National Institute for Health and Care Excellence

Final

Type 2 diabetes in adults: management (medicines update)

[F2.6] Evidence reviews for subsequent pharmacological management of type 2 diabetes – Appendix D5

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

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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.

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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.

292. Marso S, 2020

Bibliographic Reference	Marso S, P; Baeres F, M.M; Bain S, C; Goldman, B; Husain, M; Nauck M, A; Poulter N, R; Pratley R, E; Thomsen A, B; Buse J, B; Effects of Liraglutide on Cardiovascular Outcomes in Patients With Diabetes With or Without Heart Failure; Journal of the American College of Cardiology; 2020; vol. 75 (no. 10); 1128-1141

292.1. Study details

Secondary publication of another included study- see primary study for details	Parent study: Marso et al (2016) Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. The New England journal of medicine; 2016; vol. 375 (no. 4); 311-22
Other publications associated with this study included in review	Marso et al (2013). Design of the liraglutide effect and action in diabetes: evaluation of cardiovascular outcome results (LEADER) trial. American heart journal; 2013; vol. 166 (no. 5); 823-30e5 Mann et al (2017) Liraglutide and Renal Outcomes in Type 2 Diabetes. The New England journal of medicine; 2017; vol. 377 (no. 9); 839-848
Trial name / registration number	LEADER trial. ClinicalTrials.gov number, NCT01179048
Study type	Randomised controlled trial (RCT)
Study location	See parent study
Study setting	See parent study
Study dates	See parent study
Sources of funding	See parent study
Inclusion criteria	See parent study
Exclusion criteria	See parent study
Recruitment / selection of participants	See parent study

Intervention(s)	Liraglutide N=4668 Subcutaneous injection liraglutide 1.8mg once daily in addition to standard care. Concomitant therapy: Standard care targeted an HbA1c <7.0% (individualised depending on the person). If >7.0%, addition HbA1c measurement after 3 month, if still at that point treatment should be intensified. The therapy included lifestyle modifications and metformin that was considered foundational in most countries. Add-on therapy included: thiazolidinediones, sulfonylureas, alpha glucosidase inhibitors for intensification according to local labels (DPP-IV and other incretin-based therapies are not allowed). Insulin therapy should be based on local practice, including basal, basal/bolus, premix and mealtime bolus. Blood pressure target 130/80mmHg. Antihypertensive therapy: first line of ACE inhibitors or ARBs, based on the person's needs: calcium channel blockers, diuretics and others. Lipids: target LDL: <100mg/dL (<70mg/dL in people with previous cardiovascular events). Statins recommended for all people. Second-line therapy at the investigator's discretion. Antiplatelet therapy: Aspirin or clopidogrel (if aspirin intolerant) for people with previous cardiovascular events (MI, CVA or revascularisation).
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure
Strata 2: People with atherosclerotic cardiovascular disease	Mixed population
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	People at higher risk of developing cardiovascular disease
Subgroup 1: People with	Not stated/unclear

moderate or severe frailty	
Subgroup 2: Onset of type 2 diabetes mellitus	People with type 2 diabetes first diagnosed above 40 years of age
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	People with obesity
Subgroup 5: eGFR category at baseline	eGFR ≥30mL/min/1.73m2
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	Within study analyses of participants with history of heart failure at baseline (~18%), and those without history of heart failure at baseline
Comparator	Placebo N=4672 Subcutaneous injection matching placebo once daily in addition to standard care. Concomitant therapy: Standard care targeted an HbA1c <7.0% (individualised depending on the person). If >7.0%, addition HbA1c measurement after 3 month, if still at that point treatment should be intensified. The therapy included lifestyle modifications and metformin that was considered foundational in most countries. Add-on therapy included: thiazolidinediones, sulfonylureas, alpha glucosidase inhibitors for intensification according to local labels (DPP-IV and other incretin-based therapies are not allowed). Insulin therapy should be based on local practice, including basal, basal/bolus, premix and mealtime bolus. Blood pressure target 130/80mmHg. Antihypertensive therapy: first line of ACE inhibitors or ARBs, based on the person's needs: calcium channel blockers, diuretics and others. Lipids: target LDL: <100mg/dL (<70mg/dL in people with previous cardiovascular events). Statins recommended for all people. Second-line therapy at the investigator's discretion. Antiplatelet therapy: Aspirin or clopidogrel (if aspirin intolerant) for people with previous cardiovascular events (MI, CVA or revascularisation).
Number of participants	9340

Duration of follow-up	FUP 3.5-5 years, median 3.8 years
Indirectness	See parent study
Method of analysis	ITT
Additional comments	Analysis used full analysis set and a Cox regression model with treatment, HF history and the interaction between these variables as covariates.

292.2. Study arms

292.2.1. Liraglutide (N = 4668)

Subcutaneous injection liraglutide 1.8mg once daily in addition to standard care. Concomitant therapy: Standard care targeted an HbA1c <7.0% (individualised depending on the person). If >7.0%, addition HbA1c measurement after 3 month, if still at that point treatment should be intensified. The therapy included lifestyle modifications and metformin that was considered foundational in most countries. Add-on therapy included: thiazolidinediones, sulfonylureas, alpha glucosidase inhibitors for intensification according to local labels (DPP-IV and other incretin-based therapies are not allowed). Insulin therapy should be based on local practice, including basal, basal/bolus, premix and mealtime bolus. Blood pressure target 130/80mmHg. Antihypertensive therapy: first line of ACE inhibitors or ARBs, based on the person's needs: calcium channel blockers, diuretics and others. Lipids: target LDL: <100mg/dL (<70mg/dL in people with previous cardiovascular events). Statins recommended for all people. Second-line therapy at the investigator's discretion. Antiplatelet therapy: Aspirin or clopidogrel (if aspirin intolerant) for people with previous cardiovascular events (MI, CVA or revascularisation).

292.2.2. Placebo (N = 4672)

Subcutaneous injection matching placebo once daily in addition to standard care. Concomitant therapy: Standard care targeted an HbA1c <7.0% (individualised depending on the person). If >7.0%, addition HbA1c measurement after 3 month, if still at that point treatment should be intensified. The therapy included lifestyle modifications and metformin that was considered foundational in most countries. Add-on therapy included: thiazolidinediones, sulfonylureas, alpha glucosidase inhibitors for intensification according to local labels (DPP-IV and other incretin-based therapies are not allowed). Insulin therapy should be based on local practice, including basal, basal/bolus, premix and mealtime bolus. Blood pressure target 130/80mmHg. Antihypertensive therapy: first line of ACE inhibitors or ARBs, based on the person's needs: calcium channel blockers, diuretics and others. Lipids: target LDL: <100mg/dL (<70mg/dL in people with previous cardiovascular events). Statins recommended for all people. Second-line therapy at the investigator's discretion.

Antiplatelet therapy: Aspirin or clopidogrel (if aspirin intolerant) for people with previous cardiovascular events (MI, CVA or revascularisation).

293. Marso Steven, 2016

Bibliographic Reference	Marso Steven, P; Bain Stephen, C; Consoli, Agostino; Eliaschewitz Freddy, G; Jodar, Esteban; Leiter Lawrence, A; Lingvay, Ildiko; Rosenstock, Julio; Seufert, Jochen; Warren Mark, L; Woo, Vincent; Hansen, Oluf; Holst Anders, G; Pettersson, Jonas; Vilsboll, Tina; SUSTAIN-6, Investigators; Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes.; The New England journal of medicine; 2016; vol. 375 (no. 19); 1834-1844

293.1. Study details

Secondary publication of another included study- see primary study for details	This is the primary publication for the SUSTAIN-6 trial.
Other publications associated with this study included in review	Jodar, E, Michelsen, M, Polonsky, W et al. (2020) Semaglutide improves health-related quality of life versus placebo when added to standard of care in patients with type 2 diabetes at high cardiovascular risk (SUSTAIN 6). Diabetes, Obesity and Metabolism 22(8): 1339-1347
Trial name / registration number	SUSTAIN-6 / NCT01720446
Study type	Randomised controlled trial (RCT) Randomised double-blind placebo controlled parallel-group trial
Study location	230 sites in 20 countries Countries planned to participate as per protocol: Algeria, Argentina, Australia, Brazil, Bulgaria, Canada, Denmark, Germany, India, Israel, Italy, Malaysia, Mexico, Poland, Russia, Spain, Taiwan, Thailand, Turkiye, UK, USA.
Study setting	No additional information
Study dates	Participants were screened for recruitment February - December 2013. Last visit date was 15 March 2026.

Sources of funding	Novo Nordisk
Inclusion criteria	Participants with type 2 diabetes and HbA1c level of 7% or more. Antidiabetic drug naïve, or treated with one or two oral antidiabetic drug(s), or treated with human Neutral Protamine Hagedorn (NPH) insulin or long-acting insulin analogue or pre-mixed insulin, both types of insulin either alone or in combination with one or two oral antidiabetic drug(s) Age 50 years or more with established cardiovascular disease (previous cardiovascular, cerebrovascular, or peripheral vascular disease), chronic heart failure (New York Heart Association class II or III), or chronic kidney disease of stage 3 or higher. Age of 60 years or more with at least one cardiovascular risk factor.
Exclusion criteria	Type 1 diabetes. Treatment with a DPP-4 inhibitor within 30 days before screening or with a GLP-1–receptor agonist or insulin other than basal or premixed within 90 days before screening. Treatment with insulin, other than basal and pre-mixed, within 90 days prior to screening (except for short-term use). Acute decompensation of glycemic control requiring immediate intensification of treatment to prevent acute complications of diabetes (e.g. diabetes ketoacidosis) within 90 days prior to screening. History of chronic pancreatitis or idiopathic acute pancreatitis. History of acute coronary or cerebrovascular event within 90 days before randomisation. Planned revascularisation of a coronary, carotid, or peripheral artery. Chronic heart failure class IV. Long-term dialysis. End-stage liver disease. Prior or awaiting solid organ transplant. Malignant neoplasm in previous 5 years (excluding basal or squamous cell skin cancer). Personal or family history of multiple endocrine neoplasia type 2 or familial medullary thyroid carcinoma. Personal history of non-familial medullary thyroid carcinoma. Screening calcitonin ≥50ng/l. Any acute condition or exacerbation of chronic condition deemed by investigators to interfere with initial trial visits and procedures. Know / suspected hypersensitivity to trial products. Known use of non-prescribed narcotics or illicit drugs. Previous participation in the trial. Simultaneous participation in another clinical trial of another investigational agent (except for investigational stents). Receipt of any investigational medicinal product within 30 days according to local requirements. (Brazil - receipt of any investigational drug with one year prior to screening, could be waived at investigators discretion). Pregnancy / planned pregnancy, breast-feeding or non-use of contraception.
Recruitment / selection of participants	Randomisation was stratified according to CV disease status (established CVD or CKD, or cardiovascular risk factors only), insulin treatment (none, basal insulin only, or premixed insulin) and eGFR (≤30 ml or >30 ml per minute per 1.73 m2 of body-surface area) (12 strata in total).
Intervention(s)	Semaglutide 0.5 mg N=826

	Semaglutide 0.5 mg subcutaneous injection once per week. Fixed-dose escalation regimen. Starting dose of 0.25 mg for 4 weeks, then escalated to 0.5 mg. Treatment period = 104 weeks. Semaglutide 1.0 mg N=822 Semaglutide 1.0 mg subcutaneous injection once per week. Fixed-dose escalation regimen. Starting dose of 0.25 mg for 4 weeks. Escalated to 0.5 mg for 4 weeks, then escalated to 1.0 mg. Treatment period = 104 weeks. Semaglutide 0.5mg and 1.0mg combined N=1648
Cointervention	Additional non-investigational antihyperglycaemic medication (non-incretin-based therapy) could be added or adjusted.
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Subgroup analysis within study shows that 573/3297 (17.4%) had CHF class II-II, and 2724/3297 (82.6%) did not have class II/III (class IV was excluded from the trial). For the purpose of this review, we are accepting information on CHF by New York Heart Association (NYHA) class II-IV to allocate to heart failure strata. Overall >80% did not have CHF class II/III, therefore allocated to 'people without HF' stratum (see protocol cut-off rule). This also aligns with the subgroup analysis data from this trial, which will be used for the outcome of 3-item MACE to provide data for our population strata. However, the trial also reports within the baseline characteristics that 23.6% had a history of heart failure. Due to the availability of the subgroup analysis, the above proportions based on the presence of class II/III CHF have been used for allocation to the population stratum (but it should be noted that there may be additional people with heart failure but without clinical symptoms).
Strata 2: People with atherosclerotic cardiovascular disease	Mixed population Recruited "age of 50 years or more with established cardiovascular disease (previous cardiovascular, cerebrovascular, or peripheral vascular disease), chronic heart failure (New York Heart Association class II or III), or chronic kidney disease of stage 3 or higher or an age of 60 years or more with at least one cardiovascular risk factor" 1940 patients (58.8%) had established CVD without CKD, 442 (13.4%) had both CVD and CKD (therefore 2382 (72.2%) had CVD in total (<80% protocol cut-off rule) - also, by trial definition of established cardiovascular diseases, this could also include people with heart failure alone).
Strata 3: People with	Mixed population

type 2 diabetes mellitus and chronic kidney disease	Overall 28.5% participants with eGFR below 60 ml/min/1.73 m2. 353 (10.7%) had CKD only, 442 (13.4%) had both CVD and CKD (therefore 795 (24.1%) had CKD in total).
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	People at higher risk of developing cardiovascular disease Participants were aged 50 + with history of CV disease, or 60+ with one or more CV risk factors (see inclusion criteria). Overall 92.8% with hypertension.
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 People with end-stage liver disease were excluded (see appendix)
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	eGFR ≥30mL/min/1.73m2 baseline characteristics show that only 3.3% were <30ml/min/1.73m2
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	For primary composite outcome only (3 item MACE - death from cardiovascular causes, nonfatal MI or nonfatal stroke) for the following baseline characteristics: sex, age (<65 years/≥ 65 years), BMI (≤ 30kg/m²/>30kg/m²), HbA1c (≤8.5%/>8.5%), duration of diabetes (≤10 years/<10 years), region (USA/EU/rest of world), race (Asian, Black/African-American/White/Other), ethnicity (Hispanic or Latino/ not Hispanic or Latino), chronic heart failure NY Heart Association class II-III), prior MI/stroke, CV disease status (established CV disease/CV risk factors), insulin treatment (pre-mixed

	/basal/none), eGFR <30 ml/min/1.73² (MDRD), eGFR <60 ml/min/1.73² (MDRD) MDRD=modification of diet in renal disease
Comparator	Placebo 0.5 mg N=824 Volume-matched placebo. 0.5 mg subcutaneous injection once weekly. Starting dose of 0.25 mg for 4 weeks, then escalated to 0.5 mg for 4 weeks. Treatment period = 104 weeks. Placebo 1.0 mg N=825 Volume-matched placebo. 1.0 mg subcutaneous injection once per week. Starting dose of 0.25 mg for 4 weeks. Escalated to 0.5 mg for 4 weeks, then escalated to 1.0 mg. Treatment period = 104 weeks. Placebo 0.5mg and 1.0mg combined N=1649
Number of participants	3297
Duration of follow-up	104 week treatment period with 5 week follow up. Median observation time was 2.1 years.
Indirectness	No additional information.
Method of analysis	ITT
Additional comments	All results analysed using ITT, except for adverse events leading to premature treatment discontinuation, which were included in the as-treated safety analysis.

293.2. Study arms

293.2.1. Semaglutide 0.5 mg (N = 826)

Semaglutide 0.5 mg subcutaneous injection once per week. Fixed-dose escalation regimen. Starting dose of 0.25 mg for 4 weeks, then escalated to 0.5 mg. Treatment period = 104 weeks. Concomitant treatment: additional non-investigational antihyperglycaemic medication (non-incretin-based therapy) could be added or adjusted.

293.2.2. Semaglutide 1.0 mg (N = 822)

Semaglutide 1.0 mg subcutaneous injection once per week. Fixed-dose escalation regimen. Starting dose of 0.25 mg for 4 weeks. Escalated to 0.5 mg for 4 weeks, then escalated to 1.0 mg. Treatment period = 104 weeks. Concomitant treatment: additional non-investigational antihyperglycaemic medication (non-incretin-based therapy) could be added or adjusted.

293.2.3. Placebo 0.5 mg (N = 824)

Volume-matched placebo. 0.5 mg subcutaneous injection once weekly. Starting dose of 0.25 mg for 4 weeks, then escalated to 0.5 mg for 4 weeks. Treatment period = 104 weeks. Concomitant treatment: additional non-investigational antihyperglycaemic medication (non-incretin-based therapy) could be added or adjusted.

293.2.4. Placebo 1.0 mg (N = 825)

Volume-matched placebo. 1.0 mg subcutaneous injection once per week. Starting dose of 0.25 mg for 4 weeks. Escalated to 0.5 mg for 4 weeks, then escalated to 1.0 mg. Treatment period = 104 weeks. Concomitant treatment: additional non-investigational antihyperglycaemic medication (non-incretin-based therapy) could be added or adjusted.

293.2.5. Semaglutide 0.5mg and 1.0mg combined (N = 1648)

293.2.6. Placebo 0.5mg and 1.0mg combined (N = 1649)

293.3. Characteristics

293.3.1. Arm-level characteristics

Characteristic	Semaglutide 0.5 mg (N = 826)	Semaglutide 1.0 mg (N = 822)	Placebo 0.5 mg (N = 824)	Placebo 1.0 mg (N = 825)	Semaglutide 0.5mg and 1.0mg combined (N = 1648)	Placebo 0.5mg and 1.0mg combined (N = 1649)
% Male Sample size	n = 495 ; % = 59.9	n = 518 ; % = 63	n = 482 ; % = 58.5	n = 507 ; % = 61.5	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Semaglutide 0.5 mg (N = 826)	Semaglutide 1.0 mg (N = 822)	Placebo 0.5 mg (N = 824)	Placebo 1.0 mg (N = 825)	Semaglutide 0.5mg and 1.0mg combined (N = 1648)	Placebo 0.5mg and 1.0mg combined (N = 1649)
Mean age (SD) (years) Mean (SD)	64.6 (7.3)	64.7 (7.1)	64.8 (7.6)	64.4 (7.5)	NA (NA)	NA (NA)
Ethnicity Ethnicity and race Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Ethnicity: Hispanic or Latino Sample size	n = 132 ; % = 16	n = 124 ; % = 15.1	n = 117 ; % = 14.2	n = 510 ; % = 15.5	n = NA ; % = NA	*empty data*
Ethnicity: not Hispanic or Latino Sample size	n = 694 ; % = 84	n = 698 ; % = 84.9	n = 707 ; % = 85.8	n = 688 ; % = 83.4	n = NA ; % = NA	n = NA ; % = NA
Race: white Sample size	n = 693 ; % = 83.9	n = 691 ; % = 84.1	n = 676 ; % = 82	n = 676 ; % = 81.9	n = NA ; % = NA	n = NA ; % = NA
Race: Black or African American Sample size	n = 54 ; % = 6.5	n = 54 ; % = 6.6	n = 54 ; % = 6.6	n = 59 ; % = 7.2	n = NA ; % = NA	n = NA ; % = NA
Race: Asian Sample size	n = 63 ; % = 7.6	n = 58 ; % = 7.1	n = 80 ; % = 9.7	n = 72 ; % = 8.7	n = NA ; % = NA	n = NA ; % = NA
Race: Other Sample size	n = 16 ; % = 1.9	n = 19 ; % = 2.3	n = 14 ; % = 1.7	n = 18 ; % = 2.2	n = NA ; % = NA	n = NA ; % = NA
Comorbidities Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Ischaemic heart disease Sample size	n = 493 ; % = 59.7	n = 495 ; % = 60.2	n = 510 ; % = 61.9	n = 496 ; % = 60.1	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Semaglutide 0.5 mg (N = 826)	Semaglutide 1.0 mg (N = 822)	Placebo 0.5 mg (N = 824)	Placebo 1.0 mg (N = 825)	Semaglutide 0.5mg and 1.0mg combined (N = 1648)	Placebo 0.5mg and 1.0mg combined (N = 1649)
Myocardial infarction Sample size	n = 266 ; % = 32.2	n = 264 ; % = 32.1	n = 267 ; % = 32.4	n = 275 ; % = 33.3	n = NA ; % = NA	n = NA ; % = NA
Heart failure Sample size	n = 201 ; % = 24.3	n = 180 ; % = 21.9	n = 190 ; % = 23.1	n = 206 ; % = 25	n = NA ; % = NA	n = NA ; % = NA
Ischaemic stroke Sample size	n = 89 ; % = 10.8	n = 89 ; % = 10.8	n = 96 ; % = 11.7	n = 109 ; % = 13.2	n = NA ; % = NA	n = NA ; % = NA
Heamorrhagic stroke Sample size	n = 28 ; % = 3.4	n = 24 ; % = 2.9	n = 27 ; % = 3.3	n = 29 ; % = 3.5	n = NA ; % = NA	n = NA ; % = NA
Hypertension Sample size	n = 772 ; % = 93.5	n = 771 ; % = 93.8	n = 756 ; % = 91.7	n = 760 ; % = 92.1	n = NA ; % = NA	n = NA ; % = NA
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NA ; % = NA	n = NA ; % = NA
Time since type 2 diabetes diagnosed (years) Mean (SD)	14.3 (8.2)	14.1 (8.2)	14 (8.5)	13.2 (7.4)	NA (NA)	NA (NA)
HbA1c (%) Mean (SD)	8.7 (1.4)	8.7 (1.5)	8.7 (1.5)	8.7 (1.5)	NA (NA)	NA (NA)
Blood pressure (mmHg) Mean (SD)	NA (NA)	NA (NA)	NA (NA)	NA (NA)	NA (NA)	NA (NA)
Systolic blood pressure Mean (SD)	136.1 (18)	135.8 (17)	135.8 (16.2)	134.8 (17.5)	NA (NA)	NA (NA)

Characteristic	Semaglutide 0.5 mg (N = 826)	Semaglutide 1.0 mg (N = 822)	Placebo 0.5 mg (N = 824)	Placebo 1.0 mg (N = 825)	Semaglutide 0.5mg and 1.0mg combined (N = 1648)	Placebo 0.5mg and 1.0mg combined (N = 1649)
Diastolic blood pressure Mean (SD)	77.1 (9.8)	76.9 (10.2)	77.5 (9.9)	76.7 (10.2)	NA (NA)	NA (NA)
Heart rate (beats per minute) Mean (SD)	72.7 (11.22)	71.5 (10.86)	72 (10.62)	72 (10.92)	NA (NA)	NA (NA)
Smoking status Never smoked Sample size	n = 390 ; % = 47.2	n = 364 ; % = 44.3	n = 391 ; % = 47.5	n = 348 ; % = 42.2	n = NA ; % = NA	n = NA ; % = NA
Alcohol consumption Mean (SD)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Weight (kg) Mean (SD)	91.8 (20.3)	92.9 (21.1)	91.8 (20.3)	91.9 (20.8)	NA (NA)	NA (NA)
BMI Mean (SD)	32.7 (6.29)	32.9 (6.18)	32.9 (6.35)	32.7 (5.97)	NA (NA)	NA (NA)
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Semaglutide 0.5 mg (N = 826)	Semaglutide 1.0 mg (N = 822)	Placebo 0.5 mg (N = 824)	Placebo 1.0 mg (N = 825)	Semaglutide 0.5mg and 1.0mg combined (N = 1648)	Placebo 0.5mg and 1.0mg combined (N = 1649)
Cholesterol and lipid levels (mg/dL) Mean (SD)	NA (NA)	NA (NA)	NA (NA)	NA (*empty data*)	NA (NA)	NA (NA)
LDL cholesterol Geometric mean and coefficient of variation Mean (SD)	81.6 (47.1)	83.3 (41.2)	80.9 (48.1)	83.6 (48.1)	NA (NA)	NA (NA)
HDL cholesterol Geometric mean and coefficient of variation Mean (SD)	44.2 (27.76)	43.4 (26.9)	44.2 (27.3)	43.1 (26.3)	NA (NA)	NA (NA)
Albumin creatinine ratio Mean (SD)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)
eGFR mL/min/1.73m2 Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Normal eGFR ≥90 Sample size	n = 247 ; % = 29.9	n = 246 ; % = 29.9	n = 245 ; % = 29.7	n = 252 ; % = 30.5	n = NA ; % = NA	n = NA ; % = NA
Mild renal impairment eGFR 60 - <90 Sample size	n = 329 ; % = 39.8	n = 357 ; % = 43.4	n = 336 ; % = 40.8	n = 346 ; % = 41.9	n = NA ; % = NA	n = NA ; % = NA
Moderate renal impairment eGFR 30 - <60 Sample size	n = 229 ; % = 27.7	n = 194 ; % = 23.6	n = 215 ; % = 26.1	n = 194 ; % = 23.5	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Semaglutide 0.5 mg (N = 826)	Semaglutide 1.0 mg (N = 822)	Placebo 0.5 mg (N = 824)	Placebo 1.0 mg (N = 825)	Semaglutide 0.5mg and 1.0mg combined (N = 1648)	Placebo 0.5mg and 1.0mg combined (N = 1649)
Severe renal impairment eGFR 15 - <30 Sample size	n = 20 ; % = 2.4	n = 21 ; % = 2.6	n = 25 ; % = 3	n = 29 ; % = 3.5	n = NA ; % = NA	n = NA ; % = NA
Endstage renal disease eGFR <15 Sample size	n = 1 ; % = 0.1	n = 4 ; % = 0.5	n = 3 ; % = 0.4	n = 4 ; % = 0.5	n = NA ; % = NA	n = NA ; % = NA
Other antidiabetic medication used Sample size	n = 817 ; % = 98.9	n = 808 ; % = 98.3	n = 806 ; % = 97.8	n = 814 ; % = 98.7	n = NA ; % = NA	n = NA ; % = NA
Insulin (all types) Basal insulin, basal+bolus/premix insulin, bolus insulin Sample size	n = 479 ; % = 58	n = 477 ; % = 58	n = 478 ; % = 58	n = 479 ; % = 58.1	n = NA ; % = NA	n = NA ; % = NA
Basal insulin Sample size	n = 256 ; % = 31	n = 259 ; % = 31.5	n = 259 ; % = 31.4	n = 272 ; % = 33	n = NA ; % = NA	n = NA ; % = NA
Basal+bolus insulin / premix Sample size	n = 223 ; % = 27	n = 218 ; % = 26.5	n = 219 ; % = 26.6	n = 207 ; % = 25.1	n = NA ; % = NA	n = NA ; % = NA
Bolus insulin Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA
Non-insulin glucose-lowering medication (all types) Alpha glucosidase inhibitors, biguanides, combination therapy, DPP-4 inhibitors, meglitinides,	n = 695 ; % = 84.1	n = 684 ; % = 83.2	n = 696 ; % = 84.5	n = 701 ; % = 85	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Semaglutide 0.5 mg (N = 826)	Semaglutide 1.0 mg (N = 822)	Placebo 0.5 mg (N = 824)	Placebo 1.0 mg (N = 825)	Semaglutide 0.5mg and 1.0mg combined (N = 1648)	Placebo 0.5mg and 1.0mg combined (N = 1649)
SGLT-2, sulfonylureas, thiazolidinedione Sample size						
Alpha-glucosidase inhibitors Sample size	n = 9 ; % = 1.1	n = 7 ; % = 0.9	n = 16 ; % = 1.9	n = 10 ; % = 1.2	n = NA ; % = NA	n = NA ; % = NA
Biguanides Sample size	n = 617 ; % = 74.7	n = 594 ; % = 72.3	n = 586 ; % = 71.1	n = 617 ; % = 74.8	n = NA ; % = NA	n = NA ; % = NA
DPP-4 inhibitor DPP-4 was an exclusion criterion - patients randomised in error Sample size	n = 1 ; % = 0.1	n = 2 ; % = 0.2	n = 2 ; % = 0.2	n = 0 ; % = 0	n = NA ; % = NA	n = NA ; % = NA
Meglitinides Sample size	n = 25 ; % = 3	n = 23 ; % = 2.8	n = 24	n = 15 ; % = 1.8	n = NA ; % = NA	n = NA ; % = NA
SGLT2 inhibitor Sample size	n = 0 ; % = 0	n = 1 ; % = 0.1	n = 2 ; % = 0.2	n = 2 ; % = 0.2	n = NA ; % = NA	n = NA ; % = NA
Sulfonylurea Sample size	n = 349 ; % = 42.3	n = 349 ; % = 42.5	n = 363 ; % = 44.1	n = 349 ; % = 42.3	n = NA ; % = NA	n = NA ; % = NA
Thiazolidinedione Sample size	n = 14 ; % = 1.7	n = 21 ; % = 2.6	n = 18 ; % = 2.2	n = 23 ; % = 2.8	n = NA ; % = NA	n = NA ; % = NA
Glucose-lowering combination therapy Fixed-dose combination Sample size	n = 1 ; % = 0.1	n = 1 ; % = 0.1	n = 0 ; % = 0	n = 1 ; % = 0.1	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Semaglutide 0.5 mg (N = 826)	Semaglutide 1.0 mg (N = 822)	Placebo 0.5 mg (N = 824)	Placebo 1.0 mg (N = 825)	Semaglutide 0.5mg and 1.0mg combined (N = 1648)	Placebo 0.5mg and 1.0mg combined (N = 1649)
Blood pressure-lowering medication used Sample size	n = 773 ; % = 97.6	n = 809 ; % = 98.4	n = 809 ; % = 98.2	n = 810 ; % = 98.2	n = NA ; % = NA	n = NA ; % = NA
Beta-blockers Sample size	n = 475 ; % = 57.5	n = 459 ; % = 55.8	n = 475 ; % = 57.6	n = 485 ; % = 58.8	n = NA ; % = NA	n = NA ; % = NA
Calcium-channel blockers Sample size	n = 273 ; % = 33.1	n = 246 ; % = 29.9	n = 266 ; % = 32.3	n = 270 ; % = 32.7	n = NA ; % = NA	n = NA ; % = NA
ACE inhibitors Sample size	n = 420 ; % = 50.8	n = 409 ; % = 49.8	n = 402 ; % = 48.8	n = 411 ; % = 49.8	n = NA ; % = NA	n = NA ; % = NA
Angiotensin-receptor blockers Sample size	n = 274 ; % = 33.2	n = 274 ; % = 33.3	n = 266 ; % = 32.3	n = 297 ; % = 36	n = NA ; % = NA	n = NA ; % = NA
Other antihypertensives Sample size	n = 63 ; % = 7.6	n = 60 ; % = 7.3	n = 67 ; % = 8.1	n = 68 ; % = 8.2	n = NA ; % = NA	n = NA ; % = NA
Statins/lipid-lowering medication used Sample size	n = 634 ; % = 76.8	n = 629 ; % = 76.5	n = 618 ; % = 75	n = 640 ; % = 77.6	n = NA	n = NA ; % = NA
Statins Sample size	n = 600 ; % = 72.6	n = 599 ; % = 72.9	n = 590 ; % = 71.6	n = 610 ; % = 73.9	n = NA ; % = NA	n = NA ; % = NA
Ezetimibe Sample size	n = 32 ; % = 3.9	n = 31 ; % = 3.8	n = 34 ; % = 4.1	n = 32 ; % = 3.9	n = NA	n = NA ; % = NA
Other lipid-lowering drugs Sample size	n = 94 ; % = 11.4	n = 95 ; % = 11.6	n = 68 ; % = 8.3	n = 100 ; % = 12.1	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Semaglutide 0.5 mg (N = 826)	Semaglutide 1.0 mg (N = 822)	Placebo 0.5 mg (N = 824)	Placebo 1.0 mg (N = 825)	Semaglutide 0.5mg and 1.0mg combined (N = 1648)	Placebo 0.5mg and 1.0mg combined (N = 1649)
Other treatment being received Diuretics Sample size	n = 318 ; % = 38.5	n = 306 ; % = 37.2	n = 306 ; % = 37.1	n = 330 ; % = 40	n = NA ; % = NA	n = NA ; % = NA
Loop diuretics Sample size	n = 146 ; % = 17.7	n = 134 ; % = 16.3	n = 133 ; % = 16.1	n = 143 ; % = 17.3	n = NA ; % = NA	n = NA ; % = NA
Thiazides Sample size	n = 114 ; % = 13.8	n = 119 ; % = 14.5	n = 107 ; % = 13	n = 129 ; % = 15.6	n = NA ; % = NA	n = NA ; % = NA
Thiazide-like diuretics Sample size	n = 60 ; % = 7.3	n = 58 ; % = 7.1	n = 61 ; % = 7.4	n = 55 ; % = 6.7	n = NA ; % = NA	n = NA ; % = NA
Aldosterone antagonists Sample size	n = 52 ; % = 6.3	n = 45 ; % = 5.5	n = 55 ; % = 6.7	n = 42 ; % = 5.1	n = NA ; % = NA	*empty data*
Other treatment being received Anti-thrombotic treatment Sample size	n = 625 ; % = 75.7	n = 627 ; % = 76.3	n = 625 ; % = 75.8	n = 637 ; % = 77.2	n = NA ; % = NA	n = NA ; % = NA
Vitamin K agonists Sample size	n = 48 ; % = 5.8	n = 40 ; % = 4.9	n = 40 ; % = 4.9	n = 36 ; % = 4.4	n = NA ; % = NA	n = NA ; % = NA
Direct thrombin inhibitors Sample size	n = 5 ; % = 0.6	n = 4 ; % = 0.5	n = 4 ; % = 0.5	n = 5 ; % = 0.6	n = NA ; % = NA	n = NA ; % = NA
Direct factor Xa inhibitors Sample size	n = 2 ; % = 0.2	n = 1 ; % = 0.1	n = 9 ; % = 1.1	n = 1 ; % = 0.1	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Semaglutide 0.5 mg (N = 826)	Semaglutide 1.0 mg (N = 822)	Placebo 0.5 mg (N = 824)	Placebo 1.0 mg (N = 825)	Semaglutide 0.5mg and 1.0mg combined (N = 1648)	Placebo 0.5mg and 1.0mg combined (N = 1649)
ADP receptor inhibitors excluding acetylsalicyclic acid Sample size	n = 175 ; % = 21.2	n = 164 ; % = 20	n = 168 ; % = 20.4	n = 189 ; % = 22.9	n = NA ; % = NA	n = NA ; % = NA
Acetylsalicylic acid Sample size	n = 509 ; % = 61.6	n = 542 ; % = 65.9	n = 522 ; % = 63.3	n = 535 ; % = 64.8	n = NA ; % = NA	n = NA ; % = NA
SF-36 - Physical component summary Mean (SD)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	42.3 (NR)	41.4 (NR)
SF-36 - Mental component summary Mean (SD)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	47.9 (NR)	48.2 (NR)

294. Marso Steven, 2016

Bibliographic Reference	Marso Steven, P; Daniels Gilbert, H; Brown-Frandsen, Kirstine; Kristensen, Peter; Mann Johannes F, E; Nauck Michael, A; Nissen Steven, E; Pocock, Stuart; Poulter Neil, R; Ravn Lasse, S; Steinberg William, M; Stockner, Mette; Zinman, Bernard; Bergenstal Richard, M; Buse John, B; LEADER, Steering; Committee; LEADER, Trial; Investigators; Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes.; The New England journal of medicine; 2016; vol. 375 (no. 4); 311-22

