initial dose was 2 mg per day administered as a single capsule. Doses were adjusted in 2-mg increments to a maximum of 8 mg per day. Patients received therapy for 52 weeks
Number of participants	244
Duration of follow-up	52 weeks
Indirectness	24% of patients were oral antidiabetic naive
Method of analysis	ITT
Additional comments	The ITT sample included all randomized patients who received ≥1 dose of study medication and had both a baseline measurement and ≥1 efficacy measurement during the treatment period. The completer sample included those patients who had efficacy measurements at baseline and at the final visit (week 52)

450.2. Study arms

450.2.1. Pioglitazone (N = 121)

Patients received pioglitazone titrated to achieve a FBG concentration ≤7 mmol/L and a 1-hour postprandial blood glucose concentration ≤10 mmol/L. Doses were adjusted in 15-mg increments to a maximum of 45 mg per day.

450.2.2. Glimepiride (N = 123)

Patients received glimepiride titrated to achieve a FBG concentration ≤7 mmol/L and a 1-hour postprandial blood glucose concentration ≤10 mmol/L. Doses were adjusted in 2-mg increments to a maximum of 8 mg per day

450.3. Characteristics

450.3.1. Arm-level characteristics

Characteristic	Pioglitazone (N = 121)	Glimepiride (N = 123)
% Male Sample size	n = 54 ; % = 45	n = 65 ; % = 53
Mean age (SD) (Years (mean, SD)) Mean (SD)	55.1 (8)	55.7 (9.3)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Hispanic Sample size	n = 121 ; % = 0	n = 122 ; % = 99
White Sample size	n = 0 ; % = 0	n = 1 ; % = 1
Time since type 2 diabetes diagnosed (Years (mean, SD)) Mean (SD)	6.5 (6.6)	6.8 (6.9)
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Pioglitazone (N = 121)	Glimepiride (N = 123)
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Patients taking orla antidiabetics at baseline Sample size	n = 92 ; % = 76	n = 95 ; % = 77
Insulin secretagogues Sample size	n = 63 ; % = 52.1	n = 71 ; % = 57.2
Metformin Sample size	n = 27 ; % = 22.3	n = 24 ; % = 19.5
Unknown oral antidiabetic medication Sample size	n = 2 ; % = 1.6	n = 0 ; % = 0
Blood pressure-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Statins/lipid-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
statins and/or fibrates Sample size	n = 15 ; % = 12.4	n = 14 ; % = 11.4
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR

451. Tanaka, 2019

Bibliographic Reference	Tanaka, A.; Shimabukuro, M.; MacHii, N.; Teragawa, H.; Okada, Y.; Shima, K. R.; Takamura, T.; Taguchi, I.; Hisauchi, I.; Toyoda, S.; et, al.; Effect of empagliflozin on endothelial function in patients with type 2 diabetes and cardiovascular disease: results from the multicenter, randomized, placebo- controlled, double-blind EMBLEM trial; Diabetes Care; 2019; vol. 42 (no. 10); E159-E161

451.1. 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	Tanaka, Atsushi, Shimabukuro, Michio, Machii, Noritaka et al. (2020) Secondary analyses to assess the profound effects of empagliflozin on endothelial function in patients with type 2 diabetes and established cardiovascular diseases: The placebo-controlled double-blind randomized effect of empagliflozin on endothelial function in cardiovascular high risk diabetes mellitus: Multi-centre placebo-controlled double-blind randomized trial. Journal of diabetes investigation 11(6): 1551-1563 Tanaka, Atsushi, Shimabukuro, Michio, Teragawa, Hiroki et al. (2021) Reduction of estimated fluid volumes following initiation of empagliflozin in patients with type 2 diabetes and cardiovascular disease: a secondary analysis of the placebo-controlled, randomized EMBLEM trial. Cardiovascular diabetology 20(1): 105
Trial name / registration number	UMIN000024502
Study type	Randomised controlled trial (RCT)
Study location	Japan.
Study setting	Outpatient follow-up.
Study dates	No additional information.
Sources of funding	Funded by Boehringer Ingelheim and Eli Lilly and Company.
Inclusion criteria	Adults (age at least 20 years); type 2 diabetes (HbA1c 6.0-10%) with unchanged dosage of glucose-lowering agents within 1 month before consent is provided, investigator considers the person can start or

	add/switch to the trial drug; at least one of the following: congestive heart failure (NYHA class I-III systolic or diastolic heart failure) not changed NYHA classification and receiving unchanged medication within 1 month before consent is provided; history of coronary artery disease (myocardial infarction and angina) or cerebral infarction; previous coronary revascularisation (PCI and CABG); presence of coronary artery stenosis (at least 50% luminal narrowing depicted by angiography or MSCT); diagnosis of arteriosclerosis obliterans.
Exclusion criteria	Type 1 diabetes mellitus; history of DKA or diabetic coma within the last 6 months; severe renal dysfunction (eGFR <45 mL/min/1.73m2 or undergoing dialysis); serious liver dysfunction (AST/ALT 3 times higher than site reference value); NYHA class IV CHF; hypotension (SBP <90 mmHg); pituitary gland dysfunction or adrenal gland dysfunction; history of CAD, cerebrovascular disease or TIA within 3 months before consent; history of coronary revascularisation within 3 months before consent; SGLT2 inhibitor within 1 month before consent; pregnant or suspect pregnancy; lactating; history of hypersensitivity to ingredients of empagliflozin; considered inappropriate for the study by investigators for other reasons (for example: malignancy).
Recruitment / selection of participants	No additional information.
Intervention(s)	Empagliflozin N=58 Empagliflozin 10mg once daily for 24 weeks.
Cointervention	Each person's pretrial or background glucose-lowering therapy remained unchanged during the trial as long as their medical conditioned was not compromised by such an approach.
Strata 1: People with type 2 diabetes mellitus and heart failure	Mixed population "All participants had at least one CVD (myocardial infarction 24%, angina 31%, stroke 20%, and heart failure 40%)."
Strata 2: People with atherosclerotic cardiovascular disease	Mixed population "All participants had at least one CVD (myocardial infarction 24%, angina 31%, stroke 20%, and heart failure 40%)."
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.

Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe 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
Population subgroups	No additional information.
Comparator	Placebo N=59 Placebo once daily for 24 weeks.
Number of participants	117
Duration of follow-up	24 weeks
Indirectness	No additional information.

Method of analysis	Not stated/unclear
Additional comments	No additional information.

451.2. Study arms

451.2.1. Empagliflozin (N = 58)

Empagliflozin 10mg once daily for 24 weeks. Concomitant therapy: Each person's pretrial or background glucose-lowering therapy remained unchanged during the trial as long as their medical conditioned was not compromised by such an approach.

451.2.2. Placebo (N = 59)

Placebo once daily for 24 weeks. Concomitant therapy: Each person's pretrial or background glucose-lowering therapy remained unchanged during the trial as long as their medical conditioned was not compromised by such an approach.

451.3. Characteristics

451.3.1. Study-level characteristics

Characteristic	Study (N = 105)
% Male Sample size	n = NR ; % = NR
Mean age (SD) (years) Mean (SD)	64.9 (10.4)
Ethnicity Sample size	n = NR ; % = NR
Comorbidities Sample size	n = NR ; % = NR
Presence of frailty Sample size	n = NR ; % = NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	13.2 (10.9)

Characteristic	Study (N = 105)
Cardiovascular risk factors Sample size	n = NR ; % = NR
Smoking status Sample size	n = NR ; % = NR
Alcohol consumption Sample size	n = NR ; % = NR
Presence of severe mental illness Sample size	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR
Number of people with obesity Sample size	n = NR ; % = NR
Other antidiabetic medication used Sample size	n = NR ; % = NR
Blood pressure-lowering medication used Sample size	n = NR ; % = NR
Statins/lipid-lowering medication used Sample size	n = NR ; % = NR
Other treatment being received Sample size	n = NR ; % = NR

452. Tanaka, 2020

Bibliographic Reference	Tanaka, Atsushi; Shimabukuro, Michio; Machii, Noritaka; Teragawa, Hiroki; Okada, Yosuke; Shima, Kosuke R; Takamura, Toshinari; Taguchi, Isao; Hisauchi, Itaru; Toyoda, Shigeru; Matsuzawa, Yasushi; Tomiyama, Hirofumi; Yamaoka-Tojo, Minako; Ueda, Shinichiro; Higashi, Yukihito; Node, Koichi; Secondary analyses to assess the profound effects of empagliflozin on endothelial function in patients with type 2 diabetes and established cardiovascular diseases: The placebo-controlled double-blind randomized effect of empagliflozin on endothelial function in cardiovascular high risk diabetes mellitus: Multi-center placebo-controlled double-blind randomized trial.; Journal of diabetes investigation; 2020; vol. 11 (no. 6); 1551-1563

452.1. Study details

Secondary publication of another included study- see primary study for details	Tanaka, A., Shimabukuro, M., MacHii, N. et al. (2019) Effect of empagliflozin on endothelial function in patients with type 2 diabetes and cardiovascular disease: results from the multicenter, randomized, placebo- controlled, double-blind EMBLEM trial. Diabetes Care 42(10): E159-E161
Other publications associated with this study included in review	Tanaka, Atsushi, Shimabukuro, Michio, Teragawa, Hiroki et al. (2021) Reduction of estimated fluid volumes following initiation of empagliflozin in patients with type 2 diabetes and cardiovascular disease: a secondary analysis of the placebo-controlled, randomized EMBLEM trial. Cardiovascular diabetology 20(1): 105

453. Tanaka, 2021

Bibliographic Reference	Tanaka, Atsushi; Shimabukuro, Michio; Teragawa, Hiroki; Okada, Yosuke; Takamura, Toshinari; Taguchi, Isao; Toyoda, Shigeru; Tomiyama, Hirofumi; Ueda, Shinichiro; Higashi, Yukihito; Node, Koichi; Reduction of estimated fluid volumes following initiation of empagliflozin in patients with type 2 diabetes and cardiovascular disease: a secondary analysis of the placebo-controlled, randomized EMBLEM trial.; Cardiovascular diabetology; 2021; vol. 20 (no. 1); 105

453.1. Study details

Secondary publication of another included study- see primary study for details	Tanaka, A., Shimabukuro, M., MacHii, N. et al. (2019) Effect of empagliflozin on endothelial function in patients with type 2 diabetes and cardiovascular disease: results from the multicenter, randomized, placebo- controlled, double-blind EMBLEM trial. Diabetes Care 42(10): E159-E161
Other publications associated with this study included in review	Tanaka, Atsushi, Shimabukuro, Michio, Machii, Noritaka et al. (2020) Secondary analyses to assess the profound effects of empagliflozin on endothelial function in patients with type 2 diabetes and established cardiovascular diseases: The placebo-controlled double-blind randomized effect of empagliflozin on endothelial function in cardiovascular high risk diabetes mellitus: Multi-center placebo-controlled double-blind randomized trial. Journal of diabetes investigation 11(6): 1551-1563

454. Tanaka, 2017

Bibliographic Reference	Tanaka, Kenichi; Okada, Yosuke; Mori, Hiroko; Miyazaki, Megumi; Kuno, Fumi; Sonoda, Satomi; Sugai, Kei; Hajime, Maiko; Kurozumi, Akira; Narisawa, Manabu; Torimoto, Keiichi; Arao, Tadashi; Mine, Shinichiro; Tanaka, Yoshiya; Comparative analysis of the effects of alogliptin and vildagliptin on glucose metabolism in type 2 diabetes mellitus.; Endocrine journal; 2017; vol. 64 (no. 2); 179-189

454.1. 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	UMIN00001902
Study type	Randomised controlled trial (RCT)
Study location	Japan
Study setting	NR
Study dates	NR
Sources of funding	None declared
Inclusion criteria	• People with type 2 diabetes who were naïve to treatment with DPP-4 inhibitors or received sitagliptin on an outpatient basis at the University of Occupational and Environmental Health and its affiliated hospital. • People in Study 2 were people with type 2 diabetes who were on treatment with 50 mg sitagliptin

Exclusion criteria	• People with type 1 diabetes • People treated with insulin • People treated with oral DPP-4 inhibitors other than sitagliptin 50 mg/day • People with hepatic dysfunction (transaminase level at least three times higher than the normal upper limit) • People with renal dysfunction (serum creatinine >1.4 mg/dL for men and >1.2 mg/dL for women)
Recruitment / selection of participants	NR
Intervention(s)	• 25 mg/day alogliptin • 50 mg twice daily (100mg/day) vildagliptin [Participants were switched from sitagliptin to the randomised study drug.]
Cointervention	Other oral glucose-lowering agents or drug used for the control of hypertension or dyslipidaemia were not changed. Participants were instructed to stick to ideal diet tailored to their bodyweight and physical activity level.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Exclusion criteria state: "patients with renal dysfunction (serum creatinine >1.4 mg/dL for men and >1.2 mg/dL for women." No further information.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear

Subgroup 1: People with moderate or severe 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
Population subgroups	NR
Comparator	NA
Number of participants	132 participants were randomly allocated. Of 64 participants allocated to alogliptin, 62 (96.9%) completed the study, and 2 discontinued. Of 68 participants allocated to vildagliptin, 63 (92.6%) completed the study, and 5 discontinued.
Duration of follow-up	24 weeks
Indirectness	Directly applicable
Method of analysis	Not stated/unclear Method of analysis is not clear. The report states that a sensitivity analysis was conducted using LOCF.
Additional comments	Extracted data relates to Study 2. Data from Study 1 were not included as 31% of the population were treatment naïve.

454.2. Study arms

454.2.1. Alogliptin (N = 64)

454.2.2. Vildagliptin (N = 68)

454.3. Characteristics

454.3.1. Arm-level characteristics

Characteristic	Alogliptin (N = 64)	Vildagliptin (N = 68)
% Male % calculated by analyst Sample size	n = 34 ; % = 53.1	n = 38 ; % = 55.9
Mean age (SD) Mean (SD)	66.7 (10.2)	66.2 (9.9)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed Mean (SD)	10.8 (8.8)	11.7 (9.6)
Cardiovascular risk factors Nominal	NR	NR
Smoking status Nominal	NR	NR
Alcohol consumption Nominal	NR	NR
Presence of severe mental illness Nominal	NR	NR

Characteristic	Alogliptin (N = 64)	Vildagliptin (N = 68)
People with significant cognitive impairment Nominal	NR	NR
People with a learning disability Nominal	NR	NR
BMI (kg/m2) Mean (SD)	25.8 (6.4)	24.2 (4.5)
Number of people with obesity Nominal	NR	NR
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Only sitagliptin (50 mg/day) Sample size	n = 13 ; % = 20.3	n = 15 ; % = 22.1
Sulfonylurea Sample size	n = 18 ; % = 28.6	n = 19 ; % = 27.9
Metformin Sample size	n = 34 ; % = 53	n = 39 ; % = 57.4
Pioglitazone Sample size	n = 16 ; % = 25	n = 14 ; % = 20.6
Alpha-glucosidase inhibitor Sample size	n = 6 ; % = 9.4	n = 14 ; % = 20.6
Blood pressure-lowering medication used ACE-inhibitor or ARB Sample size	n = 35 ; % = 54.7	n = 33 ; % = 48.5
Statins/lipid-lowering medication used Sample size	n = 35 ; % = 54.7	n = 43 ; % = 63.2
Other treatment being received Nominal	NR	NR

455. Taskinen, 2011

Bibliographic Reference	Taskinen, M. R.; Rosenstock, J.; Tamminen, I.; Kubiak, R.; Patel, S.; Dugi, K. A.; Woerle, H. J.; Safety and efficacy of linagliptin as add-on therapy to metformin in patients with type 2 diabetes: a randomized, double-blind, placebo-controlled study; Diabetes Obes Metab; 2011; vol. 13 (no. 1); 65-74

455.1. Study details

Secondary publication of another included study- see primary study for details	No
Other publications associated with this study included in review	None
Trial name / registration number	NCT00601250
Study type	Randomised controlled trial (RCT) Double-blind, placebo-controlled, RCT
Study location	International (82 centres in 10 countries: Czech Republic, Finland, Greece, India, Israel, Mexico, New Zealand, Russia, Sweden, USA)
Study setting	Outpatient
Study dates	01/2008 to 05/2009
Sources of funding	Funded by Boehringer Ingelheim.
Inclusion criteria	• Aged 18-80 years • Type 2 diabetes diagnosis • BMI≤40 kg/m2 • Receiving stable metformin dose ≥1500 mg/day (or max tolerated dose) for ≥12 weeks before randomisation and ≤1 other oral anti-diabetes medication (unchanged for 10 weeks prior to the date of informed consent)

	• At screening, HbA1c 7-10% for those on metformin monotherapy or 6.5-9% for those on metformin combination therapy; by placebo run-in period, HbA1c 7-10% for all participants
Exclusion criteria	• Treatment in past 3-mo with: rosiglitazone, pioglitazone, a GLP-1 analogue, insulin or anti-obesity drug • Changed dosage of thyroid hormone treatment within 6 weeks or were being treated with systemic steroids at the date of informed consent • Impaired hepatic function (serum levels of either ALT, AST or ALP >3 x upper limit of normal) • Renal failure or renal impairment(serum creatinine≥135μmol/l) • Had myocardial infarction, stroke or transient ischaemic attack within 6 months of informed consent • History of acute or chronic metabolic acidosis, unstable or acute congestive heart failure, hereditary galactose intolerance or dehydration • In past 2 months, participation in another trial of an investigational drug.
Recruitment / selection of participants	Eligible participants at screening underwent 2-week placebo run-in period for those on metformin monotherapy, or a 4-week washout period (drugs other than metformin stopped) followed by 2-week placebo run-in period for those originally on metformin combination therapy. Randomisation 3:1 to linagliptin or placebo, stratified by HbA1c level (<8.5%, ≥8.5%) and metformin status at enrolment (monotherapy, combination therapy). Study visits every 6 weeks to 24 weeks, followed by additional week follow up. Those on metformin combination therapy received additional visit during start of washout period. All participants received dietary counselling. Rescue medication (sulphonylurea) permitted only during treatment period if: (weeks 0-11) confirmed glucose level >13.3 mmol/L after overnight fast, or (weeks 12-24) if confirmed glucose level 11.1 mmol/L after overnight fast or >22.2 mmol/L in randomly performed measurement. Any participant who received rescue therapy remained in trial and was not unblinded.
Intervention(s)	• Linagliptin 5 mg daily Oral linagliptin 5 mg daily for 24 weeks.
Cointervention	• Metformin≥1500 mg/day (or max tolerated dose) All participants continued on their existing metformin dose for duration of trial.
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure People with unstable or acute congestive heart failure were excluded.
Strata 2: People with atherosclerotic	Not stated/unclear

cardiovascular disease	People were excluded if they had suffered myocardial infarction, stroke or transient ischaemic attack within 6 months of giving informed consent. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear CKD not an inclusion/exclusion criteria. Patients were excluded if they had renal failure or renal impairment (serumcreatinine≥135µmol/l). CKD not reported in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe 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 Baseline characteristics reported by eGFR category (30 to <60; 60 to <90, ≥90) and 96.5% of participants had eGFR≥30 mL/min/1.73 m2, with remaining 3.5% participants having missing data for this variable.
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	

Comparator	• Placebo Oral placebo for 24 weeks.
Number of participants	N=701 randomised (N=700 received treatment, n=1 withdrew consent before treatment)
Duration of follow-up	24 weeks + 1 week follow up
Method of analysis	Per protocol Per protocol sensitivity analysis conducted for HbA1c outcome (all randomised participants in full analysis set with no important protocol violations). ITT ITT analysis for safety outcomes Modified ITT mITT primary analysis for efficacy outcomes (Full analysis set: all randomised participants who received at least one dose of trial drug and had baseline and at least one post-baseline HbA1c measurement) with LOCF for missing data. Sensitivity analysis also conducted for full analysis completer set (all randomised participants who completed 24 wks treatment with who had wk 24 HbA1c measurement).

455.2. Study arms

455.2.1. Linagliptin 5mg daily (N = 523)

Oral linagliptin 5 mg daily for 24 weeks, in addition to background metformin.

455.2.2. Placebo (N = 177)

Oral placebo for 24 weeks, in addition to background metformin.

455.3. Characteristics

455.3.1. Arm-level characteristics

Characteristic	Linagliptin 5mg daily (N = 523)	Placebo (N = 177)
% Male	n = 278 ; % = 53	n = 101 ; % = 57

Characteristic	Linagliptin 5mg daily (N = 523)	Placebo (N = 177)
Sample size		
Mean age (SD) (years) Mean (SD)	56.5 (10.1)	56.6 (10.9)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Asian Sample size	n = 114 ; % = 22	n = 32 ; % = 18
Other Sample size	n = 16 ; % = 3	n = 5 ; % = 3
White Sample size	n = 393 ; % = 75	n = 140 ; % = 79
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed (years) Sample size	n = NA ; % = NA	n = NA ; % = NA
Less than 1 year Sample size	n = 54 ; % = 11	n = 22 ; % = 13
>1 to 5 years Sample size	n = 174 ; % = 34	n = 60 ; % = 34
5+ years Sample size	n = 285 ; % = 56	n = 93 ; % = 53
Cardiovascular risk factors Nominal	NR	NR
Smoking status Nominal	NR	NR
Alcohol consumption Nominal	NR	NR

Characteristic	Linagliptin 5mg daily (N = 523)	Placebo (N = 177)
Presence of severe mental illness Nominal	NR	NR
People with significant cognitive impairment Nominal	NR	NR
People with a learning disability Nominal	NR	NR
Number of people with obesity Nominal	NR	NR
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Metformin only Sample size	n = 351 ; % = 68	n = 121 ; % = 69
Metformin combination therapy Sample size	n = 162 ; % = 32	n = 54 ; % = 31
Blood pressure-lowering medication used Nominal	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

456. Terauchi, 2020

Bibliographic Reference	Terauchi, Yasuo; Nakama, Takahiro; Spranger, Robert; Amano, Atsushi; Inoue, Takahiro; Niemoeller, Elisabeth; Efficacy and safety of insulin glargine/lixisenatide fixed-ratio combination (iGlarLixi 1:1) in Japanese patients with type 2 diabetes mellitus inadequately controlled on oral antidiabetic drugs: A randomized, 26-week, open-label, multicentre study: The LixiLan JP-O2 randomized clinical trial.; Diabetes, obesity & metabolism; 2020; vol. 22suppl4; 14-23

456.1. 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	LixiLan JP-O2 NCT02752828
Study type	Randomised controlled trial (RCT)
Study location	Japan
Study setting	No additional information.
Study dates	23/05/2016 to 12/03/2018
Sources of funding	Sanofi
Inclusion criteria	• Japanese participants with T2DM >1 year • Participants using 1 or 2 OADs (metformin, pioglitazone, α-GI, SGLT2 inhibitor, SU, glinide, DPP-4 inhibitor; for treatment with DPP-4 inhibitor, up to 3 OADs permitted) • HbA1c ≥7.5% and ≤ 9.5% • FPG ≤10.0 mmol/L • DPP-4 inhibitors were discontinued at randomization

Exclusion criteria	No additional information.
Recruitment / selection of participants	A total of 783 patients were screened. 521 were enrolled from 113 centres in Japan and were randomly assigned 1:1 to iGlarLixi or iGlar; 248 patients (95.4%) in the iGlarLixi group and 254 patients (97.3%) in the iGlar group completed the 26-week treatment period.
Intervention(s)	Insulin glargine/lixisenatide (iGlarLixi) Self-administered subcutaneous pen injection at the initial dose of 5 U iGlar/5 µg lixisenatide. Titration up to a maximum of 20 U. Patients were instructed to inject themselves before breakfast.
Cointervention	Maximum of three oral antidiabetic agents (metformin, pioglitazone, α-GI, SGLT2 inhibitor, SU, glinide, DPP-4 inhibitor; for treatment with DPP-4 inhibitor) permitted.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear
Strata 2: People with atherosclerotic cardiovascular disease	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	Not stated/unclear

moderate or severe frailty	
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
Population subgroups	No additional information.
Comparator	Insulin glargine at an initial dose of 5 U iGlar . Patients were instructed to self-administer subcutaneous injection before breakfast or at bedtime. Same titration up to a maximum of 20 U.
Number of participants	N=521
Duration of follow-up	26-week
Indirectness	
Method of analysis	Modified ITT
Additional comments	Modified intention-to-treat analysis was defined as all randomised patients who received at least one open-label randomised treatment and had both a baseline assessment and at least one post-baseline assessment of any primary or secondary efficacy variables irrespective of compliance with study protocol and procedures based on randomised treatment.

456.2. Study arms

456.2.1. Insulin glargine/lixisenatide (N = 260)

Subcutaneous injection before breakfast

456.2.2. Insulin glargine U100 (N = 261)

Subcutaneous injection before breakfast or at bedtime

456.3. Characteristics

456.3.1. Arm-level characteristics

Characteristic	Insulin glargine/lixisenatide (N = 260)	Insulin glargine U100 (N = 261)
% Male No of events	n = 174 ; % = 67	n = 167 ; % = 64
Mean age (SD) (years) Mean (SD)	59.2 (11)	60.2 (10.3)
Ethnicity No of events	n = 260 ; % = 100	n = 261 ; % = 100
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed Nominal	NR	NR
Smoking status Nominal	NR	NR
Alcohol consumption Nominal	NR	NR
Presence of severe mental illness Nominal	NR	NR

Characteristic	Insulin glargine/lixisenatide (N = 260)	Insulin glargine U100 (N = 261)
People with significant cognitive impairment Nominal	NR	NR
People with a learning disability Nominal	NR	NR
Number of people with obesity 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

457. Thrasher, 2014

Bibliographic Reference	Thrasher, J.; Daniels, K.; Patel, S.; Whetteckey, J.; Woerle, H. J.; Efficacy and safety of linagliptin in black/African American patients with type 2 diabetes: A 6-month, randomized, double-blind, placebo-controlled study; Endocrine Pract; 2014; vol. 20 (no. 5); 412-420

457.1. Study details

Secondary publication of another included study- see primary study for details	No
Other publications associated with this study included in review	None
Trial name / registration number	NCT01194830
Study type	Randomised controlled trial (RCT) Double-blind, placebo-controlled RCT
Study location	USA
Study setting	Outpatient (primary care clinics and clinical research centres)
Study dates	09/2010 to 10/2011
Sources of funding	Funded by Boehringer Ingelheim Inc
Inclusion criteria	• Aged 18-80 years • Type 2 diabetes diagnosis ≥3-mo ago • HbA1Cc 7.5-11% inclusive • BMI≤45 kg/m2 • Self-reported race as Black/African-American irrespective of ethnic group (Hispanic or non-Hispanic) • Treatment naive or stable dose (≥10 weeks) of only one blood-glucose lowering drug

Exclusion criteria	• Type 1 diabetes diagnosis • History of myocardial infarction, stroke, or transient ischemic attack ≤3 months before screening
Recruitment / selection of participants	Eligible participants entered 2-wk placebo run-in period, then randomised 1:1 to linagliptin or placebo using schedule generated by validated pseudo-random number generator. Site determined treatment assignment by allocating participants next lowest sequentially numbered medication kit. Rescue therapy (choice at investigator's discretion, excluding other DPP-4 inhibitors) initiated after 2 measurements if glucose level >240 mg/dL after overnight fast or >400 mg/dL in random measurement (weeks 1-12) or if glucose level >200 mg/dL after overnight fast or >400 mg/dL in random measurement. Participants who received rescue therapy continued in trial unless FPG remained >240 mg/dL despite rescue therapy.
Intervention(s)	• Linagliptin 5 mg daily Oral linagliptin 5 mg daily for 24 weeks.
Cointervention	• Metformin and/or sulphonylurea Participants continued on background blood-glucose lowering drugs.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear "Key clinical exclusion criteria were a history of myocardial infarction (MI), stroke, or transient ischemic attack within 3 months before screening." No further information. No information reported in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Not an inclusion/exclusion criteria. Only renal impairment (none/mild/moderate) reported in baseline characteristics, based on eGFR categories.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear

Subgroup 1: People with moderate or severe 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 At baseline all participants had eGFR>30 ml/min/1.73 m2, but not clear whether this is inclusion criteria as not sufficiently reported in article
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Comparator	• Placebo Placebo for 24 weeks
Number of participants	N=226 randomised (Full analysis set, N=208; Full analysis set - completers, N=169; Per protocol set, N=175)
Duration of follow-up	24 weeks + 1 week follow up
Indirectness	Downgrade for indirectness as ~11% of participants were treatment-naive at screening and so were not 'adding' to existing drug treatment
Method of analysis	Per protocol Per protocol sensitivity analysis (all randomised participants with no protocol violations) for primary HbA1c outcome. Modified ITT mITT LOCF analysis (full analysis set: all randomised participants treated with at least one dose of study drug, baseline HbA1c measurement and at least one post-baseline HbA1c measurement) conducted for primary efficacy and secondary outcomes. Sensitivity analysis for primary HbA1c

	outcome conducted using FAS-completer set. Safety assessments conducted on all randomised participants who received at least one study drug dose..

457.2. Study arms

457.2.1. Linagliptin 5 mg daily (N = 106)

Oral linagliptin for 24 weeks, in addition to (if any) one oral blood-glucose lowering drug.

457.2.2. Placebo (N = 120)

Oral placebo for 24 weeks, in addition to (if any) one oral blood-glucose lowering drug.

457.3. Characteristics

457.3.1. Study-level characteristics

Characteristic	**Study (N = 226)**
Comorbidities Sample size	n = NA ; % = NA
Hypertension Sample size	n = 163 ; % = 72.1
Coronary artery disease Sample size	n = 13 ; % = 5.8

457.3.2. Arm-level characteristics

Characteristic	**Linagliptin 5 mg daily (N = 106)**	**Placebo (N = 120)**
% Male Sample size	n = 60 ; % = 56.6	n = 61 ; % = 50.8
Mean age (SD) (years) Mean (SD)	53.7 (10.1)	54.1 (9.9)

Characteristic	Linagliptin 5 mg daily (N = 106)	Placebo (N = 120)
Ethnicity Black/African-American (self-reported) Sample size	n = 106 ; % = 100	n = 120 ; % = 100
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed (years) Data is for full analysis set: Linagliptin, N=98; Placebo, N=110 Sample size	n = NA ; % = NA	n = NA ; % = NA
<1 year Sample size	n = 9 ; % = 9.2	n = 5 ; % = 4.5
>1 to 5 years Sample size	n = 37 ; % = 37.8	n = 38 ; % = 34.5
>5 to 10 years Sample size	n = 23 ; % = 23.5	n = 34 ; % = 30.9
More than 10 years Sample size	n = 29 ; % = 29.6	n = 33 ; % = 30
Cardiovascular risk factors Nominal	NR	NR
Smoking status Nominal	NR	NR
Alcohol consumption Nominal	NR	NR
Presence of severe mental illness Nominal	NR	NR
People with significant cognitive impairment Nominal	NR	NR
People with a learning disability Nominal	NR	NR

Characteristic	Linagliptin 5 mg daily (N = 106)	Placebo (N = 120)
Number of people with obesity Sample size	n = 51 ; % = 54.8	n = 77 ; % = 73.3
Other antidiabetic medication used Data is for full analysis set: Linagliptin, N=98; Placebo, N=110 Sample size	n = NA ; % = NA	n = NA ; % = NA
None Sample size	n = 14 ; % = 15.3	n = 11 ; % = 10
Metformin Sample size	n = 64 ; % = 77.1	n = 78 ; % = 78.8
Sulphonylurea Sample size	n = 18 ; % = 21.7	n = 19 ; % = 19.2
Blood pressure-lowering medication used Sample size	n = 69 ; % = 64.2	n = 79 ; % = 65.8
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

458. Tinahones, 2017

Bibliographic Reference	Tinahones, F. J.; Gallwitz, B.; Nordaby, M.; Götz, S.; Maldonado-Lutomirsky, M.; Woerle, H. J.; Broedl, U. C.; Linagliptin as add-on to empagliflozin and metformin in patients with type 2 diabetes: two 24-week randomized, double-blind, double-dummy, parallel-group trials; Diabetes Obes Metab; 2017; vol. 19 (no. 2); 266-274

458.1. Study details

Secondary publication of another included study- see primary study for details	No
Other publications associated with this study included in review	None
Trial name / registration number	NCT01778049
Study type	Randomised controlled trial (RCT) Double-blind, double-dummy, parallel-group, placebo-controlled RCTs (Study 1 and Study 2)
Study location	International (114 sites in 10 countries: Argentina, Australia, Canada, Germany, Italy, Portugal, Russia, Spain, Ukraine, USA) (Study 1 and Study 2)
Study setting	Outpatient
Study dates	01/2013 to 03/2015
Sources of funding	Funded by Boehringer Ingelheim and Eli Lilly & Co. Diabetes Alliance
Inclusion criteria	• Aged ≥18 years • HbA1c 8-10.5% inclusive • On diet and exercise regimen • Receiving stable (unchanged for ≥12 weeks) dose immediate-release metformin (≥1500 mg daily, max tolerated dose, or max dose acc. to local label)

	• BMI≤45 kg/m2
Exclusion criteria	• Uncontrolled hyperglycaemia (glucose level >15.0 mmol/L after overnight fast during open-label and placebo add-on periods, confirmed by second measurement) • Treatment with anti-diabetes agent other than metformin within 12 weeks prior to randomization • eGFR <60mL/min/1.73 m2 • Hereditary galactose intolerance • Acute coronary syndrome, stroke, or transient ischemic attack within 3 months prior to consent • Any previous (within the past 2 years) or planned bariatric surgery • Treatment with anti-obesity drugs within 3 months before consent
Recruitment / selection of participants	Eligible participants for both trials were initially randomised 1:1, using third-party interactive voice and web-response system, to receive open-label empagliflozin 10 mg (Study 1) or 25 mg (Study 2) for 16 weeks, as add-on to background stable metformin dose; after 16-weeks, participants entered 1-wk open-label placebo period in which this was added to empagliflozin and metformin. Participants with HbA1c 7.5-10.5% inclusive at end of 16 weeks, and who satisfied inclusion criteria, were re-randomised using same voice/web response system (stratified by HbA1c level [<8.5%, ≥8.5%] at 16 weeks, eGFR MDRD category at 16 weeks [≥90, 60-89 mL/min/1.53 m2]). Participants who needed rescue therapy during open-label period were not eligible for double-blind period. During double-blind period, rescue therapy permitted at discretion of investigator (DPP-4 inhibitor, GLP-1 analogues and SGLT2 inhibitor not permitted). If hypoglycaemia, reduction or discontinuation of rescue therapy considered prior to reducing background metformin.
Intervention(s)	• Linagliptin 5 mg daily Oral linagliptin 5 mg daily in morning for 24 weeks, as a single-pill combination with empagliflozin, in addition to empagliflozin and metformin, plus a placebo pill.
Cointervention	• Empagliflozin 10 mg (Study 1) • Empagliflozin 25 mg (Study 2) • Metformin (Study 1 and Study 2) • Placebo All participants received open-label oral empagliflozin 10 mg or 25 mg, as a single-pill combination with linagliptin, in addition to stable metformin dose.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 2: People with	Not stated/unclear

atherosclerotic cardiovascular disease	Exclusion criteria state "acute coronary syndrome, stroke, or transient ischemic attack within 3 months prior to consent". No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Chron kidney disease was not an inclusion /exclusion criteria. No information in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Mixed population
Subgroup 5: eGFR category at baseline	eGFR ≥30mL/min/1.73m2 Exclusion criteria: eGFR≤60 ml/min/1.73 m2
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	• Placebo

	Study 1: Matching placebo daily, in morning, for 24 weeks, in addition to empagliflozin 10 mg and metformin, plus additional placebo pill Study 2: Matching placebo daily, in morning, for 24 weeks, in addition to empagliflozin 25 mg and metformin, plus additional placebo pill
Number of participants	Study 1: N=256 randomised (N=229 completers) Study 2: N=226 randomised (N=207 completers)
Duration of follow-up	24 weeks
Indirectness	None
Method of analysis	Modified ITT mITT analysis (full analysis set: all randomised participants who received at least one study drug dose, and had baseline and at least one post-baseline HbA1c measurement) for efficacy outcomes using observed cases only. Safety outcomes analysed using randomised participants who received at least one study drug dose.
Additional comments	Article reports results from 2 RCTs.

458.2. Study arms

458.2.1. Linagliptin 5 mg daily (N = 126)

Oral linagliptin 5 mg daily for 24 weeks, in addition to oral empagliflozin 10 mg and metformin (Study 1)

458.2.2. Placebo (N = 130)

Matching placebo daily for 24 weeks, in addition to oral empagliflozin 10 mg and metformin (Study 1)

458.2.3. Linagliptin 5 mg daily (N = 114)

Oral linagliptin 5 mg daily for 24 weeks, in addition to oral empagliflozin 25 mg and metformin (Study 2)

458.2.4. Placebo (N = 112)

Matching placebo daily for 24 weeks, in addition to oral empagliflozin 25 mg and metformin (Study 2)

458.3. Characteristics

458.3.1. Arm-level characteristics

Characteristic	Linagliptin 5 mg daily (N = 126)	Placebo (N = 130)	Linagliptin 5 mg daily (N = 114)	Placebo (N = 112)
% Male Sample size	n = 69 ; % = 56.6	n = 70 ; % = 56	n = 52 ; % = 47.3	n = 63 ; % = 57.3
Mean age (SD) (years) Mean (SD)	56.6 (9.5)	56.8 (9.4)	56.6 (9.8)	56.1 (10.6)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Asian Sample size	n = 0 ; % = 0	n = 1 ; % = 0.8	n = 0 ; % = 0	n = 0 ; % = 0
Black/African American Sample size	n = 2 ; % = 1.6	n = 3 ; % = 2.4	n = 3 ; % = 2.7	n = 4 ; % = 3.6
Other Sample size	n = 0 ; % = 0	n = 2 ; % = 1.6	n = 0 ; % = 0	n = 0 ; % = 0
White Sample size	n = 120 ; % = 98.4	n = 119 ; % = 95.2	n = 107 ; % = 97.3	n = 106 ; % = 96.4
Presence of frailty Nominal	NR	NR	NR	NR
Time since type 2 diabetes diagnosed Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Less than or equal to 1 year Sample size	n = 7 ; % = 5.7	n = 16 ; % = 12.8	n = 8 ; % = 7.3	n = 9 ; % = 8.2
>1 to 5 years Sample size	n = 42 ; % = 34.4	n = 40 ; % = 32	n = 31 ; % = 28.2	n = 33 ; % = 30
>5 to 10 years Sample size	n = 40 ; % = 32.8	n = 37 ; % = 29.6	n = 40 ; % = 36.4	n = 39 ; % = 35.5

Characteristic	Linagliptin 5 mg daily (N = 126)	Placebo (N = 130)	Linagliptin 5 mg daily (N = 114)	Placebo (N = 112)
More than 10 years Sample size	n = 33 ; % = 27	n = 32 ; % = 25.6	n = 31 ; % = 28.2	n = 29 ; % = 26.4
Cardiovascular risk factors Nominal	NR	NR	NR	NR
Smoking status Nominal	NR	NR	NR	NR
Alcohol consumption Nominal	NR	NR	NR	NR
Presence of severe mental illness Nominal	NR	NR	NR	NR
People with significant cognitive impairment Nominal	NR	NR	NR	NR
People with a learning disability Nominal	NR	NR	NR	NR
Number of people with obesity Nominal	NR	NR	NR	NR
Other antidiabetic medication used Nominal	NR	NR	NR	NR
Blood pressure-lowering medication used Nominal	NR	NR	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR	NR	NR
Other treatment being received Nominal	NR	NR	NR	NR

Baseline characteristic data for the following number of participants: Study 1, Linagliptin, N=122, Placebo, N=125; Study 2, Linagliptin, N=110, Placebo, N=110.

459. Tripathy, 2013

Bibliographic Reference	Tripathy, D.; Daniele, G.; Fiorentino, T. V.; Perez-Cadena, Z.; Chavez-Velasquez, A.; Kamath, S.; Fanti, P.; Jenkinson, C.; Andreozzi, F.; Federici, M.; Gastaldelli, A.; Defronzo, R. A.; Folli, F.; Pioglitazone improves glucose metabolism and modulates skeletal muscle TIMP-3-TACE dyad in type 2 diabetes mellitus: A randomised, double-blind, placebo-controlled, mechanistic study; Diabetologia; 2013; vol. 56 (no. 10); 2153-2163

459.1. Study details

Secondary publication of another included study- see primary study for details	No
Other publications associated with this study included in review	None
Trial name / registration number	NCT01223196
Study type	Randomised controlled trial (RCT) Double-blind, placebo-controlled RCT
Study location	Texas, USA
Study setting	Outpatient (clinical research unit)
Study dates	08/2009 to 12/2011
Sources of funding	Funded by Takeda.
Inclusion criteria	• Aged 18-70 years • Type 2 diabetes diagnosis • BMI 30-40 kg/m2 inclusive • HbA1c<10% • Treated with diet only, diet + metformin and/or sulphonylurea • Stable weight≥3-mo • FPG 126-270 mg/dL inclusive

	• Hematocrit >34% • Serum creatinine <1.8mg/dl • AST<2 times upper limit of normal • ALT< 2 time upper limit of normal • Alkaline phosphatase<2 times upper limit of normal
Exclusion criteria	• Previous treatment with insulin or thiazolidinediones • Presence of other major organ disease • Participates in strenuous exercise • Congestive heart failure > NYHA (New York Heart Association) class II • History of dyspnoea on exertion • Abnormal breath sounds • EKG changes other than non-specific ST-T changes in the ECG or LVH • H/O Claudication
Recruitment / selection of participants	Eligible participants randomised and allocated using central office to pioglitazone or placebo. Various metabolic tests conducted at 1, 3 and 5 months at clinical research unit after overnight fast. Before treatment phase, all participants received dietary counselling and were asked to consume standard ADA, weight-maintaining diet for duration of trial.
Intervention(s)	• Pioglitazone 15 mg daily Oral pioglitazone 15 mg daily for 26 weeks.
Cointervention	• Diet • Metformin with or without sulphonylurea All participants received diet whilst 85% of these also continued with background metformin with or without sulphonylurea.
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Exclusion criteria: NYHA class 2-4 (reported in clinicaltrials.gov record)
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.

Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe 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 Inclusion criteria: BMI 30-40 kg/m2 inclusive
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Comparator	• Placebo Oral matching placebo for 26 weeks.
Number of participants	N=29 randomised (N=20 analysed)
Duration of follow-up	26 weeks
Indirectness	Downgrade for indirectness as 15% of participants had previously received diet only.
Method of analysis	Modified ITT

	Appears to be mITT completer analysis (all randomised participants who received study drug and completed trial)
Additional comments	

459.2. Study arms

459.2.1. Pioglitazone 15 mg daily (N = 15)

Oral pioglitazone 15 mg daily, for 26 weeks, in addition to diet only, or diet and metformin with or without a sulphonylurea.

459.2.2. Placebo (N = 14)

Matching placebo for 26 weeks, in addition to diet only, or diet and metformin with or without a sulphonylurea.