294.1. Study details

Secondary publication of another included study- see primary study for details	This is the parent study of the LEADER trial - the primary data extraction is included in this record
Other publications associated with this study included in review	
Trial name / registration number	LEADER trial. ClinicalTrials.gov number, NCT01179048
Study type	Randomised controlled trial (RCT)
Study location	32 countries (Canada, USA, Mexico, Brazil, South Africa, Romania, Greece, Serbia, Italy, Austria, Spain, France, Ireland, United Kingdom, Belgium, Netherlands, Denmark, Norway, Sweden, Finland, Germany, Poland, Czech Rep, Russian Federation, China, India, Taiwan, South Korea, Australia, UAE, Turkey, Israel)
Study setting	410 sites - no further detail.
Study dates	Randomization from September 2010 through April 2012; The planned closeout of follow-up of the patients was from August 2014 through December 2015.
Sources of funding	Novo Nordisk and the National Institutes of Health
Inclusion criteria	People with type 2 diabetes who had a glycated haemoglobin level of 7.0% or more were eligible if they either had not received drugs for this condition previously or had been treated with one or more oral antihyperglycemic

	agents or insulin (human neutral protamine Hagedorn, long-acting analogue, or premixed) or a combination of these agents. The major inclusion criteria: an age of 50 years or more with at least one cardiovascular coexisting condition (coronary heart disease, cerebrovascular disease, peripheral vascular disease, chronic kidney disease of stage 3 or greater, or chronic heart failure of New York Heart Association class II or III) or an age of 60 years or more with at least one cardiovascular risk factor (investigator determined: microalbuminuria or proteinuria, hypertension and left ventricular hypertrophy, left ventricular systolic or diastolic dysfunction, or an ankle–brachial index of less than 0.9).
Exclusion criteria	Type 1 diabetes; the use of GLP-1 receptor agonists, DPP-4 inhibitors, pramlintide, or rapid-acting insulin; a familial or personal history of multiple endocrine neoplasia type 2 or medullary thyroid cancer; the occurrence of an acute coronary or cerebrovascular event within 14 days before screening and randomisation.
Recruitment / selection of participants	No additional information.
Intervention(s)	Liraglutide N=4668 Subcutaneous injection liraglutide 1.8mg once daily in addition to standard care. Concomitant therapy: Standard care targeted an HbA1c <7.0% (individualised depending on the person). If >7.0%, addition HbA1c measurement after 3 month, if still at that point treatment should be intensified. The therapy included lifestyle modifications and metformin that was considered foundational in most countries. Add-on therapy included: thiazolidinediones, sulfonylureas, alpha glucosidase inhibitors for intensification according to local labels (DPP-IV and other incretin-based therapies are not allowed). Insulin therapy should be based on local practice, including basal, basal/bolus, premix and mealtime bolus. Blood pressure target 130/80mmHg. Antihypertensive therapy: first line of ACE inhibitors or ARBs, based on the person's needs: calcium channel blockers, diuretics and others. Lipids: target LDL: <100mg/dL (<70mg/dL in people with previous cardiovascular events). Statins recommended for all people. Second-line therapy at the investigator's discretion. Antiplatelet therapy: Aspirin or clopidogrel (if aspirin intolerant) for people with previous cardiovascular events (MI, CVA or revascularisation).
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Excluded "Chronic heart failure (NYHA class IV)". 17.8% of people had heart failure I-III.
Strata 2: People with	Mixed population

atherosclerotic cardiovascular disease	Inclusion was history of CVD or CV risk factors. Majority had established cardiovascular disease (7598/9340 = 81.3%) - however, established CVD definition could include HF and CKD too, proportion with CVD alone likely to be <80% (2307 of these had CKD stage 3, with 1473 of these having both CKD and CVD, therefore 2307-1473=834 had CKD alone; therefore 7598-834=6764 had CVD (not including those with CKD alone); 6764/9340=72.4% likely to have CVD when definition doesn't include those with CKD alone).
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Baseline characteristics state 25% had chronic kidney disease but based on eGFR not CKD diagnosis.
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	People with type 2 diabetes first diagnosed above 40 years of age Most likely based on mean age and mean diabetes duration
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	People with obesity Mean BMI 32.5
Subgroup 5: eGFR category at baseline	eGFR ≥30mL/min/1.73m2 baseline characteristics show that only 2.4% were <30ml/min/1.73m2
Subgroup 6: Albuminuria	Not stated/unclear

category at baseline	
Population subgroups	No additional information.
Comparator	Placebo N=4672 Subcutaneous injection matching placebo once daily in addition to standard care. Concomitant therapy: Standard care targeted an HbA1c <7.0% (individualised depending on the person). If >7.0%, addition HbA1c measurement after 3 month, if still at that point treatment should be intensified. The therapy included lifestyle modifications and metformin that was considered foundational in most countries. Add-on therapy included: thiazolidinediones, sulfonylureas, alpha glucosidase inhibitors for intensification according to local labels (DPP-IV and other incretin-based therapies are not allowed). Insulin therapy should be based on local practice, including basal, basal/bolus, premix and mealtime bolus. Blood pressure target 130/80mmHg. Antihypertensive therapy: first line of ACE inhibitors or ARBs, based on the person's needs: calcium channel blockers, diuretics and others. Lipids: target LDL: <100mg/dL (<70mg/dL in people with previous cardiovascular events). Statins recommended for all people. Second-line therapy at the investigator's discretion. Antiplatelet therapy: Aspirin or clopidogrel (if aspirin intolerant) for people with previous cardiovascular events (MI, CVA or revascularisation).
Number of participants	9340
Duration of follow-up	Minimum follow-up period 42 months, median follow-up 3.8 years
Indirectness	Not downgraded for indirectness - 12% of people did not receive glucose lowering therapy before the trial.
Method of analysis	ITT
Additional comments	The primary and exploratory analyses for the outcomes in the time-to-event analyses were based on a Cox proportional-hazards model with treatment as a covariate

294.2. Study arms

294.2.1. Liraglutide (N = 4668)

Subcutaneous injection liraglutide 1.8mg once daily in addition to standard care. Concomitant therapy: Standard care targeted an HbA1c <7.0% (individualised depending on the person). If >7.0%, addition HbA1c measurement after 3 month, if

still at that point treatment should be intensified. The therapy included lifestyle modifications and metformin that was considered foundational in most countries. Add-on therapy included: thiazolidinediones, sulfonylureas, alpha glucosidase inhibitors for intensification according to local labels (DPP-IV and other incretin-based therapies are not allowed). Insulin therapy should be based on local practice, including basal, basal/bolus, premix and mealtime bolus. Blood pressure target 130/80mmHg. Antihypertensive therapy: first line of ACE inhibitors or ARBs, based on the person's needs: calcium channel blockers, diuretics and others. Lipids: target LDL: <100mg/dL (<70mg/dL in people with previous cardiovascular events). Statins recommended for all people. Second-line therapy at the investigator's discretion. Antiplatelet therapy: Aspirin or clopidogrel (if aspirin intolerant) for people with previous cardiovascular events (MI, CVA or revascularisation).

294.2.2. Placebo (N = 4672)

Subcutaneous injection matching placebo once daily in addition to standard care. Concomitant therapy: Standard care targeted an HbA1c <7.0% (individualised depending on the person). If >7.0%, addition HbA1c measurement after 3 month, if still at that point treatment should be intensified. The therapy included lifestyle modifications and metformin that was considered foundational in most countries. Add-on therapy included: thiazolidinediones, sulfonylureas, alpha glucosidase inhibitors for intensification according to local labels (DPP-IV and other incretin-based therapies are not allowed). Insulin therapy should be based on local practice, including basal, basal/bolus, premix and mealtime bolus. Blood pressure target 130/80mmHg. Antihypertensive therapy: first line of ACE inhibitors or ARBs, based on the person's needs: calcium channel blockers, diuretics and others. Lipids: target LDL: <100mg/dL (<70mg/dL in people with previous cardiovascular events). Statins recommended for all people. Second-line therapy at the investigator's discretion. Antiplatelet therapy: Aspirin or clopidogrel (if aspirin intolerant) for people with previous cardiovascular events (MI, CVA or revascularisation).

294.3. Characteristics

294.3.1. Arm-level characteristics

Characteristic	Liraglutide (N = 4668)	Placebo (N = 4672)
% Male Sample size	n = 3011 ; % = 64.5	n = 2992 ; % = 64
Mean age (SD) (years) Mean (SD)	64.2 (7.2)	64.4 (7.2)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Liraglutide (N = 4668)	Placebo (N = 4672)
Comorbidities Sample size	n = NA ; % = NA	n = NA ; % = NA
Heart failure Sample size	n = 835 ; % = 17.9	n = 832 ; % = 17.8
Prior myocardial infarction Sample size	n = 1464 ; % = 31.4	n = 1400 ; % = 30
Prior stroke or transient ischaemic attack Sample size	n = 730 ; % = 15.6	n = 777 ; % = 16.6
Prior revascularisation Sample size	n = 1835 ; % = 39.3	n = 1803 ; % = 38.6
>50% stenosis of coronary, carotid or lower extremity arteries Sample size	n = 1188 ; % = 25.4	n = 1191 ; % = 25.5
Documented symptomatic coronary heart disease Sample size	n = 412 ; % = 8.8	n = 406 ; % = 8.7
Documented asymptomatic cardiac ischaemic Sample size	n = 1241 ; % = 26.6	n = 1231 ; % = 26.3
NYHA II-III Sample size	n = 653 ; % = 14	n = 652 ; % = 14
Chronic kidney disease Sample size	n = 1185 ; % = 25.4	n = 1122 ; % = 24
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	12.8 (8)	12.9 (8.1)
Cardiovascular risk factors Sample size	n = 837 ; % = 17.9	n = 905 ; % = 19.4
Cardiovascular risk factors Mean (SD)	NA (NA)	NA (NA)

Characteristic	Liraglutide (N = 4668)	Placebo (N = 4672)
Microalbuminuria or proteinuria Sample size	n = 501 ; % = 10.7	n = 558 ; % = 11.9
Microalbuminuria or proteinuria Mean (SD)	NA (NA)	NA (NA)
Hypertension and left ventricular hypertrophy Sample size	n = 248 ; % = 5.3	n = 251 ; % = 5.4
Hypertension and left ventricular hypertrophy Mean (SD)	NA (NA)	NA (NA)
Left ventricular systolic or diastolic dysfunction Sample size	n = 203 ; % = 4.3	n = 191 ; % = 4.1
Left ventricular systolic or diastolic dysfunction Mean (SD)	NA (NA)	NA (NA)
Ankle-brachial index <0.9 Sample size	n = 110 ; % = 2.4	n = 116 ; % = 2.5
Ankle-brachial index <0.9 Mean (SD)	NA (NA)	NA (NA)
Systolic blood pressure mmHg Sample size	n = NA ; % = NA	n = NA ; % = NA
Systolic blood pressure mmHg Mean (SD)	135.9 (17.8)	135.9 (17.7)
Diastolic blood pressure mmHg Sample size	n = NA ; % = NA	n = NA ; % = NA
Diastolic blood pressure mmHg Mean (SD)	77.2 (10.3)	77 (10.1)
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Liraglutide (N = 4668)	Placebo (N = 4672)
Alcohol consumption Sample size	n = NA ; % = NA	n = NA ; % = NA
Presence of severe mental illness Sample size	n = NA ; % = NA	n = NA ; % = NA
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR
Weight Mean (SD)	NR (NR)	NR (NR)
BMI (kg/m2) Mean (SD)	32.5 (6.3)	32.5 (6.3)
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR
Albumin creatinine ratio Mean (SD)	NR (NR)	NR (NR)
eGFR mL/min/1.73m2 Sample size	n = NR ; % = NR	n = NR ; % = NR
Normal (eGFR >90) Sample size	n = 1620 ; % = 34.7	n = 1655 ; % = 35.4
Mild impairment (eGFR 60-89) Sample size	n = 1932 ; % = 41.4	n = 1975 ; % = 42.3
Moderate impairment (eGFR 30-59) Sample size	n = 999 ; % = 21.4	n = 935 ; % = 20
Severe impairment (eGFR <30) Sample size	n = 117 ; % = 2.5	n = 107 ; % = 2.3
Other antidiabetic medication used Sample size	n = 4113 ; % = 88.1	n = 4129 ; % = 88.4

Characteristic	Liraglutide (N = 4668)	Placebo (N = 4672)
Metformin Sample size	n = 3540 ; % = 75.8	n = 3604 ; % = 77.1
Sulfonylureas Sample size	n = 2370 ; % = 50.8	n = 2363 ; % = 50.6
Alpha glucosidase inhibitors Sample size	n = 139 ; % = 3	n = 123 ; % = 2.6
Thiazolidinedione Sample size	n = 296 ; % = 6.3	n = 279 ; % = 6
DPP4 inhibitors Sample size	n = 4 ; % = 0.1	n = 2 ; % = 0.1
GLP-1 receptor agonist Sample size	n = 0 ; % = 0	n = 2 ; % = 0.1
SGLT2 inhibitors Sample size	n = NA ; % = NA	n = NA ; % = NA
Glinides Sample size	n = 178 ; % = 3.8	n = 172 ; % = 3.7
Others Sample size	n = 0 ; % = 0	n = 1 ; % = 0.1
Insulin Sample size	n = 2038 ; % = 43.7	n = 2131 ; % = 45.6
Premix insulin Sample size	n = 445 ; % = 9.5	n = 463 ; % = 9.9
Short acting insulin Sample size	n = 42 ; % = 0.9	n = 26 ; % = 0.6
Intermediate acting insulin Sample size	n = 547 ; % = 11.7	n = 600 ; % = 12.8
Long acting insulin Sample size	n = 1041 ; % = 22.3	n = 1077 ; % = 23.1
Other insulins	n = 23 ; % = 0.5	n = 14 ; % = 0.3

Characteristic	Liraglutide (N = 4668)	Placebo (N = 4672)
Sample size		
Blood pressure-lowering medication used Sample size	n = 4329 ; % = 92.7	n = 4303 ; % = 92.1
Beta blockers Sample size	n = 2652 ; % = 56.8	n = 2529 ; % = 54.1
Calcium channel blockers Sample size	n = 1538 ; % = 32.9	n = 1479 ; % = 31.7
ACE inhibitors Sample size	n = 2417 ; % = 51.8	n = 2350 ; % = 50.3
Angiotensin receptor blockers Sample size	n = 1488 ; % = 31.9	n = 1486 ; % = 31.8
Renin inhibitors Sample size	n = 42 ; % = 0.9	n = 40 ; % = 0.9
Others Sample size	n = 468 ; % = 10	n = 454 ; % = 9.7
Diuretics Sample size	n = 1953 ; % = 41.8	n = 1953 ; % = 41.8
Loop diuretics Sample size	n = 824 ; % = 17.7	n = 837 ; % = 17.9
Thiazide diuretics Sample size	n = 829 ; % = 17.8	n = 788 ; % = 16.9
Thiazide-like diruetics Sample size	n = 325 ; % = 7	n = 355 ; % = 7.6
Aldosterone antagonists Sample size	n = 254 ; % = 5.4	n = 251 ; % = 5.4
Statins/lipid-lowering medication used Sample size	n = 3564 ; % = 76.3	n = 3515 ; % = 75.2
Statins Sample size	n = 3405 ; % = 72.9	n = 3336 ; % = 71.4

Characteristic	Liraglutide (N = 4668)	Placebo (N = 4672)
Ezetimibe Sample size	n = 165 ; % = 3.5	n = 169 ; % = 3.6
Fibrates Sample size	n = 412 ; % = 8.8	n = 432 ; % = 9.2
Niacin Sample size	n = 95 ; % = 2	n = 95 ; % = 2
Other lipid lowering drugs Sample size	n = 8 ; % = 0.2	n = 14 ; % = 0.3
Other treatment being received Sample size	n = NA ; % = NA	n = NA ; % = NA
Platelet aggregation inhibitors Sample size	n = 3205 ; % = 68.7	n = 3121 ; % = 66.8
Acetylsalicylic acid Sample size	n = 2977 ; % = 63.8	n = 2899 ; % = 62.1
Clopidogrel, Ticlopidine, Prasugrel, Ticagrelor Sample size	n = 720 ; % = 15.4	n = 745 ; % = 15.9
Other anti-thrombotic drugs Sample size	n = 314 ; % = 6.7	n = 327 ; % = 7

295. Marso, 2013

Bibliographic Reference	Marso, Steven P; Poulter, Neil R; Nissen, Steven E; Nauck, Michael A; Zinman, Bernard; Daniels, Gilbert H; Pocock, Stuart; Steinberg, William M; Bergenstal, Richard M; Mann, Johannes F E; Ravn, Lasse Steen; Frandsen, Kirstine Brown; Moses, Alan C; Buse, John B; Design of the liraglutide effect and action in diabetes: evaluation of cardiovascular outcome results (LEADER) trial.; American heart journal; 2013; vol. 166 (no. 5); 823-30e5

295.1. Study details

Secondary publication of another included study- see primary study for details	Parent study: Marso et al (2016) Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. The New England journal of medicine; 2016; vol. 375 (no. 4); 311-22
Other publications associated with this study included in review	Marso et al (2020) Effects of Liraglutide on Cardiovascular Outcomes in Patients With Diabetes With or Without Heart Failure. Journal of the American College of Cardiology; 2020; vol. 75 (no. 10); 1128-1141 Mann et al (2017) Liraglutide and Renal Outcomes in Type 2 Diabetes. The New England journal of medicine; 2017; vol. 377 (no. 9); 839-848
Trial name / registration number	LEADER trial. ClinicalTrials.gov number, NCT01179048

296. Marx, 2015

Bibliographic Reference	Marx, Nikolaus; Rosenstock, Julio; Kahn, Steven E; Zinman, Bernard; Kastelein, John J; Lachin, John M; Espeland, Mark A; Bluhmki, Erich; Mattheus, Michaela; Ryckaert, Bart; Patel, Sanjay; Johansen, Odd Erik; Woerle, Hans-Juergen; Design and baseline characteristics of the CARdiovascular Outcome Trial of LINAgliptin Versus Glimepiride in Type 2 Diabetes (CAROLINA R).; Diabetes & vascular disease research; 2015; vol. 12 (no. 3); 164-74

296.1. Study details

Secondary publication of another included study- see primary study for details	CAROLINA trial. Primary publication: Rosenstock, J, Kahn S, E, Johansen O, E et al. (2019) Effect of Linagliptin vs Glimepiride on Major Adverse Cardiovascular Outcomes in Patients with Type 2 Diabetes: The CAROLINA Randomized Clinical Trial. JAMA - Journal of the American Medical Association 322(12): 1155-1166
Other publications associated with this study included in review	NA
Trial name / registration number	CAROLINA/ NCT01243424

297. Mathieu, 2016

Bibliographic Reference	Mathieu, C.; Herrera Marmolejo, M.; Gonzalez Gonzalez, J. G.; Hansen, L.; Chen, H.; Johnsson, E.; Garcia-Sanchez, R.; Iqbal, N.; Efficacy and safety of triple therapy with dapagliflozin add-on to saxagliptin plus metformin over 52 weeks in patients with type 2 diabetes; Diabetes Obes Metab; 2016; vol. 18 (no. 11); 1134-1137

297.1. Study details

Secondary publication of another included study- see primary study for details	Mathieu 2015 Mathieu C, Ranetti AE, Li D, Ekholm E, Cook W, Hirshberg B, Chen H, Hansen L, Iqbal N. Randomized, Double-Blind, Phase 3 Trial of Triple Therapy With Dapagliflozin Add-on to Saxagliptin Plus Metformin in Type 2 Diabetes. Diabetes Care. 2015 Nov;38(11):2009-17. doi: 10.2337/dc15-0779. Epub 2015 Aug 5. PMID: 26246458.
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

298. Mathieu, 2014

Bibliographic Reference	Mathieu, C.; Rodbard, H. W.; Cariou, B.; Handelsman, Y.; Philis-Tsimikas, A.; Ocampo Francisco, A. M.; Rana, A.; Zinman, B.; A comparison of adding liraglutide versus a single daily dose of insulin aspart to insulin degludec in subjects with type 2 diabetes (BEGIN: VICTOZA ADD-ON); Diabetes Obes Metab; 2014; vol. 16 (no. 7); 636-644

298.1. 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	Multicenter trial.
Study setting	Outpatient follow-up.
Study dates	September 2011-July 2012.
Sources of funding	Sponsored by Novo Nordisk A/S.
Inclusion criteria	Informed consent; completed the end-of-treatment visit of trial NN1250-3643 with insulin degludec once daily and metformin; ability and willingness to adhere to the protocol including self-measurement of plasma glucose according to the protocol.
Exclusion criteria	Known or suspected hypersensitivity to trial product(s) or related products; previous participation in the trial; participated in NN1250-3643 and was treated with insulin glargine + metformin +/- DPP-4 inhibitor or insulin degludec + metformin + DPP-4 inhibitor; previous treatment with GLP-1 receptor agonist; impaired liver function (ALT at least 2.5 times the upper limit of normal at the end of treatment in NN1250-3643); impaired renal

	function (definition varied but generally at least serum creatinine 125 micromol/L for males, at least 110 micromol/L for females and includes GFR <60mL/min for people in France); proliferative retinopathy or maculopathy; stroke, NYHA class III-IV heart failure, myocardial infarction, unstable angina, coronary arterial bypass graft or angioplasty within the last 24 weeks prior to visit 1; recurrent severe hypoglycaemia (>1 severe event in the past 12 months) or hypoglycaemic unawareness as judged by the investigator); uncontrolled or untreated severe hypertension (systolic at least 180mmHg, diastolic at least 100mmHg); life-threatening disease (for example: cancer); females of childbearing potential who were pregnant, breast-feeding or intended to become pregnant or were not using adequate contraceptive methods; known or suspected abuse of alcohol, narcotics or illicit drugs.
Recruitment / selection of participants	People were included after completing a previous trial (NN1250-3643) if they were in the arm that received insulin degludec and metformin.
Intervention(s)	Insulin degludec/liraglutide N=88 Liraglutide 0.6mg/day increased to 1.2mg/day after 1 week and maintained until week 5. Then if the mean of three pre-breakfast FPG values were at least 5.0mmol/L, then it was increased to 1.8mg/day. From week 6 onward, if the pre-breakfast mean was at least 5.0mmol/L, either Lira could be increased to 1.8mg/day or the insulin degludec dose could be increased. Everyone continued insulin degludec as per the previous trial with the dose being titrated according to pre-breakfast plasma glucose levels. Treatments were received for 24 weeks.
Cointervention	All people received metformin throughout the trial.
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure NYHA III-IV in the exclusion criteria. Therefore, probably people with symptomatic heart failure.
Strata 2: People with atherosclerotic cardiovascular disease	People without atherosclerotic cardiovascular diseases Exclusion criteria for people with stroke, myocardial infarction, unstable angina pectoris, coronary arterial bypass graft or angioplasty within the last 24 weeks prior to visit 1.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Exclusion criteria for people with creatinine and eGFR, but not specifically people with CKD.
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	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	People without non-alcoholic fatty liver disease Based on exclusion criteria
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 degludec/insulin aspart N=89 Insulin aspart was started at 4 U once a day before the largest daily meal. Insulin aspart was titrated once weekly based on the mean of three pre-meal or bedtime SMBG values. Everyone continued insulin degludec as per the previous trial with the dose being titrated according to pre-breakfast plasma glucose levels. Treatments were received for 24 weeks. A third arm (n=236) received insulin degludec only. This arm was not included in this data extraction and analysis as the arm was a non-randomised treatment arm.

Number of participants	177 (randomised).
Duration of follow-up	24 weeks.
Indirectness	No additional information.
Method of analysis	ACA Safety analysis set - people exposed to insulin degludec + liraglutide or insulin degludec + insulin aspart. ITT Full analysis set - all randomised participants
Additional comments	No additional information.

298.2. Study arms

298.2.1. Insulin degludec/liraglutide (N = 88)

Liraglutide 0.6mg/day increased to 1.2mg/day after 1 week and maintained until week 5. Then if the mean of three pre-breakfast FPG values were at least 5.0mmol/L, then it was increased to 1.8mg/day. From week 6 onward, if the pre-breakfast mean was at least 5.0mmol/L, either Lira could be increased to 1.8mg/day or the insulin degludec dose could be increased. Everyone continued insulin degludec as per the previous trial with the dose being titrated according to pre-breakfast plasma glucose levels. Treatments were received for 24 weeks. Concomitant therapy: All people received metformin throughout the trial.

298.2.2. Insulin degludec/insulin aspart (N = 89)

Insulin aspart was started at 4 U once a day before the largest daily meal. Insulin aspart was titrated once weekly based on the mean of three pre-meal or bedtime SMBG values. Everyone continued insulin degludec as per the previous trial with the dose being titrated according to pre-breakfast plasma glucose levels. Treatments were received for 24 weeks. Concomitant therapy: All people received metformin throughout the trial.

298.3. Characteristics

298.3.1. Arm-level characteristics

Characteristic	Insulin degludec/liraglutide (N = 88)	Insulin degludec/insulin aspart (N = 89)
% Male Sample size	n = 63 ; % = 71.6	n = 53 ; % = 59.6
Mean age (SD) (years) Mean (SD)	61.1 (9.5)	60.9 (8.8)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Asian, American Indian or Alaskan native Sample size	n = 2 ; % = 2.3	n = 2 ; % = 2.2
Black Sample size	n = 6 ; % = 6.8	n = 3 ; % = 3.4
White Sample size	n = 79 ; % = 89.8	n = 83 ; % = 93.3
Other Sample size	n = 1 ; % = 1.1	n = 1 ; % = 1.1
Comorbidities Sample size	n = NA ; % = NA	n = NA ; % = NA
Diabetic neuropathy Sample size	n = 11 ; % = 12.5	n = 5 ; % = 5.6
Diabetic retinopathy Sample size	n = 3 ; % = 3.4	n = 3 ; % = 3.4
Microalbuminuria Sample size	n = 2 ; % = 2.3	n = 1 ; % = 1.1
Diabetic nephropathy Sample size	n = 1 ; % = 1.1	n = 1 ; % = 1.1
Presence of frailty Sample size	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Insulin degludec/liraglutide (N = 88)	Insulin degludec/insulin aspart (N = 89)
Time since type 2 diabetes diagnosed (years) Mean (SD)	12.9 (6.4)	11.8 (6.5)
Cardiovascular risk factors Sample size	n = NA ; % = NA	n = NA ; % = NA
Smoking status Sample size	n = NA ; % = NA	n = NA ; % = NA
Alcohol consumption Sample size	n = NA ; % = NA	n = NA ; % = NA
Presence of severe mental illness Sample size	n = NA ; % = NA	n = NA ; % = NA
People with significant cognitive impairment Sample size	n = NA ; % = NA	n = NA ; % = NA
People with a learning disability Sample size	n = NA ; % = NA	n = NA ; % = NA
Number of people with obesity Sample size	n = NA ; % = NA	n = NA ; % = NA
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
1 OAD at screening of main trial (metformin) Sample size	n = 21 ; % = 23.9	n = 10 ; % = 11.2
2 OADs at screening of main trial Sample size	n = 61 ; % = 69.3	n = 65 ; % = 73
3 OADs at screening of main trial	n = 6 ; % = 6.8	n = 14 ; % = 15.7

Characteristic	Insulin degludec/liraglutide (N = 88)	Insulin degludec/insulin aspart (N = 89)
Sample size		
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

299. Mathieu, 2015

Bibliographic Reference	Mathieu, C.; Shankar, R. R.; Lorber, D.; Umpierrez, G.; Wu, F.; Xu, L.; Golm, G. T.; Latham, M.; Kaufman, K. D.; Engel, S. S.; A randomized clinical trial to evaluate the efficacy and safety of co-administration of sitagliptin with intensively titrated insulin glargine; Diabetes Ther; 2015; vol. 6 (no. 2); 127-142

299.1. Study details

Trial name / registration number	NCT01462266
Study type	Randomised controlled trial (RCT)
Study location	Multicentre
Study setting	No additional information
Study dates	January 16 2012 and June 07 2013
Sources of funding	Merck & Co., Inc., Kenilworth, NJ, USA. A number of authors are employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. Additional authors declare funding and honoraria from multiple pharmaceutical companies
Inclusion criteria	Patients 18–80 years of age with type 2 diabetes. Patients who were diagnosed with type 2 diabetes at or after age 40 years were eligible if they had insulin therapy initiated at least 3 years after the diagnosis of diabetes. Patients diagnosed before age 40 years, or patients diagnosed after age 40 who had insulin initiated within 3 years of diagnosis, were also eligible if they had a fasting C-peptide (connecting-peptide) of [0.7 ng/mL. Patients on a stable dose of insulin glargine administered in the evening, with or without metformin (≤1500 mg/day) for ≤10 weeks and with inadequate glycemic control (defined as glycated hemoglobin [HbA1c] ≥7.5% [58.5 mmol/mol] and ≤11.0% [96.7 mmol/mol] at the screening visit) were eligible to begin single-blind placebo run-in at Week -2. Patients on a stable dose of insulin (pre-mixed insulin, or basal insulin other than insulin glargine given in the evening) with or without metformin for ≥10 weeks, with HbA1c ≥7.5% (58.5 mmol/mol) and ≤11.0% (96.7 mmol/mol) at the screening visit were eligible to begin single-blind placebo run-in after a 2-week period to switch and stabilize their insulin dose (to insulin glargine given in the evening). Patients who were on a stable dose of premixed or basal insulin with or without metformin for ≤10 weeks and were also receiving a sulfonylurea,

	with HbA1c ≥7.5% (58.5 mmol/mol) and ≤10.0% (85.8 mmol/mol) at the screening visit were also eligible to begin the single-blind placebo run-in after a 2-week period to wash-off the sulfonylurea, switch to insulin glargine and stabilize the dose if necessary (i.e., for those who were not on insulin glargine given in the evening). At the start of the single-blind placebo run-in, all patients were required to have FPG ≥7.2 mmol/L (130 mg/dL) and ≤15.0 mmol/L (270 mg/dL). Patient is not of reproductive potential or is of reproductive potential and agrees to remain abstinent or use (or have their partner use) an acceptable method of birth control within the projected duration of the study and for 14 days after the last dose of study medication.
Exclusion criteria	Patients with type 1 diabetes, a history of ketoacidosis, active liver disease, significant and active cardiovascular disease, malignancy, hematological disorders or hyperthyroidism. Patients treated with a DPP-4 inhibitor, a glucagon-like peptide-1 receptor agonist or a thiazolidinedione within the 12 weeks prior to randomization. Patients currently being treated with the daily use of pre-prandial, short-acting or rapid-acting insulin alone, or as part of a basal/bolus insulin regimen. Patients with a history of two or more episodes of hypoglycemia resulting in seizure, coma, loss of consciousness, or with recurrent (C3 times per week) episodes of hypoglycemia during the 8 weeks preceding randomization. Patients with a history of intolerance or hypersensitivity to sitagliptin, insulin, or metformin or any contraindication to sitagliptin, insulin, or metformin based upon the label of the country of the investigational site. Patients on or likely to require treatment for ≥2 consecutive weeks or repeated courses of pharmacologic doses of corticosteroids. Patients undergone a surgical procedure within 4 weeks prior to signing informed consent or has planned major surgery during the study. Patients currently participating, or have participated, in a study in which the patient received an investigational compound or used an investigational device within the prior 12 weeks of signing informed consent or is not willing to refrain from participating in another study. Patients on a weight loss program and not in the maintenance phase, or has started a weight loss medication or has undergone bariatric surgery within 12 months prior to signing the informed consent. Patients currently being treated for hyperthyroidism or patient is on thyroid hormone therapy and has not been on a stable dose for at least 6 weeks

	Patients with systolic blood pressure ≥160 mm Hg or a diastolic blood pressure ≥90 mm Hg. Patient may have blood pressure medication adjusted and may be enrolled if the patient's blood pressure no longer meets exclusion criteria. Patients with human immunodeficiency virus Patients with severe peripheral vascular disease Patients with clinically important hematological disorder (such as aplastic anemia, myeloproliferative or myelodysplastic syndromes, thrombocytopenia). Patients with a history of malignancy ≤5 years prior to signing informed consent, except for adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer. Laboratory exclusion criteria included serum creatinine C1.4 mg/dL (males) or C1.3 mg/dL (females), an estimated glomerular filtration rate <60 mL/min/1.73 m2 (calculated by modification of diet in renal disease equation), alanine aminotransferase or aspartate aminotransferase >2 times the upper limit of normal, hemoglobin <12 g/dL (male) or \11 g/ dL (female), triglycerides >600 mg/dL or thyroid-stimulating hormone outside the normal range
Recruitment / selection of participants	No additional information
Intervention(s)	Sitagliptin (n=329) Patients received 100 mg once daily sitagliptin as an oral tablet for 24 weeks
Cointervention	Insulin +/- metformin Open-label insulin glargine will be titrated in a treat-to target algorithm outlined in the protocol The dose of metformin will remain stable throughout the study period if patient was receiving metformin at Visit 1.
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	Not stated/unclear Exclusion criteria based on eGFR but no specific mention 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
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=329) Patients received the placebo as a single oral tablet for 24 weeks. Open-label insulin glargine will be titrated in a treat-to target algorithm outlined in the protocol The dose of metformin will remain stable throughout the study period if patient was receiving metformin at Visit 1.
Number of participants	660
Duration of follow-up	24 weeks
Indirectness	NA
Method of analysis	ITT
Additional comments	The population for all efficacy analyses consisted of all randomized patients who received at least one dose of study medication and had at least one measurement of the analysis endpoint at or after baseline. The primary efficacy endpoint, mean change from baseline in daily insulin dose at Week 24, was compared between the sitagliptin group and the placebo group using a longitudinal data analysis model with a constraint that both groups came from a single population with a common baseline mean. The model adjusted for the patients' use of metformin at the screening visit. Missing outcome data were handled implicitly by the model without the need for imputation. In the analysis model, the daily insulin dose for any given week was defined as the average dose from the three most recent days preceding the index date for that week. The continuous secondary endpoints of mean change from baseline in HbA1c at week 24 were analysed using a model analogous to that for the primary endpoint, including the time points of Weeks 0, 6, 12, 18, and 24.