459.3. Characteristics

459.3.1. Arm-level characteristics

Characteristic	Pioglitazone 15 mg daily (N = 15)	Placebo (N = 14)
% Male Sample size	n = 7 ; % = 63.6	n = 7 ; % = 77.8
Mean age (SD) (years) Mean (SD)	56 (2.8)	57 (2.2)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed Nominal	NR	NR
Cardiovascular risk factors	NR	NR

Characteristic	Pioglitazone 15 mg daily (N = 15)	Placebo (N = 14)
Nominal		
Smoking status Nominal	NR	NR
Alcohol consumption Nominal	NR	NR
Presence of severe mental illness Nominal	NR	NR
People with significant cognitive impairment Nominal	NR	NR
People with a learning disability Nominal	NR	NR
Number of people with obesity Data is for Pioglitazone, N=15 and Placebo, N=14 Sample size	n = 15 ; % = 100	n = 14 ; % = 100
Metformin only Sample size	n = 6 ; % = 54.5	n = 6 ; % = 66.7
Metformin + a sulphonylurea Sample size	n = 3 ; % = 27.3	n = 2 ; % = 22.2
Blood pressure-lowering medication used Nominal	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

Unless otherwise stated, baseline characteristics are for Pioglitazone, N=11, and Placebo, N=9.

460. Tuttle, 2018

Bibliographic Reference	Tuttle, K. R.; Lakshmanan, M. C.; Rayner, B.; Busch, R. S.; Zimmermann, A. G.; Woodward, D. B.; Botros, F. T.; Dulaglutide versus insulin glargine in patients with type 2 diabetes and moderate-to-severe chronic kidney disease (AWARD-7): a multicentre, open-label, randomised trial; Lancet Diabetes Endocrinol; 2018; vol. 6 (no. 8); 605

460.1. Study details

Secondary publication of another included study- see primary study for details	No
Other publications associated with this study included in review	None
Trial name / registration number	AWARD-7/NCT01621178
Study type	Randomised controlled trial (RCT) Open-label multicentre RCT with masked dulaglutide dose
Study location	International (99 sites in 9 countries: Brazil, Hungary, Mexico, Poland, Romania, South Africa, Spain, Ukraine, USA)
Study setting	Community
Study dates	08/2012 to 12/2016
Sources of funding	Eli Lilly and Co.
Inclusion criteria	• Aged ≥18 years • Diagnosis of type 2 diabetes • Moderate or severe chronic kidney disease (stages 3 or 4) • HbA1c level 7.5-10% inclusive • Treatment with insulin with or without oral antihyperglycaemic drug • Treatment with a maximum tolerated dose of angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker

Exclusion criteria	• Diagnosis of type 1 diabetes • Treatment with oral anti-hyperglycaemic drug without insulin • Treatment with GLP-1 receptor agonist or DPP-4 inhibitor • Chronic kidney disease stage 5, maintenance dialysis treatment, likely to require dialysis or kidney transplant during study, or acute kidney treatment , within 2-mo prior to randomisation
Recruitment / selection of participants	Recruited from 99 clinical research sites in 9 countries, with enrolment managed to achieve ~2:1 ratio CKD stages 3:stage 4. Participants enrolled by each clinical site and team responsible for randomisation not involved in other parts of trial. Initial 3-13 week screening and lead-in period, 52 week treatment period (22 study visits: every week for 4 weeks; every 2 weeks until week 26; every 4-6 weeks until week 52), and 4-week safety follow-up period. For participants taking insulin and oral anti-hyperglycaemic drugs before study, these drugs were discontinued in first week and pre-study insulin treatment optimized during 12-wk lead-in period.. For participants taking insulin only before study, pre-insulin treatment optimised during 3-wk lead-in period. All participants discontinued pre-study insulin regimen at randomisation. Participants randomised 1:1:1 ratio to 1 of 3 arms using computer-generated random sequence with interactive response system, stratified by baseline CKD severity (stage 3a, 3b, 4), baseline microalbuminuria, and geographical region (western USA; eastern USA; Brazil and Mexico; Hungary, Poland and Spain; Romania, South Africa and Ukraine). Rescue therapy permitted if persistent severe hyperglycaemia.
Intervention(s)	• Dulaglutide 1.5 mg weekly • Dulaglutide 0.75 mg weekly Subcutaneous injection of dulaglutide 0.75 mg or 1.5 mg weekly in skinfold of left or right abdominal wall for 52 weeks, in addition to subcutaneous injection of mealtime insulin lispro (three largest meals of day). New prefilled syringe used for each dulaglutide injection, administered at approximately same time of day each week. Investigators and participants masked to dulaglutide dose.
Cointervention	Subcutaneous injection of prandial insulin lispro at three largest meals of day. Dosing adjustment at least weekly but every 3 days permissible. Dosing adjustment based on mean of previous three self-monitored blood glucose values for given meal. If blood glucose within target range then no change. Insulin lispro titrated to target pre-prandial glucose concentration 6.7-10 mmol/L.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Exclusion criteria state: "Any of the following cardiovascular (CV) conditions within 12 weeks prior to randomization: acute myocardial infarction, New York Heart Association class III or class IV heart failure, or cerebrovascular accident (stroke)" (see supplement). No information in baseline characteristics. Unclear about class II.
Strata 2: People with atherosclerotic	Not stated/unclear Exclusion criteria state: "Any of the following cardiovascular (CV) conditions within 12 weeks prior to randomization: acute myocardial infarction, New York Heart Association class III or class IV heart failure, or

cardiovascular disease	cerebrovascular accident (stroke)" (see supplement). No information in baseline characteristics. Unclear about CV events preceding the 12 weeks and unclear about angina and PAD.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	People with chronic kidney disease The study defined the population as people with type 2 diabetes and moderate to severe chronic kidney disease (stages 3-4).
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe 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	Mixed population Inclusion criteria: moderate or severe CKD (stages 3 and 4) NKF KDOQI guidelines, defined by eGFR≥15 to <60 mL/min/1.73 m2.
Subgroup 6: Albuminuria category at baseline	Mixed population Measured UACR at baseline, includes participants in all three categories (A1-A3)
Population subgroups	Prespecified subgroup analysis by baseline UACR (A1-A3) category

Comparator	• Insulin glargine daily Subcutaneous injection of insulin glargine at bedtime for 52 weeks, in addition to subcutaneous injection of mealtime insulin lispro (three largest meals of day). Dosing adjustment for insulin glargine at least weekly but every 3 days permissible. Dosing adjustment based on mean of previous three self-monitored fasting blood glucose values. Insulin glargine doses (in this group) titrated to target self-monitored fasting blood glucose concentrations of 5.6-8.3 mmol/L.
Number of participants	N=577
Duration of follow-up	52 weeks + 4 weeks post-treatment follow up
Indirectness	None
Method of analysis	Modified ITT mITT analysis (all randomised participants who received at least one dose of study drug and had at least one post-randomisation HbA1c measurement) for efficacy analysis (HbA1c, eGFR, UACR, weight, hypoglycaemia rate). Safety analysis was in all randomised participants who received at least one dose of assigned study drug and any post-dose data).

460.2. Study arms

460.2.1. Dulaglutide 1.5 mg weekly (N = 193)

Subcutaneous injection of dulaglutide 1.5 mg weekly for 52 weeks, in addition to subcutaneous injection of titrated mealtime insulin lispro.

460.2.2. Dulaglutide 0.75 mg weekly (N = 190)

Subcutaneous injection of dulaglutide 0.75 mg weekly for 52 weeks, in addition to subcutaneous injection of titrated mealtime insulin lispro.

460.2.3. Insulin glargine (N = 194)

Subcutaneous injection of titrated insulin glargine at bedtime for 52 weeks, in addition to subcutaneous injection of titrated mealtime insulin lispro.

460.3. Characteristics

460.3.1. Arm-level characteristics

Characteristic	Dulaglutide 1.5 mg weekly (N = 193)	Dulaglutide 0.75 mg weekly (N = 190)	Insulin glargine (N = 194)
% Male Sample size	n = 104 ; % = 54	n = 104 ; % = 55	n = 93 ; % = 48
Mean age (SD) (years) Mean (SD)	64.7 (8.8)	64.7 (8.6)	64.3 (8.4)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Asian Sample size	n = 7 ; % = 4	n = 4 ; % = 2	n = 5 ; % = 3
Black/African American Sample size	n = 26 ; % = 14	n = 36 ; % = 19	n = 26 ; % = 14
Hispanic or Latino Sample size	n = 78 ; % = 41	n = 75 ; % = 39	n = 79 ; % = 41
Native American/Alaska Native Sample size	n = 12 ; % = 6	n = 17 ; % = 9	n = 18 ; % = 9
Native Hawaiian/Other Pacific Islander Sample size	n = 0 ; % = 0	n = 0 ; % = 0	n = 1 ; % = 1
Multiple Sample size	n = 10 ; % = 5	n = 7 ; % = 4	n = 6 ; % = 3
White Sample size	n = 134 ; % = 71	n = 122 ; % = 66	n = 137 ; % = 71
Comorbidities Nominal	NR	NR	NR
Presence of frailty Nominal	NR	NR	NR
Time since type 2 diabetes diagnosed Mean (SD)	17.6 (8.7)	18 (8.8)	18.7 (8.7)

Characteristic	Dulaglutide 1.5 mg weekly (N = 193)	Dulaglutide 0.75 mg weekly (N = 190)	Insulin glargine (N = 194)
Cardiovascular risk factors 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 Nominal	NR	NR	NR
Blood pressure-lowering medication used Dulaglutide 1.5 mg, N=183; Dulaglutide 0.75 mg, N=180; Insulin glargine, N=186. Sample size	n = 181 ; % = 99	n = 179 ; % = 99	n = 186 ; % = 100
Angiotensin converting enzyme inhibitors/angiotensin receptor blockers Sample size	n = 165 ; % = 90	n = 170 ; % = 94	n = 174 ; % = 94
Angiotensin converting enzyme inhibitors Sample size	n = 87 ; % = 48	n = 88 ; % = 49	n = 94 ; % = 51
Angiotensin receptor blockers Sample size	n = 91 ; % = 50	n = 96 ; % = 53	n = 86 ; % = 52

Characteristic	Dulaglutide 1.5 mg weekly (N = 193)	Dulaglutide 0.75 mg weekly (N = 190)	Insulin glargine (N = 194)
Beta blockers Sample size	n = 118 ; % = 65	n = 105 ; % = 58	n = 119 ; % = 64
Calcium channel blockers Sample size	n = 108 ; % = 59	n = 95 ; % = 53	n = 106 ; % = 57
Diuretic Sample size	n = 136 ; % = 74	n = 125 ; % = 69	n = 150 ; % = 81
Renin inhibitors Sample size	n = 2 ; % = 1	n = 1 ; % = 1	n = 0 ; % = 0
Other Sample size	n = 17 ; % = 9	n = 10 ; % = 6	n = 10 ; % = 5
Statins/lipid-lowering medication used Dulaglutide 1.5 mg, N=183; Dulaglutide 0.75 mg, N=180; Insulin glargine, N=186. Sample size	n = 143 ; % = 78	n = 134 ; % = 74	n = 140 ; % = 75
Bile acid sequestrants Sample size	n = 1 ; % = 1	n = 0 ; % = 0	n = 1 ; % = 1
Cholesterol absorption inhibitors Sample size	n = 6 ; % = 3	n = 2 ; % = 1	n = 5 ; % = 3
Fibrates Sample size	n = 38 ; % = 21	n = 25 ; % = 14	n = 21 ; % = 11
HMG-CoA reductase inhibitors Sample size	n = 129 ; % = 71	n = 128 ; % = 71	n = 131 ; % = 70
Niacin Sample size	n = 3 ; % = 2	n = 0 ; % = 0	n = 0 ; % = 0
Other treatment being received Dulaglutide 1.5 mg, N=183; Dulaglutide 0.75 mg, N=180; Insulin glargine, N=186. Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Any concomitant anti-anaemic medication	n = 36 ; % = 20	n = 29 ; % = 16	n = 34 ; % = 18

Characteristic	Dulaglutide 1.5 mg weekly (N = 193)	Dulaglutide 0.75 mg weekly (N = 190)	Insulin glargine (N = 194)
Sample size			
Iron preparations Sample size	n = 24 ; % = 13	n = 21 ; % = 12	n = 24 ; % = 13
Vitamin B12 and folic acid Sample size	n = 18 ; % = 10	n = 14 ; % = 8	n = 11 ; % = 6
Other anti-anaemic preparations (erythropoietin and analogues, or erythropoiesis-stimulating agents) Sample size	n = 5 ; % = 3	n = 15 ; % = 8	n = 10 ; % = 5

461. Umpierrez, 2006

Bibliographic Reference	Umpierrez, G.; Issa, M.; Vlajnic, A.; Glimepiride versus pioglitazone combination therapy in subjects with type 2 diabetes inadequately controlled on metformin monotherapy: results of a randomized clinical trial; Curr Med Res Opin; 2006; vol. 22 (no. 4); 751-9

461.1. Study details

Secondary publication of another included study- see primary study for details	No
Other publications associated with this study included in review	None
Trial name / registration number	Not reported
Study type	Randomised controlled trial (RCT) Open-label, parallel-group, forced titration RCT
Study location	USA (51 diabetes centres)
Study setting	Outpatient
Study dates	Not reported by conducted before 2006
Sources of funding	Sponsored by Sanofi-Aventis, Bridgewater, NJ, USA.
Inclusion criteria	• Aged 18-79 years • Type 2 diabetes diagnosis≥6-mo • Taking stable metformin dose (1000-2500 mg daily; extended-release, 500-2000 mg daily) as only oral anti-diabetic drug ≥2-mo prior to study • BMI≥24 kg/m2 • HbA1c 7.5-10% inclusive • FPG 126-235 mg/dL

	• Evidence of insulin secretory capacity (C-peptide concentration≥0.27 nmol/L during stabilisation period)
Exclusion criteria	• Treated with insulin, thiazolidinediones, or a sulphonylurea within 3 months of enrolment • History of substance abuse • Severe hypoglycaemia • Acute metabolic complications • Clinically significant abnormal baseline lab values
Recruitment / selection of participants	Eligible participants entered 2-week stabilisation period and were then randomised 1:1 to glimepiride to pioglitazone with initial 6-wk forced titration period. Participants self-monitored blood glucose at least once daily or when hypoglycaemia symptoms.
Intervention(s)	• Pioglitazone 30-45 mg daily Oral pioglitazone 30-45 mg daily for 26 weeks, in addition to metformin. Pioglitazone started at 30 mg daily and increased to max of 45 mg daily at week 12 if mean self-monitored blood glucose over prior 3 days >120 mg/dL or HbA1c≥8%.
Cointervention	• Metformin All participants continued receiving baseline metformin dose for duration of trial.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and	Not stated/unclear

high cardiovascular risk	
Subgroup 1: People with moderate or severe 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
Comparator	• Glimepiride 2-8 mg daily Oral glimepiride 2-8 mg daily for 26 weeks, in addition to metformin. Glimepiride initiated at 2 mg daily and increased during 6-wk forced titration phase to max of 8 mg daily or until mean of last 3 daily fasting self-monitored blood glucose <120 mg/dL.
Number of participants	N=210 randomised (N=203 mITT population; N=181 completers)
Duration of follow-up	26 weeks
Indirectness	None
Method of analysis	Modified ITT Efficacy and safety outcomes assessed using mITT population (all randomised participants who took at least one study drug dose and at least one post-baseline HbA1c measurement).

461.2. Study arms

461.2.1. Pioglitazone 30-45 mg daily (N = 109)

Oral pioglitazone 30-45 mg daily for 26 weeks, in addition to stable metformin.

461.2.2. Glimepiride 2-8 mg daily (N = 101)

Oral glimepiride 2-8 mg daily for 26 weeks, in addition to stable metformin.

461.3. Characteristics

461.3.1. Arm-level characteristics

Characteristic	Pioglitazone 30-45 mg daily (N = 109)	Glimepiride 2-8 mg daily (N = 101)
% Male Sample size	n = 56 ; % = 52.3	n = 53 ; % = 55.2
Mean age (SD) (years) Mean (SD)	50.4 (9.7)	47.4 (11.3)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Asian Sample size	n = 4 ; % = 3.7	n = 1 ; % = 1
Black Sample size	n = 17 ; % = 15.9	n = 13 ; % = 13.5
Hispanic Sample size	n = 2 ; % = 1.9	n = 5 ; % = 5.2
Other Sample size	n = 0 ; % = 0	n = 1 ; % = 1
White Sample size	n = 84 ; % = 78.5	n = 76 ; % = 79.2
Comorbidities Nominal	NR	NR

Characteristic	Pioglitazone 30-45 mg daily (N = 109)	Glimepiride 2-8 mg daily (N = 101)
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	5.9 (6.1)	4.9 (3.8)
Cardiovascular risk factors Nominal	NR	NR
Smoking status Nominal	NR	NR
Alcohol consumption Nominal	NR	NR
Presence of severe mental illness Nominal	NR	NR
People with significant cognitive impairment Nominal	NR	NR
People with a learning disability Nominal	NR	NR
Number of people with obesity Nominal	NR	NR
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

Baseline characteristics are for Pioglitazone, N=107, and Glimepiride, N=96.

462. Vähätalo, 2007

Bibliographic Reference	Vähätalo, M.; Rönnemaa, T.; Viikari, J.; Recognition of fasting or overall hyperglycaemia when starting insulin treatment in patients with type 2 diabetes in general practice; Scand J Prim Health Care; 2007; vol. 25 (no. 3); 147-53

462.1. 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	Finland.
Study setting	Initially inpatient and then outpatient follow-up.
Study dates	1994-1998.
Sources of funding	No additional information.
Inclusion criteria	Type 2 diabetes for more than 5 years; age 40-75 years; BMI <35 kg/m2; HbA1c >7.5%; fasting serum/plasma glucose >8.0 mmol/L; postprandial C-peptide value >0.6 nmol/L (to ensure people with type 1 diabetes were not included).
Exclusion criteria	Severe cardiac insufficiency; serum creatinine >150 micromol/L; ALT >80 IU/L.
Recruitment / selection of participants	No additional information.

Intervention(s)	Glipizide N=15 Glipizide 10 mg in the morning orally for 12 months.
Cointervention	Everyone received insulin, either NPH or Lente insulin twice daily (in the morning and at bedtime).
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Patients with severe cardiac insufficiency were excluded. No further description of cardiac insufficiency given. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe 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
Population subgroups	No additional information.
Comparator	Metformin N=26 Metformin 2.5 grams/day or the highest dose tolerated by the person for 12 months. A third arm received insulin only (n=11), but was not included in this analysis due to the comparison not being valid for the review (essentially intervention v. no treatment due to insulin being available for all treatment arms).
Number of participants	41 (52 including the insulin only arm)
Duration of follow-up	12 months
Indirectness	No additional information.
Method of analysis	Not stated/unclear
Additional comments	No additional information.

462.2. Study arms

462.2.1. Glipizide (N = 15)

Glipizide 10 mg in the morning orally for 12 months. Concomitant therapy: Everyone received insulin, either NPH or Lente insulin twice daily (in the morning and at bedtime).

462.2.2. Metformin (N = 26)

Metformin 2.5 grams/day or the highest dose tolerated by the person for 12 months. Concomitant therapy: Everyone received insulin, either NPH or Lente insulin twice daily (in the morning and at bedtime).

462.3. Characteristics

462.3.1. Arm-level characteristics

Characteristic	Glipizide (N = 15)	Metformin (N = 26)
% Male Sample size	n = NR ; % = NR	n = NR ; % = NR
Mean age (SD) Mean (SD)	NR (NR)	NR (NR)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed Mean (SD)	NR (NR)	NR (NR)
Cardiovascular risk factors Sample size	n = NR ; % = NR	n = 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	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Glipizide (N = 15)	Metformin (N = 26)
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
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR
Other antidiabetic medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Blood pressure-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Statins/lipid-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR

463. van der Meer, 2009

Bibliographic Reference	van der Meer, R. W.; Rijzewijk, L. J.; Jong, H. W.; Lamb, H. J.; Lubberink, M.; Romijn, J. A.; Bax, J. J.; Roos, A.; Kamp, O.; Paulus, W. J.; Heine, R. J.; Lammertsma, A. A.; Smit, J. W.; Diamant, M.; Pioglitazone improves cardiac function and alters myocardial substrate metabolism without affecting cardiac triglyceride accumulation and high-energy phosphate metabolism in patients with well-controlled type 2 diabetes mellitus; Circulation; 2009; vol. 119 (no. 15); 2069-77

463.1. Study details

Other publications associated with this study included in review	Jonker 2010A Jonker JT, Wang Y, de Haan W, Diamant M, Rijzewijk LJ, van der Meer RW, Lamb HJ, Tamsma JT, de Roos A, Romijn JA, Rensen PC, Smit JW. Pioglitazone decreases plasma cholesteryl ester transfer protein mass, associated with a decrease in hepatic triglyceride content, in patients with type 2 diabetes. Diabetes Care. 2010 Jul;33(7):1625-8. doi: 10.2337/dc09-1935. Epub 2010 Feb 11. PMID: 20150294; PMCID: PMC2890371. Jonker 2010B Jonker JT, Lamb HJ, van der Meer RW, Rijzewijk LJ, Menting LJ, Diamant M, Bax JJ, de Roos A, Romijn JA, Smit JW. Pioglitazone compared with metformin increases pericardial fat volume in patients with type 2 diabetes mellitus. J Clin Endocrinol Metab. 2010 Jan;95(1):456-60. doi: 10.1210/jc.2009-1441. Epub 2009 Nov 13. PMID: 19915017.
Trial name / registration number	PIRAMID / ISRCTN53177482
Study type	Randomised controlled trial (RCT)
Study location	The study was performed at two institutes in The Netherlands
Study setting	No additional information
Study dates	NR

Sources of funding	Supported by Eli Lilly, the Netherlands, which has a partnership with Takeda, the manufacturer of pioglitazone. Metformin tablets and matching placebos were provided by Merck, the Netherlands. Multiple authors report receiving funding from numerous pharmaceutical companies
Inclusion criteria	Men with uncomplicated T2DM, 45 to 65 years of age, were eligible. Inclusion criteria included glycohemoglobin level of 6.5% to 8.5% at screening, body mass index of 25 to 32 kg/m2, and blood pressure not exceeding 150/85 mm Hg (with or without the use of antihypertensive drugs).
Exclusion criteria	Exclusion criteria were any clinically significant disorder, particularly any history or complaints of cardiovascular or liver disease or diabetes-related complications, and prior use of thiazolidinediones or insulin.
Recruitment / selection of participants	No additional information
Intervention(s)	Pioglitazone (n=39) Patients were randomized to pioglitazone (15 mg once daily, titrated to 30 mg once daily after 2 weeks) for 24 weeks.
Cointervention	Glimepiride Glimepiride was titrated until a stable dose was reached during 8 weeks prior to randomisation. Glimepiride was continued throughout the entirety of the study
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear The study population is described as "T2DM men without structural heart disease or inducible ischaemia as assessed by dobutamine stress echocardiography." Exclusion criteria were "any clinically significant disorder, particularly any history or complaints of cardiovascular or liver disease or diabetes-related complications." No further information.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear The study population is described as "T2DM men without structural heart disease or inducible ischaemia as assessed by dobutamine stress echocardiography." Exclusion criteria were "any clinically significant disorder, particularly any history or complaints of cardiovascular or liver disease or diabetes-related complications." No further information.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear The study population is described as "T2DM men without structural heart disease or inducible ischaemia as assessed by dobutamine stress echocardiography." Exclusion criteria were "any clinically significant disorder, particularly any history or complaints of cardiovascular or liver disease or diabetes-related complications." No further information.
Strata 4: People with type 2	Not stated/unclear

diabetes mellitus and high cardiovascular risk	
Subgroup 1: People with moderate or severe 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
Population subgroups	NA
Comparator	Metformin (n=39) Metformin was administered initially as 500 mg twice daily, titrated to 1000 mg twice daily. Matching placebo and glimepiride was also to be taken throughout the study.
Number of participants	78
Duration of follow-up	24 weeks
Indirectness	NA

Method of analysis	Not stated/unclear
Additional comments	Between-group comparisons were performed with ANCOVA with adjustments for treatment group and baseline values. Within-group changes from baseline were assessed with independent paired t tests or Wilcoxon signed-rank tests. Mode of analysis unclear as not reported the final numbers of patients included in analyses

463.2. Study arms

463.2.1. Pioglitazone (N = 39)

Patients were randomized to pioglitazone (15 mg once daily, titrated to 30 mg once daily after 2 weeks) to be taken in addition to glimepiride for 24 weeks

463.2.2. Metformin (N = 39)

Patients were randomized to metformin, 500 mg twice daily, titrated to 1000 mg twice daily, and matching placebo to be taken in addition to glimepiride for 24 weeks

463.3. Characteristics

463.3.1. Arm-level characteristics

Characteristic	Pioglitazone (N = 39)	Metformin (N = 39)
% Male Sample size	n = 39 ; % = 100	n = 39 ; % = 100
Mean age (SD) (Years (mean, SD)) Mean (SD)	56.8 (1)	56.4 (0.9)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed (Years (mean, SD)) Mean (SD)	4 (NR)	3 (NR)
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Pioglitazone (N = 39)	Metformin (N = 39)
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Glimepiride Sample size	n = 39 ; % = 100	n = 39 ; % = 100
Blood pressure-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Any hypertensive medication Sample size	n = 19 ; % = 48.7	n = 15 ; % = 38.5
Statins/lipid-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Statins Sample size	n = 19 ; % = 48.7	n = 19 ; % = 48.7
Other treatment being received Sample size	n = NA ; % = NA	n = NA ; % = NA
Beta-blocker Sample size	n = 5 ; % = 12.8	n = 2 ; % = 5.1
Diuretic Sample size	n = 6 ; % = 15.4	n = 6 ; % = 15.4
ACE inhibitor Sample size	n = 9 ; % = 23.1	n = 9 ; % = 23.1
ARB	n = 6 ; % = 15.4	n = 3 ; % = 7.7

Characteristic	Pioglitazone (N = 39)	Metformin (N = 39)
Sample size		
Calcium antagonist Sample size	n = 1 ; % = 2.6	n = 3 ; % = 7.7

464. Van Eyk, 2019

Bibliographic Reference	Van Eyk, H. J.; Paiman, E. H. M.; Bizino, M. B.; De Heer, P.; Geelhoed-Duijvestijn, P. H.; Kharagjitsingh, A. V.; Smit, J. W. A.; Lamb, H. J.; Rensen, P. C. N.; Jazet, I. M.; A double-blind, placebo-controlled, randomised trial to assess the effect of liraglutide on ectopic fat accumulation in South Asian type 2 diabetes patients; Cardiovasc Diabetol; 2019; vol. 18 (no. 1); 87

464.1. Study details

Secondary publication of another included study- see primary study for details	N/A
Other publications associated with this study included in review	Paiman EHM, van Eyk HJ, van Aalst MMA, Bizino MB, van der Geest RJ, Westenberg JJM, Geelhoed-Duijvestijn PH, Kharagjitsingh AV, Rensen PCN, Smit JWA, Jazet IM, Lamb HJ. Effect of Liraglutide on Cardiovascular Function and Myocardial Tissue Characteristics in Type 2 Diabetes Patients of South Asian Descent Living in the Netherlands: A Double-Blind, Randomized, Placebo-Controlled Trial. J Magn Reson Imaging. 2020 Jun;51(6):1679-1688. doi: 10.1002/jmri.27009. Epub 2019 Dec 4. PMID: 31799782; PMCID: PMC7318583. EPPI ID = 13678166
Trial name / registration number	NCT02660047 Also NCT01761318 quoted in the paper
Study location	The Netherlands
Study setting	Leiden University Medical Center
Study dates	47 patients randomised between July 2015 and December 2016
Sources of funding	The study was funded by Novo Nordisk (Bagsvaerd, Denmark) Roba Metals B.V. Ijsselstein and the Cardio Vascular Imaging Group, Leiden University Medical Centre (Leiden, The Netherlands).

Inclusion criteria	• BMI ≥ 23 kg/m2 • aged 18–74 years • HbA1c ≥ 6.5% and ≤ 11.0% (≥ 47.5 and ≤ 96.4 mmol/mol) • concomitant treatment with metformin, sulfonylurea derivatives and insulin was allowed, dosage of all glucose-lowering medication needed to be stable for at least 3 months prior to participation.
Exclusion criteria	• use of glucose-lowering therapy other than those specified in the inclusion criteria • presence of renal disease • congestive heart failure New York Heart Association (NYHA) classification III–IV • uncontrolled hypertension (systolic blood pressure > 180 mmHg and/or diastolic blood pressure > 110 mmHg) • acute coronary or cerebrovascular accident within 30 days prior to study inclusion • any contra-indication for contrast enhanced MRI
Recruitment / selection of participants	Patients with type 2 diabetes and of South Asian ethnicity were recruited via advertisements and from the outpatient clinics of the Leiden University Medical Center , general practitioners, and local hospitals.
Intervention(s)	Liraglutide daily subcutaneous injection. Starting dose was 0.6 mg per day, which was titrated over 2 weeks up to a maximum dose of 1.8 mg, if tolerated.
Cointervention	Concomitant treatment with metformin, sulfonylureas and insulin was allowed, provided the dose was stable for at least 3 months prior to the trial.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Excluded "congestive heart failure New York Heart Association (NYHA) classification III–IV", otherwise unclear. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Excluded "an acute coronary or cerebrovascular accident within 30 days prior to study inclusion", prior to this unclear. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and	People without chronic kidney disease Excluded "presence of renal disease"

chronic kidney disease	
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear Only mean age and mean duration of diabetes reported.
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear Not an inclusion or exclusion criteria. No information in baseline characteristics.
Subgroup 4: People with obesity	Not stated/unclear BMI ≥ 23 kg/m2 an inclusion criteria. Only mean BMI reported in baseline characteristics.
Subgroup 5: eGFR category at baseline	Not stated/unclear No information
Subgroup 6: Albuminuria category at baseline	Not stated/unclear No information
Comparator	Placebo, daily subcutaneous injection
Number of participants	47 people randomised
Duration of follow-up	26 weeks
Indirectness	N/A

Method of analysis	ITT
Additional comments	Both ITT and per protocol analysis reported

464.2. Study arms

464.2.1. Liraglutide (N = 22)

Liraglutide 1.8 mg daily, subcutaneous administration. Starting dose was 0.6 mg per day, titrated in 2 weeks to the maximum dose of 1.8 mg per day if tolerated.

464.2.2. Placebo (N = 25)

Daily subcutaneous injection

464.3. Characteristics

464.3.1. Arm-level characteristics

Characteristic	Liraglutide (N = 22)	Placebo (N = 25)
% Male Sample size	n = 8 ; % = 36	n = 11 ; % = 44
Mean age (SD) (years) Mean (SD)	55 (11)	55 (9)
Ethnicity South Asian Sample size	n = 22 ; % = 100	n = 25 ; % = 100
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 diagnosed (years) Mean (SD)	19 (10)	17 (10)
HbA1c (%)	8.1 (0.9)	8.6 (1.1)

Characteristic	Liraglutide (N = 22)	Placebo (N = 25)
Mean (SD)		
Cardiovascular risk factors Sample size	n = NR ; % = NR	n = 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 (kg) Mean (SD)	81.9 (11)	77.8 (12.4)
BMI (kg/m2) Mean (SD)	30.4 (3.8)	28.6 (4)
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)
Triglycerides Mean (SD)	1.55 (0.86)	2.08 (1.8)
HDL cholesterol Mean (SD)	1.24 (0.33)	1.21 (0.3)

Characteristic	Liraglutide (N = 22)	Placebo (N = 25)
LDL cholesterol Mean (SD)	2 (0.65)	2.21 (0.97)
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)	NA (NA)	NA (NA)
Metformin Mean (SD)	22 (100)	23 (92)
Sulfonylurea Mean (SD)	3 (14)	5 (20)
Insulin Mean (SD)	17 (77)	19 (76)
Blood pressure-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Statins/lipid-lowering medication used Sample size	n = 17 ; % = 77	n = 20 ; % = 80
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR

465. van Eyk, 2020

Bibliographic Reference	van Eyk, Huub J; Paiman, Elisabeth H M; Bizino, Maurice B; IJzermans, Suzanne L; Kleiburg, Fleur; Boers, Tim G W; Rappel, Eline J; Burakiewicz, Jedrzej; Kan, Hermien E; Smit, Johannes W A; Lamb, Hildo J; Jazet, Ingrid M; Rensen, Patrick C N; Liraglutide decreases energy expenditure and does not affect the fat fraction of supraclavicular brown adipose tissue in patients with type 2 diabetes.; Nutrition, metabolism, and cardiovascular diseases : NMCD; 2020; vol. 30 (no. 4); 616-624

465.1. Study details

Secondary publication of another included study- see primary study for details	Bizino MB, Jazet IM, Westenberg JJM, van Eyk HJ, Paiman EHM, Smit JWA, Lamb HJ. Effect of liraglutide on cardiac function in patients with type 2 diabetes mellitus: randomized placebo-controlled trial. Cardiovasc Diabetol. 2019 Apr 30;18(1):55. doi: 10.1186/s12933-019-0857-6. Erratum in: Cardiovasc Diabetol. 2019 Aug 9;18(1):101. PMID: 31039778; PMCID: PMC6492440. EPPI ID = 13722160
Trial name / registration number	MAGNA VICTORIA / NCT01761318

466. Van Gaal, 2014

Bibliographic Reference	Van Gaal, L.; Souhami, E.; Zhou, T.; Aronson, R.; Efficacy and safety of the glucagon-like peptide-1 receptor agonist lixisenatide versus the dipeptidyl peptidase-4 inhibitor sitagliptin in young (<50 years) obese patients with type 2 diabetes mellitus; J Clin Transl Endocrinol; 2014; vol. 1 (no. 2); 31-37

466.1. Study details

Secondary publication of another included study- see primary study for details	No
Other publications associated with this study included in review	None
Trial name / registration number	NCT00976937
Study type	Randomised controlled trial (RCT) Double-blind, double-dummy, active-controlled, parallel-group RCT
Study location	International (Australia, Brazil, Canada, Chile, Guatemala, Mexico, Peru, Poland, Romania, Russian Federation, Ukraine, USA)
Study setting	Outpatient
Study dates	08/2009 to 03/2011
Sources of funding	Funded/supported by Sanofi
Inclusion criteria	• Aged ≥18 and <50 years • Type 2 diabetes diagnosis at least 1 year before screening • Obese (BMI≥30 kg/m2) • HbA1c 7-10% inclusive • Receiving stable metformin dose (≥1500 mg daily)

Exclusion criteria	• FPG >13.9 mmol/L at screening • History of unexplained pancreatitis, chronic pancreatitis, pancreatectomy, stomach/gastric surgery, inflammatory bowel disease • History of metabolic acidosis, including diabetic ketoacidosis within year prior to screening • History of myocardial infarction, stroke, or heart failure requiring hospitalization 6 months prior to screening • Amylase and/or lipase values>3 times normal laboratory range
Recruitment / selection of participants	Eligible participants randomised to lixisenatide or sitagliptin, no other information provided.
Intervention(s)	• Lixisenatide 20 mcg daily Subcutaneous injection of lixisenatide 20 mcg daily with dummy for sitagliptin tablet for 24 weeks, in addition to metformin.
Cointervention	• Metformin All participants continued on background metformin dose for duration of trial.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear "History of heart failure requiring hospitalization within 6 months prior to screening" stated in the exclusion criteria. No further information about heart failure.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear "History of myocardial infarction or stroke requiring hospitalization within 6 months prior to screening" stated in the exclusion criteria. No further information about people with CVD.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear

Subgroup 1: People with moderate or severe 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 All participants had BMI≥30 kg/m2
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Comparator	• Sitagliptin 100 mg daily Oral sitagliptin 100 mg daily and dummy for subcutaneous lixisenatide injection for 24 weeks, in addition to metformin.
Number of participants	N=319 randomised (N=292 completers)
Duration of follow-up	24 weeks
Indirectness	All participants under 50-years old and obese
Method of analysis	Modified ITT Efficacy and safety outcomes analysed using mITT populations (all randomised participants who received at least one dose study drug) with LOCF for missing data

466.2. Study arms

466.2.1. Lixisenatide 20 mcg daily (N = 158)

Subcutaneous injection of lixisenatide 20 mcg daily for 24 weeks, in addition to background metformin.

466.2.2. Sitagliptin 100 mg daily (N = 161)

Oral sitagliptin 100 mg daily for 24 weeks, in addition to background metformin.

466.3. Characteristics

466.3.1. Arm-level characteristics

Characteristic	Lixisenatide 20 mcg daily (N = 158)	Sitagliptin 100 mg daily (N = 161)
% Male Sample size	n = 55 ; % = 34.8	n = 73 ; % = 45.3
Mean age (SD) Mean (SD)	42.7 (5.2)	43.4 (4.7)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Asian Sample size	n = 1 ; % = 0.6	n = 1 ; % = 0.6
Black Sample size	n = 8 ; % = 5.1	n = 11 ; % = 6.8
Other Sample size	n = 17 ; % = 10.8	n = 22 ; % = 13.7
White Sample size	n = 132 ; % = 83.5	n = 127 ; % = 78.9
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	4.4 (3.9)	4.4 (3.6)

Characteristic	Lixisenatide 20 mcg daily (N = 158)	Sitagliptin 100 mg daily (N = 161)
Cardiovascular risk factors Nominal	NR	NR
Smoking status Nominal	NR	NR
Alcohol consumption Nominal	NR	NR
Presence of severe mental illness Nominal	NR	NR
People with significant cognitive impairment Nominal	NR	NR
People with a learning disability Nominal	NR	NR
Number of people with obesity Sample size	n = 158 ; % = 100	n = 161 ; % = 100
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

467. van Raalte, 2016

Bibliographic Reference	van Raalte, Daniel H; Bunck, Mathijs C; Smits, Mark M; Hoekstra, T; Corner, Anja; Diamant, Michaela; Eliasson, Bjorn; Marja-RiittaTaskinen; Heine, Robert J; Smith, Ulf; HanneleYki-Jarvinen; Mari, Andrea; Exenatide improves beta-cell function up to 3 years of treatment in patients with type 2 diabetes: a randomised controlled trial.; European journal of endocrinology; 2016; vol. 175 (no. 4); 345-52

467.1. Study details

Secondary publication of another included study- see primary study for details	Bunck 2009 Bunck MC, Diamant M, Cornér A, Eliasson B, Malloy JL, Shaginian RM, Deng W, Kendall DM, Taskinen MR, Smith U, Yki-Järvinen H, Heine RJ. One-year treatment with exenatide improves beta-cell function, compared with insulin glargine, in metformin-treated type 2 diabetic patients: a randomized, controlled trial. Diabetes Care. 2009 May;32(5):762-8

468. Vanderheiden, 2016

Bibliographic Reference	Vanderheiden, A.; Harrison, L.; Warshauer, J.; Li, X.; Adams-Huet, B.; Lingvay, I.; Effect of adding liraglutide vs placebo to a high-dose Insulin regimen in patients with type 2 diabetes a randomized clinical trial; JAMA Int Med; 2016; vol. 176 (no. 7); 939-947

468.1. Study details

Secondary publication of another included study- see primary study for details	No
Other publications associated with this study included in review	None
Trial name / registration number	NCT01505673
Study type	Randomised controlled trial (RCT) Double-blind, placebo-controlled, parallel-group RCT
Study location	Texas, USA
Study setting	Outpatient
Study dates	08/2012 to 02/2015
Sources of funding	Funded by Novo Nordisk
Inclusion criteria	• Aged 18 years or more • Type 2 diabetes diagnosis • HbA1c 7.5-011% inclusive • Receiving high dose (>1.5 U/kg/day) insulin • Receiving stable dose of any other anti-hyperglycaemic agents for at least 3-mo before enrolment
Exclusion criteria	• History of pancreatic disease (i.e. pancreatitis, tumors, or pancreatic surgery)

	• Lipase level>3 x above normal • Creatinine clearance≤30 mL/min/1.73 m2 • Use of incretin therapy within prior 90 days • Decompensated comorbidities
Recruitment / selection of participants	Eligible participants entered 10-day placebo run-in period then were block randomised 1:1 using computer-generated codes. All participants also received dietary and lifestyle counselling at each clinic visit.
Intervention(s)	• Liraglutide 1.8 mg daily Subcutaneous injection of liraglutide 1.8 mg daily for 6 months. Initiated at 0.6 mg daily, increased weekly by 0.6 mg daily, to 1.8 mg daily.
Cointervention	• Insulin All participants in trial continued to receive insulin for duration of trial. At randomisation, total daily dose of insulin decreased by 20% for participants with HbA1c≤8%. If no hypoglycaemia occurred, dosage increased to baseline dosage at first in-person visit 1-mo after randomisation. Dosage further titrated only for recurrent/severe/symptomatic hypoglycaemia. Following types of insulin were used: • Premixed human insulin: 48% (34/71 participants) • Basal-bolus regimen with analogue insulins: 40% (28/71 participants) • Human NPH and regular insulin combination: 8% (6/71 participants) • Regular human insulin U500: 4% (3/71 participants)
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Exclusion criteria state "Unstable or decompensated comorbidities (including but not limited to recent acute coronary or cerebrovascular accident, planned arterial revascularization, chronic heart failure NYHA class III-IV)." (See supplementary protocol.) No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Exclusion criteria state "Unstable or decompensated comorbidities (including but not limited to recent acute coronary or cerebrovascular accident, planned arterial revascularization, chronic heart failure NYHA class III-IV)" (See supplementary protocol.) No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.

Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe 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: creatinine clearance≤30 mL/min/1.73 m2
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Comparator	• Placebo Matching subcutaneous placebo injection daily for 6 months, in addition to high dose insulin.
Number of participants	N=71 randomised (N=68 completers)
Duration of follow-up	26 weeks
Indirectness	None
Method of analysis	ITT

	Safety outcomes used ITT population Modified ITT Efficacy outcomes used all randomised participants who received study medication and had at least one post-randomisation study visit, appears to assume participants continued using trial product and didn't use rescue medication

468.2. Study arms

468.2.1. Liraglutide 1.8 mg daily (N = 35)

Subcutaneous injection of liraglutide 1.8 mg daily for 6 months, in addition to high-dose (>1.5 U/kg/day) insulin.

468.2.2. Placebo (N = 36)

Matching subcutaneous placebo injection daily for 6 months, in addition to high-dose (>1.5 U/kg/day) insulin.