299.2. Study arms

299.2.1. Sitagliptin (N = 330)

Patients received 100 mg sitagliptin once daily for 24 weeks

299.2.2. Placebo (N = 330)

Patients received once daily placebo

299.3. Characteristics

299.3.1. Arm-level characteristics

Characteristic	Sitagliptin (N = 330)	Placebo (N = 330)
% Male Sitagliptin n =329, Placebo n = 329 Sample size	n = 151 ; % = 45.9	n = 164 ; % = 49.8
Mean age (SD) (Years (mean, SD)) Sitagliptin n =329, Placebo n = 329 Mean (SD)	59.3 (8.9)	58.3 (9.7)
Ethnicity Sitagliptin n =329, Placebo n = 329 Sample size	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 238 ; % = 72.3	n = 220 ; % = 66.9
Multiracial Sample size	n = 36 ; % = 10.9	n = 54 ; % = 16.4
Asian Sample size	n = 32 ; % = 9.7	n = 34 ; % = 10.3
Black Sample size	n = 18 ; % = 5.5	n = 9 ; % = 2.7
Native American or Alaska Native Sample size	n = 5 ; % = 1.5	n = 12 ; % = 3.6
Time since type 2 diabetes diagnosed (Years (mean, SD)) Sitagliptin n =329, Placebo n = 329 Mean (SD)	13.2 (6)	13.7 (6.4)
Smoking status Sitagliptin n =329, Placebo n = 329 Sample size	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Sitagliptin (N = 330)	Placebo (N = 330)
Alcohol consumption Sitagliptin n =329, Placebo n = 329 Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Sitagliptin n =329, Placebo n = 329 Sample size	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sitagliptin n =329, Placebo n = 329 Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sitagliptin n =329, Placebo n = 329 Sample size	n = NR ; % = NR	n = NR ; % = NR
Other antidiabetic medication used Sitagliptin n =329, Placebo n = 329 Sample size	n = NA ; % = NA	n = NA ; % = NA
Prior Metformin use Sample size	n = 195 ; % = 68.4	n = 189 ; % = 66.8
Prior Metformin plus sulfonylurea use Sample size	n = 90 ; % = 31.6	n = 94 ; % = 33.2
Prior sulfonoylurea use Sample size	n = 5 ; % = 11.4	n = 6 ; % = 13
Insulin Sample size	n = 329 ; % = 100	n = 329 ; % = 100
Blood pressure-lowering medication used Sitagliptin n =329, Placebo n = 329 Sample size	n = NR ; % = NR	n = NR ; % = NR
Statins/lipid-lowering medication used Sitagliptin n =329, Placebo n = 329 Sample size	n = NR ; % = NR	n = NR ; % = NR
Other treatment being received Sitagliptin n =329, Placebo n = 329 Sample size	n = NR ; % = NR	n = NR ; % = NR

300. Mathieu, 2015

Bibliographic Reference	Mathieu, Chantal; Ranetti, Aurelian Emil; Li, Danshi; Ekholm, Ella; Cook, William; Hirshberg, Boaz; Chen, Hungta; Hansen, Lars; Iqbal, Nayyar; Randomized, Double-Blind, Phase 3 Trial of Triple Therapy With Dapagliflozin Add-on to Saxagliptin Plus Metformin in Type 2 Diabetes.; Diabetes care; 2015; vol. 38 (no. 11); 2009-17

300.1. Study details

Secondary publication of another included study- see primary study for details	
Other publications associated with this study included in review	Mathieu C, Herrera Marmolejo M, González González JG, Hansen L, Chen H, Johnsson E, Garcia-Sanchez R, Iqbal N. Efficacy and safety of triple therapy with dapagliflozin add-on to saxagliptin plus metformin over 52 weeks in patients with type 2 diabetes. Diabetes Obes Metab. 2016 Nov;18(11):1134-1137. doi: 10.1111/dom.12737. Epub 2016 Aug 19. PMID: 27385192.
Trial name / registration number	NCT01646320
Study type	Randomised controlled trial (RCT)
Study location	Multicentre
Study setting	No additional information
Study dates	The first patient visit was 21 September 2012 and the last patient visit was 7 August 2014
Sources of funding	This study was funded by Bristol-Myers Squibb and AstraZeneca. Medical writing support for the preparation of the manuscript was provided by Richard Edwards, PhD, and Janet Matsuura, PhD, from Complete Healthcare Communications, Inc. (Chadds Ford, PA), with funding from AstraZeneca Numerous authors declare funding and honoraria from multiple pharmaceutical companies
Inclusion criteria	Two groups of patients (≥18 years of age) with type 2 diabetes and inadequate glycemic control were included in the open-label treatment period based on DPP-4 inhibitor use.

	Patients in stratum A had HbA1c level of 8.0–11.5% (64–102 mmol/mol) at screening and were receiving stable metformin therapy (immediate release [IR] or extended release [XR] ≥1,500 mg/day) for at least 8 weeks before screening. These patients were switched to the nearest lower or higher multiple of metformin IR 500-mg tablets and saxagliptin 5 mg/day for 16 weeks of open-label treatment. Patients in stratum B had an HbA1c level of 7.5–10.5% (58–91 mmol/mol) and were receiving stable metformin (IR or XR ≥1,500 mg/day) and a DPP-4 inhibitor at the maximum approved dose for at least 8 weeks before the screening visit. For inclusion in the 24-week double blind treatment period, patients in both stratum A and B had to have an HbA1c level of 7.0–10.5% (53–91 mmol/mol) when assessed at week 22.
Exclusion criteria	Major exclusion criteria for screening and the open-label treatment period included pregnancy, cardiovascular events within 3 months of screening, an estimated glomerular filtration rate of ,60 mL/min/1.73 m2 or a serum creatinine level of $1.5 mg/dL in men or $1.4 mg/dL in women, microscopic hematuria with no known cause in men, and significant hepatic disease. Patients were also excluded if they received any antidiabetes medication, other than metformin and DPP-4 inhibitors, for .14 days during the 12 weeks before screening
Recruitment / selection of participants	No additional information
Intervention(s)	Dapagliflozin (n=160) Patients received dapagliflozin 10 mg/ day for 52 weeks
Cointervention	Saxagliptin + Metformin Patients also received 5 mg saxagliptin per day plus ≥1500 mg metformin per day
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Cardiovascular events in the 3 months before screening but not explicit on what this means
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Cardiovascular events in the 3 months before screening but not explicit on what this means
Strata 3: People with	Not stated/unclear

type 2 diabetes mellitus and chronic kidney disease	Exclusion criteria based on eGFR and serum creatinine but no explicit mention on 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
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=160) Patients receive daily placebo as an addon to 5 mg sitagliptin daily and ≥1500 mg metformin daily for 52 weeks

Number of participants	320
Duration of follow-up	24 weeks with an extension up to 52 weeks
Indirectness	NA
Method of analysis	ITT
Additional comments	The primary efficacy data set included all randomized patients who received one or more doses of study medication during the double-blind treatment period. The primary efficacy analysis was performed using a longitudinal repeated-measures analysis with terms for baseline value, treatment group, time, stratum, the interaction of treatment group and time, and the interaction of baseline value and time, including only observations made before rescue. Point estimates and 95% CIs were calculated for the adjusted mean changes within each treatment group and for the differences in adjusted mean changes between treatment groups

300.2. Study arms

300.2.1. Dapagliflozin (N = 160)

Patients received 10 mg Dapagliflozin as add on therapy to Saxagliptin plus Metformin for 52 weeks

300.2.2. Placebo (N = 160)

Patients received placebo as an add on to Saxagliptin plus Metformin for 52 weeks

300.3. Characteristics

300.3.1. Arm-level characteristics

Characteristic	Dapagliflozin (N = 160)	Placebo (N = 160)
% Male Sample size	n = 70 ; % = 43.7	n = 76 ; % = 47.5
Mean age (SD) (Years (mean, SD)) Mean (SD)	55.2 (8.6)	55 (9.6)

Characteristic	Dapagliflozin (N = 160)	Placebo (N = 160)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 150 ; % = 93.8	n = 147 ; % = 91.9
African-American Sample size	n = 8 ; % = 5	n = 10 ; % = 6.3
Asian Sample size	n = 1 ; % = 0.6	n = 1 ; % = 0.6
Other Sample size	n = 1 ; % = 0.6	n = 2 ; % = 1.3
Time since type 2 diabetes diagnosed (Years (mean, SD)) Mean (SD)	7.2 (5.7)	8 (6.6)
Smoking status Sample size	n = NA ; % = NA	n = NA ; % = NA
Alcohol consumption Sample size	n = NA ; % = NA	n = NA ; % = NA
Presence of severe mental illness Sample size	n = NA ; % = NA	n = NA ; % = NA
People with significant cognitive impairment Sample size	n = NA ; % = NA	n = NA ; % = NA
People with a learning disability Sample size	n = NA ; % = NA	n = NA ; % = NA
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Sitagliptin + Metformin Sample size	n = 160 ; % = 100	n = 160 ; % = 100
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR

301. Matthaei, 2015

Bibliographic Reference	Matthaei, S.; Bowering, K.; Rohwedder, K.; Grohl, A.; Parikh, S.; Study, Group; Dapagliflozin improves glycemic control and reduces body weight as add-on therapy to metformin plus sulfonylurea: a 24-week randomized, double-blind clinical trial; Diabetes Care; 2015; vol. 38 (no. 3); 365-72

301.1. 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	Matthaei, S; Bowering, K; Rohwedder, K; Sugg, J; Parikh, S; Johnsson, E. Durability and tolerability of dapagliflozin over 52 weeks as add-on to metformin and sulphonylurea in type 2 diabetes.Diabetes, obesity & metabolism; 2015; vol. 17 (no. 11); 1075-84.
Trial name / registration number	NCT01392677
Study type	Randomised controlled trial (RCT)
Study location	North America (Canada) and Europe (Czech Republic, Germany, Poland, Slovak Republic, and Spain)
Study setting	No additional information.
Study dates	10/2011 - 08/2013
Sources of funding	Bristol-Myers Squibb and AstraZeneca
Inclusion criteria	Men and women who were not of childbearing potential (defined as women who were postmenopausal or who were permanently or surgically sterilized) or women of childbearing potential using a highly effective method of birth control and a negative pregnancy test 72 h prior to the start of medication and at each visit were eligible to enter the study. Patients were at least 18 years of age, had a diagnosis of type 2 diabetes, were receiving a stable-dose combination therapy of metformin ≥1,500 mg/day and a maximum tolerated dose (at least half the maximum dose according to local use) of sulfonylurea for at least 8 weeks prior to enrolment, and had inadequate glycemic control (HbA1c ≥7.0 % [53 mmol/mol] to ≤10.5% [91 mmol/ mol] at randomisation).

Exclusion criteria	Patients were excluded from the study if they had a diagnosis of type 1 diabetes, BMI ≥45.0 kg/m2 , measured serum creatinine value of ≥1.5 mg/dL (133 mmol/L) for men or ≥1.4 mg/dL (124 mmol/L) for women, unstable or rapidly progressing renal disease, cardiovascular events within 2 months prior to enrolment, congestive heart failure (New York Heart Association Class IV), systolic BP (SBP) ≥160 mmHg, or diastolic BP (DBP) ≥100 mmHg at randomisation.
Recruitment / selection of participants	Participants were
Intervention(s)	Dapagliflozin 10 mg daily Administered orally.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Excluded "congestive heart failure (New York Heart Association Class IV)", otherwise unclear. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Baseline characteristics show around 86% had a prior history of CV disease (not further defined), however, a subsequent paper Grandy 2016 states that this included hypertension.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Excluded "unstable or rapidly progressing renal disease", otherwise unclear. 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	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	
Comparator	Placebo daily Administered orally.
Number of participants	N=219
Duration of follow-up	24-week + 28-week extension with results reported in the subsidiary paper.
Indirectness	
Method of analysis	ITT

301.2. Study arms

301.2.1. Dapagliflozin 10 mg daily (N = 109)

Administered orally

301.2.2. Placebo (N = 109)

Administered orally

301.3. Characteristics

301.3.1. Arm-level characteristics

Characteristic	Dapagliflozin 10 mg daily (N = 109)	Placebo (N = 109)
% Male No of events	n = 46 ; % = 42.6	n = 60 ; % = 56
Mean age (SD) (years) Mean (SD)	61.1 (9.7)	60.9 (9.2)
White No of events	n = 104 ; % = 96.3	n = 102 ; % = 94.4
Prior history of cardiovascular disease No of events	n = 91 ; % = 84.3	n = 95 ; % = 88
Presence of frailty Nominal	NR	NR
Smoking status Nominal	NR	NR
Alcohol consumption Nominal	NR	NR
Presence of severe mental illness Nominal	NR	NR
People with significant cognitive impairment Nominal	NR	NR
People with a learning disability Nominal	NR	NR
Number of people with obesity Nominal	NR	NR
Metformin + Sulfonylurea No of events	n = 108 ; % = 100	n = 108 ; % = 100

Characteristic	Dapagliflozin 10 mg daily (N = 109)	Placebo (N = 109)
Thiazide diuretics No of events	n = 30 ; % = 27.5	n = 29 ; % = 26.6
Antihypertensives No of events	n = 89 ; % = 81.7	n = 95 ; % = 87.2
Angiotensin-receptor blockers and/or ACEi No of events	n = 75 ; % = 68.8	n = 83 ; % = 76.1

302. Matthaei, 2015

Bibliographic Reference	Matthaei, S.; Catrinoiu, D.; Celinski, A.; Ekholm, E.; Cook, W.; Hirshberg, B.; Chen, H.; Iqbal, N.; Hansen, L.; Randomized, double-blind trial of triple therapy with saxagliptin add-on to dapagliflozin plus metformin in patients with type 2 diabetes; Diabetes Care; 2015; vol. 38 (no. 11); 2018-24

302.1. 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	Matthaei, S; Aggarwal, N; Garcia-Hernandez, P; Iqbal, N; Chen, H; Johnsson, E; Chin, A; Hansen, L. One-year efficacy and safety of saxagliptin add-on in patients receiving dapagliflozin and metformin. Diabetes, obesity & metabolism; 2016; vol. 18 (no. 11); 1128-1133.
Trial name / registration number	NCT01619059
Study type	Randomised controlled trial (RCT)
Study location	US Puerto Rico Canada Romania Russia Poland Czech Republic Mexico Hungary
Study setting	No additional information.

Study dates	06/2012 - 06/2014
Sources of funding	Bristol-Myers Squibb and Astra Zeneca
Inclusion criteria	Patients with type 2 diabetes with glycated hemoglobin (HbA1c) 8.0–11.5% (64–102 mmol/mol) at screening and taking stable metformin immediate release (IR) or extended release (XR) (≥1,500 mg/day) for ≥8 weeks before screening were included. Eligible patients also had to have a C-peptide concentration ≥1.0 ng/mL and BMI ≤45.0 kg/m2 .
Exclusion criteria	Major exclusion criteria for screening and the open-label treatment period included pregnancy, cardiovascular disease within 3 months of screening, estimated glomerular filtration rate ,60 mL/min/ 1.73 m2 , or serum creatinine ≥1.5 mg/ dL in men or ≥1.4 mg/dL in women, microscopic hematuria with no known cause in men, and significant hepatic disease. Patients also were excluded if they received any antidiabetic medication other than metformin for more than 14 days during the 12 weeks before screening. Patients with uncontrolled hypertension (systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥100 mmHg) could enter the open-label period provided that their antihypertensive therapy was adjusted as appropriate. If their blood pressure remained at or above these limits, however, they could not be considered for randomization to double-blind treatment.
Recruitment / selection of participants	The study design consisted of a screening period and an open-label treatment period before randomization and a short-term (24 weeks), double-blind treatment period. Patients could then enter a long-term (28 weeks) extension, for a total of 52 weeks of triple-therapy treatment.
Intervention(s)	Saxagliptin 5 mg once daily; administered orally.
Cointervention	Dapagliflozin Metformin
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Exclusion criteria based on cardiovascular disease within 3 months but no statement of what this includes
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Exclusion criteria based on cardiovascular disease within 3 months but no statement of what this includes
Strata 3: People with type 2 diabetes mellitus and	Not stated/unclear Exclusion criteria based on eGFR and serum creatinine and based on microscopic haematuria but no statement on CKD explicitly

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
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	
Comparator	Placebo administered daily.
Number of participants	N=315
Duration of follow-up	24-week
Indirectness	

Method of analysis	Modified ITT
Additional comments	All patients who received at least one dose of study treatment were included in the efficacy analysis.

302.2. Study arms

302.2.1. Saxagliptin 5 mg daily (N = 153)

Administered orally

302.2.2. Placebo daily (N = 162)

Administered orally

302.3. Characteristics

302.3.1. Arm-level characteristics

Characteristic	Saxagliptin 5 mg daily (N = 153)	Placebo daily (N = 162)
% Male No of events	n = 73 ; % = 48	n = 76 ; % = 47
Mean age (SD) (years) Mean (SD)	54.7 (9.8)	54.5 (9.3)
White No of events	n = 136 ; % = 87	n = 141 ; % = 87
Black No of events	n = 11 ; % = 7.2	n = 9 ; % = 5.6
Asian No of events	n = 5 ; % = 3.3	n = 8 ; % = 4.9
Other No of events	n = 1 ; % = 0.7	n = 4 ; % = 2.5
Presence of frailty Nominal	NR	NR

Characteristic	Saxagliptin 5 mg daily (N = 153)	Placebo daily (N = 162)
Time since type 2 diabetes diagnosed (years) Mean (SD)	8.1 (7)	7.4 (5.8)
HbA1c (%) Mean (SD)	7.97 (0.83)	7.86 (0.93)
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)	88.1 (20)	87.9 (17.1)
BMI (kg/m2) Mean (SD)	31.4 (5.2)	31.4 (5.3)
Number of people with obesity Nominal	NR	NR
eGFR mL/min/1.73m2 Mean (SD)	92.8 (21.6)	93.9 (20.6)
Metformin + dapagliflozin No of events	n = 153 ; % = 100	n = 162 ; % = 100

303. Matthaei, 2016

Bibliographic Reference	Matthaei, S; Aggarwal, N; Garcia-Hernandez, P; Iqbal, N; Chen, H; Johnsson, E; Chin, A; Hansen, L; One-year efficacy and safety of saxagliptin add-on in patients receiving dapagliflozin and metformin.; Diabetes, obesity & metabolism; 2016; vol. 18 (no. 11); 1128-1133

303.1. Study details

Secondary publication of another included study- see primary study for details	Matthaei, S.; Catrinoiu, D.; Celinski, A.; Ekholm, E.; Cook, W.; Hirshberg, B.; Chen, H.; Iqbal, N.; Hansen, L. Randomized, double-blind trial of triple therapy with saxagliptin add-on to dapagliflozin plus metformin in patients with type 2 diabetes. Diabetes Care; 2015; vol. 38 (no. 11); 2018-24
Other publications associated with this study included in review	No additional information.
Trial name / registration number	NCT01619059
Study type	Randomised controlled trial (RCT)
Study location	
Sources of funding	
Inclusion criteria	Eligible patients were adults aged ≥18 years with T2D and inadequate glycaemic control (HbA1c 8–11.5% at screening), despite stable metformin therapy (≥1500 mg/day for at least 8 weeks before screening).

303.2. Study arms

303.2.1. Saxagliptin 5 mg daily (N = 153)

Administered orally

303.2.2. Placebo (N = 162)

Administered orally

304. Matthaei, 2015

Bibliographic Reference	Matthaei, S; Bowering, K; Rohwedder, K; Sugg, J; Parikh, S; Johnsson, E; Durability and tolerability of dapagliflozin over 52 weeks as add-on to metformin and sulphonylurea in type 2 diabetes.; Diabetes, obesity & metabolism; 2015; vol. 17 (no. 11); 1075-84

304.1. Study details

Secondary publication of another included study- see primary study for details	Parent study Matthaei 2015B
Study type	Randomised controlled trial (RCT)

305. Matthews, 2005

Bibliographic Reference	Matthews, D. R.; Charbonnel, B. H.; Hanefeld, M.; Brunetti, P.; Schernthaner, G.; Long-term therapy with addition of pioglitazone to metformin compared with the addition of gliclazide to metformin in patients with type 2 diabetes: a randomized, comparative study; Diabetes Metab Res Rev; 2005; vol. 21 (no. 2); 167-74

305.1. Study details

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	2-year efficacy results reported in: • Charbonnel, B., Schernthaner, G., Brunetti, P., Matthews, D. R., Urquhart, R., Tan, M. H., & Hanefeld, M. (2005). Long-term efficacy and tolerability of add-on pioglitazone therapy to failing monotherapy compared with addition of gliclazide or metformin in patients with type 2 diabetes. *Diabetologia*, *48*, 1093-1104. 2-year lipid/cholesterol results reported in: • Betteridge, D. J., & Verges, B. (2005). Long-term effects on lipids and lipoproteins of pioglitazone versus gliclazide addition to metformin and pioglitazone versus metformin addition to sulphonylurea in the treatment of type 2 diabetes. *Diabetologia*, *48*, 2477-2481.
Trial name / registration number	Not reported
Study type	Randomised controlled trial (RCT) Double-blind parallel-group RCTs
Study location	International (75 centres in Australia, Bulgaria, Czech Republic, France, Germany, Greece, Latvia, Poland, Romania, Turkey)
Study setting	Outpatient
Study dates	Dates not reported

Sources of funding	Takeda Europe R&D Centre and Eli Lilly and Company, USA
Inclusion criteria	• Aged 35-75 years • Diagnosis of type 2 diabetes • Diabetes inadequately managed with sulphonylurea monotherapy (≥50% maximal recommended dose or at maximal tolerated dose ≥3-mo) • Stable or worsening glycaemic control≥3-mo • HbA1c level 7.5-11% inclusive at screening • Fasting C-peptide≥1.5 ng/ml at screening • If female, postmenopausal or sterilized or using adequate contraception
Exclusion criteria	• Type 1 diabetes or ketoacidosis • History of myocardial infarction, transient ischemic attacks, or stroke in previous 6-mo • Symptomatic heart failure • Malabsorption or pancreatitis • Familial polyposis coli • Malignant disease in previous 10 years • History of, or states associated with, lactic acidosis or hypoxemia • Substance abuse • Pregnant or breast-feeding women • Previous treatment with insulin, gliclazide, pioglitazone or other sulphonylureas or thiazolidinediones
Recruitment / selection of participants	Participants block randomised using central telephone system to pioglitazone or gliclazide. Dietary advice given at baseline and instructed to adhere to disease- and body-weight-oriented diet for trial duration; participants provided with individually appropriate calories and nutrients. If weight increased>5% during treatment or HbA1c level increased >9% after dose titration completion, participants given further intensive dietary advice.
Intervention(s)	• Pioglitazone 15-45 mg daily Oral pioglitazone 15-45 mg daily for 104 months, in addition to concurrent metformin therapy. Initial 16-week forced dose-titration period (pioglitazone titrated to 30 mg and 45 mg; gliclazide titrated to 160 mg, 240 mg, and 360 (160 mg twice daily)) followed by 90-week maintenance period. No change in metformin dose from pre-study level was permitted. Cessation of titration or down titration permitted only if tolerability issues (e.g. actual hypoglycaemia or increased risk of it). Participants continued to next dose unless: (i) risk of hypoglycaemia (increase postponed for 1 visit from week 4 to week 8, or week 8 dose maintained for rest of study); (ii) reported symptomatic hypoglycaemia (one-step reduction followed by increase at next visit if possible); or (iii) adverse events requiring dose reduction (one-step reduction at weeks 8 or 12 (or week 16 for Pioglitazone v Gliclazide trial) with no further down titration).
Cointervention	• Metformin + Placebo (Gliclazide placebo for pioglitazone arm arm; Pioglitazone placebo for gliclazide arm)

	Pre-study metformin dose maintained for duration of trial with no change in dose permitted.
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Excluded "symptomatic heart failure".
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Excluded "myocardial infarction, transient ischaemic attacks or stroke in the previous 6 months", prior to this unclear. 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
Comparator	• Metformin + Placebo (Gliclazide placebo for pioglitazone arm arm; Pioglitazone placebo for gliclazide arm) Pre-study metformin dose maintained for duration of trial with no change in dose permitted.
Number of participants	N=630
Duration of follow-up	88 weeks
Indirectness	None
Method of analysis	Per protocol PP analysis (all randomised participants who received at least one dose of study drug after randomisation and who has at least one HbA1c assessment at week 72 or later) also conducted for all outcomes Modified ITT mITT LOCF analysis (all randomised participants who received at least one dose of study drug after randomisation and who has at least one post-baseline HbA1c assessment) for all outcomes
Additional comments	

305.2. Study arms

305.2.1. Pioglitazone 15-45 mg daily (N = 319)

Oral pioglitazone 15-45 mg daily + gliclazide placebo for 104 weeks, in addition to concurrent metformin therapy

305.2.2. Gliclazide 80-320 mg daily (N = 313)

Oral gliclazide 80-320 mg daily + pioglitazone placebo for 104 weeks, in addition to concurrent metformin therapy

305.3. Characteristics

305.3.1. Arm-level characteristics

Characteristic	Pioglitazone 15-45 mg daily (N = 319)	Gliclazide 80-320 mg daily (N = 313)
% Male Sample size	n = 161 ; % = 50.8	n = 154 ; % = 49.2
Mean age (SD) (years) Mean (SD)	56 (9.2)	57 (9)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Black Sample size	n = 0 ; % = 0	n = 0 ; % = 0
Caucasian Sample size	n = 315 ; % = 99.4	n = 313 ; % = 100
Other Sample size	n = 2 ; % = 0.6	n = 0 ; % = 0
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	5.8 (5.1)	5.5 (5.1)
Cardiovascular risk factors Nominal	NR	NR
Smoking status Nominal	NR	NR
Alcohol consumption Nominal	NR	NR

Characteristic	Pioglitazone 15-45 mg daily (N = 319)	Gliclazide 80-320 mg daily (N = 313)
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
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 n=317 in Pioglitazone arm.

306. Matthews, 2010

Bibliographic Reference	Matthews, D. R.; Dejager, S.; Ahren, B.; Fonseca, V.; Ferrannini, E.; Couturier, A.; Foley, J. E.; Zinman, B.; Vildagliptin add-on to metformin produces similar efficacy and reduced hypoglycaemic risk compared with glimepiride, with no weight gain: results from a 2-year study; Diabetes Obes Metab; 2010; vol. 12 (no. 9); 780-9

306.1. 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	EudraCT no. 2004-004559-21
Study type	Randomised controlled trial (RCT)
Study location	The study was conducted in 402 sites.
Study setting	Hospital setting
Study dates	No additional information
Sources of funding	Novartis Pharmaceutical Corporation
Inclusion criteria	Men, non-fertile women and women of child-bearing potential using medically approved birth control, aged 18–73 years, with type 2 diabetes mellitus inadequately controlled (HbA1c 6.5–8.5%) by metformin monotherapy. Patients must have received metformin for at least three months, at a stable maximum tolerated dose of at least 1500 mg daily for a minimum of four weeks before visit 1. Metformin dose remained unchanged throughout the study.
Exclusion criteria	A history of type 1 diabetes or secondary forms of diabetes were excluded, as were those who had experienced acute metabolic diabetic complications in the past 6 months, acute infections that might affect blood

	glucose control in the 4 weeks prior to visit 1, serious cardiac conditions (history of torsades de pointes or ventricular tachycardia; percutaneous coronary intervention in the past 3 months; myocardial infarction, coronary artery bypass surgery, unstable angina or stroke in the past 6 months; congestive heart failure requiring pharmacological treatment; second- or third-degree atrioventricular block or prolonged QTc) or clinically significant liver or renal disease. Any of the following laboratory abnormalities at screening also precluded participation: alanine aminotransferase or aspartate aminotransferase >3 times the upper limit of normal, direct bilirubin >1.3 times upper limit of normal, serum creatinine levels ≥132 µmol/l in men or ≥123 µmol/l in women, clinically significant thyroid-stimulating hormone outside of normal range at screening; or fasting triglycerides >7.9 mmol/l.
Recruitment / selection of participants	Patients were randomized to receive either vildagliptin or glimepiride in addition to metformin.
Intervention(s)	Glimepiride up to 6 mg daily
Cointervention	All participants also received metformin.
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Exclusion criteria for congestive heart failure requiring pharmacological treatment
Strata 2: People with atherosclerotic cardiovascular disease	People without atherosclerotic cardiovascular diseases Exclusion criteria for people with percutaneous coronary intervention in the past 3 months, myocardial infarction, coronary artery bypass surgery, unstable angina or stroke in the past 6 months.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Mixed population Around 50% of people had a mild-moderate renal insufficiency
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	
Comparator	Vildagliptin 50 mg twice daily, administered orally.
Number of participants	N=3118
Duration of follow-up	2-year
Indirectness	
Method of analysis	Modified ITT
Additional comments	All patients who received at least one dose of study drug and had at least one postbaseline efficacy assessment (primary or secondary).

306.2. Study arms

306.2.1. Glimepiride 2-6 mg (N = 1556)

Administered daily, orally

306.2.2. Vildagliptin 50 mg (N = 1562)

Administered twice daily, orally

306.3. Characteristics

306.3.1. Study-level characteristics

Characteristic	Study (N = 3118)
Angiotensin Converting Enzyme (ACE) inhibitors No of events	n = 1434 ; % = 46
Angiotensin II blocker (ARB) No of events	n = 811 ; % = 26
ACE-inhibitor or ARB + diuretic No of events	n = 780 ; % = 25

306.3.2. Arm-level characteristics

Characteristic	Glimepiride 2-6 mg (N = 1556)	Vildagliptin 50 mg (N = 1562)
% Male No of events	n = 838 ; % = 53.9	n = 829 ; % = 53.1
Mean age (SD) (years) Mean (SD)	57.5 (9.19)	57.5 (9.07)
Caucasian No of events	n = 1343 ; % = 86.3	n = 1364 ; % = 87.3
Black No of events	n = 19 ; % = 1.2	n = 18 ; % = 1.2
Asian No of events	n = 46 ; % = 3	n = 44 ; % = 2.8

Characteristic	Glimepiride 2-6 mg (N = 1556)	Vildagliptin 50 mg (N = 1562)
Hispanic or Latino No of events	n = 133 ; % = 8.5	n = 129 ; % = 8.3
Other No of events	n = 15 ; % = 1	n = 7 ; % = 0.4
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	5.7 (5)	5.7 (5.2)
Current smoker No of events	n = 255 ; % = 16.4	n = 263 ; % = 16.8
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
Albumin creatinine ratio Nominal	NR	NR
Metformin No of events	n = 1556 ; % = 100	n = 1562 ; % = 100

307. Mattoo, 2005

Bibliographic Reference	Mattoo, V.; Eckland, D.; Widel, M.; Duran, S.; Fajardo, C.; Strand, J.; Knight, D.; Grossman, L.; Oakley, D.; Tan, M.; Metabolic effects of pioglitazone in combination with insulin in patients with type 2 diabetes mellitus whose disease is not adequately controlled with insulin therapy: results of a six-month, randomized, double-blind, prospective, multicenter, parallel-group study; Clin Ther; 2005; vol. 27 (no. 5); 554-67

307.1. Study details

Trial name / registration number	No additional information.
Study type	Randomised controlled trial (RCT)
Study setting	Hospital
Study dates	No additional information.
Sources of funding	Sponsored by Eli Lilly and Company, Indianapolis, Indiana, and Takeda Europe R&D Centre, London, United Kingdom.
Inclusion criteria	Patients in this study had type 2 diabetes mellitus diagnosed according to World Health Organization criteria, 11 used insulin therapy (with or without an oral anti-hyperglycemic medication [OAM]) for >3 months, had an HbA1c value >7.5% at screening, and were >30 years old at the time of diabetes diagnosis.
Exclusion criteria	Persons were excluded who had: type 1 diabetes mellitus, clinical signs or symptoms of any chronic systemic condition (liver disease, diminished cardiac function, renal impairment, transplantation or dialysis, HIV infection), or signs or symptoms of drug or alcohol abuse. Previous thiazolidinedione use, systemic glucocorticoid therapy, nicotinic acid at a dose >500 rag/d, or therapy for a malignancy other than basal cell or squamous cell skin cancer were also reasons for exclusion. Women who were breastfeeding or pregnant were excluded, as were women of childbearing potential who were not actively practicing birth control.
Recruitment / selection of participants	Patients with HbA1c values >7.0 % after insulin intensification (the end of the insulin intensification period was considered to be baseline) were randomised to pioglitazone (30 mg) + insulin or placebo + insulin. The intent of the insulin intensification period was to exclude patients who could obtain glycemic control with insulin alone.
Intervention(s)	Pioglitazone 30 mg (oral) + insulin (subcutaneous) daily

Cointervention	Insulin
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Exclusion criteria on diminished cardiac function but no information on what this means
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Exclusion criteria on diminished cardiac function but no information on what this means
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Exclusion criteria on renal impairment but no information on what this means
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	A2 (ACR 30-300 mg/g or 3-30mg/mmol)
Comparator	Placebo (oral) + insulin (subcutaneous) daily
Number of participants	N=289
Duration of follow-up	6 months
Method of analysis	Modified ITT
Additional comments	The ITT sample was defined as all randomized patients who received at least 1 dose of study medication and had both a baseline measurement and at least 1 efficacy measurement during the treatment period.

307.2. Study arms

307.2.1. Pioglitazone 30 mg daily (N = 142)

Administered orally

307.2.2. Placebo (N = 147)

Administered orally

307.3. Characteristics

307.3.1. Arm-level characteristics

Characteristic	Pioglitazone 30 mg daily (N = 142)	Placebo (N = 147)
% Male No of events	n = 62 ; % = 43.7	n = 63 ; % = 42.9
Mean age (SD) (years) Mean (SD)	58.8 (7.4)	58.9 (5.9)

Characteristic	Pioglitazone 30 mg daily (N = 142)	Placebo (N = 147)
White No of events	n = 137 ; % = 96.5	n = 142 ; % = 96.6
Other No of events	n = 5 ; % = 3.5	n = 5 ; % = 3.4
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed (Months) Mean (SD)	163.4 (81)	160.9 (73.7)
Smoking status Nominal	NR	NR
Alcohol consumption Nominal	NR	NR
Presence of severe mental illness Nominal	NR	NR
People with significant cognitive impairment Nominal	NR	NR
People with a learning disability Nominal	NR	NR
Number of people with obesity 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

308. Mazzone, 2006

Bibliographic Reference	Mazzone, T.; Meyer, P. M.; Feinstein, S. B.; Davidson, M. H.; Kondos, G. T.; D'Agostino, R. B.; Perez, A.; Provost, J. C.; Haffner, S. M.; Effect of pioglitazone compared with glimepiride on carotid intima-media thickness in type 2 diabetes: a randomized trial; JAMA; 2006; vol. 296 (no. 21); 2572-81

308.1. 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	Sam, S et al. Pioglitazone-Mediated Changes in Lipoprotein Particle Composition Are Predicted by Changes in Adiponectin Level in Type 2 Diabete. J Clin Endocrinol Metab. 2012 Jan; 97(1): E110–E114.
Trial name / registration number	CHICAGO/NCT00225264
Study type	Randomised controlled trial (RCT)
Study location	US, Chicago at 28 clinical sites.
Study setting	Hospital
Study dates	10/2003 - 05/2006
Sources of funding	Takeda Pharmaceuticals North America Inc, Lincolnshire, Ill, sponsored and funded this study and provided the study drugs.
Inclusion criteria	Individuals eligible for participation were men and women between the ages of 45 and 85 years with type 2 diabetes mellitus by American Diabetes Association criteria who were newly diagnosed with type 2 diabetes mellitus that was diet-controlled or treated with sulfonylurea or metformin monotherapy, sulfonylurea/ metformin combination therapy, or any of these plus insulin. Individuals taking medication for glycemia were included if they had HbA1c values of 6.5% or greater and less than 9%; those not taking medication for glycemia were included if they had HbA1c values of greater than 6.5% and less than 10%.

Exclusion criteria	Exclusion criteria included symptomatic coronary artery disease, cerebrovascular disease, or peripheral artery disease; functional New York Heart Association class III or IV heart failure; left ventricular dysfunction measured as left ventricular ejection fraction less than 40%; current use of diuretics or angiotensin-converting enzyme inhibitors for the treatment of heart failure; or significant cardiac valvular disease. Individuals also were excluded if they had been treated with a thiazolidinedione within 12 weeks of treatment randomization; did not respond to or were intolerant of sulfonylurea or thiazolidinedione treatment; required more than 2 oral agents for glycemic control; had unexplained microscopic hematuria, a triglycerides level greater than 500 mg/dL (5.7 mmol/ L), elevated serum creatinine level, decreased hemoglobin level, an alanine transaminase level of 2.5 or more times the upper limit of normal; had active liver disease or jaundice; or weighed more than 135 kg or had a body mass index (calculated as weight in kilograms divided by height in meters squared) greater than 45.
Recruitment / selection of participants	Patients were recruited from a large US city. Patients who were newly diagnosed with type 2 diabetes that was diet-controlled or treated with sulfonylurea or metformin monotherapy, sulfonylurea/ metformin combination therapy, or any of these plus insulin were randomly assigned 1:1 to pioglitazone (15-45 mg daily) or glimepiride (1-4 mg daily).
Intervention(s)	Pioglitazone 15-45 mg/d The initial dose was based on sulfonylurea use and dose at study entry.
Cointervention	Metformin ± sulfonylurea ± insulin
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Excluded "functional New York Heart Association class III or IV heart failure" but other HF unclear. Less than 2 % had congestive heart failure.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Excluded "symptomatic coronary artery disease, cerebrovascular disease, or peripheral artery disease". However, baseline characteristics show history of CVD, breakdown by type of CVD only and unclear if any overlap to calculate overall proportion.
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	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	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	
Comparator	Glimepiride 1-4mg /d The initial dose was based on sulfonylurea use and dose at study entry.
Number of participants	N=462
Duration of follow-up	73 weeks
Indirectness	In total around 10% of patients in this study were oral antidiabetic treatment naïve.

Method of analysis	ITT

308.2. Study arms

308.2.1. Pioglitazone 15 - 45 mg daily (N = 232)

Administered orally

308.2.2. Glimepiride 1-4 mg daily (N = 230)

Administered orally

308.3. Characteristics

308.3.1. Arm-level characteristics

Characteristic	Pioglitazone 15 - 45 mg daily (N = 232)	Glimepiride 1-4 mg daily (N = 230)
% Male No of events	n = 146 ; % = 63.5	n = 143 ; % = 62.7
Mean age (SD) (years) Mean (SD)	59.3 (8)	59.9 (8.2)
White No of events	n = 137 ; % = 59.6	n = 149 ; % = 65.4
Black No of events	n = 71 ; % = 30.9	n = 61 ; % = 26.8
Oriental/Asian No of events	n = 21 ; % = 9.1	n = 18 ; % = 7.9
Hispanic/Latino No of events	n = 21 ; % = 9.1	n = 22 ; % = 9.6
Hypertension No of events	n = 156 ; % = 67.8	n = 166 ; % = 72.8
Myocardial infarction No of events	n = 18 ; % = 7.8	n = 31 ; % = 13.6

Characteristic	Pioglitazone 15 - 45 mg daily (N = 232)	Glimepiride 1-4 mg daily (N = 230)
Stroke/transient ischemic attack No of events	n = 9 ; % = 3.9	n = 8 ; % = 3.5
Angina No of events	n = 14 ; % = 6.1	n = 20 ; % = 8.8
Cardiac arrythmia No of events	n = 15 ; % = 6.5	n = 13 ; % = 5.7
Congestive heart failure No of events	n = 2 ; % = 0.9	n = 4 ; % = 1.8
Peripheral arterial disease No of events	n = 3 ; % = 1.3	n = 4 ; % = 1.8
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	8 (7.6)	7.5 (6.8)
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
Sulfonylurea monotherapy No of events	n = 39 ; % = 17	n = 32 ; % = 14

Characteristic	Pioglitazone 15 - 45 mg daily (N = 232)	Glimepiride 1-4 mg daily (N = 230)
Sulfonylurea/metformin combination therapy No of events	n = 79 ; % = 34.3	n = 73 ; % = 32
Metformin monotherapy No of events	n = 67 ; % = 29.1	n = 74 ; % = 32.5
Insulin No of events	n = 30 ; % = 13	n = 28 ; % = 12.3
Renin-angiotensin system blockers No of events	n = 124 ; % = 53.9	n = 137 ; % = 60.1
Beta blockers No of events	n = 50 ; % = 21.7	n = 48 ; % = 21.1
Calcium channel blockers No of events	n = 46 ; % = 20	n = 44 ; % = 19.3
Other No of events	n = 11 ; % = 4.8	n = 15 ; % = 6.6
Any lipid-reducing agent No of events	n = 142 ; % = 61.7	n = 140 ; % = 61.4
Statin therapy No of events	n = 125 ; % = 54.3	n = 128 ; % = 56.1
Diuretics No of events	n = 52 ; % = 22.6	n = 78 ; % = 34.2

309. McCluskey, 2004

Bibliographic Reference	McCluskey, D.; Touger, M. S.; Melis, R.; Schleusener, D. S.; McCluskey, D.; Results of a randomized, double-blind, placebo-controlled study administering glimepiride to patients with type 2 diabetes mellitus inadequately controlled with rosiglitazone monotherapy; Clin Ther; 2004; vol. 26 (no. 11); 1783-90

309.1. 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	US (17 sites)
Study setting	No additional information.
Study dates	No additional information.
Sources of funding	No additional information.
Inclusion criteria	Men and women aged 18 to 80 years who had type 2 diabetes mellitus for >1 year were eligible for inclusion if their disease was managed with rosiglitazone 4 or 8 mg for >2 months before study entry. None of the subjects had received insulin. Patients were required to have a screening HbA1c value between 7.5% and 9.5% and a baseline BMI between 26 and 42 kg/m2. All enrollees had to demonstrate evidence of insulin secretory capacity (fasting C-peptide >0.27 nmol/L during the stabilization period) and to have FPG levels between 126 and 235 mg/dL at randomization. All patients signed informed consent forms prior to the conduct of any study-related procedures.

Exclusion criteria	Individuals who required insulin therapy, were receiving other sulfonylureas, or had a history of sulfonylurea hypersensitivity were excluded.
Recruitment / selection of participants	Patients with uncontrolled type 2 diabetes mellitus on rosiglitazone were recruited and randomly assigned to glimepiride or placebo.
Intervention(s)	Glimepiride 2-8 mg daily, administered orally. Glimepiride was titrated over a maximum of 2 sequential biweekly steps to 4 and 8 mg.
Cointervention	Rosiglitazone 4 or 8 mg daily at study entry.
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	Not stated/unclear

2 diabetes mellitus	
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	No additional information.
Comparator	Placebo daily, administered orally.
Number of participants	N=40
Duration of follow-up	30-week
Indirectness	
Method of analysis	Not stated/unclear

309.2. Study arms

309.2.1. Glimepiride 2-8 mg daily (N = 25)

Administered orally

309.2.2. Placebo daily (N = 15)

Administered orally

309.3. Characteristics

309.3.1. Arm-level characteristics

Characteristic	Glimepiride 2-8 mg daily (N = 25)	Placebo daily (N = 15)
% Male No of events	n = 11 ; % = 44	n = 6 ; % = 4
Mean age (SD) (years) Mean (SD)	60.2 (7.8)	50.8 (9.7)
White No of events	n = 24 ; % = 96	n = 12 ; % = 80
Other No of events	n = 1 ; % = 4	n = 3 ; % = 20
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed Mean (SD)	7.2 (8.8)	4.6 (4)
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
Rosiglitazone No of events	n = 25 ; % = 100	n = 15 ; % = 100

Characteristic	Glimepiride 2-8 mg daily (N = 25)	Placebo daily (N = 15)
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

310. McGill, 2013

Bibliographic Reference	McGill, J. B.; Sloan, L.; Newman, J.; Patel, S.; Sauce, C.; Eynatten, M.; Woerle, H. J.; Long-term efficacy and safety of linagliptin in patients with type 2 diabetes and severe renal impairment: a 1-year, randomized, double-blind, placebo-controlled study; Diabetes Care; 2013; vol. 36 (no. 2); 237-44

310.1. Study details

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	NA
Trial name / registration number	NR
Study type	Randomised controlled trial (RCT)
Study location	53 sites in six countries (Australia, Hong Kong, Israel, New Zealand, Ukraine, and U.S.)
Study setting	NR
Study dates	11 December 2008 to 5 January 2011
Sources of funding	Boehringer Ingelheim
Inclusion criteria	• Women (non-fertile or using a medically approved birth control method) and men aged 18–80 years, previously diagnosed with type 2 diabetes • Treated with glucose-lowering agents, including insulin, sulfonylurea, glinides, pioglitazone, and a-glucosidase inhibitors. Existing glucose-lowering therapy must have remained unchanged for 8 weeks before study entry. • Participants fulfilled the criteria for severe RI (CKD stage 4/5) at screening, having an estimated glomerular filtration rate (eGFR) calculated by the Modification of Diet in Renal Disease study

	equation of <30 mL/min/1.73 m2 (while not receiving chronic dialysis). • Participants had an HbA1c >7 and <=10% (>53 and <=86 mmol/mol) • BMI <=45 kg/m2
Exclusion criteria	• Myocardial infarction (MI), stroke, or transient ischemic attack within the previous 6 months • Any requirement for acute dialysis within the previous 3 months • Renal transplantation • Impaired hepatic function • U se of any other DPP-4 inhibitor or anti-obesity drug within the previous 3 months
Recruitment / selection of participants	Study participants who met the eligibility criteria at screening and at the end of the 2-week placebo run-in period were randomized (1:1) to receive double-blind treatment.
Intervention(s)	Linagliptin 5 mg/day
Cointervention	Glucose-lowering background therapy
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	People with chronic kidney disease Inclusion of people with severe renal impairment (eGFR <30)
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 Participants fulfilled the criteria for severe RI (CKD stage 4/5) at screening, having an estimated glomerular filtration rate (eGFR) calculated by the Modification of Diet in Renal Disease study equation of <30 mL/min/1.73 m2 (while not receiving chronic dialysis).
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	NA
Comparator	Placebo
Number of participants	133 participants randomised. Out of 68 participants randomised to Linagliptin, 19 discontinued, 49 completed, and 66 were in the full-analysis set. Out of 65 participants randomised to placebo, 17 discontinued, 48 completed, and 62 were in the full analysis set.
Duration of follow-up	12 weeks and 52 months
Indirectness	Directly applicable
Method of analysis	ITT Although not explicitly stated, it appears that ITT analysis was conducted. Change from baseline scores in HbA1c were calculated using ANCOVA with treatment and glucose-lowering background drugs as fixed-classification effects and continuous HbA1c and renal function at baseline as linear covariates. Analysis was performed on the full analysis set (FAS)

	using last observation carried forward (LOCF) to impute missing data. The FAS included randomized participants who received >=1 dose of treatment and who had both a baseline and >=1 on-treatment HbA1c measurement. Safety data were analysed in the treated set using descriptive statistics. The TS included randomized participants who receive >=1 does of treatment.
Additional comments	Power calculations showed that 50 patients were required in each arm to achieve a power of 93% to detect a 0.7% difference in HbA1c change from baseline to week 12.

310.2. Study arms

310.2.1. Linagliptin (N = 68)

310.2.2. Placebo (N = 65)

310.3. Characteristics

310.3.1. Arm-level characteristics

Characteristic	Linagliptin (N = 68)	Placebo (N = 65)
% Male Sample size	n = 45 ; % = 66.2	n = 35 ; % = 53.8
Mean age (SD) Mean (SD)	64 (10.9)	64.9 (9.6)
Ethnicity Sample size	n = NA	n = NA
White Sample size	n = 53 ; % = 77.9	n = 45 ; % = 69.2
Asian Sample size	n = 8 ; % = 11.8	n = 11 ; % = 16.9
Black/African-American Sample size	n = 6 ; % = 8.8	n = 7 ; % = 10.8
Other	n = 2 ; % = 3.1	n = 1 ; % = 1.5

Characteristic	Linagliptin (N = 68)	Placebo (N = 65)
Sample size		
Comorbidities Sample size	n = NA	n = NA
Hypertension Sample size	n = 64 ; % = 94.1	n = 65 ; % = 100
Diabetic nephropathy Sample size	n = 60 ; % = 88.2	n = 62 ; % = 95.4
Diabetic retinopathy Sample size	n = 43 ; % = 63.2	n = 35 ; % = 53.8
Metabolic syndrome Sample size	n = 37 ; % = 54.4	n = 40 ; % = 61.5
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed Duration >5 years Sample size	n = 64 ; % = 97	n = 59 ; % = 95.2
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 BMI >=30 kg/m2 Sample size	n = 50 ; % = 73.5	n = 38 ; % = 58.5
eGFR mL/min/1.73m2	n = NA	n = NA

Characteristic	Linagliptin (N = 68)	Placebo (N = 65)
Sample size		
30-60 mL/min/1.73 m2 Sample size	n = 5 ; % = 7.4	n = 14 ; % = 21.5
15-30 mL/min/1.73 m2 Sample size	n = 55 ; % = 80.9	n = 45 ; % = 69.2
<15 ml/min/1.73 m2 Sample size	n = 8 ; % = 11.8	n = 6 ; % = 9.2
Other antidiabetic medication used Sample size	n = NA	n = NA
Insulin monotherapy Sample size	n = 39 ; % = 57.4	n = 46 ; % = 70.8
Insulin combination therapy Sample size	n = 15 ; % = 22.1	n = 9 ; % = 13.8
Sulfonylurea monotherapy Sample size	n = 9 ; % = 13.2	n = 7 ; % = 10.8
Sulfonylurea combination therapy with any other OAD(s) Sample size	n = 4 ; % = 5.9	n = 2 ; % = 3
Glitazone Sample size	n = 0 ; % = 0	n = 1 ; % = 1.5
Alpha-glucosidase inhibitor + glinide Sample size	n = 1 ; % = 1.5	n = 0 ; % = 0
Blood pressure-lowering medication used n calculated by analyst Sample size	n = 64 ; % = 94.1	n = 65 ; % = 100
Statins/lipid-lowering medication used Sample size	n = 53 ; % = 77.9	n = 52 ; % = 80
Other treatment being received Acetylsalicylic acid Sample size	n = 45 ; % = 67.6	n = 45 ; % = 69.2

311. McGuire Darren, 2019

Bibliographic Reference	McGuire Darren, K; Alexander John, H; Johansen Odd, Erik; Perkovic, Vlado; Rosenstock, Julio; Cooper Mark, E; Wanner, Christoph; Kahn Steven, E; Toto Robert, D; Zinman, Bernard; Baanstra, David; Pfarr, Egon; Schnaidt, Sven; Meinicke, Thomas; George Jyothis, T; von Eynatten, Maximilian; Marx, Nikolaus; CARMELINA, Investigators; Linagliptin Effects on Heart Failure and Related Outcomes in Individuals With Type 2 Diabetes Mellitus at High Cardiovascular and Renal Risk in CARMELINA.; Circulation; 2019; vol. 139 (no. 3); 351-361

311.1. Study details

Secondary publication of another included study- see primary study for details	This study is a part of the CARMELINA trial. For the full data extraction please see the primary study. Rosenstock, Julio, Perkovic, Vlado, Johansen Odd, Erik et al. (2019) Effect of Linagliptin vs Placebo on Major Cardiovascular Events in Adults With Type 2 Diabetes and High Cardiovascular and Renal Risk: The CARMELINA Randomized Clinical Trial. JAMA 321(1): 69-79
Other publications associated with this study included in review	Perkovic, V, Toto, R, Cooper M, E et al. (2020) Effects of linagliptin on cardiovascular and kidney outcomes in people with normal and reduced kidney function: Secondary analysis of the carmelina randomized trial. Diabetes Care 43(8): 1803-1812 Rosenstock, Julio, Perkovic, Vlado, Alexander John, H et al. (2018) Rationale, design, and baseline characteristics of the CArdiovascular safety and Renal Microvascular outcomE study with LINAgliptin (CARMELINA R): a randomized, double-blind, placebo-controlled clinical trial in patients with type 2 diabetes and high cardio-renal risk. Cardiovascular diabetology 17(1): 39
Trial name / registration number	CARMELINA. ClinicalTrials.gov = NCT01897531

311.2. Study arms

311.2.1. Linagliptin - Heart failure, Ejection fraction <50% (N = 148)

Linagliptin 5mg once daily initially for 12 weeks, then 24 week periods until the study end, median end follow up of 2.2 years. Concomitant therapy: Majority received at least 1 background glucose-lowering therapy in addition to the new therapy, as well as a large number of people receiving antihypertensive medication, aspirin and statins (see characteristics table).

311.2.2. Linagliptin - Heart failure, Ejection fraction ≥50% (N = 312)

Linagliptin 5mg once daily initially for 12 weeks, then 24 week periods until the study end, median end follow up of 2.2 years. Concomitant therapy: Majority received at least 1 background glucose-lowering therapy in addition to the new therapy, as well as a large number of people receiving antihypertensive medication, aspirin and statins (see characteristics table).

311.2.3. Placebo - Heart failure, Ejection fraction <50% (N = 142)

Placebo once daily initially for 12 weeks, then 24 weeks periods until the study end, median end follow up of 2.2 years. Concomitant therapy: Majority received at least 1 background glucose-lowering therapy in addition to the new therapy, as well as a large number of people receiving antihypertensive medication, aspirin and statins (see characteristics table).

311.2.4. Placebo - Heart failure, Ejection fraction ≥50% (N = 345)

Placebo once daily initially for 12 weeks, then 24 weeks periods until the study end, median end follow up of 2.2 years. Concomitant therapy: Majority received at least 1 background glucose-lowering therapy in addition to the new therapy, as well as a large number of people receiving antihypertensive medication, aspirin and statins (see characteristics table).

312. McGuire, 2016

Bibliographic Reference	McGuire, Darren K; Van de Werf, Frans; Armstrong, Paul W; Standl, Eberhard; Koglin, Joerg; Green, Jennifer B; Bethel, M Angelyn; Cornel, Jan H; Lopes, Renato D; Halvorsen, Sigrun; Ambrosio, Giuseppe; Buse, John B; Josse, Robert G; Lachin, John M; Pencina, Michael J; Garg, Jyotsna; Lokhnygina, Yuliya; Holman, Rury R; Peterson, Eric D; Association Between Sitagliptin Use and Heart Failure Hospitalization and Related Outcomes in Type 2 Diabetes Mellitus: Secondary Analysis of a Randomized Clinical Trial.; JAMA cardiology; 2016; vol. 1 (no. 2); 126-35

312.1. Study details

Secondary publication of another included study- see primary study for details	TECOS trial. Green et al (2015) Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes. The New England journal of medicine; 2015; vol. 373 (no. 3); 232-42
Other publications associated with this study included in review	Bethel M, A, Engel S, S, Stevens S, R et al. (2019) Progression of glucose-lowering diabetes therapy in TECOS. Endocrinology, Diabetes and Metabolism 2(1): e00053 Green, Jennifer B, Bethel, M Angelyn, Paul, Sanjoy K et al. (2013) Rationale, design, and organization of a randomized, controlled Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) in patients with type 2 diabetes and established cardiovascular disease. American heart journal 166(6): 983-989e7 Nauck Michael, A, McGuire Darren, K, Pieper Karen, S et al. (2019) Sitagliptin does not reduce the risk of cardiovascular death or hospitalization for heart failure following myocardial infarction in patients with diabetes: observations from TECOS. Cardiovascular diabetology 18(1): 116
Trial name / registration number	TECOS ClinicalTrials.gov number NCT00790205

313. McGuire, 2025

Bibliographic Reference	McGuire DK; Marx N; Mulvagh SL; Deanfield JE; Inzucchi SE; Pop-Busui R; Mann JFE; Emerson SS; Poulter NR; Engelmann MDM; Ripa MS; Hovingh GK; Brown-Frandsen K; Bain SC; Cavender MA; Gislum M; David JP; Buse JB; ; Oral Semaglutide and Cardiovascular Outcomes in High-Risk Type 2 Diabetes.; The New England journal of medicine; 2025; vol. 392 (no. 20)

313.1. Study details

Secondary publication of another included study- see primary study for details	
Other publications associated with this study included in review	McGuire DK, Busui RP, Deanfield J, Inzucchi SE, Mann JFE, Marx N, Mulvagh SL, Poulter N, Engelmann MDM, Hovingh GK, Ripa MS, Gislum M, Brown-Frandsen K, Buse JB. Effects of oral semaglutide on cardiovascular outcomes in individuals with type 2 diabetes and established atherosclerotic cardiovascular disease and/or chronic kidney disease: Design and baseline characteristics of SOUL, a randomized trial. Diabetes Obes Metab. 2023 Jul;25(7):1932-1941. doi: 10.1111/dom.15058. Epub 2023 Apr 11. PMID: 36945734. Marx N, Deanfield JE, Mann JFE, Arechavaleta R, Bain SC, Bajaj HS, Bayer Tanggaard K, Birkenfeld AL, Buse JB, Davicevic-Elez Z, Desouza C, Emerson SS, Engelmann MDM, Hovingh GK, Inzucchi SE, Jhund PS, Mulvagh SL, Pop-Busui R, Poulter NR, Rasmussen S, Tu ST, McGuire DK; SOUL Study Group. Oral Semaglutide and Cardiovascular Outcomes in People With Type 2 Diabetes, According to SGLT2i Use: Prespecified Analyses of the SOUL Randomized Trial. Circulation. 2025 Jun 10;151(23):1639-1650. doi: 10.1161/CIRCULATIONAHA.125.074545. Epub 2025 Mar 29. PMID: 40156843; PMCID: PMC12144549.
Trial name / registration number	SOUL / NCT03914326
Study type	Randomised controlled trial (RCT)
Study location	33 countries in Africa, Asia, Europe, Latin and North America and the Middle East
Study setting	Not specified
Study dates	17th June 2019 and 24th March 2021
Sources of funding	Novo Nordisk

Inclusion criteria	All inclusion criteria are based on the participants' medical records, except for inclusion criterion for glycated haemoglobin (HbA1c; local laboratory or point-of-care device). Participants are eligible to be included in the trial only if all of the following criteria apply: 1. Informed consent obtained before commencing any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial 2. Male or female, age ≥50 years at the time of signing informed consent 3. Diagnosed with type 2 diabetes 4. HbA1c 47-86 mmol/mol (6.5%-10.0%; both inclusive)† 5. At least one of the below conditions (a-d): a. Coronary artery disease (CAD), defined as at least one of the following: i. Prior myocardial infarction (MI) ii. Prior coronary revascularization procedure iii. ≥50% stenosis in ≥1 coronary artery documented by cardiac catheterization or computed tomography (CT) coronary angiography iv. CAD with ischaemia documented by stress test with any imaging modality. b. Cerebrovascular disease defined as at least one of the following: i. Prior stroke ii. Prior carotid artery revascularization procedure iii. ≥50% stenosis in carotid artery documented by invasive angiography, magnetic resonance (MR) angiography, CT angiography or Doppler ultrasound. c. Symptomatic peripheral arterial disease (PAD), defined as at least one of the following: i. Intermittent claudication with an ankle-brachial index <0.85 at rest ii. Intermittent claudication with a ≥50% stenosis in peripheral artery (excluding carotid) documented by invasive angiography, MR angiography, CT angiography or Doppler ultrasound

	iii. Prior peripheral artery revascularization procedure (excluding carotid) iv. Lower extremity amputation at or above ankle due to atherosclerotic disease. d. Chronic kidney disease (CKD) defined as: i. Estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m2‡.1 †Latest available, and no more than 30 days old, local laboratory assessment based on medical records or point of care measurement. ‡Based on medical records using the latest available, and no more than 6 months old, assessment.
Exclusion criteria	All exclusion criteria are based on the participants' medical records, except for exclusion criterion 3, urine pregnancy test. Participants are excluded from the trial if any of the following criteria apply: 1. Known or suspected hypersensitivity to trial product or related products 2. Previous participation in this trial. Participation is defined as randomization 3. Woman who is pregnant, breast-feeding, or intends to become pregnant or is of child-bearing potential and not using a highly effective contraceptive method 4. Participation in any clinical trial of an approved or nonapproved investigational medicinal product within 30 days before screening§ 5. Any disorder, which in the investigator's opinion, might jeopardize participants' safety or compliance with the protocol 6. Any of the following: MI, stroke, hospitalization for unstable angina pectoris or transient ischaemic attack within the past 60 days prior to the day of screening 7. Planned coronary, carotid or peripheral artery revascularization 8. Heart failure (HF) presently classified as being in New York Heart Association (NYHA) class IV 9. Treatment with any glucagon-like peptide-1 receptor agonist (GLP-1RA) within 30 days before screening 10. Uncontrolled and potentially unstable diabetic retinopathy or maculopathy, verified by a retinal examination performed within the past 90 days prior to screening or in the period between screening and

	randomization. Pharmacologic pupil dilation is a requirement, unless using a digital retinal photography camera specified for nondilated examination 11. Presence or history of malignant neoplasm within 5 years prior to the day of screening. Basal and squamous cell skin cancer and any carcinoma in situ is allowed 12. Personal or first-degree relative(s) history of multiple endocrine neoplasia 2 or medullary thyroid cancer 13. End-stage kidney disease or chronic or intermittent haemodialysis or peritoneal dialysis 14. History of major surgical procedures involving the stomach or small intestine potentially affecting absorption of drugs and/or nutrients, as judged by the investigator. §Simultaneous participation in a trial with the primary objective of evaluating an approved or nonapproved investigational medicinal product for prevention or treatment of coronavirus disease (COVID-19) or postinfectious conditions is allowed, if the last dose of the investigational medicinal product has been received more than 30 days before screening.
Recruitment / selection of participants	Not recorded
Intervention(s)	Semaglutide (n=4825) Patients received oral semaglutide for a mean of 47.5 months with an initial dose of 3mg for 4 weeks, followed by 7 mg for an additional 4 weeks, and finally a dose of 14 mg once daily for the remainder of the the trial
Cointervention	75.7% of all patients were receiving metformin
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear
Strata 2: People with atherosclerotic cardiovascular disease	Mixed population
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	People without chronic kidney disease
Strata 4: People with	Mixed population

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	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	Placebo (N=4825) Patients received oral placebo for a mean of 47.5 months
Number of participants	9650
Duration of follow-up	Mean follow up of 47.5 months
Method of analysis	ITT
Additional comments	Efficacy analyses were performed in the intention-to-treat population, which included all the individual participants who had undergone randomization, regardless of adherence to oral semaglutide or placebo or changes to background medications. Data from the participants who withdrew from the trial, died, or were lost to follow-up were censored at the time of withdrawal, death, or last contact, respectively

313.2. Study arms

313.2.1. Semaglutide (N = 4825)

Individuals received 3 mgs oral semaglutide for 4 weeks followed by 7 mg for 4 weeks and then 14 mgs for the rest of the trial (mean 47.5 months total)

313.2.2. Placebo (N = 4825)

Patients received oral placebo for a mean of 47.5 months

313.3. Characteristics

313.3.1. Arm-level characteristics

Characteristic	Semaglutide (N = 4825)	Placebo (N = 4825)
% Male Sample size	n = 3449 ; % = 71.5	n = 3441 ; % = 70.7
Mean age (SD) (years (mean)) Mean (SD)	66.1 (7.6)	66.1 (7.5)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Ethnicity - white Sample size	n = 3327 ; % = 69	n = 3321 ; % = 68.8
Ethnicity - Black Sample size	n = 124 ; % = 2.6	n = 128 ; % = 2.7
Ethnicity - Asian Sample size	n = 1134 ; % = 23.5	n = 1121 ; % = 23.2
Ethnicity - American Indian or Alaska Native Sample size	n = 7 ; % = 0.1	n = 12 ; % = 0.2
Ethnicity - Native Hawaiian or Pacific Islander Sample size	n = 4 ; % = 0.08	n = 5 ; % = 0.1
Ethnicity - Other	n = 185 ; % = 3.8	n = 192 ; % = 4

Characteristic	Semaglutide (N = 4825)	Placebo (N = 4825)
Sample size		
Ethnicity - Not reported Sample size	n = 44 ; % = 0.9	n = 46 ; % = 1
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed (years (mean)) Mean (SD)	14.7 (NR)	14.6 (NR)
Smoking status Sample size	n = 545 ; % = 11.3	n = 584 ; % = 12.1
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR
Other antidiabetic medication used Sample size	n = NR ; % = NR	n = NR ; % = NR

314. McMurray, 2018

Bibliographic Reference	McMurray, J. J. V.; Ponikowski, P.; Bolli, G. B.; Lukashevich, V.; Kozlovski, P.; Kothny, W.; Lewsey, J. D.; Krum, H.; Effects of vildagliptin on ventricular function in patients with type 2 diabetes mellitus and heart failure: A randomized placebo-controlled trial; JACC: heart failure; 2018; vol. 6 (no. 1); 8-17

314.1. Study details

Secondary publication of another included study- see primary study for details	Not applicable
Other publications associated with this study included in review	Not applicable
Trial name / registration number	VIVIDD (Vildagliptin in Ventricular Dysfunction Diabetes)
Study type	Randomised controlled trial (RCT)
Study location	Czechia, Denmark, Estonia, Germany, Greece, Guatemala, India, Italy, Latvia, Lithuania, Poland, Romania, Russian Federation, Singapore, Slovakia [Taken from Clinicaltials.gov]
Study setting	Novartis Investigative Site [Taken from Clinicaltrials.gov]
Study dates	May 2009 to August 2012
Sources of funding	Novartis
Inclusion criteria	• Men and women between 18 and 85 years of age with type 2 diabetes • Hemoglobin A1c: 6.5% to 10.0% [48.0 to 86.0 mmol/mol] • Body mass index ranging from 22 to 42 kg/m2 • With heart failure with a reduced ejection fraction (<40%), and in New York Heart Association (NYHA) functional class I to III

Exclusion criteria	• NYHA functional class IV • A fasting plasma glucose concentration of ≥15 mmol/l • Receiving thiazolidinedione or incretin therapy • A recent cardiovascular event or procedure • Creatinine clearance of <30 ml/min • Liver disease or elevated transaminases or bilirubin.
Recruitment / selection of participants	Not reported
Intervention(s)	Vildagliptin 50 mg twice daily, oral (50 mg once daily if treated with a sulfonylurea)
Cointervention	Individuals continued their usual diet, exercise regimen, and drug therapy for diabetes (if taking drug therapy)
Strata 1: People with type 2 diabetes mellitus and heart failure	People with heart failure People with heart failure NHYA class I-III were included. People with class IV were excluded. Baseline table reports 89.8% in vildagliptin group and 90% in placebo group had class II or III.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear People with recent cardiovascular event or procedure were excluded. Baseline characteristics table report MI, angina, CABG, PCI, and stroke, but it is not possible to determine the number of participants who had more than one event.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear CKD not an inclusion/exclusion criteria. CKD not reported in 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	Mixed population Baseline characteristics table shows that 42.2 and 39.7% of participants in the intervention and control group respectively had obesity.
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	Patients with heart failure and reduced ejection fraction
Comparator	Placebo, oral
Number of participants	254 participants were randomized
Duration of follow-up	16 and 52 weeks
Indirectness	Directly applicable - 12.5% intervention and 7.1% participants were on diet alone
Method of analysis	Not stated/unclear Although the report presented per-protocol, intent-to-treat, and full-set analyses for the LVEF outcome, the type of analyses used to present the other outcomes was unclear.
Additional comments	Study sample size was calculated based upon 90% power and a 1-sided significance level of 0.025 to declare noninferiority of vildagliptin compared with placebo for the effect of treatment of LVEF, using a margin of -3.5% and an expected difference between the 2 treatments of 0%. It was calculated that a total of 172 patients with at least 1 LVEF measurement after randomization were required.