468.3. Characteristics

468.3.1. Arm-level characteristics

Characteristic	Liraglutide 1.8 mg daily (N = 35)	Placebo (N = 36)
% Male Sample size	n = 12 ; % = 34	n = 14 ; % = 39
Mean age (SD) (years) Mean (SD)	52.8 (8.1)	55.5 (6.6)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Asian Sample size	n = 0 ; % = 0	n = 1 ; % = 3
Black/African-American Sample size	n = 11 ; % = 31	n = 15 ; % = 42
Hispanic	n = 9 ; % = 26	n = 9 ; % = 25

Characteristic	Liraglutide 1.8 mg daily (N = 35)	Placebo (N = 36)
Sample size		
White Sample size	n = 15 ; % = 43	n = 11 ; % = 31
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed (years) Median (IQR)	16 (12 to 23)	18 (13 to 27)
Cardiovascular risk factors Nominal	NR	NR
Smoking status Current smoker Sample size	n = 6 ; % = 17.1	n = 1 ; % = 2.8
Alcohol consumption Nominal	NR	NR
Presence of severe mental illness Nominal	NR	NR
People with significant cognitive impairment Nominal	NR	NR
People with a learning disability Nominal	NR	NR
Number of people with obesity Nominal	NR	NR
Other antidiabetic medication used Metformin use Sample size	n = 28 ; % = 80	n = 22 ; % = 61
Blood pressure-lowering medication used	n = 33 ; % = 94	n = 34 ; % = 94

Characteristic	Liraglutide 1.8 mg daily (N = 35)	Placebo (N = 36)
Sample size		
Statins/lipid-lowering medication used Sample size	n = 28 ; % = 80	n = 32 ; % = 89
Other treatment being received Nominal	NR	NR

469. Verma, 2019

Bibliographic Reference	Verma, S.; Mazer, C. D.; Yan, A. T.; Mason, T.; Garg, V.; Teoh, H.; Zuo, F.; Quan, A.; Farkouh, M. E.; Fitchett, D. H.; et, al.; Effect of empagliflozin on left ventricular mass in patients with type 2 diabetes and coronary artery disease: the EMPA-HEART CardioLink-6 randomized clinical trial; Circulation; 2019

469.1. 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	NCT02998970.
Study type	Randomised controlled trial (RCT)
Study location	Canada.
Study setting	Outpatient follow-up.
Study dates	September 2016 to June 30th 2017.
Sources of funding	Boehringer Ingelheim (Canada) Ltd.
Inclusion criteria	Male and female subjects between 40 and 80 years of age; history of type 2 diabetes; HbA1c 6.5-10% within 3 months of the screening visit; established cardiovascular disease, defined as previous myocardial infarction at least 6 months ago or previous cardiovascular revascularisation at least 2 months ago; any background antihyperglycaemic therapy (which has been stable for at least 2 months); evidence of a personally signed and dated informed consent document; willing and able to comply with trial procedures.

Exclusion criteria	Female subjects who are pregnant, lactating or of child bearing potential or pre-menopausal women; type 1 diabetes; subjects treated with SGLT-2 inhibitors, GLP1 receptor agonist, or saxagliptin; frequent episodes (>4/month) of moderate hypoglycaemia as defined by the Canadian Diabetes Association 2013 Clinical PRactice Guidelines for the Prevention and Management of Diabetes; any episode of severe hypoglycaemia within the past 12 months, as also defined by the Canadian Diabetes Association 2013 Clinical Practice Guidelines for the PRevention and Management of Diabetes; Subjects in whom coronary revascularisation by either PCI or bypass surgery is being contemplated within 6 months or who have undergone revascularisation in the prior 2 months; MDRD eGFR <60mL/min/1.73m2 at screening; significant allergy or known intolerance to SGLT2 inhibitors or any ingredient in the formulations; clinically significant or unstable medical condition that might limit their ability to complete the study (including hepatic disease); any malignancy not considered cured; blood donation within 4 weeks prior to screening; subjects who have participated in studies of an investigational drug or device within 30 days prior to the screening visit; conditions preventing safe MRI imaging; LVEF <30%; NYHA class IV or recent hospitalisation for decompensated HF (<3 months); unstable coronary syndromes; moderate or severe aortic stenosis, aortic regurgitation, mitral stenosis or mitral regurgitation.
Recruitment / selection of participants	No additional information.
Intervention(s)	Empagliflozin N=49 Empagliflozin 10mg/day in additional to usual care.
Cointervention	Concomitant therapy: People were allowed to receive anti-hyperglycaemic therapy. Adjustment to baseline therapy was allowed while on the study. If HbA1c exceeds 10 or there is an increase of greater than 1%, intensification will be initiated. DPP4 inhibitors or basal insulin can be added if this is not done already.
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Exclusion criteria state: LVEF <30% on the most recent assessment within 6 months NYHA Class IV or recent hospitalization for decompensated HF (<3 months) Baseline characteristics table reports heart failure among 6% participants overall.
Strata 2: People with atherosclerotic cardiovascular disease	People with atherosclerotic cardiovascular diseases Inclusion criteria state: "Established cardiovascular disease, defined as previous myocardial infarction ≥ 6 months ago, or previous coronary revascularization ≥ 2 months ago."

Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear People with eGFR< 60 ml/min/1.73 m2 at screening were excluded. No further information about CKD in the inclusion/exclusion criteria. Baseline characteristics table reports 4% people overall had nephropathy. No other information about CKD reported.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe 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
Population subgroups	No additional information.

Comparator	Placebo N=48 Matching placebo.
Number of participants	97
Duration of follow-up	6 months.
Indirectness	No additional information.
Method of analysis	ITT
Additional comments	No additional information.

469.2. Study arms

469.2.1. Empagliflozin (N = 49)

Empagliflozin 10mg/day in additional to usual care. Concomitant therapy: People were allowed to receive anti-hyperglycaemic therapy. Adjustment to baseline therapy was allowed while on the study. If HbA1c exceeds 10 or there is an increase of greater than 1%, intensification will be initiated. DPP4 inhibitors or basal insulin can be added if this is not done already.

469.2.2. Placebo (N = 48)

Matching placebo. Concomitant therapy: People were allowed to receive anti-hyperglycaemic therapy. Adjustment to baseline therapy was allowed while on the study. If HbA1c exceeds 10 or there is an increase of greater than 1%, intensification will be initiated. DPP4 inhibitors or basal insulin can be added if this is not done already.

469.3. Characteristics

469.3.1. Arm-level characteristics

Characteristic	Empagliflozin (N = 49)	Placebo (N = 48)
% Male Sample size	n = 44 ; % = 90	n = 46 ; % = 96

Characteristic	Empagliflozin (N = 49)	Placebo (N = 48)
Mean age (SD) (years) Median (IQR)	64 (57 to 69)	64 (56 to 72)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR
Comorbidities Sample size	n = NA ; % = NA	n = NA ; % = NA
Heart failure Sample size	n = 2 ; % = 4	n = 4 ; % = 8
Hypertension Sample size	n = 45 ; % = 92	n = 43 ; % = 90
Nephropathy Sample size	n = 0 ; % = 0	n = 2 ; % = 4
Stroke or TIA Sample size	n = 8 ; % = 16	n = 6 ; % = 13
Peripheral artery disease Sample size	n = 2 ; % = 4	n = 3 ; % = 6
Presence of frailty Sample size	n = NA ; % = NA	n = NA ; % = NA
Time since type 2 diabetes diagnosed Median (IQR)	7.9 (7.5 to 8.4)	7.9 (7.3 to 8.7)
Smoking status Sample size	n = 20 ; % = 41	n = 22 ; % = 46
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

Characteristic	Empagliflozin (N = 49)	Placebo (N = 48)
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Metformin Sample size	n = 47 ; % = 96	n = 44 ; % = 92
Insulin Sample size	n = 12 ; % = 25	n = 12 ; % = 25
Blood pressure-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
ACEI/ARB Sample size	n = 40 ; % = 82	n = 41 ; % = 85
Diuretic Sample size	n = 2 ; % = 4	n = 6 ; % = 13
Beta-blocker Sample size	n = 38 ; % = 78	n = 39 ; % = 81
Calcium channel blocker Sample size	n = 6 ; % = 12	n = 15 ; % = 31
Statins/lipid-lowering medication used Sample size	n = 47 ; % = 96	n = 46 ; % = 96
Other treatment being received Sample size	n = NA ; % = NA	n = NA ; % = NA
ASA/P2Y12 inhibitor Sample size	n = 40 ; % = 82	n = 41 ; % = 85

470. Vianna, 2018

Bibliographic Reference	Vianna, A. G. D.; Lacerda, C. S.; Pechmann, L. M.; Polesel, M. G.; Marino, E. C.; Faria-Neto, J. R.; A randomized controlled trial to compare the effects of sulphonylurea gliclazide MR (modified release) and the DPP-4 inhibitor vildagliptin on glycemic variability and control measured by continuous glucose monitoring (CGM) in Brazilian women with type 2 diabetes; Diabetes Research and Clinical Practice; 2018; vol. 139; 357-365

470.1. Study details

Secondary publication of another included study- see primary study for details	Parent study for the BoneGlic Trial.
Other publications associated with this study included in review	Vianna et al., (2017). Vildagliptin has the same safety profile as a sulfonylurea on bone metabolism and bone mineral density in post-menopausal women with type 2 diabetes: a randomized controlled trial. Diabetology & metabolic syndrome; 2017; vol. 9; 35.
Trial name / registration number	BoneGlic Trial (NCT01679899)
Study type	Randomised controlled trial (RCT)
Study location	One centre, Brazil
Study setting	Curitiba Diabetes Center
Study dates	October 2012 to October 2014
Sources of funding	investigator-initiated trial research funds from Novartis Pharmaceuticals
Inclusion criteria	Postmenopausal women diagnosed with T2D treated with metformin; age ≥40 years old and glycated hemoglobin (HbA1c) ≥6.5% (48 mmol/mol) at randomization
Exclusion criteria	An acute cardiovascular event (cardiac, cerebral or peripheral), chronic dialysis and/or renal transplantation, serum creatinine >1.5 mg/dL, human immunodeficiency virus infection, severe autoimmune disease, chronic treatment with oral steroids (>30 consecutive days), current or previous treatment with incretin mimetics (iDPP-4 or GLP-1 receptor agonists),

	current or previous treatment with pioglitazone or rosiglitazone, body mass index (BMI) >50 kg/m2, HbA1c ≥9%, chronic or alcoholic liver disease, plasma triglycerides >1000 mg/dL (11.3 mmol/L), serum 25-hidroxi-vitamin D (25-OH-vit.D) <20 ng/mL, abnormal levels of parathyroid hormone (PTH), serum cortisol, insulin-like growth factor 1 (IGF-1) or growth hormone (GH) and history of previous fragility fracture
Recruitment / selection of participants	Recruited via media outlets, including online and newspaper advertisements, flyers, radio announcements or after a search for T2D treatment at the research centre
Intervention(s)	Vildagliptin Gliclazide
Cointervention	Metformin
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear "Exclusion criteria included an acute cardiovascular event (cardiac, cerebral or peripheral)." Heart failure is not specifically mentioned. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear "Exclusion criteria included an acute cardiovascular event (cardiac, cerebral or peripheral)." No further details given.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Exclusion criteria state "chronic dialysis and/ or renal transplantation, serum creatinine >1.5 mg/dL." No further information about CKD.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type	Not stated/unclear

2 diabetes mellitus	
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
Population subgroups	NR
Comparator	NA
Number of participants	42
Duration of follow-up	12 months
Indirectness	None
Method of analysis	ACA
Additional comments	19/21 Vildagliptin group analysed, 18/21 Gliclazide group analysed.

470.2. Study arms

470.2.1. Vildagliptin 100 mg (N = 21)

administered at 50 mg orally twice daily

470.2.2. Gliclazide MR 120mg (N = 21)

Gliclazide modified release administered at 120 mg orally once daily. If the maximum dose of gliclazide MR was not tolerated or was otherwise associated with unacceptable adverse events, a dose reduction to 60 mg once daily was allowed at the discretion of the investigator.

470.3. Characteristics

470.3.1. Arm-level characteristics

Characteristic	Vildagliptin 100 mg (N = 21)	Gliclazide MR 120mg (N = 21)
% Male Nominal	NR	NR
Mean age (SD) Mean (SD)	62.8 (6.4)	61 (5.3)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Caucasian Sample size	n = 18 ; % = 85.7	n = 19 ; % = 90.4
Black Sample size	n = 2 ; % = 9.5	n = 1 ; % = 4.8
Hispanic or Latino Sample size	n = 1 ; % = 4.8	n = 1 ; % = 4.8
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed Mean (SD)	NR (NR)	NR (NR)
Cardiovascular risk factors Nominal	NR	NR
Smoking status Nominal	NR	NR
Alcohol consumption Mean (SD)	NR (NR)	NR (NR)
Presence of severe mental illness Nominal	NR	NR

Characteristic	Vildagliptin 100 mg (N = 21)	Gliclazide MR 120mg (N = 21)
People with significant cognitive impairment Nominal	NR	NR
People with a learning disability Nominal	NR	NR
Number of people with obesity Nominal	NR	NR
Other antidiabetic medication used Mean (SD)	NA (NA)	NA (NA)
Metformin daily dose mg Mean (SD)	1640.5 (664.2)	1742.9 (626.4)
Blood pressure-lowering medication used Nominal	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

471. Vianna, 2017

Bibliographic Reference	Vianna, Andre Gustavo Daher; de Lacerda, Claudio Silva; Pechmann, Luciana Muniz; Polesel, Michelle Garcia; Marino, Emerson Cestari; Borba, Victoria Zeghbi Cochenski; Barreto, Fellype de Carvalho; Vildagliptin has the same safety profile as a sulfonylurea on bone metabolism and bone mineral density in post-menopausal women with type 2 diabetes: a randomized controlled trial.; Diabetology & metabolic syndrome; 2017; vol. 9; 35

471.1. Study details

Secondary publication of another included study- see primary study for details	Parent study: Vianna et al., (2018). A randomized controlled trial to compare the effects of sulphonylurea gliclazide MR (modified release) and the DPP-4 inhibitor vildagliptin on glycemic variability and control measured by continuous glucose monitoring (CGM) in Brazilian women with type 2 diabetes. Diabetes Research and Clinical Practice; 2018; vol. 139; 357-365
Other publications associated with this study included in review	NA
Trial name / registration number	BoneGlic Trial (NCT01679899)
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear "Exclusion criteria included an acute cardiovascular event (cardiac, cerebral or peripheral)." Heart failure is not specifically mentioned. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear "Exclusion criteria included an acute cardiovascular event (cardiac, cerebral or peripheral)." No further details given.
Strata 3: People with type 2 diabetes mellitus and	Not stated/unclear Exclusion criteria state "chronic dialysis and/ or renal transplantation, serum creatinine >1.5 mg/dL." No further information about CKD.

chronic kidney disease	
Population subgroups	

472. Vilsbøll, 2010

Bibliographic Reference	Vilsbøll, T.; Rosenstock, J.; Yki-Järvinen, H.; Cefalu, W. T.; Chen, Y.; Luo, E.; Musser, B.; Andryuk, P. J.; Ling, Y.; Kaufman, K. D.; Amatruda, J. M.; Engel, S. S.; Katz, L.; Efficacy and safety of sitagliptin when added to insulin therapy in patients with type 2 diabetes; Diabetes Obes Metab; 2010; vol. 12 (no. 2); 167-77

472.1. Study details

Secondary publication of another included study- see primary study for details	No
Other publications associated with this study included in review	None
Trial name / registration number	Sitagliptin Study 051/NCT 00395343
Study type	Randomised controlled trial (RCT) Double-blind, placebo-controlled, parallel-group RCT
Study location	International (100 clinical sites in 24 countries: Australia, Belgium, Bulgaria, Canada, Colombia, Croatia, Denmark, Finland, France, Hungary, India, Ireland, Israel, Italy, Malaysia, New Zealand, Portugal, Russian Federation, South Africa, Serbia, Spain, Taiwan, Thailand, USA)
Study setting	Outpatient
Study dates	12/2006 to 10/2008
Sources of funding	Funded by Merck & Co., Inc.
Inclusion criteria	• Aged≥21 years • BMI>20 to <43 kg/m2 • Taking (long- or intermediate- acting or premixed) insulin (≥15 IU daily) with or without metformin (≥1500 mg daily) • HbA1c 7.5-11% inclusive

Exclusion criteria	• Type 1 diabetes • FPG<130 mg/dl • Unstable cardiac disease (including new or worsening signs or symptoms of coronary heart disease within 3 months of study entry or any of the following within 6 months of study entry: acute coronary syndrome, stroke or ischaemic event; coronary artery intervention, or NYHA Class II-IV congestive heart failure) • Significant renal impairment (creatinine clearance<50 ml/min) • Elevated ALT or AST (more than 2x upper limit of normal) or elevated triglycerides (>600 mg/dl) • Treatment with oral antihyperglycaemic agents (except metformin) or exenatide within 8 – 12 weeks of study entry
Recruitment / selection of participants	Eligible participants entered 2-wk single-blind placebo run-in period, then had baseline measurements and randomised 1:1 using computer-generated allocation schedule to sitagliptin or placebo (proportion of participants on insulin + metformin capped at 75% and those on premixed insulin capped at 25%). Rescue therapy permitted if glycaemic goals not met.
Intervention(s)	• Sitagliptin 100 mg daily Oral sitagliptin 100 mg daily for 24 weeks, in addition to insulin.
Cointervention	• Insulin All participants continued receiving stable insulin dose, with or without metformin, for duration of trial. Insulin dose unchanged except in case of or to prevent hypoglycaemia.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear NYHCA Class II-IV congestive heart failure within 6 months of study entry was an exclusion criterion. No information about heart failure prior to study entry. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Exclusion criteria state: "Unstable cardiac disease (including new or worsening signs or symptoms of coronary heart disease within 3 months of study entry or any of the following within 6 months of study entry: acute coronary syndrome, stroke or ischaemic event; coronary artery intervention, or NYHA Class II-IV congestive heart failure)." No further information about previous events. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Exclusion criteria state "significant renal impairment (creatinine clearance<50ml/min)." No further information. No information in baseline characteristics.

Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe 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
Comparator	• Placebo Matching placebo daily for 24 weeks, in addition to insulin.
Number of participants	N=641 randomised (N=564 completers)
Duration of follow-up	24 weeks
Indirectness	None
Method of analysis	Modified ITT

	Efficacy outcomes use full analysis set (all randomised participants with at least one study drug dose and both baseline and at least one post-baseline measurement) using observed data only; safety set used all randomised participants with at least one study drug dose.

472.2. Study arms

472.2.1. Sitagliptin 100 mg daily (N = 322)

Oral sitagliptin 100 mg daily for 24 weeks, in addition to insulin.

472.2.2. Placebo (N = 319)

Matching placebo daily for 24 weeks, in addition to insulin.

472.3. Characteristics

472.3.1. Arm-level characteristics

Characteristic	Sitagliptin 100 mg daily (N = 322)	Placebo (N = 319)
% Male Sample size	n = 157 ; % = 49	n = 169 ; % = 53
Mean age (SD) (years) Mean (SD)	58.3 (9.1)	57.2 (9.3)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Asian Sample size	n = 55 ; % = 17	n = 61 ; % = 19
Black Sample size	n = 21 ; % = 6	n = 23 ; % = 7
Other Sample size	n = 18 ; % = 6	n = 16 ; % = 5
White Sample size	n = 228 ; % = 71	n = 219 ; % = 69

Characteristic	Sitagliptin 100 mg daily (N = 322)	Placebo (N = 319)
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	13 (7)	12 (6)
Cardiovascular risk factors Nominal	NR	*empty data*
Smoking status Nominal	NR	NR
Alcohol consumption Nominal	NR	NR
Presence of severe mental illness Nominal	NR	NR
People with significant cognitive impairment Nominal	NR	NR
People with a learning disability Nominal	NR	NR
Number of people with obesity Nominal	NR	NR
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Premixed insulin Sample size	n = 87 ; % = 27	n = 82 ; % = 26
Long-acting or intermediate-acting insulin Sample size	n = 235 ; % = 73	n = 237 ; % = 74
Metformin	n = 229 ; % = 71	n = 233 ; % = 73

Characteristic	Sitagliptin 100 mg daily (N = 322)	Placebo (N = 319)
Sample size		
Blood pressure-lowering medication used Nominal	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

473. Vilsboll, 2019

Bibliographic Reference	Vilsboll, Tina; Ekholm, Ella; Johnsson, Eva; Dronamraju, Nalina; Jabbour, Serge; Lind, Marcus; Dapagliflozin Plus Saxagliptin Add-on Therapy Compared With Insulin in Patients With Type 2 Diabetes Poorly Controlled by Metformin With or Without Sulfonylurea Therapy: A Randomized Clinical Trial.; Diabetes care; 2019; vol. 42 (no. 8); 1464-1472

473.1. Study details

Secondary publication of another included study- see primary study for details	No
Other publications associated with this study included in review	Two-year follow-up data reported in: • Vilsbøll, T., Ekholm, E., Johnsson, E., Garcia-Sanchez, R., Dronamraju, N., Jabbour, S. A., & Lind, M. (2020). Efficacy and safety of dapagliflozin plus saxagliptin versus insulin glargine over 52 weeks as add-on to metformin with or without sulphonylurea in patients with type 2 diabetes: A randomized, parallel-design, open-label, Phase 3 trial. Diabetes, Obesity and Metabolism, 22(6), 957-968.
Trial name / registration number	NCT02551874
Study type	Randomised controlled trial (RCT) Open-label, active-controlled, parallel-group RCT
Study location	International (112 centres in 11 countries: Czech Republic, Denmark, Germany, Hungary, Mexico, Poland, Romania, South Africa, Spain, Sweden, USA)
Study dates	10/2015 to 10/2016
Sources of funding	Funded by AstraZeneca.
Inclusion criteria	• Type 2 diabetes diagnosis • HbA1c 8-12% inclusive • Receiving stable dose of metformin (≥1500 mg daily) with or without a stable dose of a sulphonylurea (≥50% max dose) for at least 8 weeks before screening • BMI≤45 kg/m2 at screening