314.2. Study arms

314.2.1. Vildagliptin (N = 128)

314.2.2. Placebo (N = 126)

314.3. Characteristics

314.3.1. Arm-level characteristics

Characteristic	Vildagliptin (N = 128)	Placebo (N = 126)
Mean age (SD) Mean (SD)	62.9 (8.5)	63.4 (10.2)
Time since type 2 diabetes diagnosed (years) Mean (SD)	9.5 (8.1)	9.1 (7.8)
HbA1c (%) Mean (SD)	7.8 (0.95)	7.8 (1.07)
Blood pressure (mmHg) Systolic blood pressure Mean (SD)	130.4 (16.3)	127.9 (15.3)
Heart rate (beats/min) Mean (SD)	73.1 (10.1)	73.5 (9.3)
Smoking status Current smoker Sample size	n = 21 ; % = 16.4	n = 9 ; % = 7.1
BMI (kg/m²) Mean (SD)	29.6 (4.6)	29.3 (4.7)
Number of people with obesity Sample size	n = 54 ; % = 42.2	n = 50 ; % = 39.7
Sulfonylurea Sample size	% = 46.9	% = 53.2
Metformin Sample size	% = 36.7	% = 32.5

Characteristic	Vildagliptin (N = 128)	Placebo (N = 126)
AGI Sample size	% = 0.8	% = 3.2
Glinide Sample size	% = 1.6	% = 0
Any oral anti-diabetes therapy Sample size	% = 63.3	% = 68.3
ACE inhibitor Sample size	% = 71.8	% = 61.9
ARB Sample size	% = 23.4	% = 28.6
Beta-blockers Sample size	% = 79.7	% = 76.2
Diuretic (loop) Sample size	% = 71.1	% = 70.7
Mineralocorticoid receptor antagonist Sample size	% = 46.1	% = 37.3
Digitalis glycoside Sample size	% = 28.9	% = 23
Implantable cardioverter-defibrillator Sample size	% = 9.4	% = 7.9
Cardiac resynchronization therapy Sample size	% = 10.2	% = 11.9
Insulin - monotherapy Sample size	% = 24.2	% = 24.6
Insulin - any Sample size	% = 35.2	% = 33.3
Diet only Sample size	% = 12.5	% = 7.1
% Female Sample size	n = 29 ; % = 22.7	n = 30 ; % = 23.8

Characteristic	Vildagliptin (N = 128)	Placebo (N = 126)
Blood pressure (mmHg) Diastolic blood pressure Mean (SD)	77.6 (8.9)	77.2 (8.7)
Class I Sample size	n = 13 ; % = 10.2	n = 12 ; % = 9.5
Class II Sample size	n = 68 ; % = 53.1	n = 66 ; % = 52.4
Class III Sample size	n = 47 ; % = 36.7	n = 48 ; % = 38.1

315. Meneghini, 2010

Bibliographic Reference	Meneghini, L. F.; Traylor, L.; Schwartz, S. L.; Improved glycemic control with insulin glargine versus pioglitazone as add-on therapy to sulfonylurea or metformin in patients with uncontrolled type 2 diabetes mellitus; Endocr Pract; 2010; vol. 16 (no. 4); 588-99

315.1. 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	US
Study setting	Medical centres (60 in total)
Study dates	11/2001 - 02/2005
Sources of funding	One of the authors is employed by Sanofi Aventis group and editorial support was also provided by the Sanofi Aventis U.S. group which suggests that they provided at least some funding towards the study.
Inclusion criteria	Included men and women 18 to 79 years old who had had type 2 diabetes for at least 6 months, with A1C levels ≥8.0% to ≤12.0% despite ≥3 months of treatment with a stable dose of either a sulfonylurea (at least half of the maximally labelled dose) or metformin (1 to 2.5 g/d). Patients were also required to have a demonstrated ability and willingness to inject insulin and to perform self-monitoring of blood glucose at least twice daily with use of a plasma-referenced glucose meter.
Exclusion criteria	• Stroke, myocardial infarction, angina, and/or cardiovascular surgical procedure within the previous 12 months

	and/or: • Congestive heart failure • Impaired renal function or liver disease • Treatment with nonselective b-adrenergic blocking agents • Acute infection • History or current signs of severe peripheral edema • Current or history of acute or chronic metabolic acidosis • History of hypoglycemia unawareness • Planned radiologic studies necessitating administration of contrast agents • Women who were pregnant, breastfeeding, or failing to use adequate contraception, if applicable • Body mass index <25 kg/m2 • Treatment with systemic corticosteroids or large doses of inhaled corticosteroids • Treatment with any diabetes medication other than those required in this study • History of cancer within the previous 5 years (except adequately treated basal cell carcinoma and adequately treated cervical carcinoma in situ) • Current or history of addiction or alcohol abuse within the past 2 years Diagnosis of dementia • Presence of any condition that may interfere with study completion or the inability to comply with study procedures
Recruitment / selection of participants	This study included men and women 18 to 79 years old who had had type 2 diabetes for at least 6 months, with A1C levels ≥8.0% to ≤12.0% despite ≥3 months of treatment with a stable dose of either a sulfonylurea (at least half of the maximally labelled dose) or metformin (1 to 2.5 g/d). Patients were randomized in a parallel-group, 2-arm, noninferiority, open-label study consisting of a 2-week screening period and a 48-week treatment phase, conducted at 60 medical centres.
Intervention(s)	Pioglitazone 15 mg - 45 mg daily. The starting dosage of pioglitazone was a single dose of 15 mg/daily titrated upward in 15-mg increments at weeks 6, 12, and 18 up to a maximum of 45 mg/daily.
Cointervention	• Sulfonylurea (glyburide/glipizide/glimepiride) • Metformin
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Exclusion criteria for congestive heart failure
Strata 2: People with atherosclerotic	People without atherosclerotic cardiovascular diseases Exclusion criteria for stroke, myocardial infarction, angina and/or cardiovascular surgical procedure within the previous 12 months

cardiovascular disease	
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Exclusion criteria for impaired renal function but not clear as to what this means
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	Insulin glargine (n=121)
Number of participants	N=247

Duration of follow-up	48 weeks
Indirectness	No additional information.
Method of analysis	Modified ITT
Additional comments	Originally designed to be a 24-week study, a revision of the titration algorithm and an extension of an additional 24 weeks (instituted through a protocol amendment) were implemented to allow patients to optimise their glycemic control fully.

315.2. Study arms

315.2.1. Pioglitazone 15 mg - 45 mg daily (N = 126)

Administered orally

315.2.2. Insulin glargine titrated (N = 121)

Administered subcutaneously at bedtime

315.3. Characteristics

315.3.1. Arm-level characteristics

Characteristic	Pioglitazone 15 mg - 45 mg daily (N = 126)	Insulin glargine titrated (N = 121)
% Male No of events	n = 62 ; % = 49	n = 58 ; % = 48
Mean age (SD) Mean (SD)	51.8 (9.8)	52.9 (10.6)
White No of events	n = 82 ; % = 65.1	n = 77 ; % = 63.6
African American No of events	n = 23 ; % = 18.3	n = 25 ; % = 20.7
Hispanic No of events	n = 19 ; % = 15.1	n = 17 ; % = 14

Characteristic	Pioglitazone 15 mg - 45 mg daily (N = 126)	Insulin glargine titrated (N = 121)
Other No of events	n = 2 ; % = 1.6	n = 2 ; % = 1.6
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 Nominal	NR	NR
Glyburide No of events	n = 11 ; % = 8.7	n = 11 ; % = 9.1
Glipizide No of events	n = 27 ; % = 21.4	n = 25 ; % = 20.7
Glimepiride No of events	n = 13 ; % = 10.3	n = 13 ; % = 10.7

316. Meneilly, 2017

Bibliographic Reference	Meneilly, G. S.; Roy-Duval, C.; Alawi, H.; Dailey, G.; Bellido, D.; Trescoli, C.; Hurtado, H. M.; Guo, H.; Pilorget, V.; Perfetti, R.; Simpson, H.; Jesien, K.; Smith, S.; Lixisenatide therapy in older patients with type 2 diabetes inadequately controlled on their current antidiabetic treatment: The GetGoal-O randomized trial; Diabetes Care; 2017; vol. 40 (no. 4); 485-493

316.1. Study details

Trial name / registration number	GetGoal-O / NCT01798706
Study type	Randomised controlled trial (RCT)
Study location	73 centres in 13 countries
Study setting	No additional information
Study dates	NR
Sources of funding	Sanofi. Numerous authors declare funding and honoraria from multiple pharmaceutical companies
Inclusion criteria	Key inclusion criteria included diagnosis of type 2 diabetes inadequately controlled with a current antidiabetic treatment regimen, age ≥70 years at the time of signing the informed consent, at least 3 months on the current antidiabetic treatment regimen, and the ability to be compliant and to complete study procedures, including self-injection. Permitted antidiabetic therapies were metformin, sulfonylurea (except glibenclamide .10 mg and gliclazide .160 mg), meglitinide (except repaglinide >6 mg), pioglitazone, and basal insulin.
Exclusion criteria	Key exclusion criteria included HbA1c ≤7% (≤53 mmol/mol) and >10% (>86 mmol/mol); however, because the threshold of 7% (53 mmol/mol) may not be appropriate for all older patients , inclusion was also based on the investigator's assessment of the individual patient, FPG >13.9 mmol/L at screening, basal insulin therapy combined with either a sulfonylurea or meglitinide, severe renal impairment (eGFR <30 mL/min/1.73 m2) at visit 6 (week 21), amylase and/or lipase >3 times the upper limit of normal at visit 6 (week 21), and a history of severe hypoglycemia associated with unawareness of symptoms or leading to unconsciousness, coma, or seizure ≤6 months before screening. Patients at risk for malnutrition as defined by a score of <12 on the Mini-Nutritional Assessment-Short Form or with moderate to severe cognitive impairment as defined by a score of <24 on the Mini Mental State Examination were excluded also.
Recruitment / selection of participants	No additional information

Intervention(s)	Lixisenatide (n=176) Lixisenatide was self administered once daily by subcutaneous injection 30–60 min before breakfast. Lixisenatide treatment was initiated at the starting dose of 10 mg once daily for 2 weeks and then increased to the maintenance dose of 20 mg, which was continued until the end of the treatment period. If the target maintenance dose was not tolerated, the lixisenatide dose could be reduced to 10 mg during the first 8 weeks of treatment. Thereafter, the maintenance dose was kept stable
Cointervention	Oral antidiabetic drug therapy: In patients who were receiving basal insulin at the start of the study and whose HbA1c was 7.0–8.0% (53–64 mmol/mol) inclusive, the basal insulin dose was reduced by 20% when lixisenatide was initiated to avoid hypoglycemia. Between study weeks 4 and 12, the insulin dose was titrated according to self-monitored plasma glucose values, and the dose was permitted to be increased to the baseline value in the absence of hypoglycemia. Patients with HbA1c between 7.0% (53 mmol/mol) and 8.5% (69 mmol/ mol) who were receiving a sulfonylurea at baseline were required to reduce the sulfonylurea dose by 25% for the first 4 weeks of lixisenatide therapy. Similarly, the sulfonylurea dose could be titrated back to the baseline dose by week 12, provided that no hypoglycemia occurred. Patients whose HbA1c was greater than the upper limits of the ranges described above did not have a mandated dose reduction of insulin or sulfonylurea at the time of lixisenatide initiation, but doses could be reduced in the case of two or more symptomatic or one severe symptomatic hypoglycemic episode.
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 Exclusion criteria for severe renal impairment (eGFR <30 mL/min/1.73m2) but not explicitly for CKD and not for all stages of CKD
Strata 4: People with type 2 diabetes	Not stated/unclear

mellitus and high cardiovascular risk	
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	eGFR ≥30mL/min/1.73m2
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	NA
Comparator	Placebo (n=173) Placebo was self administered once daily by subcutaneous injection 30–60 min before breakfast for 24 weeks Background oral antidiabetic drug therapy: In patients who were receiving basal insulin at the start of the study and whose HbA1c was 7.0–8.0% (53–64 mmol/mol) inclusive, the basal insulin dose was reduced by 20% when lixisenatide was initiated to avoid hypoglycemia. Between study weeks 4 and 12, the insulin dose was titrated according to self-monitored plasma glucose values, and the dose was permitted to be increased to the baseline value in the absence of hypoglycemia. Patients with HbA1c between 7.0% (53 mmol/mol) and 8.5% (69 mmol/ mol) who were receiving a sulfonylurea at baseline were required to reduce the sulfonylurea dose by 25% for the first 4 weeks of lixisenatide therapy. Similarly, the sulfonylurea dose could be titrated back

	to the baseline dose by week 12, provided that no hypoglycemia occurred. Patients whose HbA1c was greater than the upper limits of the ranges described above did not have a mandated dose reduction of insulin or sulfonylurea at the time of lixisenatide initiation, but doses could be reduced in the case of two or more symptomatic or one severe symptomatic hypoglycemic episode.
Number of participants	350
Duration of follow-up	24 weeks
Indirectness	NA
Method of analysis	Modified ITT
Additional comments	Efficacy analyses were performed for the modified intention-to-treat population, which was defined as all randomized patients who received at least one dose of study drug and had both a baseline assessment and at least one postbaseline assessment of any primary or secondary efficacy variables irrespective of compliance with the study protocol and procedures. Efficacy assessments were obtained during the on-treatment period (before medication was taken in the event of rescue therapy), unless otherwise specified.

316.2. Study arms

316.2.1. Lixisenatide (N = 176)

Lixisenatide was self administered once daily by subcutaneous injection 30–60 min before breakfast. Treatment was initiated at the starting dose of 10 mg once daily for 2 weeks and then increased to the maintenance dose of 20 mg, which was continued until the end of the treatment period of 24 weeks

316.2.2. Placebo (N = 174)

Placebo was self administered once daily by subcutaneous injection 30–60 min before breakfast for 24 weeks

316.3. Characteristics

316.3.1. Arm-level characteristics

Characteristic	Lixisenatide (N = 176)	Placebo (N = 174)
% Male Sample size	n = 92 ; % = 52.3	n = 90 ; % = 51.7
Mean age (SD) (Years (mean, SD)) Mean (SD)	74 (4)	74.4 (3.8)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 128 ; % = 72.7	n = 122 ; % = 70.1
Time since type 2 diabetes diagnosed (Years (mean, SD)) Mean (SD)	13.6 (7.3)	14.6 (7.9)
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 = 0 ; % = 0	n = 0 ; % = 0
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR
Basal insulin +/- OADs Sample size	n = 54 ; % = 30.7	n = 55 ; % = 31.6
Metformin +/- OADs (except sulfonylurea) Sample size	n = 52 ; % = 29.5	n = 57 ; % = 32.8
Sulfonlyurea + Metformin +/- OADs Sample size	n = 59 ; % = 33.5	n = 51 ; % = 29.3

Characteristic	Lixisenatide (N = 176)	Placebo (N = 174)
Sulfonlyurea +/- OADs (except Metformin) Sample size	n = 11 ; % = 6.3	n = 8 ; % = 4.6
OADs (except Metformin and Sulfonylurea) Sample size	n = 0 ; % = 0	n = 1 ; % = 0.6
Blood pressure-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Renin angiotensin system agents Sample size	n = 130 ; % = 73.9	n = 128 ; % = 73.6
Statins/lipid-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Lipid-modifying agents Sample size	n = 110 ; % = 62.5	n = 108 ; % = 62.1
Other treatment being received Sample size	n = NA ; % = NA	n = NA ; % = NA
Analgesics Sample size	n = 114 ; % = 64.8	n = 112 ; % = 64.4
Topical products for joint and muscular pain Sample size	n = 98 ; % = 55.7	n = 104 ; % = 59.8
Anti-thrombotic agents Sample size	n = 94 ; % = 53.4	n = 103 ; % = 59.2

317. Mentz, 2017

Bibliographic Reference	Mentz, Robert J; Bethel, M Angelyn; Gustavson, Stephanie; Thompson, Vivian P; Pagidipati, Neha J; Buse, John B; Chan, Juliana C; Iqbal, Nayyar; Maggioni, Aldo P; Marso, Steve P; Ohman, Peter; Poulter, Neil; Ramachandran, Ambady; Zinman, Bernard; Hernandez, Adrian F; Holman, Rury R; Baseline characteristics of patients enrolled in the Exenatide Study of Cardiovascular Event Lowering (EXSCEL).; American heart journal; 2017; vol. 187; 1-9

317.1. Study details

Secondary publication of another included study- see primary study for details	Holman Rury, R; Bethel M, Angelyn; Mentz Robert, J et al. (2017) Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes. The New England journal of medicine; 2017; vol. 377 (no. 13); 1228-1239
Other publications associated with this study included in review	Holman, R. R., Bethel, M. A., George, J., et al. (2016). Rationale and design of the EXenatide Study of Cardiovascular Event Lowering (EXSCEL) trial. American heart journal, 174, 103–110.
Trial name / registration number	EXSCEL trial. ClinicalTrials.gov number, NCT01144338

318. Merker, 2015

Bibliographic Reference	Merker, L; Haring, H-U; Christiansen, A V; Roux, F; Salsali, A; Kim, G; Meinicke, T; Woerle, H J; Broedl, U C; Empagliflozin as add-on to metformin in people with Type 2 diabetes.; Diabetic medicine : a journal of the British Diabetic Association; 2015; vol. 32 (no. 12); 1555-67

318.1. Study details

Secondary publication of another included study- see primary study for details	Parent study Haring 2014

319. Miller, 2019

Bibliographic Reference	Miller, Eden; Doshi, Ankur; Gron, Randi; Jodar, Esteban; Orsy, Petra; Ranthe, Mattis F; Sugimoto, Danny; Tentolouris, Nikolaos; Viljoen, Adie; Billings, Liana K; IDegLira improves patient-reported outcomes while using a simple regimen with fewer injections and dose adjustments compared with basal-bolus therapy.; Diabetes, obesity & metabolism; 2019; vol. 21 (no. 12); 2643-2650

319.1. Study details

Secondary publication of another included study- see primary study for details	Subsidiary study of Billings 2018, EPPI ID = 13679055 Billings LK, Doshi A, Gouet D, Oviedo A, Rodbard HW, Tentolouris N, Grøn R, Halladin N, Jodar E. Efficacy and Safety of IDegLira Versus Basal-Bolus Insulin Therapy in Patients With Type 2 Diabetes Uncontrolled on Metformin and Basal Insulin: The DUAL VII Randomized Clinical Trial. Diabetes Care. 2018 May;41(5):1009-1016. doi: 10.2337/dc17-1114. Epub 2018 Feb 26. PMID: 29483185.
Other publications associated with this study included in review	N/A
Trial name / registration number	DUAL VII / NCT02420262
Study location	

320. Miras, 2019

Bibliographic Reference	Miras, A. D.; Perez-Pevida, B.; Aldhwayan, M.; Kamocka, A.; McGlone, E. R.; Al-Najim, W.; Chahal, H.; Batterham, R. L.; McGowan, B.; Khan, O.; et, al.; Adjunctive liraglutide treatment in patients with persistent or recurrent type 2 diabetes after metabolic surgery (GRAVITAS): a randomised, double-blind, placebo-controlled trial; Lancet Diabetes Endocrinol; 2019; vol. 7 (no. 7); 549-559

320.1. Study details

Trial name / registration number	GRAVITAS / ISRCTN 13643081
Study type	Randomised controlled trial (RCT)
Study location	London, UK
Study setting	All assessments and interventions took place at the NIHR Imperial Clinical Research Facility at Hammersmith Hospital, UK
Study dates	February 2016 to November 2018
Sources of funding	JP Moulton Charitable Foundation. Liraglutide and Placebo pens provided by Novo Nordisk. Multiple authors declare funding and honoraria from numerous pharmaceutical companies
Inclusion criteria	Obese patients with persistent or recurrent T2DM that had undergone Roux-en-Y gastric bypass or vertical sleeve gastrectomy aged 18-70 and HbA1c >48mmol/l (>6.5%).
Exclusion criteria	Key exclusion criteria included current treatment with GLP-1 RA or dipeptidyl peptidase 4 (DPP-4) inhibitors, the presence of anatomical or endocrinological pathology causing suboptimal weight loss or weight regain (e.g. gastro-gastric fistula, hypothyroidism or Cushing's syndrome), specific contraindication to the use of GLP-1 RA, pregnancy and breastfeeding.
Recruitment / selection of participants	Patients were recruited from the Imperial College Healthcare NHS Trust, Guy's and St Thomas's NHS Foundation Trust, University College London Hospitals NHS Foundation Trust, St George's University Hospitals NHS Trust and Chelsea and Westminster Hospital NHS Foundation Trust.
Intervention(s)	Liraglutide (n=53) The starting dose was 0·6 mg/day . The dose was increased by 0·6 mg/day each week as tolerated, such that between trial week 6 and 26 all patients administered 1·8 mg/day or their maximum tolerated dose. Doses were self administered subcutaneous injections using a pen device
Cointervention	Glucose lowering agents ± Insulin

	The management of glucose-lowering agents (GLAs) was based on the NICE guideline NG28.
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 non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	People with obesity

Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Comparator	Placebo (n=27) Patients self administered placebo via subcutaneous injection using a pend device for 24 weeks Patients also received glucose lowering agents as per NICE guideline (NG28) and / or insulin (no additional information)
Number of participants	80
Duration of follow-up	24 weeks
Indirectness	NA
Method of analysis	ITT
Additional comments	The principal statistical analysis presented is a complete-cases analysis excluding patients who did not complete the final study visit at week 26. For the intention to treat (ITT) dataset analysis, imputation was done for the main clinical outcomes of the study (HbA1c, weight). Missing data was assumed to be missing at random (MAR). Where the missing value occurred at the baseline visit, available data from the screening visit was used. If the missing value occurred at the end of a time series, a Last Observation Carried Forward rule was used. Missing data within a time series was imputed using a mean imputation rule. Primary statistical comparisons were performed with a multivariable linear regression analysis for each of the following outcomes (change from baseline to week 26 of HbA1c, weight, systolic and diastolic BP, lipid parameters, King's Obesity Staging Criteria score) using the treatment assignment (Liraglutide or Placebo), baseline values of the outcome variable and type of surgery (VSG or RYGB) as covariates.

320.2. Study arms

320.2.1. Liraglutide (N = 53)

Patients received up to 1.8 mg liraglutide per day subcutaneously for 24 weeks

320.2.2. Placebo (N = 27)

Patients received placebo subcutaneously for 24 weeks

320.3. Characteristics

320.3.1. Arm-level characteristics

Characteristic	Liraglutide (N = 53)	Placebo (N = 27)
% Male Sample size	n = 20 ; % = 37.8	n = 13 ; % = 48.1
Mean age (SD) (Years (mean, SD)) Mean (SD)	54.8 (9.4)	57.2 (8.1)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed (Years (mean, SD)) Mean (SD)	16.4 (7)	19.6 (8)
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
1 oral glucose lowering agent (GLA) Sample size	n = 13 ; % = 25	n = 5 ; % = 19
2 GLAs	n = 30 ; % = 57	n = 15 ; % = 56

Characteristic	Liraglutide (N = 53)	Placebo (N = 27)
Sample size		
3 GLAs Sample size	n = 2 ; % = 4	n = 1 ; % = 4
Insulin Sample size	n = 15 ; % = 28	n = 6 ; % = 22
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

321. Moeinzadeh, 2021

Bibliographic Reference	Moeinzadeh, F.; Iraj, B.; Mortazavi, M.; Ramezani, P.; The Renoprotective Effect of Linagliptin in Type 2 Diabetic Patients with Severely Increased Albuminuria; Iranian journal of Kidney Diseases; 2021; vol. 15 (no. 5); 344-350

321.1. Study details

Secondary publication of another included study- see primary study for details	NR
Other publications associated with this study included in review	NR
Trial name / registration number	Study protocol approved by ethics committee IRCT20090905002417N23
Study type	Randomised controlled trial (RCT)
Study location	Iran
Study setting	Nephrology clinic, Alzahra Hospital
Study dates	NR
Sources of funding	NR
Inclusion criteria	• Adult (≥ 18 years) with type 2 diabetic • a eGFR of 30 to 60 mL/min/ 1.73m2 or urinary albumin excretion of more than 300 mg/24h
Exclusion criteria	Unstable doses of anti-hypertensive medications, poor compliance, impaired hepatic function, pancreatitis, use of any other DPP-4 inhibitor, using weight control, and immunosuppressive medications during last 3 months.

Recruitment / selection of participants	140 patients were screened and 136 patient were randomised. All patients were completely informed about study objectives and signed an informed consent form before the enrolment. Patients who met the inclusion criteria were subjected to a 6-month treatment period.
Intervention(s)	5 mg/d Linagliptin
Cointervention	Doses of other glucose-lowering medication were reduced in patients who experienced hypoglycaemia during the study period.
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	People with chronic kidney disease Inclusion criteria of people with severely increased albuminuria (>300mg/24hr) and reduced eGFR (eGFR 30-60 mL/min/1.73m2). People referred to nephrology clinic.
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 eGFR 30-60 mL/min/1.73 m2
Subgroup 6: Albuminuria category at baseline	A3 (ACR >300mg/g or >30mgmmol)
Population subgroups	Subgroup analysis was conducted based on Statin and angiotensin II receptor blocker (ARB) use.
Comparator	Placebo
Number of participants	136 participants were randomised. Out of 68 participants in the intervention arm, 6-month follow-up was completed for 68 participants, and data were analysed for 62 participants. Out of 68 participants in the control arm, 2 participants were excluded due to gastrointestinal symptoms, and 3 were excluded due to poor compliance. Therefore, in the control arm, 63 participants completed 6-month follow-up, and 59 participants were analysed.
Duration of follow-up	6 months
Indirectness	Indirectly applicable - the study did not specifically recruit participants that were currently receiving treatment for T2D. However, a high proportion of participants were receiving insulin and/or oral anti-hypoglycaemic agents.
Method of analysis	Not stated/unclear The method of analysis was unclear. The participant flow diagram states that 62 participants out of 68 participants randomised to the intervention group, and 59 out of 68 participants randomised to the control group were included in the analysis. However, the participant flow diagram also states that 68 out of 68 participants randomised to the intervention group and 68 out of 68 participants randomised to the control group completed the 6-month follow-up, and it is unclear why all these participants were not included in the analysis.
Additional comments	None

321.2. Study arms

321.2.1. Linagliptin (N = 68)

321.2.2. Placebo (N = 68)

321.3. Characteristics

321.3.1. Arm-level characteristics

Characteristic	Linagliptin (N = 68)	Placebo (N = 68)
% Male n calculated by analyst. Reported characteristics were for analysed patients only. Linagliptin n=62, placebo n=59. Sample size	n = 40 ; % = 58.8	n = 28 ; % = 47.7
Mean age (SD) Mean (SD)	62.16 (12.82)	58.06 (13.15)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed Reported characteristics were for analysed patients only. Linagliptin n=62, placebo n=59. Sample size	n = 13.68 ; % = 9.13	n = 10.87 ; % = 6.53
Smoking status Nominal	NR	NR
Alcohol consumption Nominal	NR	NR
Presence of severe mental illness Nominal	NR	NR

Characteristic	Linagliptin (N = 68)	Placebo (N = 68)
People with significant cognitive impairment Nominal	NR	NR
People with a learning disability Nominal	NR	NR
Number of people with obesity Nominal	NR	NR
eGFR mL/min/1.73m2 Nominal	NR	NR
Other antidiabetic medication used Reported characteristics were for analysed patients only. Linagliptin n=62, placebo n=59. Sample size	n = NA	n = NA
Insulin Sample size	n = 13 ; % = 20.9	n = 11 ; % = 18.8
Oral hypoglycaemic agents Sample size	n = 29 ; % = 46.3	n = 41 ; % = 68.8
Both Sample size	n = 20 ; % = 32.8	n = 7 ; % = 12.4
Blood pressure-lowering medication used Reported characteristics were for analysed patients only. Linagliptin n=62, placebo n=59. Sample size	n = NA	n = NA
Angiotensin-converting-enzyme (ACE) inhibitor Sample size	n = 40 ; % = 65	n = 21 ; % = 35
Angiotensin II receptor blocker (ARB) Sample size	n = 48 ; % = 78.2	n = 13 ; % = 21.8
Statins Sample size	n = 40 ; % = 64.6	n = 21 ; % = 35.4
Statins/lipid-lowering medication used Nominal	NR	NR

Characteristic	Linagliptin (N = 68)	Placebo (N = 68)
Other treatment being received Nominal	NR	NR

322. Moon, 2014

Bibliographic Reference	Moon, J. S.; Ha, K. S.; Yoon, J. S.; Lee, H. W.; Lee, H. C.; Won, K. C.; The effect of glargine versus glimepiride on pancreatic beta-cell function in patients with type 2 diabetes uncontrolled on metformin monotherapy: Open-label, randomized, controlled study; Acta Diabetol; 2014; vol. 51 (no. 2); 277-285

322.1. 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	NCT00562172
Study type	Randomised controlled trial (RCT)
Study location	Korea
Study setting	Hospital
Study dates	09/2007 to 10/2009
Sources of funding	
Inclusion criteria	Patients with type 2 diabetes, aged 18–75 years, with HbA1c 7.5–12.0 % (58–108 mmol/ mol), BMI\35 kg/m2 , and who received metformin treatment at a dose of >1,000 mg/day for [3 months, prior to enrolment, were eligible.
Exclusion criteria	Patient with type 1 diabetes, gestational diabetes or diabetes with identifiable secondary causes, significant renal impairment (serum creatinine C 1.5 mg/ dL [133 lmol/L] in men, and 1.4 mg/dl [124 lmol/L] in women), or alanine aminotransferase/aspartate aminotransferase (ALT/AST) [3 times the upper limit of its normal range at study entry.

	Patients taking medications (other than antidiabetic medications) known to affect glycemic control, such as glucocorticoids, were also excluded.
Recruitment / selection of participants	Participants with type 2 diabetes uncontrolled on metformin monotherapy were screened and recruited from 10 hospitals to the multi-centre trial conducted in Korea. Participants were randomised to glimepiride or insulin glargine in a 1:1 ratio.
Intervention(s)	Glimepiride 1-8 mg daily
Cointervention	Metformin dose >1,000 mg daily
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 Exclusion criteria for significant renal impairment based on creatinine but not explicitly 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
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	Insulin glargine; titrated every three days by 2 IU after starting at 0.2 U/kg of body weight to target a fasting blood glucose (FBG) level of 90–130 mg/dL. Administered subcutaneously.
Number of participants	N= 75
Duration of follow-up	52-week study
Indirectness	None
Method of analysis	Modified ITT
Additional comments	Analysis was performed on all randomised patients who received at least one does of study medication and who had both baseline and follow-up measurements.

322.2. Study arms

322.2.1. Glimepiride 1-8 mg daily (N = 36)

Administered orally

322.2.2. Insulin glargine daily (N = 39)

Administered subcutaneously

322.3. Characteristics

322.3.1. Arm-level characteristics

Characteristic	Glimepiride 1-8 mg daily (N = 36)	Insulin glargine daily (N = 39)
% Male No of events	n = 17 ; % = 47.1	n = 12 ; % = 31.6
Mean age (SD) Mean (SD)	54.9 (8.6)	51.3 (8.1)
Korean No of events	n = 36 ; % = 100	n = 39 ; % = 100
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed (Months) Mean (SD)	95.6 (72.2)	79 (59.9)
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
Albumin creatinine ratio	NR	NR

Characteristic	Glimepiride 1-8 mg daily (N = 36)	Insulin glargine daily (N = 39)
Nominal		
Metformin No of events	n = 36 ; % = 100	n = 39 ; % = 100
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

323. Morikawa, 2011

Bibliographic Reference	Morikawa, A.; Ishizeki, K.; Iwashima, Y.; Yokoyama, H.; Muto, E.; Oshima, E.; Sekiguchi, M.; Miura, T.; Itoh, H.; Haneda, M.; Pioglitazone reduces urinary albumin excretion in renin-angiotensin system inhibitor-treated type 2 diabetic patients with hypertension and microalbuminuria: the APRIME study; Clin Exp Nephrol; 2011; vol. 15 (no. 6); 848-53

323.1. 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	UMIN000004367. APRIME study (Asahikawa Prospective Pioglitazone in Microalbuminuria Effect)
Study type	Randomised controlled trial (RCT)
Study location	Japan
Study setting	Hospital
Study dates	1/1/2005-1/6/2008
Sources of funding	Takeda Pharmaceutical Company, Japan
Inclusion criteria	1.Type 2 diabetic patient 2.Patient who is treated with diet alone, insulin or oral hypoglycemic agents except metformin and/or pioglitazone (only clinically used thiazolidinedione in Japan). If metformin and/or pioglitazone had already been administered, they were withdrawn from patient at 4 weeks before screening. 3.HbA1c between 6.9% and 9.4% with stable glycemic control 4.Patient who is receiving anti-hypertensive treatment with RAS-Is over 12 weeks. 5.Patient with microalbuminuria (defined by twice measured urinary

	albumin-to-creatinine ratio of 30 mg/gCr or greater and less than 300 mg/gCr in first morning urine samples in the screening period. Age-lower limit: 20 years-old<= Age-upper limit: 70 years-old >=
Exclusion criteria	1.serum creatinine >1.5 mg/dl at baseline 2.a history of side effects with pioglitazone or metformin. 3.present or past history of congestive heart failure, myocardial infarction, pulmonary embolism. 4.alanine aminotransferase (ALT) or aspartate aminotransferase (AST) values > twofold the upper limit of normal. 5.pregnancy
Recruitment / selection of participants	Type 2 diabetic patients, aged 20–70 years, inadequately treated with diet alone, with insulin or with oral hypoglycemic agents except metformin and/or pioglitazone
Intervention(s)	After treatment of hypertension at least 12 weeks with angiotensin receptor blockers (ARBs) or angiotensin converting enzyme inhibitors (ACE-Is) in usual dose, patients receive pioglitazone 15mg/day. Pioglitazone dose is titrated up to 30 mg after 4 weeks and maintained to 52 weeks of treatment.
Cointervention	Diet only (<20%), insulin or other OAHs. Angiotensin receptor blockers (ARBs) or angiotensin converting enzyme inhibitors (ACE-Is) in usual dose
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear
Strata 2: People with atherosclerotic cardiovascular disease	People without atherosclerotic cardiovascular diseases No events at baseline
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear People with microalbuminuria but not explicitly stated that people have CKD
Strata 4: People with type 2 diabetes	Not stated/unclear

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	eGFR ≥30mL/min/1.73m2 Baseline eGFR (ml/min/1.73 m2) 79 ± 3.4 and 75 ± 3.3 indicates these values are comfortably above 30.
Subgroup 6: Albuminuria category at baseline	A2 (ACR 30-300 mg/g or 3-30mg/mmol) microalbuminuria (defined by twice measured UACR C30 mg/g Cr and \300 mg/ g Cr in first-morning urine samples in the screening period)
Population subgroups	NA
Comparator	After treatment of hypertension at least 12 weeks with angiotensin receptor blockers (ARBs) or angiotensin converting enzyme inhibitors (ACE-Is) in usual dose, patients receive metformin 500 or 750mg/day. Metformin dose is titrated up to 750mg/day to achieve HbA1c less than 6.9%, and maintained to 52 weeks of treatment.
Number of participants	70 randomised. Because two of the randomized patients were withdrawn before the start of therapy, the actual number of patients was 36 in the pioglitazone group and 32 in the metformin group. Five patients (n = 4 with pioglitazone; n = 1 with metformin) were not eligible for ITT analysis due to missing post-baseline data
Duration of follow-up	52 weeks
Indirectness	None

Method of analysis	Modified ITT
Additional comments	intention-to-treat (ITT) analysis with last observation carried forward. The ITT population included all randomized patients who had at least one post-baseline data point for any parameter. Safety and tolerability were assessed in all patients who received at least one dose of study medicine.

323.2. Study arms

323.2.1. Pioglitazone (N = 32)

pioglitazone 15mg/day. Pioglitazone dose is titrated up to 30 mg after 4 weeks

323.2.2. Metformin (N = 31)

metformin 500 or 750mg/day. Metformin dose is titrated up to 750mg/day to achieve HbA1c less than 6.9%

323.3. Characteristics

323.3.1. Arm-level characteristics

Characteristic	Pioglitazone (N = 32)	Metformin (N = 31)
% Male Nominal	75	67.7
Mean age (SD) Mean (SD)	62.5 (1.8)	62.4 (1.5)
Ethnicity Nominal	NR	NR
Retinopathy Nominal	53.1	61.3
Neuropathy Nominal	46.9	54.8
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed (years)	9.5 (1)	11.6 (1.3)

Characteristic	Pioglitazone (N = 32)	Metformin (N = 31)
Mean (SD)		
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
People with significant cognitive impairment Nominal	NR	NR
People with a learning disability Nominal	NR	NR
Number of people with obesity Nominal	NR	NR
Albumin creatinine ratio Mean (95% CI)	143 (84 to 202)	111 (85 to 139)
eGFR mL/min/1.73m2 Mean (SD)	79 (3.4)	75 (3.3)
Diet only Nominal	21.9	16.1
Sulfonlyurea Nominal	59.4	64.5
Alpha glucosidase inhibitors Nominal	21.9	16.1
Glinide Nominal	9.4	3.2
insulin or analog Nominal	15.6	16.1

Characteristic	Pioglitazone (N = 32)	Metformin (N = 31)
Calcium-channel blocker Nominal	53.1	41.9
Diuretic Nominal	6.3	9.7
alpha blocker Nominal	3.5	6.5
Beta blocker Nominal	3.5	6.5
Statin Nominal	31.1	41.9
Fibrate Nominal	3.1	6.5
Renin angiotensin system blockers Nominal	100	100

324. Mosenzon, 2019

Bibliographic Reference	Mosenzon, O.; Blicher, T. M.; Rosenlund, S.; Eriksson, J. W.; Heller, S.; Hels, O. H.; Pratley, R.; Sathyapalan, T.; Desouza, C.; Abramof, R.; et, al.; Efficacy and safety of oral semaglutide in patients with type 2 diabetes and moderate renal impairment (PIONEER 5): a placebo-controlled, randomised, phase 3a trial; Lancet Diabetes Endocrinol; 2019; vol. 7 (no. 7); 515-527

324.1. Study details

Secondary publication of another included study- see primary study for details	Not applicable
Other publications associated with this study included in review	Not applicable
Trial name / registration number	PIONEER 5 European Clinical Trials Database, EudraCT 2015-005326-19 ClinicalTrials.gov, number NCT02827708.
Study type	Randomised controlled trial (RCT)
Study location	88 sites in Denmark, Finland, Israel, Poland, Russia, Sweden, the UK, and the USA
Study setting	Not reported
Study dates	Screening was conducted between Sept 20, 2016, and Sept 29, 2017
Sources of funding	Novo Nordisk
Inclusion criteria	• Aged 18 years or older with type 2 diabetes (diagnosed ≥90 days before screening) • HbA1c of 7.0 to 95% (53–80 mmol/mol) • Moderate renal impairment (Chronic Kidney Disease-Epidemiology Collaboration [CKD-EPI] stage 3), defined as an eGFR of 30–59 mL/min per 1.73 m2, calculated by use of the CKD-EPI formula • Required to be able to provide informed consent

	• Required to be treated with stable doses of one of the following regimens for 90 days before screening: metformin (≥1500 mg or maximum tolerated dose), a sulfonylurea (at least half of the maximum approved dose or maximum tolerated dose), or both; or basal insulin with or without metformin.
Exclusion criteria	• Rapidly progressing renal disease or known nephrotic albuminuria (>2200 mg per 24 h or >2200 mg/g) • Family or personal history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma • History of malignant neoplasms within the past 5 years • History of pancreatitis; myocardial infarction, stroke, or admission to hospital for unstable angina or transient ischaemic attack within the past 180 days, • New York Heart Association Class IV heart failure • Proliferative retinopathy or maculopathy (determined by fundus photography or dilated fundoscopy 90 days or fewer before randomisation and requiring acute treatment).
Recruitment / selection of participants	Not reported
Intervention(s)	Once-daily oral semaglutide escalated to 14 mg. Oral semaglutide was initiated at a 3 mg dose, then escalated to 7 mg at 4 weeks, and 14 mg at 8 weeks. No dose adjustment of study drug were permitted during the trial. [Both groups were instructed to take the medication in the morning in a fasted state with up to half a glass of water (approximately 120 mL), 30 min before any other food, beverage, or other oral medication.]
Cointervention	• Background glucose-lowering medication throughout the trial. Patients receiving metformin and sulfonylureas were required to maintain the same dose level and frequency as at trial entry. Patients receiving basal insulin were recommended to have the dose decreased by 20% after random assignment to treatment group to minimise the risk of hypoglycaemic episodes. • Up-titration of basal insulin (to a dose not exceeding that at randomisation) was permitted in weeks 10–16, after the maximum dose of oral semaglutide was reached. • Patients with persistent and unacceptable hyperglycaemia were offered treatment intensification with rescue medication, as an add-on to assigned treatment.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Exclusion criteria for NYHA class IV heart failure but unclear about other stages

Strata 2: People with atherosclerotic cardiovascular disease	People without atherosclerotic cardiovascular diseases Exclusion criteria for admission with myocardial infarction, stroke, unstable angina or TIA within the past 180 days
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	People with chronic kidney disease CKD stage 3
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	Mixed population

Population subgroups	Moderate renal impairment
Comparator	Placebo
Number of participants	Intervention: 163 participants assigned, 163 received treatment, 30 discontinued treatment, 5 withdrew from trial, 133 completed treatment, 127 completed treatment without rescue medication, 158 completed trial Comparator: 161 participants assigned, 161 received treatment, 20 discontinued treatment, 5 withdrew from trial, 141 completed treatment, 127 completed treatment without rescue medication, 156 completed trial
Duration of follow-up	26 weeks
Indirectness	Directly applicable
Method of analysis	ITT HbA1c and bodyweight outcomes were analyses by analysis of covariance using data irrespective of discontinuation of trial product or initiation of rescue medication using a pattern mixture model with multiple imputation to handle missing data at week 26 for both confirmatory endpoints. Binary endpoints were analysed using a logistic regression model, and for the treatment policy estimand, missing data were imputed similarly as for the continuous endpoints. Safety endpoints during the on-treatment and in-trial periods using data from all participants exposed to a study drug (the safety analysis set). Sensitivity analyses were performed on the primary and confirmatory secondary endpoints, primarily to assess the effect of missing data.
Additional comments	• The primary estimand was treatment policy, which was defined as effect regardless of treatment discontinuation or rescue medication. • The secondary estimand was trial product policy, which was defined as effect on treatment without rescue medication. • Patients who prematurely discontinued their allocated treatment (eg, due to adverse events) were switched to an appropriate locally approved treatment selected at the investigator's discretion, excluding GLP-1 receptor agonists. All participants were asked to complete the protocol-specified visit schedule, regardless of premature discontinuation of allocated treatment or use of rescue medication, unless consent was withdrawn. • Sample size was calculated to ensure a power of 90% or more for testing superiority of oral semaglutide versus placebo in change of HbA1c for the treatment policy estimand.

324.2. Study arms

324.2.1. Semaglutide (N = 163)

324.2.2. Placebo (N = 161)

324.3. Characteristics

324.3.1. Arm-level characteristics

Characteristic	Semaglutide (N = 163)	Placebo (N = 161)
% Male Sample size	n = 83 ; % = 51	n = 73 ; % = 45
Mean age (SD) Mean (SD)	71 (8)	70 (8)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 158 ; % = 97	n = 152 ; % = 94
Black or African American Sample size	n = 4 ; % = 2	n = 9 ; % = 6
Asian Sample size	n = 1 ; % = 1	n = 0 ; % = 0
Hispanic or Latino Sample size	n = 7 ; % = 4	n = 14 ; % = 9
Time since type 2 diabetes diagnosed (years) Mean (SD)	14.1 (8.6)	13.9 (7.4)
HbA1c (%) Mean (SD)	8 (0.7)	7.9 (0.7)
Cardiovascular risk factors Nominal	NR	NR
Smoking status Nominal	NR	NR

Characteristic	Semaglutide (N = 163)	Placebo (N = 161)
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)	91.3 (17.8)	90.4 (17.5)
BMI (kg/m2) Mean (SD)	32.2 (5.4)	32.6 (5.5)
Number of people with obesity Nominal	NR	NR
Albumin creatinine ratio Median (IQR)	19.2 (7.4 to 114.9)	14.1 (5.5 to 90.8)
eGFR mL/min/1.73m2 Mean (SD)	47 (10)	48 (10)
Other antidiabetic medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Metfomin/metformin hydrochloride Sample size	n = 132 ; % = 81	n = 110 ; % = 68.3
Sulfonlyureas Sample size	n = 65 ; % = 39.9	n = 66 ; % = 41
Insulin and analogues - Long-acting Sample size	n = 59 ; % = 36.2	n = 55 ; % = 34.2
Insulin and analogues - intermediate-acting Sample size	n = 13 ; % = 8	n = 11 ; % = 6.8
Insulin and analogues - fast-acting	n = 0 ; % = 0	n = 1 ; % = 0.6

Characteristic	Semaglutide (N = 163)	Placebo (N = 161)
Sample size		
Insulin and analogues - combined Sample size	n = 1 ; % = 0.6	n = 0 ; % = 0
Repaglinide Sample size	n = 0 ; % = 0	n = 1 ; % = 0.6
Blood pressure-lowering medication used Nominal	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

325. Mosenzon, 2017

Bibliographic Reference	Mosenzon, Ofri; Leibowitz, Gil; Bhatt Deepak, L; Cahn, Avivit; Hirshberg, Boaz; Wei, Cheryl; Im, KyungAh; Rozenberg, Aliza; Yanuv, Ilan; Stahre, Christina; Ray Kausik, K; Iqbal, Nayyar; Braunwald, Eugene; Scirica Benjamin, M; Raz, Itamar; Effect of Saxagliptin on Renal Outcomes in the SAVOR-TIMI 53 Trial.; Diabetes care; 2017; vol. 40 (no. 1); 69-76

325.1. Study details

Secondary publication of another included study- see primary study for details	Parent study: Scirica et al (2013) Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. The New England journal of medicine; 2013; vol. 369 (no. 14); 1317-26
Other publications associated with this study included in review	NA
Trial name / registration number	SAVOR-TIMI ClinicalTRials.gov number NCT01107886
Study type	Randomised controlled trial (RCT)
Study location	See parent study
Study setting	See parent study
Study dates	See parent study
Inclusion criteria	
Exclusion criteria	See parent study
Recruitment / selection of participants	See parent study
Intervention(s)	See parent study

Strata 1: People with type 2 diabetes mellitus and heart failure	Mixed population See parent study
Strata 2: People with atherosclerotic cardiovascular disease	Mixed population See parent study
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	People at higher risk of developing cardiovascular disease See parent study
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Mixed population See parent study
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Mixed population See parent study

Subgroup 5: eGFR category at baseline	Mixed population See parent study for details. Results in this paper include: Mean change in ACR by baseline eGFR categories (<30, 30-50, >50) for saxagliptin and placebo at 1 and 2 y.
Subgroup 6: Albuminuria category at baseline	Mixed population Outcomes (change in categorical ACR reported according to ACR category at baseline (in line with A1/2/3) ie <30mg/g, 30-300 mg/g, >300 mg/g
Population subgroups	Additional analyses available on correlation between changes in ACR and changes in HbA1c (on treatment analysis)
Comparator	Matching placebo
Number of participants	16492
Duration of follow-up	2.1 years (median, IQR 1.8-2.3)
Indirectness	No concerns
Method of analysis	ITT
Additional comments	Baseline characteristics according to category of ACR (<30, 30-300, >300 mg/g) are reported.

325.2. Study arms

325.2.1. Saxagliptin (N = 8280)

Saxagliptin at dose of 5mg daily or 2.5mg daily in patients with an estimated GFR<=50ml per minute

325.2.2. Placebo (N = 8212)

Matching placebo

326. Mosenzon, 2019

Bibliographic Reference	Mosenzon, Ofri; Wiviott Stephen, D; Cahn, Avivit; Rozenberg, Aliza; Yanuv, Ilan; Goodrich Erica, L; Murphy Sabina, A; Heerspink Hiddo J, L; Zelniker Thomas, A; Dwyer Jamie, P; Bhatt Deepak, L; Leiter Lawrence, A; McGuire Darren, K; Wilding John P, H; Kato Eri, T; Gause-Nilsson Ingrid A, M; Fredriksson, Martin; Johansson Peter, A; Langkilde Anna, Maria; Sabatine Marc, S; Raz, Itamar; Effects of dapagliflozin on development and progression of kidney disease in patients with type 2 diabetes: an analysis from the DECLARE-TIMI 58 randomised trial.; The lancet. Diabetes & endocrinology; 2019; vol. 7 (no. 8); 606-617

326.1. Study details

Secondary publication of another included study- see primary study for details	Mosenzon 2019A. DECLARE-TIMI 58 trial. Wiviott Stephen, D, Raz, Itamar, Bonaca Marc, P et al. (2019) Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. The New England journal of medicine 380(4): 347-357
Other publications associated with this study included in review	Wiviott et al. (2018) The design and rationale for the Dapagliflozin Effect on Cardiovascular Events (DECLARE)-TIMI 58 Trial. American heart journal; 2018; vol. 200; 83-89 Zelniker T, A, Bonaca M, P, Furtado R, H.M et al. (2020) Effect of dapagliflozin on atrial fibrillation in patients with type 2 diabetes mellitus: Insights from the DECLARE-TIMI 58 Trial. Circulation: 1227-1234 Zelniker, Thomas A, Raz, Itamar, Mosenzon, Ofri et al. (2021) Effect of Dapagliflozin on Cardiovascular Outcomes According to Baseline Kidney Function and Albuminuria Status in Patients With Type 2 Diabetes: A Prespecified Secondary Analysis of a Randomized Clinical Trial. JAMA cardiology 6(7): 801-810 Cahn et al. (2021) Cardiovascular, Renal, and Metabolic Outcomes of Dapagliflozin Versus Placebo in a Primary Cardiovascular Prevention Cohort: Analyses From DECLARE-TIMI 58. Diabetes care; 2021; vol. 44 (no. 5); 1159-1167
Trial name / registration number	DECLARE-TIMI 58 trial. ClinicalTrials.gov number, NCT01730534

326.2. Study arms

326.2.1. Dapagliflozin (N = 8582)

Oral dapagliflozin 10mg daily for median follow up of 4.2 years. Concomitant therapy: A variety of other medication was used concomitantly, including other glucose-lowering therapies. For more information see the baseline characteristics table.

326.2.2. Placebo (N = 8578)

Oral matching placebo daily for a median follow up of 4.2 years. Concomitant therapy: A variety of other medication was used concomitantly, including other glucose-lowering therapies. For more information see the baseline characteristics table.

327. Moses, 2014

Bibliographic Reference	Moses, R. G.; Kalra, S.; Brook, D.; Sockler, J.; Monyak, J.; Visvanathan, J.; Montanaro, M.; Fisher, S. A.; A randomized controlled trial of the efficacy and safety of saxagliptin as add-on therapy in patients with type 2 diabetes and inadequate glycaemic control on metformin plus a sulphonylurea; Diabetes Obes Metab; 2014; vol. 16 (no. 5); 443-450

327.1. 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	EudraCT Number: 2010-019428-30 Protocol number: D1680L00006
Study type	Randomised controlled trial (RCT)
Study location	Conducted in 35 outpatient centres in the following countries: • Australia • Canada • India • Korea • Thailand • UK
Study setting	Outpatient centre
Study dates	06/2010 - 06/2011
Sources of funding	Bristol-Myers Squibb and Astra Zeneca

Inclusion criteria	• ≥18 years old with type 2 diabetes • BMI ≤40 kg/m2 • Inadequate glycaemic control [HbA1c, 7.0–10.0% (53–86 mmol/mol)] on combination therapy with a stable maximum tolerated dose of metformin immediate release (IR) or extended release (XR) (≥1500 mg, either formulation) plus a sulphonylurea (≥50% of the maximum recommended dose) daily for ≥8 weeks before screening. • Women of childbearing potential were required to be using an adequate method of contraception and have a negative urine pregnancy test at visit 2 and each visit thereafter.
Exclusion criteria	• Symptoms of poorly controlled diabetes; • Estimated creatinine clearance (CrCl) <1.0 ml/s or creatinine kinase ≥10 times upper limit of normal (ULN) at visit 2 • Congestive heart failure (New York Heart Association class III or IV and/or left ventricular ejection fraction <40%); active liver disease and/or significant abnormal liver function (aspartate aminotransferase >3 times ULN and/or alanine aminotransferase >3 times ULN and/or bilirubin >34.2 µmol/l at visit 2); history of haemoglobinopathies; history of alcohol abuse or drug abuse ≤12 months before screening; use of insulin, DPP-4 inhibitors, GLP-1 analogues or oral antidiabetic agents other than metformin and sulphonylureas currently or within 3 months of screening; treatment with systemic glucocorticoids other than replacement therapy; treatment with cytochrome P450 3A4 inducers or potent 3A4 or 3A5 inhibitors; and pregnancy or breast-feeding.
Recruitment / selection of participants	Patients with type 2 diabetes from 35 outpatient centres in Australia, Canada, India, Korea, Thailand and the UK were recruited and randomised to saxagliptin or placebo.
Intervention(s)	Saxagliptin 5 mg daily, administered orally
Cointervention	Metformin and sulphonylurea
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Congestive heart failure (NYHA class III-IV and/or LVEF <40%)
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear
Strata 3: People with type 2	Not stated/unclear

diabetes mellitus and 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	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	
Comparator	Placebo administered orally
Number of participants	N=257
Duration of follow-up	24 weeks

Method of analysis	ITT
Additional comments	

327.2. Study arms

327.2.1. Saxagliptin 5 mg daily (N = 129)

Administered orally

327.2.2. Placebo daily (N = 128)

Administered orally

327.3. Characteristics

327.3.1. Arm-level characteristics

Characteristic	Saxagliptin 5 mg daily (N = 129)	Placebo daily (N = 128)
% Male No of events	n = 80 ; % = 62	n = 74 ; % = 57.8
Mean age (SD) Mean (SD)	57.2 (9.6)	56.8 (11.5)
White No of events	n = 59 ; % = 45.7	n = 57 ; % = 44.5
Asian No of events	n = 70 ; % = 54.3	n = 71 ; % = 55.5
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed Nominal	NR	NR
Smoking status	NR	NR

Characteristic	Saxagliptin 5 mg daily (N = 129)	Placebo daily (N = 128)
Nominal		
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 = 129 ; % = 100	n = 128 ; % = 100
Sulfonylurea No of events	n = 129 ; % = 100	n = 128 ; % = 100
Blood pressure-lowering medication used Nominal	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

328. Moses, 2017

Bibliographic Reference	Moses, RG; Round, E; Shentu, Y; Golm, GT; O'Neill, EA; Gantz, I; Engel, SS; Kaufman, KD; Goldstein, BJ; A randomized clinical trial evaluating the safety and efficacy of sitagliptin added to the combination of sulfonylurea and metformin in patients with type 2 diabetes mellitus and inadequate glycemic control; J Diabetes; 2017; vol. 8 (no. 5); 701-711

328.1. 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	NCT01076075
Study type	Randomised controlled trial (RCT)
Study location	USA
Study setting	Not reported.
Study dates	06/2010 - 01/2012
Sources of funding	Merck & Co., Inc. (Kenilworth, NJ, USA).
Inclusion criteria	• Type 2 diabetes mellitus • Hemoglobin A1C of ≥7.5% and ≤10.5% • Currently taking a stable dose of metformin (at least 1500 mg/day) and either glimepiride (at least 2 mg/day) or gliclazide (at least 50% of maximum registered dose) for at least 10 weeks prior to study start • Male, or a female who is highly unlikely to conceive

Exclusion criteria	Patients were excluded for the following reasons: • if they had type 1 diabetes mellitus, • a history of ketoacidosis, • previous treatment with either a DPP-4 inhibitor or a GLP-1 receptor agonist • required insulin therapy within 12 weeks prior to signing informed consent • they had a significant cardiovascular disorder within the prior 3months • renal impairment (estimated creatinine clearance <60mL/min) • elevated (>2-fold the upper limit of normal) alanine aminotransferase or aspartate aminotransferase, or fasting fingerstick glucose <7.2 mmol/L or >14.4mmol/L at randomisation.
Recruitment / selection of participants	Patients with uncontrolled type 2 diabetes mellitus from 48 sites in 9 countries and on a stable dose of either glimepiride or gliclazide and metformin for 10 weeks prior to screening for the study were randomised 1:1 to either sitagliptin 100 mg/day or matching placebo.
Intervention(s)	Sitagliptin 100 mg once daily; administered orally.
Cointervention	Metformin and sulfonylurea (glimepiride/gliclazide). Patients continued on their pre-study stable doses of sulfonylurea and metformin, which were to remain stable unless down-titration of sulfonylurea was required to manage hypoglycemia.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear
Strata 2: People with atherosclerotic cardiovascular disease	People without atherosclerotic cardiovascular diseases Exclusion criteria for significant cardiovascular disorder
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Exclusion criteria for people with renal impairment (estimated creatinine clearance <60mL/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
Comparator	Placebo daily; administered orally.
Number of participants	N=427
Duration of follow-up	24 weeks
Indirectness	No additional information.
Method of analysis	Modified ITT

328.2. Study arms

328.2.1. Sitagliptin 100 mg daily (N = 213)

Administered orally

328.2.2. Placebo once daily (N = 214)

Administered orally

328.3. Characteristics

328.3.1. Arm-level characteristics

Characteristic	Sitagliptin 100 mg daily (N = 213)	Placebo once daily (N = 214)
% Male No of events	n = 95 ; % = 45.2	n = 98 ; % = 46.2
Mean age (SD) (years) Mean (SD)	54.4 (9.6)	55.4 (10.2)
Hispanic or Latino No of events	n = 2 ; % = 1	n = 0 ; % = 0
Not Hispanic or Latino % No of events	n = 208 ; % = 99	n = 212 ; % = 100
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	7.5 (5.4)	8 (5.3)
HbA1c (%) Mean (SD)	8.4 (0.8)	8.4 (0.9)
Smoking status Nominal	NR	NR
Alcohol consumption	NR	NR

Characteristic	Sitagliptin 100 mg daily (N = 213)	Placebo once daily (N = 214)
Nominal		
Presence of severe mental illness Nominal	NR	NR
People with significant cognitive impairment Nominal	NR	NR
People with a learning disability Nominal	NR	NR
Number of people with obesity Nominal	NR	NR
Metformin No of events	n = 210 ; % = 100	n = 212 ; % = 100
Glimepiride No of events	n = 126 ; % = 60	n = 126 ; % = 59.4
Gliclazide No of events	n = 84 ; % = 40	n = 86 ; % = 40.6
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

329. Muller-Wieland, 2018

Bibliographic Reference	Muller-Wieland, D.; Kellerer, M.; Cypryk, K.; Skripova, D.; Rohwedder, K.; Johnsson, E.; Garcia-Sanchez, R.; Kurlyandskaya, R.; Sjostrom, C. D.; Jacob, S.; et, al.; Efficacy and safety of dapagliflozin or dapagliflozin plus saxagliptin versus glimepiride as add-on to metformin in patients with type 2 diabetes; Diabetes Obes Metab; 2018; vol. 20 (no. 11); 2598-2607

329.1. Study details

Trial name / registration number	DapaZu / NCT02471404
Study type	Randomised controlled trial (RCT)
Study location	194 centres in Germany, the Czech Republic, Hungary, Poland and Slovakia
Study setting	No additional information
Study dates	September 21, 2015 to March 13, 2017
Sources of funding	AstraZeneca; Numerous authors declare honoraria and funding from multiple pharmaceutical companies.
Inclusion criteria	Men and women, aged 18 to <75 years, were eligible for inclusion in the study if they fulfilled the following criteria: diagnosis of type 2 diabetes; stable metformin dose (≥1500 mg/day) for ≥8 weeks prior to enrolment; BMI ≤45 kg/m2 ; fasting plasma glucose ≤ 270 mg/ dL (≤15 mmol/L); C-peptide ≥1.0 ng/mL (≥0.33 nmol/L); HbA1c, 7.5% to 10.5%.
Exclusion criteria	Major exclusion criteria included: a cardiovascular event during the 3 months prior to screening; creatinine clearance rate of <60 mL/minute; severe uncontrolled hypertension, defined as SBP ≥180 mm Hg and/or diastolic blood pressure ≥110 mm Hg at any visit up to and including randomization; presence or history of severe congestive heart failure (New York Heart Association Class III and IV), decompensated or acute congestive heart failure, and/or left ventricular ejection fraction ≤40%
Recruitment / selection of participants	No additional information
Intervention(s)	Dapagliflozin (n = 314) Patients received 10 mg dapagliflozin once daily orally with matching placebo for 52 weeks

	Dapagliflozin + Saxagliptin (n = 312) Dapagliflozin 10 mg and saxagliptin 5 mg were taken orally, once daily as add-on therapy to metformin for 52 weeks
Cointervention	Metformin; All patients received background therapy with Metformin (≥1500 mg/day)
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Exclusion criteria for NYHA III-IV heart failure, decompensated or acute heart failure and LVEF less than or equal to 40%
Strata 2: People with atherosclerotic cardiovascular disease	People without atherosclerotic cardiovascular diseases Exclusion criteria for a cardiovascular event in the last 3 months
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Exclusion criteria for creatinine clearance of <60mL/min but not explicitly 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
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=313) Glimepiride treatment (1-6 mg) was initiated at 1 mg/day and was titrated upwards or downwards in 1 mg increments at subsequent visits, in accordance with prescribing information. The glimepiride/placebo dose was titrated to achieve an individualized FPG target, agreed by the patient and investigator at the start of treatment; a general target of approximately 110 mg/dL (6.1 mmol/L) was proposed in the study protocol. In order to reflect real-life clinical practice as closely as possible, glimepiride titration was allowed for the duration of the study (52 weeks). Patients received matching placebo plus background therapy with Metformin ≥1500 mg/ day
Number of participants	939
Duration of follow-up	52 weeks
Indirectness	NA
Method of analysis	ITT
Additional comments	All efficacy analyses were conducted on the full analysis set (FAS), which comprised randomized patients who received at least 1 dose of study medication and for whom there were a baseline value and at least 1 post-baseline efficacy value. Analyses were performed using values prior to rescue treatment or discontinuation. The primary efficacy variable was analysed using a mixed-model repeated measures model with fixed effects for treatment group and covariates. Safety analyses were performed on the safety analysis set, which comprised patients who received at least 1 dose of study medication, regardless of rescue treatment; safety data were summarized using descriptive statistics

329.2. Study arms

329.2.1. Dapagliflozin (N = 314)

Patients received 10 mg dapagliflozin once daily orally as add-on therapy to metformin for 52 weeks

329.2.2. Dapagliflozin + Saxagliptin (N = 312)

Dapagliflozin 10 mg and saxagliptin 5 mg were taken orally, once daily as add-on therapy to metformin for 52 weeks

329.2.3. Glimepiride (N = 313)

Glimepiride treatment was initiated at 1 mg/day and was titrated upwards or downwards in 1 mg increments at subsequent visits, to achieve an individualized FPG target, agreed by the patient and investigator at the start of treatment; a general target of approximately 110 mg/dL (6.1 mmol/L) was proposed in the study protocol. Titration was allowed for the 52 week trial period as add-on therapy to metformin

329.3. Characteristics

329.3.1. Arm-level characteristics

Characteristic	Dapagliflozin (N = 314)	Dapagliflozin + Saxagliptin (N = 312)	Glimepiride (N = 313)
% Male Sample size	n = 202 ; % = 64.3	n = 190 ; % = 60.9	n = 208 ; % = 66.5
Mean age (SD) (Years (mean, SD)) Mean (SD)	57.4 (9.4)	59.2 (7.9)	58.6 (8.4)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed (Years (mean, SD)) Mean (SD)	6.9 (5.2)	7.3 (5.9)	6.7 (5.1)
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Dapagliflozin (N = 314)	Dapagliflozin + Saxagliptin (N = 312)	Glimepiride (N = 313)
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 = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Metformin Sample size	n = 314 ; % = 100	n = 312 ; % = 100	n = 313 ; % = 100
Blood pressure-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
ACE inhibitors Sample size	n = 143 ; % = 45.7	n = 163 ; % = 52.2	n = 164 ; % = 52.6
Angiotensin II antagonists Sample size	n = 96 ; % = 30.7	n = 70 ; % = 22.4	n = 74 ; % = 23.7
Beta blockers Sample size	n = 114 ; % = 36.4	n = 110 ; % = 35.3	n = 104 ; % = 33.3
Thiazides (plain) Sample size	n = 39 ; % = 12.5	n = 41 ; % = 13.1	n = 48 ; % = 15.4
Statins/lipid-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Other treatment being received	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Dapagliflozin (N = 314)	Dapagliflozin + Saxagliptin (N = 312)	Glimepiride (N = 313)
Sample size			

330. Nahra, 2021

Bibliographic Reference	Nahra, R.; Wang, T.; Gadde, K. M.; Oscarsson, J.; Stumvoll, M.; Jermutus, L.; Hirshberg, B.; Ambery, P.; Effects of Cotadutide on Metabolic and Hepatic Parameters in Adults With Overweight or Obesity and Type 2 Diabetes: A 54-Week Randomized Phase 2b Study; Diabetes Care; 2021; vol. 44 (no. 6); 1433-1442

330.1. Study details

Trial name / registration number	NCT03235050
Study type	Randomised controlled trial (RCT)
Study location	120 sites in 8 countries; Bulgaria, Canada, Czech Republic, Germany, Mexico, Russia, Slovakia and the US
Study setting	No additional information
Study dates	2 August 2017 and 14 June 2019
Sources of funding	AstraZeneca. A number of authors are also employees of AstraZeneca
Inclusion criteria	Eligible participants were aged ≥18 years, had a BMI ≥25 kg/m2 , were diagnosed with type 2 diabetes and inadequate blood glucose control (HbA1c level 7.0–10.5% [53–91 mmol/mol], inclusive), and had AST and ALT levels <3 times the upper limit of normal
Exclusion criteria	Participants were excluded if they had received a GLP-1 receptor mono-agonist within the previous 30 days or five half-lives of the drug (whichever was longer), received daily subcutaneous insulin for >2 weeks within 90 days prior to screening, or were currently participating in another interventional study. Participants with alcohol dependence were also excluded from this study
Recruitment / selection of participants	No additional information
Intervention(s)	Liraglutide (n=110) Liraglutide administration, with commercially available multiuse 3- mL pen injectors, was open-label. Liraglutide was initiated at a dose of 0.6 mg and up-titrated by an additional 0.6 mg weekly until a daily dose of 1.8 mg was reached. Treatment with Liraglutide was for a minimum of 54 weeks
Cointervention	Metformin Patients received a stable background of metformin that was maintained throughout the study duration

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 non-alcoholic fatty liver disease	People with non-alcoholic fatty liver disease
Subgroup 4: People with obesity	Not stated/unclear

Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	All patients had NAFLD
Comparator	Placebo (n=112) Patients received once daily injection of placebo for a minimum of 54 weeks. Patients also received a stable dose of metformin as background therapy throughout the trial
Number of participants	834 patients in total; however for the purposes of this study, those patients assigned to either Liraglutide or Placebo = 222
Duration of follow-up	58 weeks; 54 weeks treatment therapy plus an additional 4 week follow-up
Indirectness	NA
Method of analysis	Per protocol ITT
Additional comments	Primary and secondary efficacy end points were initially planned to be assessed using the intent-to-treat (ITT) population. The ITT population was defined as those participants who received any study drug and were analysed according to the randomly assigned treatment group. Secondary efficacy analyses were based on the per-protocol population, which included only participants who did not discontinue the study drug during the relevant treatment period and excluded those with important protocol violations Analyses performed on the per-protocol population are presented to address the confounding effect of treatment adherence owing to the high proportion of treatment discontinuations. The as-treated population was defined as those participants who received any study drug and were analysed according to the treatment received. All safety analyses were performed in the as-treated population. Additional ad hoc analyses were performed in the per-protocol population. PLEASE NOTE; For the purposes of this analyses, only data from the Liraglutide and Placebo arms are included. No data for the cotadutide arms have been extracted

330.2. Study arms

330.2.1. Liraglutide (N = 110)

Patients received once daily subcutaneous injections of liraglutide, initiated at a dose of 0.6 mg and uptitrated by an additional dose of 0.6 mg until a daily dose of 1.8 mg was reached. Treatment was for a minimum of 54 weeks

330.2.2. Placebo (N = 112)

Patients received once daily injection of placebo for a minimum of 54 weeks

330.3. Characteristics

330.3.1. Arm-level characteristics

Characteristic	Liraglutide (N = 110)	Placebo (N = 112)
% Male Sample size	n = 50 ; % = 46	n = 57 ; % = 51
Mean age (SD) (Years (mean, SD)) Mean (SD)	55.5 (9.8)	57.3 (9.5)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Asian Sample size	n = 1 ; % = 0.9	n = 1 ; % = 0.9
Black Sample size	n = 3 ; % = 2.7	n = 0 ; % = 0
White Sample size	n = 103 ; % = 94	n = 107 ; % = 96
Other Sample size	n = 3 ; % = 2.7	n = 4 ; % = 3.6
Time since type 2 diabetes diagnosed (Years (mean, SD)) Mean (SD)	7.6 (6.1)	7.6 (5)

Characteristic	Liraglutide (N = 110)	Placebo (N = 112)
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Metformin Sample size	n = 110 ; % = 100	n = 112 ; % = 100
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

331. Nakaguchi, 2020

Bibliographic Reference	Nakaguchi, H.; Kondo, Y; Kyohara, M; Konishi, H; Oiwa, K; Terauchi, Y; Effects of liraglutide and empagliflozin added to insulin therapy in patients with type 2 diabetes: a randomized controlled study ELLENA-IT study; J Diabetes Invest; 2020

331.1. Study details

Secondary publication of another included study- see primary study for details	
Trial name / registration number	UMIN000027614
Study type	Randomised controlled trial (RCT)
Study location	Yokahama Japan
Study setting	No additional information
Study dates	NR
Sources of funding	Self-procurement with no subsidy
Inclusion criteria	(i) outpatients with type 2 diabetes, aged 20–80 years; (ii) patients of either sex; (iii) patients without GLP-1RA, SGLT2i or dipeptidyl peptidase-4 inhibitor (DPP4i) treatment for >8 weeks before intervention (if DPP4i was taken orally, it was washed out for 8 weeks before the start of the study); (iv) patients under insulin therapy glycemic control: 7.0% ≤ HbA1c ≤ 9.5%; (v) fasting plasma C-peptide ≥0.5 ng/mL or casual plasma C- peptide ≥1.0 ng/mL; (vi) patients that provided voluntary written consent for participation in this study
Exclusion criteria	(i) type 1 diabetes or secondary forms of diabetes; (ii) fasting plasma glucose (FPG) <70 mg/dL;

	(iii) renal dysfunction (eGFR<30 mL/min/1.73 m2); (iv) steroid medication; (v) hepatic dysfunction (aspartate transaminase and/or alanine aminotransferase >3 times the upper limit of normal); (vi) active malignant neoplasm; (vii) severe infection or injury; (viii) hypersensitivity to liraglutide or empagliflozin; (ix) pregnant or intending to become pregnant during this study; (x) unable to obtain informed consent for this study; and (xi) inadequate use of this therapy
Recruitment / selection of participants	The participants included patients who visited Yokohama City University Hospital and Yokohama Chuo Hospital from June 2017 to May 2019
Intervention(s)	Liraglutide (n=30) Patients received a starting dose of Liraglutide 0.3 mg/day, followed by 0.6 mg/day after 1 week and 0.9 mg/day after another week in addition to any prior treatment. If no side-effects appeared, a final maintenance dose of 0.9 mg/day was continued for up to 24 weeks. If side-effects occurred during the dose increase, the dose was decreased by 0.3 mg and treatment was continued, if possible. Patients subcutaneously injected themselves with liraglutide at approximately the same time each day.
Cointervention	Insulin Insulin dose was maintained for 24 weeks of the trial; with dose increases when marked hyperglycaemia was sustained.
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	Not stated/unclear

diabetes mellitus and chronic kidney disease	Exclusion criteria for renal dysfunction (eGFR <30mL/min/1.73m2) but no other 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	NA
Comparator	Empagliflozin (n=30) Patients received 10 mg/day empagliflozin treatment for 24 weeks in addition to any prior treatment. If glycemic control was inadequate (FBG ≥180 mg/dL or HbA1c ≥8.5%) at 12 weeks after the initiation of the intervention, the dosage was increased to 25 mg/ day empagliflozin.

	Insulin dose was maintained for 24 weeks of the trial; with dose increases when marked hyperglycaemia was sustained.
Number of participants	64
Duration of follow-up	24 weeks
Indirectness	NA
Method of analysis	ITT
Additional comments	Analysis of the main evaluation items was carried out using the full analysis set method.