	• FPG≤270 mg/dL at baseline
Exclusion criteria	• Type 1 diabetes • Cardiovascular disease (including myocardial infarction; cardiac surgery or revascularizations; valvular disease or repair; unstable angina; unstable congestive heart failure; transient ischemic attack or significant cerebrovascular disease; unstable or previously undiagnosed arrhythmia; congestive heart failure [NYHA III and IV]; unstable or acute congestive heart failure;and/or known left ventricular ejection fraction of≤40%) within 3 months of screening • Severe hepatic insufficiency • Medical history of diabetic ketoacidosis or renal impairment (defined as creatinine clearance <60 mL/min or serum creatinine≥1.5 mg/dL in men or ≥1.4 mg/dL in women)
Recruitment / selection of participants	After 2-wk screening period, eligible participants entered 2-wk lead in period in which they received instruction in diet, exercise, and self-monitoring of glucose levels, then were randomised 1:1 to dapagliflozin + saxagliptin or insulin using interactive voice response system, stratified by sulphonylurea and background metformin use. Randomisation schedules kept by Bristol-Myers Squibb.
Intervention(s)	• Dapagliflozin 10 mg daily + Saxagliptin 5 mg daily Oral dapagliflozin and saxagliptin tablet for 24 weeks, in addition to metformin.
Cointervention	• Metformin All participants continued previous metformin dose regimen unchanged, with or without sulphonylurea, for duration of trial.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Cardiovascular disease stated in exclusion criteria. Study definition of cardiovascular disease includes unstable congestive heart failure; congestive heart failure defined as New York Heart Association Functional Classification III and IV; unstable or acute congestive heart failure; and/or known left ventricular ejection fraction of 40%) within 3 months of screening. Baseline characteristics table reports 1.6% had recent congestive heart failure (within 3 months of screening visit). No information about NYHA class II heart failure or heart failure before the 3 months period.
Strata 2: People with atherosclerotic	Not stated/unclear Exclusion criteria state "Cardiovascular disease (including myocardial infarction; cardiac surgery or revascularizations; valvular disease or repair;

cardiovascular disease	unstable angina; unstable congestive heart failure; transient ischemic attack or significant cerebrovascular disease; unstable or previously undiagnosed arrhythmia; congestive heart failure defined as New York Heart Association Functional Classification III and IV; unstable or acute congestive heart failure; and/or known left ventricular ejection fraction of 40%) within 3 months of screening." Baseline characteristics table reports the following recent vascular history (within 3 months of the screening visit): coronary bypass grafting (1.4%), carotid endarterectomy or stenting (1.9%), cerebrovascular accident (1.7%), hospitalisation for unstable angina (0.6%), PCI (2.8%), previous MI (3.6%), TIA (1.1%). No information about events before the 3 months.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear The study excluded people with "a medical history of renal impairment (defined as creatinine clearance <60mL/min or serum creatinine ≥1.5mg/dL in men or ≥1.4mg/dL in women)." No further information.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe 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 Exclusion criteria: eGFR≤40%
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Comparator	• Insulin glargine U100 Subcutaneous insulin glargine U100 injection for 24 weeks, in addition to metformin. Insulin initiated at 0.2 U/kg weight or ≥10 U/day. Participants self-titrated dose in 2U increments every 3 days until week 8 with FPG target 100 mg/dL. Goal at week 12 to reach stable insulin dose so investigator could increase insulin dose to help achieve target. Open label rescue therapy permitted if FPG>200 mg/dL. Subgroup of participants received masked continuous glucose monitoring sensor for 7 days before lead-in period.
Number of participants	N=650 randomised (N=584 completers after 24-wks; N=600 entered long-term treatment; N=557 completers after 52-wks)
Duration of follow-up	24 and 52 weeks
Indirectness	None
Method of analysis	Modified ITT Efficacy and safety outcomes use mITT population (all randomised participants who received at least one study drug dose) using observed cases only

473.2. Study arms

473.2.1. Dapagliflozin 10 mg daily + Saxagliptin 5 mg daily (N = 322)

Oral dapagliflozin 10 mg daily + oral saxagliptin 5 mg daily tablets for 52 weeks, in addition to metformin.

473.2.2. Insulin (N = 319)

Subcutaneous Insulin glargine U100 (Sanofi) daily for 52 weeks, in addition to metformin.

473.3. Characteristics

473.3.1. Arm-level characteristics

Characteristic	Dapagliflozin 10 mg daily + Saxagliptin 5 mg daily (N = 322)	Insulin (N = 319)
% Male Sample size	n = 176 ; % = 54.3	n = 171 ; % = 53.6
Mean age (SD) (years) Mean (SD)	55.7 (9.52)	55.3 (9.63)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
African American Sample size	n = 28 ; % = 8.6	n = 35 ; % = 11
American Indian Sample size	n = 12 ; % = 3.7	n = 6 ; % = 1.9
Asian Sample size	n = 12 ; % = 3.7	n = 12 ; % = 3.8
Native Hawaiian Sample size	n = 0 ; % = 0	n = 1 ; % = 0.3
Other Sample size	n = 9 ; % = 2.8	n = 11 ; % = 3.4
White Sample size	n = 263 ; % = 81.2	n = 254 ; % = 79.6
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	9.6 (6.5)	9.3 (6.2)
Cardiovascular risk factors	NR	NR

Characteristic	Dapagliflozin 10 mg daily + Saxagliptin 5 mg daily (N = 322)	Insulin (N = 319)
Nominal		
Smoking status Nominal	NR	NR
Alcohol consumption Nominal	NR	NR
Presence of severe mental illness Nominal	NR	NR
People with significant cognitive impairment Nominal	NR	NR
People with a learning disability Nominal	NR	NR
Number of people with obesity Nominal	NR	NR
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Fast-acting insulin and analogues for injection Sample size	n = 4 ; % = 1.2	n = 2 ; % = 0.6
GLP-1 receptor agonist Sample size	n = 1 ; % = 0.3	n = 2 ; % = 0.6
Long-acting insulin and analogues for injection Sample size	n = 2 ; % = 0.6	n = 1 ; % = 0.3
Insulin glargine Sample size	n = 2 ; % = 0.6	n = 1 ; % = 0.3
Oral blood glucose-lowering combination drug therapy Sample size	n = 2 ; % = 0.6	n = 0 ; % = 0
Alpha-glucosidase inhibitors Sample size	n = 1 ; % = 0.3	n = 0 ; % = 0

Characteristic	Dapagliflozin 10 mg daily + Saxagliptin 5 mg daily (N = 322)	Insulin (N = 319)
Intermediate-acting insulin and analogues for injection Sample size	n = 1 ; % = 0.3	n = 0 ; % = 0
Isophane insulin human injection Sample size	n = 1 ; % = 0.3	n = 0 ; % = 0
Blood pressure-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
ACE inhibitors Sample size	n = 112 ; % = 34.6	n = 123 ; % = 38.6
Beta-blockers Sample size	n = 61 ; % = 18.8	n = 65 ; % = 20.4
Angiotensin II antagonists Sample size	n = 44 ; % = 13.6	n = 35 ; % = 11
Statins/lipid-lowering medication used Sample size	n = 142 ; % = 43.8	*empty data*
Other treatment being received Sample size	n = NA ; % = NA	n = NA ; % = NA
Platelet aggregation inhibitors (excluding heparin) Sample size	n = 77 ; % = 23.8	n = 83
Proprionic acid derivatives Sample size	n = 41 ; % = 12.7	n = 39 ; % = 12.2
Proton pump inhibitors Sample size	n = 39 ; % = 12	n = 41 ; % = 12.9
Anilides Sample size	n = 44 ; % = 13.6	n = 35 ; % = 11

474. Vilsboll, 2020

Bibliographic Reference	Vilsboll, Tina; Ekholm, Ella; Johnsson, Eva; Garcia-Sanchez, Ricardo; Dronamraju, Nalina; Jabbour, Serge A; Lind, Marcus; Efficacy and safety of dapagliflozin plus saxagliptin versus insulin glargine over 52 weeks as add-on to metformin with or without sulphonylurea in patients with type 2 diabetes: A randomized, parallel-design, open-label, Phase 3 trial.; Diabetes, obesity & metabolism; 2020; vol. 22 (no. 6); 957-968

474.1. Study details

Secondary publication of another included study- see primary study for details	Yes, see primary study: • Vilsbøll, T., Ekholm, E., Johnsson, E., Dronamraju, N., Jabbour, S., & Lind, M. (2019). Dapagliflozin plus saxagliptin add-on therapy compared with insulin in patients with type 2 diabetes poorly controlled by metformin with or without sulfonylurea therapy: a randomized clinical trial. *Diabetes Care*, *42*(8), 1464-1472.
Other publications associated with this study included in review	See above
Trial name / registration number	NCT02551874
Study type	Randomised controlled trial (RCT) Open-label, active-controlled, parallel-group RCT

474.2. Study arms

474.2.1. Dapagliflozin 10 mg daily + Saxagliptin 5 mg daily (N = 322)

Oral dapagliflozin 10 mg daily + oral saxagliptin 5 mg daily tablets for 52 weeks, in addition to metformin.

474.2.2. Insulin (N = 319)

Subcutaneous insulin U100 (Sanofi) for 52 weeks, in addition to metformin.

475. Wada, 2022

Bibliographic Reference	Wada, Takashi; Mori-Anai, Kazumi; Takahashi, Akiko; Matsui, Takahiro; Inagaki, Masaya; Iida, Mitsutaka; Maruyama, Ken; Tsuda, Hidetaka; Effect of canagliflozin on the decline of estimated glomerular filtration rate in chronic kidney disease patients with type 2 diabetes mellitus: A multicenter, randomized, double-blind, placebo-controlled, parallel-group, phase III study in Japan.; Journal of diabetes investigation; 2022; vol. 13 (no. 12); 1981-1989

475.1. Study details

Trial name / registration number	ClinicalTrials.gov: NCT03436693
Study type	Randomised controlled trial (RCT)
Study location	Japan
Study setting	Unspecified clinical setting
Study dates	February 15 2018 - January 21, 2021
Sources of funding	Mitsubishi Tanabe Pharma Corporation
Inclusion criteria	• Glycated hemoglobin(HbA1c) of ≥6.5% and ≤12.0% • eGFR of ≥30 mL/min/1.73m2 and <90 mL/min/1.73m2 • The median UACR of the first morning void urine samples is ≥300 mg/g Cr and ≤5000 mg/g Cr • Patients who are taking on angiotensin-converting enzyme inhibitor (ACE-I) or angiotensin receptor blocker (ARB) • Patients who are under dietary management and taking therapeutic exercise for diabetes • 30 Years and older
Exclusion criteria	• Type I diabetes, diabetes mellitus resulting from pancreatic disorder, or secondary diabetes • A diagnosis of non-diabetic renal disease • Hereditary glucose-galactose malabsorption or primary renal glucosuria • Class IV heart failure symptoms according to New York Heart Association (NYHA) functional classification • Severe hepatic disorder or severe renal disorder • Blood potassium level >5.5 mmoL/L • Stable blood pressure (diastolic blood pressure (DBP) ≥180mmHg or systolic blood pressure (SBP) ≥100mmHg)

Recruitment / selection of participants	No information provided
Intervention(s)	The patients received the placebo once daily during the run-in period and 100 mg canagliflozin, taken orally before or after breakfast, once daily during the 104-week treatment period.
Cointervention	All patients were required to receive an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker at the maximum approved dose for at least 5 weeks before the screening period. Diet and exercise therapies continued unchanged from ≥12 weeks before the first day of the treatment period to the end of the study.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Exclusion criteria state: "Concurrent or history of heart failure of New York Heart Association class IV." No further information.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Exclusion criteria state: "Myocardial infarction, cerebrovascular disorder, revascularization procedure (e.g., stent or bypass), or unstable angina within 12 weeks before the beginning of the treatment period. Electrocardiogram findings within 12 weeks before the beginning of the treatment period that would require urgent diagnostic evaluation or intervention." No further information about events preceding the 12 weeks.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	People with chronic kidney disease The study defines the population as people with type 2 diabetes and CKD. Inclusion criteria state: "eGFR (as calculated by the equation for estimating Japanese GFR) of ≥30 and<90mL/min/1.73m2,and a median urinary albumin-to creatinine ratio (UACR) of ≥300 and ≤5,000mg/g creatinine." Exclusion criteria state: "Patients with non-diabetic renal disease, a history of nephrectomy or renal transplantation, or a history of hemodialysis therapy were excluded." Baseline characteristics reports average duration of diabetic nephropathy as 4.64 years ±3.75

Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe 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	A3 (ACR >300mg/g or >30mgmmol)
Comparator	The patients received the placebo once daily during the run-in period and the matching placebo, taken orally before or after breakfast, once daily during the 104-week treatment period.
Number of participants	308 underwent randomization to receive either canagliflozin (154 patients) or the placebo (154 patients)
Duration of follow-up	treatment (104 weeks) and follow-up (4 weeks)
Indirectness	None

Method of analysis	Not stated/unclear
Additional comments	Some post hoc analyses

475.2. Study arms

475.2.1. Canagliflozin (N = 154)

100 mg canagliflozin once daily

475.2.2. Placebo (N = 154)

Matching placebo once daily

475.3. Characteristics

475.3.1. Arm-level characteristics

Characteristic	Canagliflozin (N = 154)	Placebo (N = 154)
% Male Nominal	74.7	83.8
Mean age (SD) Mean (SD)	62.5 (10.5)	62.4 (11.1)
Japanese % Nominal	100	100
Hypertension % Nominal	100	100
History of fracture % Nominal	34.4	32.5
Time since type 2 diabetes diagnosed (years) Mean (SD)	15.43 (8.64)	16.49 (8.98)
HbA1c (%)	7.75 (1.1)	7.77 (1.05)

Characteristic	Canagliflozin (N = 154)	Placebo (N = 154)
Mean (SD)		
Systolic BP, mmHg Mean (SD)	140.8 (15)	140.8 (15)
Diastolic BP mmHg Mean (SD)	78.7 (11)	79 (9.9)
BMI Mean (SD)	26.7 (4.4)	27.1 (4.5)
Albumin creatinine ratio Median (IQR)	712 (422 to 1433)	630 (418 to 1239)
eGFR mL/min/1.73m2 Mean (SD)	56.3 (15.5)	55.2 (13.6)

476. Wägner, 2019

Bibliographic Reference	Wägner, A. M.; Miranda-Calderin, G.; Ugarte-Lopetegui, M. A.; Marrero-Santiago, H.; Suarez-Castellano, L.; Lopez-Madrazo, M. J.; Alberiche-Ruano, M. P.; Abselam Ahmed, N.; Aleman, C.; Castellot-Martin, A.; Diez Del Pino, A.; Novoa-Mogollon, F. J; Effect of liraglutide on physical performance in type 2 diabetes: results of a randomized, double-blind, controlled trial (LIPER2); Diabetes Metab; 2019; vol. 45 (no. 3); 268-275

476.1. Study details

Other publications associated with this study included in review	Wagner 2016 Wägner AM, Miranda-Calderín G, Ugarte-Lopetegui MA, Marrero-Santiago H, Suárez-Castellano L, Alberiche-Ruano MDP, Castillo-García N, López-Madrazo MJ, Alemán C, Martínez-Mancebo C, López-Ríos L, Díez Del Pino A, Nóvoa-Mogollón FJ. Effect of liraglutide on physical performance in type 2 diabetes (LIPER2): A randomised, double-blind, controlled trial. Contemp Clin Trials Commun. 2016 Jun 24;4:46-51. doi: 10.1016/j.conctc.2016.06.007. PMID: 29736469; PMCID: PMC5935879.
Trial name / registration number	LIPER / Eudract_number:2012-005197-6
Study type	Randomised controlled trial (RCT)
Study location	Single centre
Study setting	No additional information
Study dates	June 2013 to August 2016
Sources of funding	Funding and Drug supplies; Novo Nordisk
Inclusion criteria	T2D patients treated with oral agents, a maximum of 2 intermediate or long acting insulin injections per day or a combination of both. HbA1c between 7% and 10%.
Exclusion criteria	Severe renal failure (estimated glomerular filtration rate <30 ml/min), liver failure (Child-Pugh score > 6 points), present or planned pregnancy or breastfeeding or inadequate contraception, intolerance or allergy to liraglutide, familial or personal history of medullary thyroid cancer or type 2 multiple endocrine neoplasia, personal history of pancreatitis, triglyceride concentrations above 500 mg/dl or alcohol intake >40 g/day, known active malignancy, treatment with GLP1 agonists or DPP4 inhibitors in the previous 3 months, known coronary artery disease with exercise-induced ischaemia, planned revascularisations in the following 6 months, severe symptoms of heart failure (NYHA class IV), impossibility to perform a cycle ergometry or factors potentially interfering with adherence to treatment or follow-up.

Recruitment / selection of participants	Patients were identified and invited to participate in the outpatient clinics at the Endocrinology Department and at the primary care centres to which the hospital is the referral centre.
Intervention(s)	Liraglutide (n= 12) Patients received Liraglutide 1.2 - 1.8 mg/day as a daily, self-administered subcutaneous injection using a pre-filled injection pen containing 3 ml (18 mg). The aimed dose was 1.8 mg/d, but 1.2 mg/d was accepted if the higher dose was not tolerated. Participants administered 0.6 mg/d during the first week, increased to 1.2 mg/d during the second week and to 1.8 mg/ d during the third week.
Cointervention	Oral antidiabetic medication Patients continued with their oral agents prescribed from the beginning of the trial.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Exclusion criteria state: "severe symptoms of heart failure (NYHA class IV)" (see appendix). No information in baseline characteristics. Unclear regarding class II and III.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Exclusion criteria state: "known coronary artery disease with exercise-induced ischaemia" Baseline characteristics reports coronary artery disease and TIA.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear CKD not an inclusion/exclusion criteria. Exclusion criteria state: "severe renal failure (estimated glomerular filtration rate <30 ml/min)"
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe 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
Population subgroups	NA
Comparator	Placebo (n=12) Patients received Placebo as a daily, self-administered subcutaneous injection for 6 months. Patients continued to receive oral antidiabetic medication
Number of participants	24
Duration of follow-up	6 months
Indirectness	NA
Method of analysis	Per protocol ITT
Additional comments	Analysis performed in an intention to treat and per-analysis plan

476.2. Study arms

476.2.1. Liraglutide (N = 12)

Patients received Liraglutide 1.2 - 1.8 mg/day as a daily, self-administered subcutaneous injection using a pre-filled injection for 6 months

476.2.2. Placebo (N = 12)

Patients received Placebo as a daily, self-administered subcutaneous injection for 6 months

476.3. Characteristics

476.3.1. Arm-level characteristics

Characteristic	Liraglutide (N = 12)	Placebo (N = 12)
% Male Sample size	n = 4 ; % = 33.33	n = 5 ; % = 41.67
Mean age (SD) (Years (mean, SD)) Mean (SD)	52.6 (13.8)	53.2 (9.7)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed (Years (mean, SD)) Mean (SD)	7.42 (4.1)	10 (7.2)
Smoking status Sample size	n = 2 ; % = 16.67	n = 3 ; % = 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
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Liraglutide (N = 12)	Placebo (N = 12)
Metformin Sample size	n = 12 ; % = 100	n = 12 ; % = 100
Sulphonylurea Sample size	n = 5 ; % = 41.67	n = 5 ; % = 41.67
Repaglinide Sample size	n = 2 ; % = 16.67	n = 0 ; % = 0
Insulin Sample size	n = 7 ; % = 58.34	n = 3 ; % = 25
Blood pressure-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Renin-angiotensin axis inhibitor Sample size	n = 8 ; % = 66.67	n = 10 ; % = 83.34
Statins/lipid-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Statin Sample size	n = 6 ; % = 50	n = 7 ; % = 58.34
Other treatment being received Sample size	n = NA ; % = NA	n = NA ; % = NA
Aspirin Sample size	n = 7 ; % = 58.34	n = 7 ; % = 58.34

477. Wagner, 2016

Bibliographic Reference	Wagner, Ana Maria; Miranda-Calderin, Guillermo; Ugarte-Lopetegui, Miren Arantza; Marrero-Santiago, Hector; Suarez-Castellano, Laura; Alberiche-Ruano, Maria Del Pino; Castillo-Garcia, Nuria; Lopez-Madrazo, Maria Jose; Aleman, Carolina; Martinez-Mancebo, Carla; Lopez-Rios, Laura; Diez Del Pino, Alicia; Novoa-Mogollon, Francisco Javier; Effect of liraglutide on physical performance in type 2 diabetes (LIPER2): A randomised, double-blind, controlled trial.; Contemporary clinical trials communications; 2016; vol. 4; 46-51

477.1. Study details

Secondary publication of another included study- see primary study for details	W?gner 2019 Wägner AM, Miranda-Calderín G, Ugarte-Lopetegui MA, Marrero-Santiago H, Suárez-Castellano L, López-Madrazo MJ, Alberiche-Ruano MP, Abselam Ahmed N, Alemán C, Castellot-Martín A, Díez Del Pino A, Nóvoa-Mogollón FJ. Effect of liraglutide on physical performance in type 2 diabetes: Results of a randomized, double-blind, controlled trial (LIPER2). Diabetes Metab. 2019 Jun;45(3):268-275. doi: 10.1016/j.diabet.2018.08.010. Epub 2018 Sep 14. PMID: 30223083.