331.2. Study arms

331.2.1. Liraglutide (N = 30)

Patients received a starting dose of Liraglutide 0.3 mg/day, followed by 0.6 mg/day after 1 week and 0.9 mg/day after another week. If no side-effects appeared, a final maintenance dose of 0.9 mg/day was continued for up to 24 weeks. Patients subcutaneously injected themselves at approximately the same time each day.

331.2.2. Empagliflozin (N = 31)

Patients received 10 - 25 mg Empagliflozin for 24 weeks.

331.3. Characteristics

331.3.1. Arm-level characteristics

Characteristic	Liraglutide (N = 30)	Empagliflozin (N = 31)
% Male Sample size	n = 21 ; % = 70	n = 21 ; % = 67.7
Mean age (SD) (Years (mean, SD)) Mean (SD)	67.2 (9)	66.3 (9.5)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Liraglutide (N = 30)	Empagliflozin (N = 31)
Time since type 2 diabetes diagnosed (Years (mean, SD)) Mean (SD)	18.8 (9.9)	19 (10.1)
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Sulfonylurea Sample size	n = 1 ; % = 3.3	n = 0 ; % = 0
Glinide Sample size	n = 3 ; % = 10	n = 1 ; % = 3.2
Thiazolidine Sample size	n = 4 ; % = 13.3	n = 2 ; % = 6.5
Alpha glucosidase inhibitors Sample size	n = 5 ; % = 16.7	n = 9 ; % = 29
Metformin Sample size	n = 8 ; % = 26.7	n = 15 ; % = 48.4
DPP-4 inhibitor Sample size	n = 14 ; % = 46.7	n = 12 ; % = 38.7
Insulin Sample size	n = 30 ; % = 100	n = 31 ; % = 100

Characteristic	Liraglutide (N = 30)	Empagliflozin (N = 31)
Blood pressure-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
ARB or ACE inhibitor Sample size	n = 17 ; % = 56.7	n = 23 ; % = 74.2
Calcium-channel blocker Sample size	n = 16 ; % = 53.3	n = 17 ; % = 54.8
alpha blocker Sample size	n = 3 ; % = 10	n = 2 ; % = 6.5
Beta blockers Sample size	n = 3 ; % = 10	n = 2 ; % = 6.5
Diuretic Sample size	n = 5 ; % = 16.7	n = 4 ; % = 12.9
Others Sample size	n = 3 ; % = 10	n = 0 ; % = 0
Statins/lipid-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Statin Sample size	n = 17 ; % = 56.7	n = 23 ; % = 74.2
Fibrate Sample size	n = 0 ; % = 0	n = 1 ; % = 3.2
Small intestine transporter inhibitor Sample size	n = 5 ; % = 16.7	n = 4 ; % = 12.9
Others Sample size	n = 1 ; % = 3.3	n = 2 ; % = 6.5
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR

332. Natali, 2017

Bibliographic Reference	Natali, Andrea; Nesti, Lorenzo; Fabiani, Iacopo; Calogero, Enrico; Di Bello, Vitantonio; Impact of empagliflozin on subclinical left ventricular dysfunctions and on the mechanisms involved in myocardial disease progression in type 2 diabetes: rationale and design of the EMPA-HEART trial.; Cardiovascular diabetology; 2017; vol. 16 (no. 1); 130

332.1. Study details

Secondary publication of another included study- see primary study for details	Nesti L, Pugliese NR, Sciuto P, Trico D, Dardano A, Baldi S, Pinnola S, Fabiani I, Di Bello V, Natali A. Effect of empagliflozin on left ventricular contractility and peak oxygen uptake in subjects with type 2 diabetes without heart disease: results of the EMPA-HEART trial. Cardiovasc Diabetol. 2022 Sep 12;21(1):181. doi: 10.1186/s12933-022-01618-1. PMID: 36096863; PMCID: PMC9467417.

333. Nathan, 2022

Bibliographic Reference	Nathan, David M; Lachin, John M; Balasubramanyam, Ashok; Burch, Henry B; Buse, John B; Butera, Nicole M; Cohen, Robert M; Crandall, Jill P; Kahn, Steven E; Krause-Steinrauf, Heidi; Larkin, Mary E; Rasouli, Neda; Tiktin, Margaret; Wexler, Deborah J; Younes, Naji; Glycemia Reduction in Type 2 Diabetes - Glycemic Outcomes.; The New England journal of medicine; 2022; vol. 387 (no. 12); 1063-1074

333.1. Study details

Secondary publication of another included study- see primary study for details	Group, Grade Study Research, Nathan, D. M., Lachin, J. M. et al. (2022) Glycemia Reduction in Type 2 Diabetes - Microvascular and Cardiovascular Outcomes. New England Journal of Medicine 387(12): 1075-1088
Other publications associated with this study included in review	NA
Trial name / registration number	The GRADE Study [NCT01794143]

334. Nauck Michael, 2019

Bibliographic Reference	Nauck Michael, A; McGuire Darren, K; Pieper Karen, S; Lokhnygina, Yuliya; Strandberg Timo, E; Riefflin, Axel; Delibasi, Tuncay; Peterson Eric, D; White Harvey, D; Scott, Russell; Holman Rury, R; Sitagliptin does not reduce the risk of cardiovascular death or hospitalization for heart failure following myocardial infarction in patients with diabetes: observations from TECOS.; Cardiovascular diabetology; 2019; vol. 18 (no. 1); 116

334.1. Study details

Secondary publication of another included study- see primary study for details	TECOS trial. Green et al (2015) Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes. The New England journal of medicine; 2015; vol. 373 (no. 3); 232-42
Other publications associated with this study included in review	Bethel M, A, Engel S, S, Stevens S, R et al. (2019) Progression of glucose-lowering diabetes therapy in TECOS. Endocrinology, Diabetes and Metabolism 2(1): e00053 Green, Jennifer B, Bethel, M Angelyn, Paul, Sanjoy K et al. (2013) Rationale, design, and organization of a randomized, controlled Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) in patients with type 2 diabetes and established cardiovascular disease. American heart journal 166(6): 983-989e7 McGuire, Darren K, Van de Werf, Frans, Armstrong, Paul W et al. (2016) Association Between Sitagliptin Use and Heart Failure Hospitalization and Related Outcomes in Type 2 Diabetes Mellitus: Secondary Analysis of a Randomized Clinical Trial. JAMA cardiology 1(2): 126-35
Trial name / registration number	TECOS ClinicalTrials.gov number NCT00790205

335. Nauck, 2007

Bibliographic Reference	Nauck, M. A.; Duran, S.; Kim, D.; Johns, D.; Northrup, J.; Festa, A.; Brodows, R.; Trautmann, M.; A comparison of twice-daily exenatide and biphasic insulin aspart in patients with type 2 diabetes who were suboptimally controlled with sulfonylurea and metformin: a non-inferiority study; Diabetologia; 2007; vol. 50 (no. 2); 259-67

335.1. Study details

Trial name / registration number	NCT00082407)
Study type	Randomised controlled trial (RCT)
Study location	13 countries
Study setting	No additional information
Study dates	November 2003 and April 2005
Sources of funding	Industry initiated study. A number of authors are employees of Eli Lilly and Amlyn Pharmaceuticals or declare funding and / or honoraria from Eli Lilly and Amlyn Pharmaceuticals
Inclusion criteria	Eligible patients were between 30 and 75 years of age and had suboptimal glycaemic control despite receiving optimally effective metformin and sulfonylurea therapy for at least 3 months. Inclusion criteria included, at the time of screening, HbA1c levels ≥7.0 and ≤11.0%, a BMI ≥25 and ≤40 kg/m2 , and a history of stable body weight (≤10% variation for ≥3 months).
Exclusion criteria	(1) had had more than three episodes of severe hypoglycaemia within 6 months prior to screening; (2) had used any prescription drug to promote weight loss within 3 months; or (3) had been treated with insulin, thiazolidinediones, alpha-glucosidase inhibitors or meglitinides for longer than 2 weeks within 3 months.
Recruitment / selection of participants	Patients were recruited through advertising
Intervention(s)	Exenatide (n= 253) Patients used a multi-use pen to subcutaneously inject (within 15 min before morning and evening meals) a fixed dose of 5 µg twice daily for 4 weeks and 10 µg twice daily for the remaining 48 weeks. If frequent nausea developed (daily episodes for >1 week duration), patients had the option to decrease their dose to 5 µg twice daily.

Cointervention	Metformin + Sulfonylurea Patients received optimally effective pre-study metformin and sulfonylurea dosages; if hypoglycaemia events occurred, investigators reduced the sulfonylurea dose by approximately 50% for patients on exenatide or adapted the insulin dose for patients on insulin.
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 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=248) Patients subcutaneously injected premixed insulin before the morning and evening meals. Investigators chose the starting insulin dose for patients, and contacted patients at regular intervals to discuss glycaemic control. A forced titration schedule was not used in this trial. Investigators were instructed to adjust insulin doses to achieve an optimal balance between glycaemic control and risk of hypoglycaemia as dictated by best clinical practice. Patients entering this study maintained optimally effective pre-study metformin and sulfonylurea dosages if hypoglycaemia events occurred, investigators reduced the sulfonylurea dose by approximately 50% for patients on exenatide or adapted the insulin dose for patients on insulin
Number of participants	501
Duration of follow-up	52 weeks
Indirectness	NA
Method of analysis	ITT
Additional comments	Two analysis sets were predefined for the analysis of HbA1c: (1) an intention-to-treat (ITT) sample, defined as patients who received at least one dose of study medication and had at least one post-baseline measurement of HbA1c; and (2) a per-protocol sample, defined as patients who had at least 12 weeks of exposure to study medication and no violations of screening criteria or discontinuation criteria. In non-inferiority trials, non-ITT analyses provide protection from type 1 error risk, and greater confidence is evoked when conclusions from ITT and per-protocol datasets are consistent

335.2. Study arms

335.2.1. Exenatide (N = 253)

Patients injected a fixed dose of 5 ug twice daily for 4 weeks and 10 ug twice daily for the remaining 48 weeks

335.2.2. Insulin (N = 248)

Patients subcutaneously injected premixed insulin before the morning and evening meals for 52 weeks

335.3. Characteristics

335.3.1. Arm-level characteristics

Characteristic	Exenatide (N = 253)	Insulin (N = 248)
% Male Sample size	n = 134 ; % = 53	n = 122 ; % = 49
Mean age (SD) (Years (mean, SD)) Mean (SD)	59 (9)	58 (9)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed (Years (mean, SD)) Mean (SD)	9.8 (6.3)	10 (6.2)
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	Exenatide (N = 253)	Insulin (N = 248)
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
Metformin + a sulphonylurea Sample size	n = 253 ; % = 100	n = 248 ; % = 100
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

336. Nauck, 2009

Bibliographic Reference	Nauck, M. A.; Ellis, G. C.; Fleck, P. R.; Wilson, C. A.; Mekki, Q.; Efficacy and safety of adding the dipeptidyl peptidase-4 inhibitor alogliptin to metformin therapy in patients with type 2 diabetes inadequately controlled with metformin monotherapy: a multicentre, randomised, double-blind, placebo-controlled study; Int J Clin Pract; 2009; vol. 63 (no. 1); 46-55

336.1. Study details

Trial name / registration number	NCT00286442
Study type	Randomised controlled trial (RCT)
Study location	115 sites in 15 countries
Study setting	No additional information
Study dates	NR
Sources of funding	Takeda Global Research and Development Center, Inc. A number of authors are employees of Takeda Global Research and Development Center, Inc. The primary authors declares honoraria from numerous pharmaceutical companies
Inclusion criteria	Men and women (aged 18-80 years) with an historical diagnosis of T2DM and inadequate glycaemic control (HbA1c between 7.0% and 10.0%) despite ≥3 months stable metformin monotherapy regimen (≥1500 mg per day for at least 8 weeks). BMI of 23 - 45 kg⁄m2; a C-peptide concentration ≥0.26 nmol/l (0.8 ng⁄ml) and serum creatinine <1.5 mg⁄dl (men) or <1.4 mg⁄dl (women). FPG < 275 mg⁄dl (< 15.3 mmol⁄l) and ≥75% compliance with the single-blind placebo regimen
Exclusion criteria	Patients who had used antidiabetic agents other than metformin within the 3 months prior to screening. Patients with a urine albumin⁄creatinine ratio ≥113 mg⁄mol (≥1000 mg⁄g); a history of cancer (other than squamous cell or basal cell carcinoma of the skin that had not been in full remission for at least 5 years); laser treatment for proliferative diabetic retinopathy within 6 months; a history of treated diabetic gastroparesis; New York Heart Association Class III or IV heart failure; or history of coronary angioplasty, coronary stent placement, coronary bypass surgery or myocardial infarction within 6 months were also excluded. The use of oral or systemically injected glucocorticoids or the use of weight-loss drugs within the 3 months prior to randomisation was prohibited
Recruitment / selection of participants	No additional information

Intervention(s)	Alogliptin 12.5 mg (n=213) Alogliptin 25 mg (n=210) Patients received once daily doses of 12.5mg or 25mg alogliptin for 26 weeks
Cointervention	Metformin Patients were switched from their own metformin medication to open-label treatment with an equivalent dose of a generic immediate release metformin formulation (≥1500 mg daily, except those with intolerance to this dose whereupon the patients maximum tolerated dose was used)
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Exclusion criteria for NYHA class III or IV heart failure
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 Exclusion criteria for people with a urine albumin/creatinine ratio above or equal to 113mg/mol but no other information and no explicit mention 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	Not stated/unclear

2 diabetes mellitus	
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Mixed population
Population subgroups	NA
Comparator	Placebo (n=104) Patients received placebo in addition to metformin for 26 weeks
Number of participants	527
Duration of follow-up	26 weeks
Indirectness	NA
Method of analysis	ITT
Additional comments	All efficacy analyses were based on the full analysis set (FAS), defined as all patients receiving randomised treatment assignment. For a particular variable, the FAS included all patients who had a baseline assessment and at least one post-baseline efficacy assessment. The safety set included all patients who took at least one dose of double-blind study drug.

336.2. Study arms

336.2.1. Alogliptin 12.5 mg (N = 213)

Patients received 12.5 mg alogliptin in combination with metformin for 26 weeks

336.2.2. Alogliptin 25 mg (N = 210)

Patients received 25 mg alogliptin in combination with metformin for 26 weeks

336.2.3. Placebo (N = 104)

Patients received placebo in combination with metformin for 26 weeks

336.3. Characteristics

336.3.1. Arm-level characteristics

Characteristic	Alogliptin 12.5 mg (N = 213)	Alogliptin 25 mg (N = 210)	Placebo (N = 104)
% Male Sample size	n = 101 ; % = 47.4	n = 114 ; % = 54.3	n = 50 ; % = 48
Mean age (SD) (Years (mean, SD)) Mean (SD)	55 (11)	54 (11)	56 (11)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 170 ; % = 80	n = 159 ; % = 76	n = 79 ; % = 76
African-American Sample size	n = 5 ; % = 2	n = 12 ; % = 6	n = 7 ; % = 7
Asian Sample size	n = 17 ; % = 8	n = 19 ; % = 9	n = 6 ; % = 6
Other race Sample size	n = 21 ; % = 10	n = 20 ; % = 9	n = 12 ; % = 11
Hispanic or Latino Sample size	n = 66 ; % = 31	n = 68 ; % = 32	n = 25 ; % = 24
Not hispanic or latino Sample size	n = 147 ; % = 69	n = 142 ; % = 68	n = 79 ; % = 76

Characteristic	Alogliptin 12.5 mg (N = 213)	Alogliptin 25 mg (N = 210)	Placebo (N = 104)
Time since type 2 diabetes diagnosed (Years (mean, SD)) Mean (SD)	6 (5)	6 (4)	6 (5)
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 Sample size	n = 213 ; % = 100	n = 210 ; % = 100	n = 104 ; % = 100
Blood pressure-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Statins/lipid-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR

337. Nauck, 2007

Bibliographic Reference	Nauck, M. A.; Meininger, G.; Sheng, D.; Terranella, L.; Stein, P. P.; Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, compared with the sulfonylurea, glipizide, in patients with type 2 diabetes inadequately controlled on metformin alone: a randomized, double-blind, non-inferiority trial; Diabetes Obes Metab; 2007; vol. 9 (no. 2); 194-205

337.1. Study details

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	Krobot, Karl J, Ferrante, Shannon Allen, Davies, Michael J et al. (2012) Lower risk of hypoglycemia with sitagliptin compared to glipizide when either is added to metformin therapy: a pre-specified analysis adjusting for the most recently measured HbA(1c) value. Current medical research and opinion 28(8): 1281-7 Seck, T., Nauck, M., Sheng, D. et al. (2010) Safety and efficacy of treatment with sitagliptin or glipizide in patients with type 2 diabetes inadequately controlled on metformin: a 2-year study. Int J Clin Pract 64(5): 562-76
Trial name / registration number	Sitagliptin Protocol 024 [NCT00094770]
Study type	Randomised controlled trial (RCT)
Study location	Multinational study
Study setting	NR
Study dates	NR
Sources of funding	Merck & Co.
Inclusion criteria	• Men and women aged 18 to 78 years with type 2 diabetes • Eligible patients were those who were not currently on an OHA, were taking any OHA in monotherapy or were taking metformin in combination with another OHA

Exclusion criteria	• History of type 1 diabetes • Insulin use within 8 weeks of screening • Renal function impairment inconsistent with the use of metformin or a fasting plasma glucose (FPG) (or a fasting fingerstick glucose) at or just prior to randomization >15.0 mmol/l (270 mg/dl)
Recruitment / selection of participants	• Patients who were already on metformin ≥1500 mg/day and had an HbA1c ≥6.5 and ≤10% directly entered a 2-week placebo run-in period and were eligible to be randomized. • Patients not currently on an OHA, patients on an OHA other than metformin monotherapy at a dose ≥1500 mg/day or patients on metformin in combination with another OHA entered a metformin monotherapy treatment titration and dose-stable period of at least 8 weeks. • Patients with an HbA1c ≥6.5 and ≤10% after the metformin dose-stable period entered a 2-week single-blind placebo run-in period. Following this 2-week period, eligible patients had baseline measurements and then were randomized in a 1 : 1 ratio to the addition of sitagliptin 100 mg once daily or glipizide (at an initial dose of 5 mg/day).
Intervention(s)	• Sitagliptin 100 mg once daily • Glipizide - starting dose of 5 mg/day and up-titrated according to protocol-specified criteria to a potential maximum dose of 20 mg/day. During the first 18 weeks of treatment, glipizide was up-titrated, in 3-week intervals, if premeal fingerstick glucose values were >6.1 mmol/l (110 mg/dl). Up-titration of glipizide could be withheld if the investigator considered that it would place the patient at risk of hypoglycaemia. Glipizide could also be down-titrated at any point in the study to prevent recurrent hypoglycaemic events.
Cointervention	• Other treatments for hyperglycaemia were prohibited during the study. • Concurrent lipid lowering and antihypertensive medications, thyroid medications, hormone replacement therapy and birth control medications were allowed but were expected to remain at stable doses. • Patients received counselling on exercise and a diet consistent with American Diabetes Association recommendations
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 Not an inclusion/exclusion criteria. No information in baseline characteristics.

cardiovascular disease	
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 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	NA

Number of participants	2,141 patients were screened, 969 were excluded, and 1,172 patients were randomised. Of 588 participants allocated to sitagliptin, 202 participants discontinued, and 386 completed. Of 584 participants allocated to glipizide, 172 discontinued and 412 completed.
Duration of follow-up	52 and 104 weeks
Indirectness	Directly applicable
Method of analysis	Per protocol The PP cohort consisted of patients who completed the 2-year treatment period and did not have any reasons for exclusion from this cohort, including the absence of baseline data, the absence of treatment data at the end of the 2nd year, or major protocol violations (e.g. drug compliance <75%; change in metformin dose; addition of non-study antihyperglycemic agents). For efficacy endpoints, an analysis of covariance (ANCOVA) model was used to compare the treatment groups, focusing on change from baseline at the end of the 2nd year, with baseline values and prior antihyperglycemic agent status as covariates. The differences in least squares (LS) mean change (or percent change) from baseline to the end of the 2nd year and 95% confidence intervals (CI) were provided for the between-group comparisons. ITT Described as all-patients treated cohort - included all randomised patients who received at least one dose of study treatment and who had both a baseline and at least one postbaseline measurement. Missing values were imputed by the last observation carried forward approach. Other Safety data were were evaluated in the all-patients-as-treated cohort, which is defined as all randomised patients who received at least one dose of study medication. It is unclear whether this analysis relates to the treatment allocated or the treatment received.
Additional comments	NA

337.2. Study arms

337.2.1. Sitagliptin (N = 588)

337.2.2. Glipizide (N = 584)

337.3. Characteristics

337.3.1. Arm-level characteristics

Characteristic	Sitagliptin (N = 588)	Glipizide (N = 584)
% Male Sample size	n = 336 ; % = 57.1	n = 358 ; % = 61.3
Mean age (SD) (years) Mean (SD)	56.8 (9.3)	56.6 (9.8)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Caucasian Sample size	n = 432 ; % = 73.5	n = 434 ; % = 74.3
Black Sample size	n = 41 ; % = 7	n = 35 ; % = 6
Hispanic Sample size	n = 43 ; % = 7.3	n = 46 ; % = 7.9
Asian Sample size	n = 50 ; % = 8.5	n = 49 ; % = 8.4
Other Sample size	n = 22 ; % = 3.7	n = 20 ; % = 3.4
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed Mean (SD)	6.5 (6.1)	6.2 (5.4)
Cardiovascular risk factors Nominal	NR	NR
Smoking status Nominal	NR	NR
Alcohol consumption	NR	NR

Characteristic	Sitagliptin (N = 588)	Glipizide (N = 584)
Nominal		
Presence of severe mental illness Nominal	NR	NR
People with significant cognitive impairment Nominal	NR	NR
People with a learning disability Nominal	NR	NR
Other antidiabetic medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Dual therapy Sample size	n = 177 ; % = 30.1	n = 159 ; % = 27.2
Monotherapy Sample size	n = 386 ; % = 65.6	n = 397 ; % = 68
absence Sample size	n = 25 ; % = 4.3	n = 28 ; % = 4.8
Blood pressure-lowering medication used Nominal	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

338. Nauck, 2011

Bibliographic Reference	Nauck, M. A.; Prato, S.; Meier, J. J.; Durán-García, S.; Rohwedder, K.; Elze, M.; Parikh, S. J.; Dapagliflozin versus glipizide as add-on therapy in patients with type 2 diabetes who have inadequate glycemic control with metformin: a randomized, 52-week, double-blind, active-controlled noninferiority trial; Diabetes Care; 2011; vol. 34 (no. 9); 2015-22

338.1. Study details

Secondary publication of another included study- see primary study for details	This is the parent study.
Other publications associated with this study included in review	4 year follow-up data: Del Prato et al. (2015). Long-term glycaemic response and tolerability of dapagliflozin versus a sulphonylurea as add-on therapy to metformin in patients with type 2 diabetes: 4-year data. Diabetes, obesity & metabolism; 2015; vol. 17 (no. 6); 581-590.
Trial name / registration number	NCT00660907
Study type	Randomised controlled trial (RCT)
Study location	95 sites in 10 countries: Argentina, 17 centres; France, 7; Germany, 16; U.K., 12; Italy, 3; Mexico, 4; the Netherlands, 10; South Africa, 10; Spain, 6; and Sweden, 10.
Study setting	NR
Study dates	From 31 March 2008 (52 week study with 156 week extension period)
Sources of funding	Supported by AstraZeneca and Bristol-Myers Squibb
Inclusion criteria	Men and women aged ≥18 years with inadequately controlled type 2 diabetes (HbA1c >6.5 and ≤10%) while receiving metformin or metformin and one other OAD administered up to half-maximal dose for at least 8 weeks before enrolment; a fasting plasma glucose (FPG) ≤15 mmol/L and C-peptide concentration of ≥0.33 nmol/L
Exclusion criteria	Receiving metformin monotherapy at a stable dose of ,1,500 mg/day or at a variable dose, or combined with another OAD. Type 1 diabetes; diabetes insipidus; corticosteroid-induced type 2 diabetes; a history of diabetic ketoacidosis or hyperosmolar non-ketotic coma; poorly controlled diabetes

	characterized by polyuria/polydipsia with >10% weight loss; use of insulin within 1 year of enrolment, except in the case of hospitalization or use in gestational diabetes. Body mass index (BMI) >45.0 kg/m2 ; calculated creatinine clearance <60 mL/min; urine albumin: creatinine ratio >203.4 mg/mmol; aspartate aminotransferase and/or alanine aminotransferase and/or creatine kinase ≥3 × upper limit of normal range; serum total bilirubin >34 µmol/L; hemoglobin (Hb) ≤11 g/dL for men and ≤10 g/dL for women; abnormal thyroid stimulating hormone level; systolic blood pressure ≥180 mmHg and/or diastolic blood pressure ≥110 mmHg; cardiovascular event within 6 months of enrolment; congestive heart failure; congenital renal glycosuria; significant renal, hepatic, respiratory, haematological, oncological, endocrine, immunological (including hypersensitivity to study medications), and alcohol and/or substance misuse disorders; pregnancy and/or lactation; use of systemic corticosteroids equivalent to >10 mg of oral prednisolone within 30 days of enrolment; a history of bariatric surgery; and use of weight loss medication within 30 days of enrolment
Recruitment / selection of participants	NR
Intervention(s)	Dapagliflozin
Cointervention	Receiving metformin monotherapy at a stable dose of ,1,500 mg/day or at a variable dose, or combined with another OAD, entered an 8-week stabilization period during which other OADs were discontinued and the metformin dose was stabilized to 1,500–2,500 mg/day in all patients. Patients who were already receiving a stable dose of metformin monotherapy (1,500–2,500 mg/day) for at least 8 weeks before enrolment skipped the dose-stabilization period. Once patients were stabilized, no further changes in the metformin dose were allowed.
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Excluded "congestive heart failure".
Strata 2: People with atherosclerotic cardiovascular disease	People without atherosclerotic cardiovascular diseases Excluded "cardiovascular event within 6 months", prior unclear. Baseline characteristics show <20% had a prior history of CVD (excluding hypertension only).
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Excluded "calculated creatinine clearance <60 mL/min", otherwise unclear. Baseline characteristics give eGFR categories only.

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 Around 56% had a BMI ≥30
Subgroup 5: eGFR category at baseline	eGFR ≥30mL/min/1.73m2
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	NA
Comparator	Glipizide
Number of participants	814
Duration of follow-up	52 week (then 156 week extension)
Indirectness	None

Method of analysis	Modified ITT
Additional comments	The safety analysis set, consisting of all patients who received one or more doses of the investigational product (dapa = 406; glip = 408), and the full analysis set, consisting of all randomized patients who received one or more doses of the investigational product and who had a non-missing baseline and one or more postbaseline efficacy value for one or more efficacy variable (dapa = 400, glip = 401). Primary, key secondary, and exploratory end points were analysed using the full analysis set. Missing values at week 52 were replaced using the LOCF method (dapa 322 completed, glip 314 completed, 84 and 94 not completed respectively at 52 weeks). Numbers completing the 48 month period were dapa=161 (39.7%) and glip=141 (34.6%).

338.2. Study arms

338.2.1. Dapagliflozin (N = 406)

Commenced treatment at dapagliflozin 2.5 mg. During an 18-week period and at 21-day intervals, patients were up-titrated to the next dosage level if FPG was ≥6.1 mmol/L. Level 2 was dapagliflozin 5 mg , and level 3 was dapagliflozin at 10mg. Up-titration continued until the maximum tolerable dose level was reached. After the 18-week titration period, patients entered a 34-week maintenance period, during which no further uptitration was allowed. However, patients could be down-titrated to the preceding level or potentially down to level 0 (placebo for both arms) in the event of recurrent hypoglycemia.

338.2.2. Glipizide (N = 408)

Commenced treatment at glipizide at 5 mg. During an 18-week period and at 21-day intervals, patients were up-titrated to the next dosage level if FPG was ≥6.1 mmol/L. Level 2 was glipizide 10 mg, and level 3 was glipizide 20 mg. Up-titration continued until the maximum tolerable dose level was reached (20mg limit for glipizide). After the 18-week titration period, patients entered a 34-week maintenance period, during which no further up-titration was allowed. However, patients could be down-titrated to the preceding level or potentially down to level 0 (placebo for both arms) in the event of recurrent hypoglycemia.

338.3. Characteristics

338.3.1. Arm-level characteristics

Characteristic	Dapagliflozin (N = 406)	Glipizide (N = 408)
% Male Sample size	n = 221 ; % = 55.3	n = 220 ; % = 54.9
Mean age (SD) Mean (SD)	58 (9)	59 (10)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 327 ; % = 81.8	n = 323 ; % = 80.5
Black Sample size	n = 26 ; % = 6.5	n = 24 ; % = 6
Asian Sample size	n = 27 ; % = 6.8	n = 34 ; % = 8.5
Other Sample size	n = 20 ; % = 5	n = 20 ; % = 5
Comorbidities Sample size	n = NA ; % = NA	n = NA ; % = NA
Prior history of CVD (excluding hypertension only) Sample size	n = 72 ; % = 18	n = 78 ; % = 19.5
Nephropathy Sample size	n = 15 ; % = 3.8	n = 10 ; % = 2.5
Microalbuminuria Sample size	n = 42 ; % = 10.5	n = 39 ; % = 9.7
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed Mean (SD)	6 (5)	7 (6)

Characteristic	Dapagliflozin (N = 406)	Glipizide (N = 408)
Cardiovascular risk factors Sample size	n = NA ; % = NA	n = NA ; % = NA
Hypertension Sample size	n = 282 ; % = 70.5	n = 282 ; % = 70.3
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR
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
BMI Sample size	n = NA ; % = NA	n = NA ; % = NA
≥25 kg/m2 Sample size	n = 380 ; % = 95	n = 364 ; % = 90.8
≥30 kg/m2 Sample size	n = 228 ; % = 57	n = 222 ; % = 55.4
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 monotherapy Sample size	n = 265 ; % = 65.3	n = 275 ; % = 67.6
Metformin + 1 OAD Sample size	n = 141 ; % = 34.7	n = 132 ; % = 32.4
Blood pressure-lowering medication used	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Dapagliflozin (N = 406)	Glipizide (N = 408)
Sample size		
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

339. Nauck, 2009

Bibliographic Reference	Nauck, M.; Frid, A.; Hermansen, K.; Shah, N. S.; Tankova, T.; Mitha, I. H.; Zdravkovic, M.; During, M.; Matthews, D. R.; Efficacy and safety comparison of liraglutide, glimepiride, and placebo, all in combination with metformin, in type 2 diabetes; Diabetes Care; 2009; vol. 32 (no. 1); 84-90

339.1. Study details

Trial name / registration number	LEAD-2 / NCT00318461
Study type	Randomised controlled trial (RCT)
Study location	170 sites in 21 countries
Study setting	No additional information
Study dates	NR
Sources of funding	A number of authors were supported by Novo Nordisk. Numerous authors declare funding and honoraria
Inclusion criteria	Adult subjects with type 2 diabetes were screened and enrolled if they were 18–80 years of age, had A1C between 7 and 11% (pre-study OAD monotherapy for ≥3 months) or between 7 and 10% (pre-study combination OAD therapy for ≥3 months), and had BMI ≥40 kg/m2
Exclusion criteria	Subjects were excluded if they had used insulin during the previous 3 months (except short-term treatment).
Recruitment / selection of participants	No additional information
Intervention(s)	Liraglutide 0.6 mg (n = 242) Liraglutide 1.2 mg (n = 241) Liraglutide 1.8 mg (n = 242) Patients received Liraglutide injected subcutaneously once daily at any time of the day in the upper arm, abdomen, or thigh using a pen injector device. Subjects were encouraged to inject liraglutide at the same time each day.

	Glimepiride (n=242) Patients received up to 4 mg Glimepiride (with 1-, 2-, and 4-mg doses at weeks 1, 2, and 3) orally once daily with the first meal of the day
Cointervention	Metformin. Patients received Metformin at a maintenance dose titrated prior to study therapy commencement however , metformin could be decreased to a minimum of 1,500 mg/day in the case of unacceptable hypoglycemia or other adverse events but had to be maintained between 1,500 and 2000 mg/day during the maintenance period.
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 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=122) Patients received glimepiride oral placebo plus a liraglutide placebo injection for the duration of the trial
Number of participants	1087
Duration of follow-up	2 years; An initial 26 weeks followed by an 18 months extension period
Indirectness	NA
Method of analysis	ITT
Additional comments	The analyses of efficacy end points were based on the intent-to-treat population defined as subjects who were exposed to at least one dose of trial product and had one postbaseline measurement of the parameter. Each end point was analysed using an ANCOVA model with treatment, country, and previous antidiabetic treatment as fixed effects and baseline as the covariate. Missing data were imputed as the last observation carried forward.