478. Wang, 2020

Bibliographic Reference	Wang, Q.; Wang, D.; Cheng, A.; Sun, F. Y.; Li, Z.; Comparison between the effects of sitagliptin and liraglutide on blood glucose and cognitive function of patients with both type 2 diabetes mellitus and post-stroke mild cognitive impairment; Int J Clin Experimental Med; 2020; vol. 13 (no. 2); 1219-1227

478.1. 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	Linyi Peoples Hospital, Linyi, China
Study setting	No additional information
Study dates	No additional information
Sources of funding	NR
Inclusion criteria	(1) Patients meeting the T2DM diagnosis criteria; (2) Patients meeting the diagnosis criteria of post-stroke cognitive impairment; (3) Patients meeting the diagnosis criteria of MCI. The diagnosis covered four items: 1) The mini-mental state examination; 2) The Montreal cognitive assessment 3) The patients complained about their own memory deterioration or their family members complained about the patients' memory deterioration; 4) The activity of daily living. A patient

	meeting the requirements of the four items meantime could be diagnosed with MCI; (4) Patients getting a score between 0 and 42 points after being assessed using the National Institutes of Health Stroke Scale (5) Patients meeting the following requirements: they had diabetes before suffering from stroke, and had taken sulfonylureas, metformin or insulin for blood glucose reduction, but they had not received DPP-4 inhibitors or GLP-1. Meantime, they showed a stable condition after suffering from stroke and being treated, and they met the diagnosis of post-stroke cognitive impairment based on detection.
Exclusion criteria	(1) Patients allergic to sitagliptin or liraglutide; (2) Patients with a history of craniocerebral trauma, epilepsy, or cerebrovascular disease; (3) Patients unable to cooperate for the cognitive function evaluation; (4) Patients under the influence of glucocorticoid on blood glucose; (5) Patients comorbid with severe hypertension, coronary heart disease, or hyperlipidemia; (6) Patients comorbid with a malignant tumour; (7) Patients with a mental disease that affects cognition.
Recruitment / selection of participants	Patients with T2DM accompanied by cognitive impairment within 6 months after stroke admitted to the department of neurology of Linyi People's Hospital from January 2017 to June 2018 were recruited
Intervention(s)	Sitagliptin (n=30) Patients received 100 mg of sitagliptin orally once a day, one tablet each time for 6 months
Cointervention	No information reported
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Study population was people with T2DM and post-stroke cognitive impairment.

	Exclusion criteria state: “patients with a history of cerebrovascular disease” and “patients comorbid with coronary heart disease”. From baseline characteristics table, there was a mix of people with ischaemic stroke (32 people) and hemorrhagic stroke (28 people). No information about PAD.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	People at higher risk of developing cardiovascular disease
Subgroup 1: People with moderate or severe 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	
Population subgroups	NA
Comparator	Liraglutide (n = 30) Patients received Liraglutide through subcutaneous injection at an initial amount of 0.6 mg/d, and an amount of 1.2 mg/d after one week for the treatment term of 6 months
Number of participants	60
Duration of follow-up	6 months
Indirectness	NA
Method of analysis	Not stated/unclear
Additional comments	Method of analysis not reported

478.2. Study arms

478.2.1. Sitagliptin (N = 30)

Patients received 100 mg sitagliptin orally once a day for 6 months

478.2.2. Liraglutide (N = 30)

Patients received liraglutide as subcutaneous injection at an initial amount of 06 mg per day, and then 1.2 mg per day after one week of treatment. Patients received liraglutide for 6 months

478.3. Characteristics

478.3.1. Arm-level characteristics

Characteristic	Sitagliptin (N = 30)	Liraglutide (N = 30)
% Male Sample size	n = 17 ; % = 56.7	n = 14 ; % = 46.7

Characteristic	Sitagliptin (N = 30)	Liraglutide (N = 30)
Mean age (SD) (Years (mean, SD)) Mean (SD)	67.2 (7.1)	66.1 (5.9)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed (Years (mean, SD)) Mean (SD)	8.19 (3.05)	8.99 (2.65)
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 = 30 ; % = 100	n = 30 ; % = 100
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR
Other antidiabetic medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
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

479. Wang, 2017

Bibliographic Reference	Wang, W.; Ning, G.; Ma, J.; Liu, X.; Zheng, S.; Wu, F.; Xu, L.; O'Neill, E. A.; Fujita, K. P.; Engel, S. S.; Kaufman, K. D.; Shankar, R. R.; A randomized clinical trial of the safety and efficacy of sitagliptin in patients with type 2 diabetes mellitus inadequately controlled by acarbose alone; Curr Med Res Opin; 2017; vol. 33 (no. 4); 693-699

479.1. 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	NCT01177384
Study type	Randomised controlled trial (RCT)
Study location	China Romania Korea Malaysia India Philippines
Study setting	Hospital
Study dates	01/2011 - 04/2013
Sources of funding	Merck & Co., Inc., Kenilworth, NJ, USA

Inclusion criteria	Patients were male or female and ≥18 years of age (and ≤65 years of age for patients in India).Patients were either on acarbose alone at a stable dose of at least 50 mg three times a day (t.i.d.) for ≥10 weeks with glycated hemoglobin (HbA1c) ≥7.0% and ≤10.0% at screening, or on acarbose at a stable dose of at least 50 mg t.i.d. for ≥10 weeks in combination with another antihyperglycemic agent (except a peroxisome proliferator-activated receptor – gamma [PPAR-c] agonist, a DPP-4 inhibitor, insulin, or a GLP-1 receptor agonist) with HbA1c ≥6.5% and ≤9.5% at screening, and with HbA1c ≥7.0% and ≤10.0% after an 8 week period when the other AHA was washed out. Patients had to have fasting finger-stick glucose of ≥7.2 and ≥15.0 mmol/L (≥130 and ≤270 mg/dL) at the randomisation visit.
Exclusion criteria	Type 1 diabetes or a history of ketoacidosis, active liver disease, significant and active cardiovascular disease, hematological disorders, had been previously treated with a DPP-4 inhibitor or a GLP-1 receptor agonist, or had been treated with a PPAR-c agonist or insulin within 12 weeks prior to randomization. Patients with an estimated glomerular filtration rate <60 mL/ min/1.73 m2 (calculated using the Modification of Diet in Renal Disease equation18), alanine aminotransferase or aspartate aminotransferase >2 times the upper limit of normal, hemoglobin <11 g/dL (male) or <10 g/dL (female), triglycerides >600 mg/dL, or thyroid-stimulating hormone outside the normal range were also excluded from the study.
Recruitment / selection of participants	Patients with uncontrolled type 2 diabetes taking acarbose (50 mg three times daily) were enrolled from 31 trial centers from 6 countries were randomised 1:1 ratio to sitagliptin or placebo.
Intervention(s)	Sitagliptin 100 mg daily Administered orally
Cointervention	Acarbose 50 mg three times daily Administered orally
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Exclusion criteria state "Patients were excluded from the study if they had significant and active cardiovascular disease." No further details about what conditions this includes. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Exclusion criteria state "Patients were excluded from the study if they had significant and active cardiovascular disease." No further details about what conditions this includes. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.

chronic kidney disease	
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe 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
Population subgroups	
Comparator	Placebo daily Administered orally.
Number of participants	N=381
Duration of follow-up	24-week

Indirectness	No additional information.
Method of analysis	Modified ITT

479.2. Study arms

479.2.1. Sitagliptin 100 mg daily (N = 191)

Administered orally

479.2.2. Placebo (N = 189)

Administered orally

479.3. Characteristics

479.3.1. Arm-level characteristics

Characteristic	Sitagliptin 100 mg daily (N = 191)	Placebo (N = 189)
% Male No of events	n = 97 ; % = 50.8	n = 97 ; % = 51.3
Mean age (SD) (years) Mean (SD)	56.5 (8.9)	57.8 (9.5)
Asian No of events	n = 171 ; % = 89.5	n = 170 ; % = 89.9
White No of events	n = 20 ; % = 10.5	n = 19 ; % = 10.1
Not hispanic or latino No of events	n = 191 ; % = 100	n = 189 ; % = 100
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed Mean (SD)	7.4 (4.9)	8.2 (5.7)

Characteristic	Sitagliptin 100 mg daily (N = 191)	Placebo (N = 189)
Smoking status Nominal	NR	NR
Alcohol consumption Nominal	NR	NR
Presence of severe mental illness Nominal	NR	NR
People with significant cognitive impairment Nominal	NR	NR
People with a learning disability Nominal	NR	NR
Weight (kg) Mean (SD)	68.9 (14.4)	69.3 (12.8)
BMI (kg/m2) Mean (SD)	25.9 (4.6)	26 (4.4)
Number of people with obesity Nominal	NR	NR
Acarbose No of events	n = 191 ; % = 100	n = 189 ; % = 100

480. Wang, 2016

Bibliographic Reference	Wang, W.; Yang, J.; Yang, G.; Gong, Y.; Patel, S.; Zhang, C.; Izumoto, T.; Ning, G.; Efficacy and safety of linagliptin in Asian patients with type 2 diabetes mellitus inadequately controlled by metformin: A multinational 24-week, randomized clinical trial; J Diabetes; 2016; vol. 8 (no. 2); 229-237

480.1. Study details

Secondary publication of another included study- see primary study for details	No
Other publications associated with this study included in review	None
Trial name / registration number	NCT01215097
Study type	Randomised controlled trial (RCT) Double-blind, placebo-controlled, parallel-group RCT
Study location	International (19 centres in China, Philippines and Malaysia)
Study setting	Outpatient
Study dates	11/2010 to 04/2012
Sources of funding	Funded by Boehringer Ingelheim
Inclusion criteria	• Aged 18-80 years inclusive • Type 2 diabetes diagnosis • Receiving stable metformin dose (≥1500 mg daily or max tolerated dose) with or without one other oral anti-diabetes drug • HbA1c 7-10% inclusive at start of placebo run-in period • BMI≤45 kg/m2 at screening

Exclusion criteria	• Myocardial infarction, stroke, or transient ischemic attack≤6 months prior to informed consent • Unstable or acute congestive heart failure • Impaired hepatic function at screening • Confirmed hyperglycemia (glucose≥240 mg/dL) after overnight fasting during the wash-out or run-in periods • Treatment with a thiazolidinedione, insulin, GLP-1 agonist, DPP-4 inhibitor, or anti-obesity drug • Recent alcohol and/or drug abuse • Current treatment with systemic steroids • Renal failure or impairment at screening • Participation in another trial≤2-mo prior to informed consent
Recruitment / selection of participants	Eligible participants on metformin only entered 2-wk placebo run-in period, whilst those on metformin combination therapy discontinued other oral antidiabetic drug and entered 4-wk washout period before entering 2-wk placebo run-in period. Participants eligible at end of run in then randomised 2:1, stratified by HbA1c level (<8.5%, ≥8.5%) at beginning of placebo run-in period) and previous treatment (metformin only, metformin combination therapy), using computer-generated randomisation sequence provided by interactive voice-response system.. Participants and investigators remained blinded to treatment for duration of trial. Rescue medication (glimepiride) permitted. Participants discontinued if fasting plasma glucose remained uncontrolled despite rescue therapy.
Intervention(s)	• Linagliptin 5 mg daily Oral linagliptin 5 mg daily for 24 weeks, in addition to metformin.
Cointervention	• Metformin All participants continued receiving metformin at baseline dose (≥1500 mg daily or max tolerated dose) for duration of trial. Participants receiving additional oral antidiabetic drugs at baseline discontinued them and entered 4-wk washout period before 2-wk placebo run-in period.
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Exclusion criteria state "patients were ineligible to participate if they had unstable or acute congestive heart failure."
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Exclusion criteria state: "patients were ineligible to participate if they had experienced myocardial infarction, stroke, or transient ischaemic attack ≤6 months prior to informed consent." NO information about CVD in the preceding 6 months. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and	Not stated/unclear "Renal failure or impairment at screening" stated as an exclusion criteria. No further information about CKD.

chronic kidney disease	
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe 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 participants had eGFR≥30 ml/min/1,73 m2 at baseline
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Comparator	• Placebo Matching placebo daily for 24 weeks, in addition to metformin.
Number of participants	N=306 randomised (N=305 received treatment; N=279 completers)
Duration of follow-up	24 weeks
Indirectness	None

Method of analysis	Modified ITT Efficacy outcomes use full analysis set (all randomised participants who received at least one study drug dose and had baseline and at least one post-baseline measurement) with LOCF for missing values. Safety outcomes analysed using all randomised participants with at least one study drug dose.

480.2. Study arms

480.2.1. Linagliptin 5 mg daily (N = 205)

Oral linagliptin 5 mg daily for 24 weeks, in addition to metformin.

480.2.2. Placebo (N = 101)

Matching placebo daily for 24 weeks, in addition to metformin.

480.3. Characteristics

480.3.1. Arm-level characteristics

Characteristic	Linagliptin 5 mg daily (N = 205)	Placebo (N = 101)
% Male Sample size	n = 102 ; % = 49.8	n = 50 ; % = 50
Mean age (SD) Mean (SD)	55.1 (10.7)	56.5 (8.7)
Ethnicity Country of origin Sample size	n = NA ; % = NA	n = NA ; % = NA
China Sample size	n = 187 ; % = 89.8	n = 80 ; % = 80
Malaysia Sample size	n = 13 ; % = 6.3	n = 11 ; % = 11
Philippines Sample size	n = 8 ; % = 3.9	n = 9 ; % = 9

Characteristic	Linagliptin 5 mg daily (N = 205)	Placebo (N = 101)
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Less than 1 year Sample size	n = 33 ; % = 16.3	n = 19 ; % = 19.6
>1 to 5 years Sample size	n = 83 ; % = 40.9	n = 32 ; % = 33
5+ years Sample size	n = 87 ; % = 42.9	n = 46 ; % = 47.4
Cardiovascular risk factors Nominal	NR	NR
Smoking status Nominal	NR	NR
Alcohol consumption Nominal	NR	NR
Presence of severe mental illness Nominal	NR	NR
People with significant cognitive impairment Nominal	NR	NR
People with a learning disability Nominal	NR	NR
Number of people with obesity Nominal	NR	NR
Other antidiabetic medication used At baseline Sample size	n = NA ; % = NA	n = NA ; % = NA
Metformin only Sample size	n = 135 ; % = 66.5	n = 62 ; % = 63.9

Characteristic	Linagliptin 5 mg daily (N = 205)	Placebo (N = 101)
Sulphonylurea Sample size	n = 54 ; % = 26.6	n = 28 ; % = 28.9
Alpha-glucosidase inhibitors Sample size	n = 8 ; % = 3.9	n = 4 ; % = 4.1
Other antidiabetes drugs Sample size	n = 6 ; % = 3	n = 3 ; % = 3.1
Blood pressure-lowering medication used Nominal	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

Baseline data for Age, Gender, Ethnicity are for N=100 in the placebo group because one participant in this group did not receive treatment; Baseline data for other characteristics are for the following number of participants: LINA, N=203; Placebo, N=97.

481. Wang, 2023

Bibliographic Reference	Wang, Weimin; Yan, Xin; Cheng, Zhifeng; Zhang, Qiqi; Wang, Rui; Deng, Yuying; Ma, Jianhua; Zhu, Dalong; Efficacy and safety of adding once-weekly dulaglutide to basal insulin for inadequately controlled type 2 diabetes in Chinese patients (AWARD-CHN3): A randomized, double-blind, placebo-controlled, phase III trial.; Diabetes, obesity & metabolism; 2023

481.1. 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	NCT04591626
Study type	Randomised controlled trial (RCT)
Study location	China
Study setting	University
Study dates	12/2020 - 04/2022
Sources of funding	Eli Lilly and Company
Inclusion criteria	• have type 2 diabetes • are men or nonpregnant women aged ≥18 years at screening • have been treated with basal insulin glargine once daily and metformin and/or acarbose for at least 3 months prior to screening • doses of once daily insulin glargine and oral antidiabetic medication must be stable during the 3-month period prior to screening. Insulin glargine dose is considered stable when all doses during this period are within the range defined by ±20% of the most commonly used insulin glargine dose during this same period. Doses of

	metformin and/or acarbose are considered stable when doses are unchanged during the same period, and the doses should be in the inclusive range of the half maximum to maximum approved daily dose per the locally-approved label • have an HbA1c value ≥7.0% and ≤11.0% as assessed by the central laboratory at screening • require further insulin glargine dose increase at baseline per the titrated treated-to-target algorithm based on the self-monitored blood glucose data (fasting blood glucose ≥5.6mmol/L) collected during the prior week • have stable weight (±5%) ≥3 months prior to screening • have BMI between ≥19.0 and ≤35.0 kg/m2 at screening
Exclusion criteria	• type 1 diabetes • history of ≥1 episode of ketoacidosis or hyperosmolar state/coma • history of severe hypoglycemia and/or hypoglycemia unawareness within the 6 months prior to screening • any of the following CV conditions within the 2 months prior to screening: acute myocardial infarction, New York Heart Association (NYHA) Class III or Class IV heart failure, or cerebrovascular accident (stroke) • a known clinically significant gastric emptying abnormality (eg, severe diabetic gastroparesis or gastric outlet obstruction) or have undergone or plan to have a gastric bypass (bariatric) surgery or restrictive bariatric surgery (eg, Lap-Band®) during the course of the study, or chronically take drugs that directly affect gastrointestinal motility • a history of chronic pancreatitis or acute idiopathic pancreatitis, or were diagnosed with any type of acute pancreatitis within the 3 months prior to screening • for participants on metformin or metformin and acarbose, have renal disease or renal dysfunction (eGFR [CKD-EPI] <45 mL/min/1.73 m2), as determined by the central laboratory; for participants on acarbose, have renal disease or renal dysfunction (eGFR [CKD-EPI] <25 mL/min/1.73 m2), as determined by the central laboratory • have any self or family history of type 2A or type 2B multiple endocrine neoplasia (MEN 2A or 2B) syndrome in the absence of known C-cell hyperplasia (the only exception for this exclusion will be for participants whose family members with MEN 2A or 2B syndrome have a known RET mutation and the potential participant for the study is negative for the RET mutation) • have any self or family history of medullary C-cell hyperplasia, focal hyperplasia, or carcinoma (including sporadic, familial, or part of MEN 2A or 2B syndrome) • have serum calcitonin ≥20 pg/mL at screening, as determined by the central laboratory • have any hematologic condition that may interfere with HbA1c measurement (eg, hemolytic anemias, sickle-cell disease) • have been treated with any other antihyperglycemia regimen, other than basal insulin glargine once daily and metformin and/or acarbose, within the 3 months prior to screening or between screening and baseline

Recruitment / selection of participants	Patients with type two diabetes
Intervention(s)	Dulaglutide 1.5 mg once weekly Administered subcutaneously.
Cointervention	Basal insulin glargine once daily Administered subcutaneously.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear
Strata 2: People with atherosclerotic cardiovascular disease	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 moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with	Not stated/unclear

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
Population subgroups	No additional information.
Comparator	Placebo once weekly administered subcutaneously.
Number of participants	N=291
Duration of follow-up	28-week.
Indirectness	Directly applicable
Method of analysis	ITT
Additional comments	All randomised patients were included in the analysis.

481.2. Study arms

481.2.1. Dulaglutide 5 mg once weekly (N = 144)

Administered subcutaneously

481.2.2. Placebo once weekly (N = 147)

Administered subcutaneously

481.3. Characteristics

481.3.1. Arm-level characteristics

Characteristic	Dulaglutide 5 mg once weekly (N = 144)	Placebo once weekly (N = 147)
% Male No of events	n = 92 ; % = 64	n = 90 ; % = 61
Mean age (SD) (years) Mean (SD)	57.8 (9.3)	58.3 (9.5)
Chinese No of events	n = 144 ; % = 100	n = 147 ; % = 100
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	11.2 (6)	12.4 (6.9)
Smoking status Nominal	NR	NR
Alcohol consumption Nominal	NR	NR
Presence of severe mental illness Nominal	NR	NR
People with significant cognitive impairment Nominal	NR	NR
People with a learning disability Nominal	NR	NR
Number of people with obesity Nominal	NR	NR
Metformin No of events	n = 75 ; % = 52.1	n = 77 ; % = 52.4
Acarbose only	n = 13 ; % = 9	n = 14 ; % = 9.5

Characteristic	Dulaglutide 5 mg once weekly (N = 144)	Placebo once weekly (N = 147)
No of events		
Metformin + acarbose No of events	n = 56 ; % = 38.9	n = 56 ; % = 38.1
Blood pressure-lowering medication used Nominal	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

482. Wang, 2022

Bibliographic Reference	Wang, Weiqing; Agner, Bue F Ross; Luo, Bin; Liu, Lei; Liu, Ming; Peng, Yongde; Qu, Shen; Stachlewska, Karolina Amelia; Wang, Guixia; Yuan, Guoyue; Zhang, Qiu; Ning, Guang; DUAL I China: Improved glycemic control with IDegLira versus its individual components in a randomized trial with Chinese participants with type 2 diabetes uncontrolled on oral antidiabetic drugs.; Journal of diabetes; 2022; vol. 14 (no. 6); 401-413

482.1. 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	DUAL I/NCT03172494
Study type	Randomised controlled trial (RCT)
Study location	China
Study setting	Hospital
Study dates	05/2017 - 12/2018
Sources of funding	Novo Nordisk
Inclusion criteria	Chinese people with T2D, aged ≥18 years, with HbA1c 53.0 to 85.8 mmoL/moL (7.0%- 10.0%), BMI ≤ 40 kg/m2 , and on a stable dose of metformin (≥1500 mg or the maximum tolerated) ± one other oral antidiabetic treatment (α-glucosidase inhibitor, sulfonylurea, glinide, or thiazolidinedione; at least half the local-label maximum approved dose) for ≥60 days before screening
Exclusion criteria	Current treatment with other diabetic medications, previous insulin use (except short-term treatment at investigator's discretion), and anticipated

	initiation/change in concomitant medications affecting glucose metabolism. Individuals with renal or liver impairment were excluded.
Recruitment / selection of participants	Patients with inadequately controlled type 2 diabetes from 38 sites in mainland China were recruited and randomised in a 2:1:1 ration to IDegLira or degludec or liraglutide; all administered once daily subcutaneously. Patients were on metformin (≥ 1500 mg) or maximum tolerated ± one other oral antidiabetic (alpha-glucosidase inhibitor, sulfonylurea, glinide, thiazolidinedione; at least half the local-label maximum approved dose) for ≥60 days before screening. After randomisation all patients continued with metformin but discontinues other oral antidiabetics.
Intervention(s)	IDegLira (insulin degludec/liraglutide), initiated at 10 dose steps (10 U degludec:0.36 mg liraglutide) Administered once daily subcutaneously.
Cointervention	Metformin (≥ 1500 mg) daily. Administered orally.
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure
Strata 2: People with atherosclerotic cardiovascular disease	People without atherosclerotic cardiovascular diseases
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	People without chronic kidney disease

Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe 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
Population subgroups	
Comparator	Degludec once daily given as 10 U initially. Liraglutide once daily, started as 0.6 mg then increased weekly by 0.6 mg up to a maximum dose of 1.8 mg. Administered subcutaneously
Number of participants	N=720

Duration of follow-up	26-week
Indirectness	No additional information.
Method of analysis	Modified ITT
Additional comments	Full analysis set - some form of mITT

482.2. Study arms

482.2.1. IDegLira (degludec/liraglutide) once daily (N = 361)

Administered subcutaneously. Initiated at 10 dose steps (10 U degludec:0.36 mg liraglutide)

482.2.2. Degludec once daily (N = 179)

Administered subcutaneously. Given as 10 U initially and then titrated.

482.2.3. Liraglutide 1.8 mg once daily (N = 180)

Administered subcutaneously. Started as 0.6 mg then increased weekly by 0.6 mg up to a maximum dose of 1.8 mg.

482.3. Characteristics

482.3.1. Arm-level characteristics

Characteristic	IDegLira (degludec/liraglutide) once daily (N = 361)	Degludec once daily (N = 179)	Liraglutide 1.8 mg once daily (N = 180)
% Male No of events	n = 219 ; % = 60.7	n = 100 ; % = 55.9	n = 108 ; % = 60
Mean age (SD) Mean (SD)	54.5 (10.3)	55.7 (10.2)	54.1 (10.2)
Ethnicity Nominal	NR	NR	NR

Characteristic	IDegLira (degludec/liraglutide) once daily (N = 361)	Degludec once daily (N = 179)	Liraglutide 1.8 mg once daily (N = 180)
Presence of frailty 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

483. Wang, 2019

Bibliographic Reference	Wang, Weiqing; Nevarez, Luis; Filippova, Ekaterina; Song Ki, Ho; Tao, Bei; Gu, Liqun; Wang, Feng; Li, Pengfei; Yang, Jun; Efficacy and safety of once-weekly dulaglutide versus insulin glargine in mainly Asian patients with type 2 diabetes mellitus on metformin and/or a sulphonylurea: a 52-week open-label, randomized phase III trial; Diabetes Obes Metab; 2019; vol. 21 (no. 2); 234-243

483.1. Study details

Trial name / registration number	NCT01648582
Study type	Randomised controlled trial (RCT)
Study location	45 sites in China, Russia, Mexico and South Korea
Study setting	No additional information
Study dates	NR
Sources of funding	Elli Lilly and Company. A number of authors are employees of Elli Lilly and Company
Inclusion criteria	Patients aged ≥18 years with a diagnosis of T2DM for at least 6 months, a body mass index ≥19.0 and ≤35.0 kg/m2 and HbA1c ≥53.0 mmol/mol (7.0%; considered inadequate glycaemic control) and ≤96.7 mmol/mol (11.0%), who had been taking metformin and/or a sulphonylurea for at least 3 months and were on a stable therapeutic dose (at least half the maximum dose according to the product information in the country of treatment) for at least 8 weeks before screening
Exclusion criteria	Patients were excluded from the study if they had type 1 diabetes, had a clinically significant gastric emptying abnormality, had a history of pancreatitis, had a serum calcitonin concentration ≥20 ng/L (or 5.83 pmol/L), were taking insulin treatment or had been treated with a GLP-1 receptor agonist within 3 months before screening.
Recruitment / selection of participants	No additional information
Intervention(s)	Dulaglutide 0.75 mg (n=257) Dulaglutide 1.5 mg (n=258) Patients in the two dulaglutide treatment groups received a fixed, double-blind dose of dulaglutide (either 1.5 or 0.75 mg) once weekly as a subcutaneous injection.

Cointervention	Metformin and / or sulphonylurea: Patients continued taking their usual oral antidiabetic medication dose and regimen throughout the treatment period
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe 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
Population subgroups	NA
Comparator	Insulin (n=259) Patients started their once daily subcutaneous injection before bedtime. The initial dose of glargine was determined from the patient's average plasma-equivalent fasting plasma glucose (FPG) from the previous 2 to 4 days. The initial dose of glargine was 6 IU/day, with an average FPG of ≥7.8 mmol/L and was reduced by 1 to 2 IU/d with an average FPG of <7.8 mmol/L at the investigator's discretion. The patients measured FPG every morning and were instructed to adjust insulin doses to achieve the target FPG range of 4.0 to 5.6 mmol/L. Patients continued taking their usual OAM (metformin and/or a sulphonylurea) dose and regimen throughout the treatment period.
Number of participants	774
Duration of follow-up	52 weeks
Indirectness	NA
Method of analysis	Modified ITT
Additional comments	Efficacy analyses were based on a modified intention-to-treat (mITT) population, consisting of all randomized patients who had a baseline HbA1c measurement and at least one post-baseline HbA1c measurement for the respective analysis period (week 26 and week 52) and received at least one dose of injectable study drug. Safety analyses were based on the as-treated population (the safety analysis set) consisting of all randomized patients who received one dose of the study drug. The changes from baseline in efficacy endpoints and body weight at weeks 26 and 52 were analysed using a mixed model with repeated measures (MMRM) with restricted maximum likelihood on MITT analysis set. The change from baseline value was the dependent variable; treatment, country, pre-study therapy, visit and the treatment-by-visit interaction were fixed effects, and baseline value was a covariate and patient was a

	random effect. The percentage of patients achieving HbA1c targets (with LOCF for the missing endpoint HbA1c) and of patients experiencing AEs or hypoglycaemia were analysed using Fisher's exact test

483.2. Study arms

483.2.1. Dulaglutide 0.75 mg (N = 257)

Patients received a fixed, double-blind dose of dulaglutide 0.75 mg once weekly as a subcutaneous injection. for 52 weeks

483.2.2. Dulaglutide 1.5 mg (N = 258)

Patients received a fixed, double-blind dose of dulaglutide 1.5 mg once weekly as a subcutaneous injection. for 52 weeks

483.2.3. Insulin (N = 259)

Patients received insulin glargine group as a once daily subcutaneous injection before bedtime. The initial dose of glargine was 6 IU/day, with an average FPG of ≥7.8 mmol/L and was reduced by 1 to 2 IU/d with an average FPG of <7.8 mmol/L at the investigator's discretion. The patients measured FPG every morning and were instructed to adjust insulin doses to achieve the target FPG range of 4.0 to 5.6 mmol/L

483.3. Characteristics

483.3.1. Arm-level characteristics

Characteristic	Dulaglutide 0.75 mg (N = 257)	Dulaglutide 1.5 mg (N = 258)	Insulin (N = 259)
% Male Dulaglutide 0.75mg n = 252, Dulaglutide 1.5 mg n = 253, Insulin n = 250 Sample size	n = 143 ; % = 56.7	n = 135 ; % = 53.4	n = 139 ; % = 57.6
Mean age (SD) (Years (mean, SD)) Mean (SD)	54.5 (10)	55 (9.6)	55.4 (9.2)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Dulaglutide 0.75 mg (N = 257)	Dulaglutide 1.5 mg (N = 258)	Insulin (N = 259)
Time since type 2 diabetes diagnosed (Years (mean, SD)) Mean (SD)	8.1 (5.3)	7.9 (4.8)	8.4 (5.3)
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
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Metformin only Dulaglutide 0.75mg n = 252, Dulaglutide 1.5 mg n = 253, Insulin n = 250 Sample size	n = 101 ; % = 40	n = 106 ; % = 41.9	n = 101 ; % = 40.2
Sulphonylureas only Dulaglutide 0.75mg n = 252, Dulaglutide 1.5 mg n = 253, Insulin n = 250 Sample size	n = 29 ; % = 12.4	n = 31 ; % = 11.5	n = 28 ; % = 11.2
Metformin + sulphonylureas Dulaglutide 0.75mg n = 252, Dulaglutide 1.5 mg n = 253, Insulin n = 250 Sample size	n = 120 ; % = 47.6	n = 118 ; % = 46.6	n = 122 ; % = 48.6
Blood pressure-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Dulaglutide 0.75 mg (N = 257)	Dulaglutide 1.5 mg (N = 258)	Insulin (N = 259)
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

484. Wang, 2020

Bibliographic Reference	Wang, X.; Zhang, H.; Zhang, Q.; Guan, M.; Sheng, S.; Mo, W.; Zou, M.; Li, J.; Bi, J.; Tang, X.; Zeng, H.; He, J.; Xu, G.; Li, P.; Xue, Y.; Exenatide and Renal Outcomes in Patients with Type 2 Diabetes and Diabetic Kidney Disease; American Journal of Nephrology; 2020; vol. 51 (no. 10); 806-814

484.1. Study details

Secondary publication of another included study- see primary study for details	No
Other publications associated with this study included in review	None
Trial name / registration number	NCT02690883
Study type	Randomised controlled trial (RCT) Open-label parallel-group RCT
Study location	4 hospitals in Guangzhou, China
Study setting	Outpatient
Study dates	03/2016 to 04/2019
Sources of funding	AstraZeneca China and 3SBio Inc. funded study and provided drugs and examination items during follow up.
Inclusion criteria	• Aged 18-80 years inclusive • Diagnosis of T2DM • HbA1c 7.0-11.0% inclusive • BMI 18-35 kg/m2 inclusive • Blood pressure 90/60-160/100 mmHg • Macroalbuminuria (24h-UAER >0.3 g/24h after 3 months treatment with sulphonylureas, metformin, AG-inhibitor, meglitinides or insulin) • eGFR ≥30 mL/min per 1.73m2

	• Informed consent prior to any study specific procedures
Exclusion criteria	• Women who are pregnant or who are intending to become pregnant during study; not using highly effective, medically approved birth control methods if currently lactating, or of child-bearing potential • Diagnosis or history of Type 1 diabetes mellitus, diabetes resulting from pancreatic injury or secondary forms of diabetes • Acute metabolic diabetic complications (e.g. ketoacidosis or hyperosmolar coma) within past 6 months • Previous treatment with thiazolidinediones, DPP-4 inhibitors or GLP-1 receptor agonists within past 3 months • Hypersensitivity reaction to exenatide • Blood amylase and/or lipase >2ULN • Hyperkalemia (K+ >5.5 mmol/L) • Diabetic retinopathy • Triglycerides (fasting) >4.5 mmol/L (400 mg/dL) at screening or within 4 weeks prior to screening • Clinically apparent liver disease characterized by ALT or AST >3ULN confirmed on two consecutive measurements within 4 weeks prior to screening • Significant cardiovascular history within 3 months prior to screening defined as: myocardial infarction, coronary angioplasty or bypass graft(s), valvular disease or repair, unstable angina pectoris, transient ischemic attack, or cerebrovascular accident • Congestive heart failure defined as NYHA class III or IV • History of chronic pancreatitis or idiopathic acute pancreatitis • History of medullary thyroid carcinoma
Recruitment / selection of participants	Participants recruited from 4 hospitals in Guangzhou. Three-day screening phase and eligible participants entered 2-week run-in phase in which all glucose-lowering drugs (except exenatide and insulin) were stopped and basal insulin titrated twice every week based on self-monitored fasting blood glucose levels. Block randomisation 1:1 to 1 of 2 arms. Eligible participants referred by physician to nurse, who obtained allocation from researcher not involved in clinical work and who maintained allocation sequence.
Intervention(s)	• Exenatide 10 mcg twice daily Subcutaneous injection of exenatide 5 mcg twice daily for 4 weeks, then titrated up to 10 mcg twice daily for remaining 20 weeks, in addition to insulin glargine.
Cointervention	Insulin glargine
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear "Congestive heart failure defined as NYHA class III or IV" stated in the exclusion criteria (in supplementary information). No information in baseline characteristics.

Strata 2: People with atherosclerotic cardiovascular disease	Mixed population Exclusion criteria (supplementary information state): "Significant cardiovascular history within the past 3 months prior to screening defined as: myocardial infarction, coronary angioplasty or bypass graft(s), valvular disease or repair, unstable angina pectoris, transient ischemic attack, or cerebrovascular accident." Baseline characteristics table and results report 27.2% with history of cardiovascular disease.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	People with chronic kidney disease Study population is people with type 2 diabetes and diabetic kidney disease. Study inclusion criteria (in supplementary info) state: "24h-UAER >0.3 g/24h after 3 months treatment with several hypoglycemic agents (sulphonylureas, metformin, AG-inhibitor, meglitinides or insulin) and eGFR ≥30 mL/min per 1.73m2"
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe 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 Inclusion criteria: eGFR ≥30 mL/min/1.73m2
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Comparator	• Insulin lispro three times daily Standard dose administered according to "dose used in previous antihyperglycemic therapies" and further titrated every 4-weeks to match target fasting plasma glucose level.
Number of participants	N=92
Duration of follow-up	24 weeks
Indirectness	None
Method of analysis	Modified ITT mITT analysis (all randomised participants with at least 1 non-missing baseline and 1 post-baseline assessment) for efficacy outcomes (change in UAER, UACR, HbA1c, weight, blood pressure). Safety analysis conducted for all participants who took at least 1 dose of study drug.
Additional comments	

484.2. Study arms

484.2.1. Exenatide 10 mcg twice daily (N = 46)

Subcutaneous injection of exenatide 10 mcg for 24 weeks, in addition to insulin glargine.

484.2.2. Insulin lispro thrice daily (N = 46)

Insulin lispro thrice daily for 24 weeks titrated at 4-wk intervals to match target fasting plasma glucose, in addition to insulin glargine.

484.3. Characteristics

484.3.1. Arm-level characteristics

Characteristic	Exenatide 10 mcg twice daily (N = 46)	Insulin lispro thrice daily (N = 46)
% Male Sample size	n = 35 ; % = 76.1	n = 29 ; % = 63
Mean age (SD) Mean (SD)	55.9 (8.9)	56.2 (8)
Ethnicity Nominal	NR	NR
Comorbidities Sample size	n = NA ; % = NA	n = NA ; % = NA
Cardiovascular disease Sample size	n = 12 ; % = 26.1	n = 13 ; % = 28.3
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed Mean (SD)	10.9 (6.2)	11.4 (7)
Cardiovascular risk factors Sample size	n = NA ; % = NA	n = NA ; % = NA
Hyperlipdaemia Sample size	n = 35 ; % = 76.1	n = 35 ; % = 76.1
Hypertension Sample size	n = 39 ; % = 84.8	n = 36 ; % = 78.4
Smoking status Current smoker Sample size	n = 23 ; % = 50	n = 18 ; % = 39.1
Alcohol consumption Nominal	NR	NR
Presence of severe mental illness Nominal	NR	NR

Characteristic	Exenatide 10 mcg twice daily (N = 46)	Insulin lispro thrice daily (N = 46)
People with significant cognitive impairment Nominal	NR	NR
People with a learning disability Nominal	NR	NR
Number of people with obesity Nominal	NR	NR
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Alpha-glucosidase inhibitors Sample size	n = 13 ; % = 28.3	n = 11 ; % = 23.9
Insulin Sample size	n = 36 ; % = 78.3	n = 33 ; % = 71.7
Metformin Sample size	n = 18 ; % = 39.1	n = 17 ; % = 37
Sulphonylureas Sample size	n = 6 ; % = 13	n = 8 ; % = 17.4
Blood pressure-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Any blood pressure-lowering medication Sample size	n = 42 ; % = 91.3	n = 41 ; % = 89.1
Angiotensin-converting enzyme inhibitor/angiotensin II receptor blockers Sample size	n = 40 ; % = 87	n = 40 ; % = 87
Calcium-channel blockers Sample size	n = 28 ; % = 60.9	n = 28 ; % = 60.9
Statins/lipid-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Any lipid-lowering drug	n = 42 ; % = 91.3	n = 40 ; % = 87

Characteristic	Exenatide 10 mcg twice daily (N = 46)	Insulin lispro thrice daily (N = 46)
Sample size		
Statins Sample size	n = 41 ; % = 89.1	n = 39 ; % = 84.8
Other treatment being received Sample size	n = NA ; % = NA	n = NA ; % = NA
Any anti-platelet drug Sample size	n = 42 ; % = 91.3	n = 41 ; % = 89.1
Aspirin Sample size	n = 19 ; % = 41.3	n = 10 ; % = 21.7
Beta blockers Sample size	n = 9 ; % = 19.6	n = 4 ; % = 8.7
Diuretics Sample size	n = 6 ; % = 13	n = 7 ; % = 15.2

485. Wang, 2020

Bibliographic Reference	Wang, X.; Zhao, X.; Gu, Y.; Zhu, X.; Yin, T.; Tang, Z.; Yuan, J.; Chen, W.; OuYang, R.; Yao, L.; Zhang, R.; Yuan, J.; Zhou, R.; Sun, Y.; Cui, S.; Effects of Exenatide and Humalog Mix25 on Fat Distribution, Insulin Sensitivity, and beta-Cell Function in Normal BMI Patients with Type 2 Diabetes and Visceral Adiposity; Journal of Diabetes Research; 2020; vol. 2020; 9783859

485.1. Study details

Trial name / registration number	ChiCTR-IPR-14005568
Study type	Randomised controlled trial (RCT)
Study location	Nantong University, Nantong, China
Study setting	All study procedures and visits were conducted in the Endocrinology Internal Medicine Laboratory of the Affiliated Hospital of Nantong University, China.
Study dates	NR
Sources of funding	AstraZeneca and 3SBio Inc.
Inclusion criteria	T2DM patients who had received a stable dose of any oral antidiabetes drug (except for thiazolidinediones and dipeptidase-4 inhibitors) for at least 3 months, an HbA1c level of ≥7.0% to <10.0% at screening or within 4 weeks before screening, a BMI of ≥18.5 to <25 kg/m2 , and a WC of >85 cm for male or >80 cm for female subjects, respectively.
Exclusion criteria	(1) current pregnancy, lactation, or child-bearing potential (female subjects); (2) diagnosis or a history of type 1 diabetes mellitus or secondary forms of diabetes; (3) acute metabolic complications of diabetes; (4) treatment with glucocorticoids; (5) a triglyceride level > 4:5 mmol/L; (6) clinically acute or chronic liver disease; (7) moderate/severe renal impairment or end-stage renal disease;

	(8) significant history of cardiovascular disease; (9) history of chronic pancreatitis, idiopathic acute pancreatitis or gastrointestinal disease and acute or chronic thyroid diseases; (10) diagnosis and/or treatment of malignancy within the past 5 years; (11) history of organ transplant or acquired immunodeficiency syndrome; and (12) history of alcohol abuse or illegal drug abuse within the past 12 months.
Recruitment / selection of participants	Patients were enrolled in the study at the Endocrinology department of the Affiliated Hospital of Nantong University between January 2015 and September 2016
Intervention(s)	Exenatide (n=49) A 5 μg dose was injected subcutaneously twice daily for 4 weeks, after which a 10 μg dose was injected subcutaneously twice daily for 20 additional weeks
Cointervention	The doses of concurrent medications were adjusted by the investigators if required during patient study visits
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Exclusion criteria state "significant history of cardiovascular disease", but no further information.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Exclusion criteria state "significant history of cardiovascular disease", but no further information.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Exclusion criteria state "moderate/severe renal impairment or end-stage renal disease." No further information.
Strata 4: People with type 2 diabetes mellitus and high	Not stated/unclear

cardiovascular risk	
Subgroup 1: People with moderate or severe 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
Population subgroups	NA
Comparator	Insulin (n=46) Humalog Mix25 was injected subcutaneously before morning and evening meals for 24 weeks. The patients were contacted once weekly by investigators to discuss glycaemic control. The starting doses of humalog Mix25 were 0.4 IU/kg per day (twice daily) and were then gradually adjusted for target glucose values (fasting plasma glucose < 7:0 mmol/L and 2 h plasma blood glucose < 10:0 mmol/L) by the investigators
Number of participants	95
Duration of follow-up	24 weeks
Indirectness	NA

Method of analysis	Per protocol
Additional comments	Analysis poorly described but analysis appears to be per protocol

485.2. Study arms

485.2.1. Exenatide (N = 49)

Patients received exenatide as a 5 µg dose injected subcutaneously twice daily for 4 weeks, after which a 10 µg dose was injected twice daily for 20 additional weeks

485.2.2. Insulin (N = 46)

Patients received a starting doses of Insulin lispro of 0.4 IU/kg per day(twice daily) which were gradually adjusted for target fasting plasma glucose < 7:0 mmol/L and 2 h plasma blood glucose < 10:0 mmol/L. Insulin was injected subcutaneously before morning and evening meals for 24 weeks.

485.3. Characteristics

485.3.1. Arm-level characteristics

Characteristic	Exenatide (N = 49)	Insulin (N = 46)
% Male Sample size	n = 31 ; % = 63.2	n = 23 ; % = 50
Mean age (SD) (Years (mean, SD)) Mean (SD)	56.1 (11.14)	60.37 (10.83)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed (Years (mean, SD)) Mean (SD)	NR (NR)	NR (NR)
Smoking status Sample size	n = 19 ; % = 39.8	n = 13 ; % = 28.3

Characteristic	Exenatide (N = 49)	Insulin (N = 46)
Alcohol consumption Sample size	n = 22 ; % = 44.9	n = 24 ; % = 52.2
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Sulfonlyureas Sample size	n = 18 ; % = 36.7	n = 17 ; % = 36.9
Biguanides Sample size	n = 27 ; % = 55.1	n = 17 ; % = 37
Glinides Sample size	n = 4 ; % = 8.2	n = 4 ; % = 8.7
Glucosidase inhibitors Sample size	n = 7 ; % = 14.3	n = 10 ; % = 21.7
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