339.2. Study arms

339.2.1. Liraglutide 0.6 mg (N = 242)

Patients received 0.6 mg Liraglutide once daily for 2 years

339.2.2. Liraglutide 1.2 mg (N = 241)

Patients received 1.2 mg Liraglutide once daily for 2 years

339.2.3. Liraglutide 1.8 mg (N = 242)

Patients received 1.8 mg Liraglutide once daily for 2 years

339.2.4. Glimepiride (N = 244)

Patients received 4.0 mg Glimepiride once daily for 2 years

339.2.5. Placebo (N = 122)

Patients received oral placebo daily for 2 years

339.3. Characteristics

339.3.1. Arm-level characteristics

Characteristic	Liraglutide 0.6 mg (N = 242)	Liraglutide 1.2 mg (N = 241)	Liraglutide 1.8 mg (N = 242)	Glimepiride (N = 244)	Placebo (N = 122)
% Male Sample size	n = 150 ; % = 62	n = 130 ; % = 54	n = 143 ; % = 59	n = 139 ; % = 57	n = 73 ; % = 60
Mean age (SD) (Years (mean, SD)) Mean (SD)	56 (11)	57 (9)	57 (9)	57 (9)	56 (9)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Caucasian Sample size	n = 203 ; % = 84	n = 212 ; % = 88	n = 213 ; % = 88	n = 217 ; % = 89	n = 107 ; % = 88

Characteristic	Liraglutide 0.6 mg (N = 242)	Liraglutide 1.2 mg (N = 241)	Liraglutide 1.8 mg (N = 242)	Glimepiride (N = 244)	Placebo (N = 122)
Black Sample size	n = 4 ; % = 2	n = 9 ; % = 4	n = 5 ; % = 2	n = 4 ; % = 2	n = 3 ; % = 3
Asian/Pacific islander Sample size	n = 31 ; % = 13	n = 18 ; % = 8	n = 17 ; % = 7	n = 22 ; % = 9	n = 9 ; % = 7
Other Sample size	n = 4 ; % = 2	n = 2 ; % = 1	n = 5 ; % = 2	n = 1 ; % = 1	n = 3 ; % = 3
Time since type 2 diabetes diagnosed (Years (mean, SD)) Mean (SD)	7 (5)	7 (5)	8 (5)	8 (5)	8 (6)
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Metformin monotherapy Sample size	n = 70 ; % = 29	n = 78 ; % = 32	n = 72 ; % = 30	n = 82 ; % = 34	n = 38 ; % = 31

Characteristic	Liraglutide 0.6 mg (N = 242)	Liraglutide 1.2 mg (N = 241)	Liraglutide 1.8 mg (N = 242)	Glimepiride (N = 244)	Placebo (N = 122)
Sulfonylurea monotherapy Sample size	n = 9 ; % = 4	n = 12 ; % = 5	n = 11 ; % = 5	n = 7 ; % = 3	n = 3 ; % = 2
Repaglinide monotherapy Sample size	n = 2 ; % = 1	n = 1 ; % = 0.5	n = 0 ; % = 0	n = 0 ; % = 0	n = 0 ; % = 0
Combniation therapy Sample size	n = 161 ; % = 67	n = 150 ; % = 62	n = 159 ; % = 66	n = 155 ; % = 63	n = 81 ; % = 66
Blood pressure-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Statins/lipid-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR

340. Nauck, 2014

Bibliographic Reference	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

340.1. 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	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. 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 **(N.B. this study was a dose finding study, where patients randomised to 7 different doses of dulaglutide, this study has been included but as a separate study altogether because it included only a small subset of the total number of patients included in the AWARD-5 trial; after the dose selection occurred, 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.)**
Trial name / registration number	AWARD-5/NCT00734474
Study type	Randomised controlled trial (RCT)
Study location	US, Canada, France, Germany, India, Korea, Mexico, Poland, Puerto Rico, Romania, Russian, Spain and Taiwan.
Study setting	Hospital

Study dates	08/2008 - 07/2012
Sources of funding	Eli Lilly and company
Inclusion criteria	Eligible patients were those 18–75 years old, had type 2 diabetes (≥6 months) with an HbA1c value of >8% (64 mmol/mol) and ≤9.5% (80 mmol/mol) on diet and exercise alone or ≥7% (53 mmol/mol) and ≤9.5% (80 mmol/mol) on oral antihyperglycaemic medication monotherapy or combination therapy (metformin plus another oral antihyperglycaemic), a BMI between 25 and 40 kg/m2 , and a stable weight during the 3-month period before entering the study.
Exclusion criteria	Taking GLP-1 receptor agonists during the 6 months prior to screening or were on chronic insulin therapy. The protocol was approved by local ethics review boards, and all patients provided written informed consent. The study was conducted in compliance with the Declaration of Helsinki and the International Conference on Harmonization guideline on good clinical practices.
Recruitment / selection of participants	Patients aged 18 - 75 years old with uncontrolled type 2 diabetes were randomised in a 2:2:2:1 ratio to dulaglutide 1.5 mg, dulaglutide 0.75 mg, sitagliptin 100 mg or placebo (replaced with sitagliptin after 26-weeks).
Intervention(s)	Dulaglutide 0.75 mg - 1.5 mg weekly Administered subcutaneously.
Cointervention	
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	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	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	
Comparator	Sitagliptin 100 mg daily or placebo daily Both administered orally.
Number of participants	N=1098
Duration of follow-up	104 weeks
Indirectness	

Method of analysis	ITT
Additional comments	All randomised patients were included in the analysis.

340.2. Study arms

340.2.1. Dulaglutide 1.5 mg weekly (N = 304)

Administered subcutaneously

340.2.2. Dulaglutide 0.75 mg weekly (N = 302)

Administered subcutaneously

340.2.3. Sitagliptin 100 mg daily (N = 315)

Administered orally

340.2.4. Placebo daily (N = 177)

Administered orally

340.3. Characteristics

340.3.1. Arm-level characteristics

Characteristic	Dulaglutide 1.5 mg weekly (N = 304)	Dulaglutide 0.75 mg weekly (N = 302)	Sitagliptin 100 mg daily (N = 315)	Placebo daily (N = 177)
% Male No of events	n = 146 ; % = 48	n = 134 ; % = 44	n = 151 ; % = 48	n = 90 ; % = 51
Mean age (SD) (year) Mean (SD)	54 (10)	54 (10)	54 (10)	55 (9)
Aboriginal No of events	n = 0 ; % = 0	n = 0 ; % = 0	n = 1 ; % = 1	n = 0 ; % = 0

Characteristic	Dulaglutide 1.5 mg weekly (N = 304)	Dulaglutide 0.75 mg weekly (N = 302)	Sitagliptin 100 mg daily (N = 315)	Placebo daily (N = 177)
Black No of events	n = 16 ; % = 5	n = 12 ; % = 4	n = 7 ; % = 2	n = 9 ; % = 5
White No of events	n = 157 ; % = 52	n = 162 ; % = 54	n = 158 ; % = 50	n = 91 ; % = 51
East Asian No of events	n = 50 ; % = 16	n = 47 ; % = 16	n = 52 ; % = 17	n = 28 ; % = 16
Hispanic No of events	n = 54 ; % = 18	n = 51 ; % = 17	n = 67 ; % = 21	n = 38 ; % = 22
Native-American No of events	n = 0 ; % = 0	n = 0 ; % = 0	n = 1 ; % = 1	n = 0 ; % = 0
West-Asian No of events	n = 27 ; % = 9	n = 30 ; % = 10	n = 28 ; % = 9	n = 11 ; % = 6
Presence of frailty Nominal	NR	NR	NR	NR
Time since type 2 diabetes diagnosed Mean (SD)	7 (6)	7 (5)	7 (5)	7 (5)
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
Number of people with obesity	NR	NR	NR	NR

Characteristic	Dulaglutide 1.5 mg weekly (N = 304)	Dulaglutide 0.75 mg weekly (N = 302)	Sitagliptin 100 mg daily (N = 315)	Placebo daily (N = 177)
Nominal				
One medication class No of events	n = 203 ; % = 67	n = 193 ; % = 64	n = 218 ; % = 69	n = 114 ; % = 64
Two medication classes No of events	n = 83 ; % = 27	n = 89 ; % = 30	n = 76 ; % = 24	n = 49 ; % = 28
More than two medication classes No of events	n = 4 ; % = 1	n = 2 ; % = 1	n = 0 ; % = 0	n = 4 ; % = 2

341. Nauck, 2013

Bibliographic Reference	Nauck, M; Frid, A; Hermansen, K; Thomsen, A B; During, M; Shah, N; Tankova, T; Mitha, I; Matthews, D R; Long-term efficacy and safety comparison of liraglutide, glimepiride and placebo, all in combination with metformin in type 2 diabetes: 2-year results from the LEAD-2 study.; Diabetes, obesity & metabolism; 2013; vol. 15 (no. 3); 204-12

341.1. Study details

Secondary publication of another included study- see primary study for details	Nauck 2009B Nauck M, Frid A, Hermansen K, Shah NS, Tankova T, Mitha IH, Zdravkovic M, Düring M, Matthews DR; LEAD-2 Study Group. Efficacy and safety comparison of liraglutide, glimepiride, and placebo, all in combination with metformin, in type 2 diabetes: the LEAD (liraglutide effect and action in diabetes)-2 study. Diabetes Care. 2009 Jan;32(1):84-90. doi: 10.2337/dc08-1355. Epub 2008 Oct 17. PMID: 18931095; PMCID: PMC2606836.

342. Nauck, 2016

Bibliographic Reference	Nauck, Michael; Rizzo, Manfredi; Johnson, Andrew; Bosch-Traberg, Heidrun; Madsen, Jesper; Cariou, Bertrand; Once-Daily Liraglutide Versus Lixisenatide as Add-on to Metformin in Type 2 Diabetes: A 26-Week Randomized Controlled Clinical Trial.; Diabetes care; 2016; vol. 39 (no. 9); 1501-9

342.1. 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	NCT01973231
Study type	Randomised controlled trial (RCT)
Study location	56 sites in nine countries of the European Union (Czech Republic, Finland, France, Germany, Hungary, Italy, Latvia, Lithuania, and U.K.)
Study setting	NR
Study dates	24 October 2013 to 19 November 2014
Sources of funding	Sponsored by Novo Nordisk A/S
Inclusion criteria	Males and females with type 2 diabetes, age ≥18 years, HbA1c 7.5−10.5% (58−91 mmol/mol), and BMI ≥20 kg/m2, who were on unchanged metformin treatment at the maximum tolerated dose (1,000 to 3,000 mg/day) for at least 90 days prior to screening.
Exclusion criteria	female patients of child-bearing potential who was pregnant, breast-feeding, or intending to become pregnant or not using adequate contraception and patients who were previously treated with a GLP-1 RA, who were treated with glucose-lowering agents other than metformin within 90 days of screening or who had a history of chronic pancreatitis or idiopathic acute pancreatitis, a screening calcitonin value ≥50 ng/L,

	personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2, impaired liver function (alanine aminotransferase ≥2.5 times the upper normal limit [UNL]), impaired renal function (estimated glomerular filtration rate <60 mL/min/1.73 m2 per MDRD formula), or any chronic disorder or severe disease that in the opinion of the investigator might jeopardize the patient's safety or compliance with the protocol.
Recruitment / selection of participants	NR
Intervention(s)	liraglutide, lixisenatide
Cointervention	Metformin treatment at the maximum tolerated dose (1,000 to 3,000 mg/day) for at least 90 days prior to screening
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 Exclusion criteria for impaired renal function (eGFR <60mL/min/1.73 m2) but not explicitly 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 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	NA
Comparator	NA
Number of participants	404
Duration of follow-up	26-week
Indirectness	None
Method of analysis	ITT Modified ITT
Additional comments	The full analysis set (FAS) included all randomized patients. The safety analysis set (SAS) included all patients receiving at least one dose of any of the trial products. All efficacy end points were summarized and analysed using the FAS, and all safety end points were summarized and analysed using the SAS.

342.2. Study arms

342.2.1. Liraglutide (N = 202)

Liraglutide 1.8 mg administered once daily subcutaneously at any time of the day irrespective of meals, but time of injection was to be consistent throughout the trial. Add-on to metformin. Started at 0.6 mg/day, with weekly dose escalations of 0.6 mg/day until the maintenance dose of 1.8 mg/day was reached. If patients could not tolerate the dose of liraglutide 1.8 mg, they were to discontinue the trial product. Patients meeting predefined hyperglycemia criteria were offered rescue treatment

(suitable marketed products or attempt to further increase metformin dose) at the discretion of the investigator as add-on to the trial product during the remainder of the trial.

342.2.2. Lixisenatide (N = 202)

Lixisenatide 20 µg administered once daily within 1 h prior to the morning or evening meal. Add-on to metformin. After a starting dose of 10 µg, the lixisenatide dose was escalated to 20 µg from day 15. If patients could not tolerate the dose of lixisenatide 20 µg, they were to discontinue the trial product. Patients meeting predefined hyperglycemia criteria were offered rescue treatment (suitable marketed products or attempt to further increase metformin dose) at the discretion of the investigator as add-on to the trial product during the remainder of the trial.

342.3. Characteristics

342.3.1. Arm-level characteristics

Characteristic	Liraglutide (N = 202)	Lixisenatide (N = 202)
% Male Sample size	n = NR ; % = 65	n = NR ; % = 55
Mean age (SD) Mean (SD)	56.3 (10.6)	56.1 (10)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed Mean (SD)	6.5 (5.3)	6.3 (5)
Cardiovascular risk factors Sample size	n = NR ; % = NR	n = NR ; % = NR
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Liraglutide (N = 202)	Lixisenatide (N = 202)
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
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
Metfomin Sample size	n = 202 ; % = 100	n = 202 ; % = 100
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

343. Neal, 2013

Bibliographic Reference	Neal, Bruce; Perkovic, Vlado; de Zeeuw, Dick; Mahaffey, Kenneth W; Fulcher, Greg; Stein, Peter; Desai, Mehul; Shaw, Wayne; Jiang, Joel; Vercruysse, Frank; Meininger, Gary; Matthews, David; Rationale, design, and baseline characteristics of the Canagliflozin Cardiovascular Assessment Study (CANVAS)--a randomized placebo-controlled trial.; American heart journal; 2013; vol. 166 (no. 2); 217-223e11

343.1. Study details

Secondary publication of another included study- see primary study for details	Mahaffey Kenneth, W, Neal, Bruce, Perkovic, Vlado et al. (2018) Canagliflozin for Primary and Secondary Prevention of Cardiovascular Events: Results From the CANVAS Program (Canagliflozin Cardiovascular Assessment Study). Circulation 137(4): 323-334
Other publications associated with this study included in review	Neal, Bruce, Perkovic, Vlado, Matthews David, R et al. (2017) Rationale, design and baseline characteristics of the CANagliflozin cardioVascular Assessment Study-Renal (CANVAS-R): A randomized, placebo-controlled trial. Diabetes, obesity & metabolism 19(3): 387-393 Radholm, Karin, Figtree, Gemma, Perkovic, Vlado et al. (2018) Canagliflozin and Heart Failure in Type 2 Diabetes Mellitus: Results From the CANVAS Program. Circulation 138(5): 458-468 Zhou, Z, Lindley R, I, Radholm, K et al. (2019) Canagliflozin and Stroke in Type 2 Diabetes Mellitus: Results from the Randomized CANVAS Program Trials. Stroke 50(2): 396-404
Trial name / registration number	CANVAS Program combines the CANVAS trial (NCT01032629) and the CANVAS-R trial (NCT01989754)

344. Neal, 2017

Bibliographic Reference	Neal, Bruce; Perkovic, Vlado; Matthews David, R; Mahaffey Kenneth, W; Fulcher, Greg; Meininger, Gary; Erondu, Ngozi; Desai, Mehul; Shaw, Wayne; Vercruysse, Frank; Yee, Jacqueline; Deng, Hsiaowei; de Zeeuw, Dick; CANVAS-R Trial Collaborative, Group; Rationale, design and baseline characteristics of the CANagliflozin cardioVascular Assessment Study-Renal (CANVAS-R): A randomized, placebo-controlled trial.; Diabetes, obesity & metabolism; 2017; vol. 19 (no. 3); 387-393

344.1. Study details

Secondary publication of another included study- see primary study for details	Mahaffey Kenneth, W, Neal, Bruce, Perkovic, Vlado et al. (2018) Canagliflozin for Primary and Secondary Prevention of Cardiovascular Events: Results From the CANVAS Program (Canagliflozin Cardiovascular Assessment Study). Circulation 137(4): 323-334
Other publications associated with this study included in review	Neal, Bruce; Perkovic, Vlado; de Zeeuw, Dick et al. (2013) Rationale, design, and baseline characteristics of the Canagliflozin Cardiovascular Assessment Study (CANVAS)--a randomized placebo-controlled trial. American heart journal; 2013; vol. 166 (no. 2); 217-223e11 Radholm, Karin, Figtree, Gemma, Perkovic, Vlado et al. (2018) Canagliflozin and Heart Failure in Type 2 Diabetes Mellitus: Results From the CANVAS Program. Circulation 138(5): 458-468 Zhou, Z, Lindley R, I, Radholm, K et al. (2019) Canagliflozin and Stroke in Type 2 Diabetes Mellitus: Results from the Randomized CANVAS Program Trials. Stroke 50(2): 396-404
Trial name / registration number	CANVAS Program combines the CANVAS trial (NCT01032629) and the CANVAS-R trial (NCT01989754)

345. Nesti, 2022

Bibliographic Reference	Nesti, L.; Pugliese, N. R.; Sciuto, P.; Trico, D.; Dardano, A.; Baldi, S.; Pinnola, S.; Fabiani, I.; Di Bello, V.; Natali, A.; Effect of empagliflozin on left ventricular contractility and peak oxygen uptake in subjects with type 2 diabetes without heart disease: results of the EMPA-HEART trial; Cardiovascular Diabetology; 2022; vol. 21 (no. 1)

345.1. Study details

Other publications associated with this study included in review	Natali A, Nesti L, Fabiani I, Calogero E, Di Bello V. Impact of empagliflozin on subclinical left ventricular dysfunctions and on the mechanisms involved in myocardial disease progression in type 2 diabetes: rationale and design of the EMPA-HEART trial. Cardiovasc Diabetol. 2017 Oct 12;16(1):130. doi: 10.1186/s12933-017-0615-6. PMID: 29025406; PMCID: PMC5639750.
Trial name / registration number	EMPA-HEART / EUDRACT Code 2016-002225-10
Study type	Randomised controlled trial (RCT)
Study location	Single centre in Pisa, Italy.
Study setting	Outpatients
Study dates	July 2017 to July 2019
Sources of funding	Supported at 49% by an unrestricted grant from Boehringer Ingelheim
Inclusion criteria	• Male or female affected by type 2 diabetes mellitus (T2D). • Age ≥ 40 and ≤ 80 years. • HbA1c levels ≥ 53 (7%) and ≤ 69 mmol/mol (8.5%). • On stable (since 3 months) antidiabetic therapy with either Metformin alone or Metformin + basal insulin (this constraint is determined by the present Italian prescription rules). • On stable (since 3 months) cardio-active therapies (e.g. anti-hypertensive drugs, diuretics, drugs for asthma or migraine prophylaxis). • Preserved kidney function as defined by eGFR ≥ 45 ml min−1 1.73 m2 . • Preserved left ventricular function as defined by EF ≥ 50%.

Exclusion criteria	(a) impaired kidney function (CK-EPI eGFR<50 mL/ min/1.76m2) (b) any heart disease defined as presence of clinically relevant cardiovascular symptom, cardiac or vascular disease or valvular defects, history of coronary artery disease or evidence of stress-induced ischemia, reduced (≤50%) 2D LV ejection fraction (LVEF), cardiac autonomic neuropathy (c) any pulmonary, muscular, or orthopaedic diseases potentially limiting exercise capacity. •• Patients with type 1 diabetes mellitus. •• Pregnancy or active breast feeding. •• History of hospitalization for acute coronary syndrome or heart failure. •• Respiratory insufficiency or history of clinically significant respiratory diseases (chronic obstructive pulmonary disease). •• NYHA class III and IV or other symptoms of heart failure (breathlessness, orthopnoea, paroxysmal nocturnal dyspnoea, fatigue, increased time to recover after exercise, ankle swelling) unrelated to most common non-cardiac causes
Recruitment / selection of participants	No additional information
Intervention(s)	Empagliflozin (n=22) Patients will receive 26 weeks of treatment with empagliflozin 10 mg daily as add on to the background therapy
Cointervention	Metformin and or basal insulin: Patients were on stable metformin and / or basal insulin
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Excluded "any heart disease defined as presence of clinically relevant cardiovascular symptom, cardiac or vascular disease or valvular defects, history of coronary artery disease or evidence of stress-induced ischemia, reduced (≤50%) 2D LV ejection fraction (LVEF), cardiac autonomic neuropathy"
Strata 2: People with atherosclerotic	People without atherosclerotic cardiovascular diseases Excluded "any heart disease defined as presence of clinically relevant cardiovascular symptom, cardiac or vascular disease or valvular defects, history of coronary artery disease or evidence of stress-induced ischemia,

cardiovascular disease	reduced (≤50%) 2D LV ejection fraction (LVEF), cardiac autonomic neuropathy". No person had peripheral artery disease (as assessed by ankle-brachial index)
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Excluded “impaired kidney function (CK-EPI eGFR<50 mL/ min/1.76m2)> < 50 mL/ min/1.76m2)”, otherwise unclear. 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	Sitagliptin (n=22) Patients received 26 weeks of treatment with 100 mg sitagliptin in addition to background therapy or metformin and / or basal insulin
Number of participants	56
Duration of follow-up	26 weeks
Indirectness	NA
Method of analysis	Not stated/unclear
Additional comments	Analysis not clearly stated however the exclusion of patients from analysis owing to abandoning trial and unreliable data suggests per protocol analysis

345.2. Study arms

345.2.1. Empagliflozin (N = 27)

Patients received 10 mg empagliflozin per day for 6 months

345.2.2. Sitagliptin (N = 29)

Patients received 100 mg Sitagliptin per day for 6 months

345.3. Characteristics

345.3.1. Arm-level characteristics

Characteristic	Empagliflozin (N = 27)	Sitagliptin (N = 29)
% Male Empagliflozin n = 22, Sitagliptin n = 22 Sample size	n = 19 ; % = 86	n = 19 ; % = 86
Mean age (SD) (Years (mean, SD)) Empagliflozin n = 22, Sitagliptin n = 22 Mean (SD)	61.6 (9.6)	61.8 (10.1)

Characteristic	Empagliflozin (N = 27)	Sitagliptin (N = 29)
Ethnicity Empagliflozin n = 22, Sitagliptin n = 22 Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed (Years (mean, SD)) Empagliflozin n = 22, Sitagliptin n = 22 Mean (SD)	7.8 (6.9)	11.1 (8.8)
Smoking status Empagliflozin n = 22, Sitagliptin n = 22 Sample size	n = 6 ; % = 27	n = 4 ; % = 18
Alcohol consumption Empagliflozin n = 22, Sitagliptin n = 22 Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Empagliflozin n = 22, Sitagliptin n = 22 Sample size	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Empagliflozin n = 22, Sitagliptin n = 22 Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Empagliflozin n = 22, Sitagliptin n = 22 Sample size	n = NR ; % = NR	n = NR ; % = NR
Other antidiabetic medication used Empagliflozin n = 22, Sitagliptin n = 22 Sample size	n = NA ; % = NA	n = NA ; % = NA
Metformin Sample size	n = 20 ; % = 91	n = 20 ; % = 91
Insulin Sample size	n = 11 ; % = 25	n = 7 ; % = 32
Statins/lipid-lowering medication used Empagliflozin n = 22, Sitagliptin n = 22 Sample size	n = NA ; % = NA	n = NA ; % = NA
Statin	n = 18 ; % = 81	n = 14 ; % = 63

Characteristic	Empagliflozin (N = 27)	Sitagliptin (N = 29)
Sample size		
Other treatment being received Empagliflozin n = 22, Sitagliptin n = 22 Sample size	n = NA ; % = NA	n = NA ; % = NA
ACEI/ARB Sample size	n = 16 ; % = 53	n = 11 ; % = 50
Beta blockers Sample size	n = 5 ; % = 23	n = 5 ; % = 23
CCB Sample size	n = 6 ; % = 27	n = 4 ; % = 18
ASA Sample size	n = 4 ; % = 41	n = 7 ; % = 32
Thiazide diuretics Sample size	n = 3 ; % = 14	n = 2 ; % = 9
Furosemide Sample size	n = 0 ; % = 0	n = 1 ; % = 5

346. Ning, 2016

Bibliographic Reference	Ning, G.; Li, L.; Ma, J.; Lv, X.; Yang, M.; Wang, W.; Woloschak, M.; Lukashevich, V.; Kothny, W.; Vildagliptin as add-on therapy to insulin improves glycemic control without increasing risk of hypoglycemia in Asian, predominantly Chinese, patients with type 2 diabetes mellitus; J Diabetes; 2016; vol. 8 (no. 3); 345-353

346.1. Study details

Other publications associated with this study included in review	
Trial name / registration number	NCT01582230
Study type	Randomised controlled trial (RCT)
Study location	22 centres in China, Thailand, Philippines, and Singapore
Study setting	No additional information
Study dates	April 2012 to May 2013
Sources of funding	Novartis Pharma AG (Basel, Switzerland). Five authors are also employed by Novartis and may be eligible for Novartis stock and stock options
Inclusion criteria	Men and women aged 18–80 years, with a BMI of 20–40 kg/m2 , inadequate glycemic control (HbA1c 7.5%– 11.0%), and on a stable dose (maximum ≤1 unit/kg per day) of basal long-acting, intermediate-acting, or premixed insulin with or without concomitant metformin therapy (≥1500 mg daily or a maximally tolerated dose) for at least 12 weeks before the screening period were enrolled in the study.
Exclusion criteria	Patients with fasting plasma glucose (FPG) levels >240 mg/dL (13.3 mmol/L), patients on rapid- or short-acting insulin except in premixed formulations with intermediate- or long-acting insulin, patients receiving insulin more frequently than twice daily or a total insulin dose >1 unit/kg per day for the past 12 weeks before screening, or patients using DPP-4 inhibitors, glucagon-like peptide-1 (GLP-1) analogues or mimetics, and oral antidiabetic drugs, except metformin in the past 6 months, were excluded from the study. Patients with a history or evidence of ketoacidosis, lactic acidosis, congestive heart failure (New York Heart Association Class III or IV), significant renal impairment (estimated glomerular filtration rate <30 mL/min per 1.73 m2) or elevated (>2× upper limit of normal) alanine aminotransferase or aspartate aminotransferase

Recruitment / selection of participants	No additional information
Intervention(s)	Vildagliptin (n=146) Patients received 50 mg vildagliptin twice daily for 24 weeks
Cointervention	Insulin ± Metformin Patients remained on a stable dose (maximum ≤1 unit/kg per day) of basal long-acting, intermediate-acting, or premixed insulin with or without concomitant metformin therapy (≥1500 mg daily or a maximally tolerated dose) throughout the trial
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Exclusion criteria for congestive heart failure (NYHA class III-IV)
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 Exclusion criteria for significant renal impairment (eGFR <30mL/min/1.73m2) but not explicitly 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

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=147) Patients received placebo for 24 weeks Insulin ± Metformin Patients remained on a stable dose (maximum ≤1 unit/kg per day) of basal long-acting, intermediate-acting, or premixed insulin with or without concomitant metformin therapy (≥1500 mg daily or a maximally tolerated dose) throughout the trial
Number of participants	293
Duration of follow-up	24 weeks
Indirectness	NA
Method of analysis	ITT
Additional comments	Efficacy analyses were performed on the full analysis set (FAS), which consisted of all randomized patients who received at least one dose of the study medication and had at least one post-randomization efficacy parameter measurement. Analysis of covariance (ANCOVA) was performed for the primary endpoint with treatment, population, metformin use, and insulin type (long- or intermediate-acting vs premixed) as the classification factors and baseline HbA1c as the covariate. The change in FPG from baseline to Week 24 (secondary endpoint) was analysed using the same model as for the primary endpoint (ANCOVA)

346.2. Study arms

346.2.1. Vildagliptin (N = 146)

Patients received 50 mg vildagliptin twice a day for 24 weeks in addition to basal/premix insulin with or without metformin

346.2.2. Placebo (N = 147)

Patients received a placebo twice a day for 24 weeks in addition to basal/premix insulin with or without metformin

346.3. Characteristics

346.3.1. Arm-level characteristics

Characteristic	Vildagliptin (N = 146)	Placebo (N = 147)
% Male Sample size	n = 61 ; % = 41.8	n = 66 ; % = 44.9
Mean age (SD) (Years (mean, SD)) Mean (SD)	57.8 (9.1)	58.4 (9.6)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Chinese Sample size	n = 120 ; % = 82.2	n = 121 ; % = 82.3
Indian (Indian subcontinent) Sample size	n = 2 ; % = 1.4	n = 0 ; % = 0
Other Sample size	n = 24 ; % = 16.4	n = 26 ; % = 17.7
Time since type 2 diabetes diagnosed (Years (mean, SD)) Mean (SD)	11.2 (7.3)	11.4 (6.7)
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Vildagliptin (N = 146)	Placebo (N = 147)
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
Long acting insulin Sample size	n = 46 ; % = 31.5	n = 46 ; % = 31.3
Intermediate acting insulin Sample size	n = 11 ; % = 7.5	n = 12 ; % = 8.2
Premixed insulin Sample size	n = 89 ; % = 61	n = 89 ; % = 60.5
Concomitant Metformin Sample size	n = 104 ; % = 71.2	n = 104 ; % = 70.7
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

347. Nissen, 2008

Bibliographic Reference	Nissen, S. E.; Nicholls, S. J.; Wolski, K.; Nesto, R.; Kupfer, S.; Perez, A.; Jure, H.; Larochellière, R.; Staniloae, C. S.; Mavromatis, K.; Saw, J.; Hu, B.; Lincoff, A. M.; Tuzcu, E. M.; Comparison of pioglitazone vs glimepiride on progression of coronary atherosclerosis in patients with type 2 diabetes: the PERISCOPE randomized controlled trial; JAMA; 2008; vol. 299 (no. 13); 1561-73

347.1. 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	NCT00225277. PERISCOPE.
Study type	Randomised controlled trial (RCT)
Study location	Multicentre trial.
Study setting	Outpatient follow-up.
Study dates	August 2003-March 2006.
Sources of funding	Financially supported by Takeda Pharmaceuticals North America Inc.
Inclusion criteria	People aged 35 to 85 years; baseline HbA1c of 6.0-9.0% (if taking a glucose-lowering medication) or 6.5-10% (if not currently receiving drug therapy); required to have coronary angiography performed for clinical indications that demonstrated at least 1 angiographic stenosis with at least 20% narrowing; a "target vessel" for IVUS examination was required to have less than 50% obstruction throughout a 40-mm or longer segment.
Exclusion criteria	Type 1 diabetes; taking 3 or more antidiabetic medications; received any thiazolidinedione within the past 12 weeks; serum creatinine level of >2.0 mg/dL; triglyceride level of more than 500mg/dL; uncontrolled hypertension

	(blood pressure >160/100mmHg despite therapy); active liver disease; a left main coronary artery stenosis of more than 50%. Use of thiazolidinediones, sulfonylureas or other insulin secretagogue.
Recruitment / selection of participants	No additional information.
Intervention(s)	Glimepiride N=273 Glimepiride 1mg if people were naive to glucose lowering therapy at screening or taking less than glimepiride 2mg/day (or an equivalent dosage of another sulfonylurea) at baseline. Glimepiride at a starting dosage of 2mg for those taking 2mg/day or more of glimepiride (or the equivalent) or metformin monotherapy. At the subsequent visits the study drug was increased to the next level (2mg or 4mg of glimepiride). The study drug was titrated to the maximum dose by 16 weeks, if tolerated. Total duration of 18 months.
Cointervention	Concomitant therapy: Metformin, insulin or both could be added or increased in dosage at the discretion of the investigator to achieve the target HbA1c level of less than 7.0%. If a person experienced hypoglycaemic symptoms, other glucose lowering therapies were reduced to maintain maximal dosages of study medication.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear
Strata 2: People with atherosclerotic cardiovascular disease	People with atherosclerotic cardiovascular diseases People with coronary heart disease
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Exclusion criteria for serum creatinine >2.0mg/dL but not explicitly 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
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	Pioglitazone N=270 Pioglitazone 15mg if people were naive to glucose lowering therapy at screening or taking less than glimepiride 2mg/day (or an equivalent dosage of another sulfonylurea) at baseline. Pioglitazone at a starting dosage of 30mg for those taking 2mg/day or more of glimepiride (or the equivalent) or metformin monotherapy. At the subsequent visits the study drug was increased to the next level (30mg or 45mg of glimepiride). The study drug was titrated to the maximum dose by 16 weeks, if tolerated. Total duration of 18 months.
Number of participants	543
Duration of follow-up	18 months.
Indirectness	No additional information.
Method of analysis	Modified ITT

Additional comments	No additional information.

347.2. Study arms

347.2.1. Glimepiride (N = 273)

Glimepiride 1mg if people were naive to glucose lowering therapy at screening or taking less than glimepiride 2mg/day (or an equivalent dosage of another sulfonylurea) at baseline. Glimepiride at a starting dosage of 2mg for those taking 2mg/day or more of glimepiride (or the equivalent) or metformin monotherapy. At the subsequent visits the study drug was increased to the next level (2mg or 4mg of glimepiride). The study drug was titrated to the maximum dose by 16 weeks, if tolerated. Total duration of 18 months. Concomitant therapy: Metformin, insulin or both could be added or increased in dosage at the discretion of the investigator to achieve the target HbA1c level of less than 7.0%. If a person experienced hypoglycaemic symptoms, other glucose lowering therapies were reduced to maintain maximal dosages of study medication.

347.2.2. Pioglitazone (N = 270)

Pioglitazone 15mg if people were naive to glucose lowering therapy at screening or taking less than glimepiride 2mg/day (or an equivalent dosage of another sulfonylurea) at baseline. Pioglitazone at a starting dosage of 30mg for those taking 2mg/day or more of glimepiride (or the equivalent) or metformin monotherapy. At the subsequent visits the study drug was increased to the next level (30mg or 45mg of glimepiride). The study drug was titrated to the maximum dose by 16 weeks, if tolerated. Total duration of 18 months. Concomitant therapy: Metformin, insulin or both could be added or increased in dosage at the discretion of the investigator to achieve the target HbA1c level of less than 7.0%. If a person experienced hypoglycaemic symptoms, other glucose lowering therapies were reduced to maintain maximal dosages of study medication.

347.3. Characteristics

347.3.1. Arm-level characteristics

Characteristic	Glimepiride (N = 273)	Pioglitazone (N = 270)
% Male Sample size	n = 180 ; % = 65.9	n = 186 ; % = 68.9
Mean age (SD) (years)	60 (9.4)	59.7 (9.1)

Characteristic	Glimepiride (N = 273)	Pioglitazone (N = 270)
Mean (SD)		
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 220 ; % = 80.6	n = 225 ; % = 83.3
Black Sample size	n = 27 ; % = 9.9	n = 30 ; % = 11.1
Asian Sample size	n = 16 ; % = 5.9	n = 12 ; % = 4.4
Native American Sample size	n = 10 ; % = 3.7	n = 3 ; % = 1.1
Comorbidities Sample size	n = NA ; % = NA	n = NA ; % = NA
Hypertension Sample size	n = 250 ; % = 91.6	n = 225 ; % = 83.3
Prior myocardial infarction Sample size	n = 70 ; % = 25.6	n = 83 ; % = 30.7
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed (Months) Median (IQR)	71 (30 to 131)	70 (27 to 129)
Smoking status Sample size	n = NA ; % = NA	n = NA ; % = NA
Current Sample size	n = 53 ; % = 19.4	n = 31 ; % = 11.5
Past Sample size	n = 119 ; % = 43.6	n = 147 ; % = 54.4
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Glimepiride (N = 273)	Pioglitazone (N = 270)
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Metformin Sample size	n = 174 ; % = 63.7	n = 176 ; % = 65.2
Insulin Sample size	n = 63 ; % = 23.1	n = 49 ; % = 18.1
Blood pressure-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Beta-blocker Sample size	n = 211 ; % = 77.3	n = 205 ; % = 75.9
ACE inhibitor or ARB Sample size	n = 229 ; % = 83.9	n = 217 ; % = 80.4
Statins/lipid-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Statin Sample size	n = 224 ; % = 82	n = 220 ; % = 81.5
Other lipid-lowering agent Sample size	n = 17 ; % = 6.2	n = 13 ; % = 4.8
Other treatment being received Sample size	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Glimepiride (N = 273)	Pioglitazone (N = 270)
Aspirin Sample size	n = 251 ; % = 91.9	n = 242 ; % = 89.6

348. Nogueira, 2014

Bibliographic Reference	Nogueira, K. C.; Furtado, M.; Fukui, R. T.; Correia, M. R. S.; Dos Santos, R. F.; Andrade, J. L.; Da Silva, M. E. R.; Left ventricular diastolic function in patients with type 2 diabetes treated with a dipeptidyl peptidase-4 inhibitor- a pilot study; Diabetol Metab Syndr; 2014; vol. 6 (no. 1)

348.1. Study details

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	NA
Trial name / registration number	NR
Study type	Randomised controlled trial (RCT)
Study location	Unclear- appears to be Brazil
Study setting	NR
Study dates	NR
Sources of funding	grants from Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP)
Inclusion criteria	Outpatients with type 2 diabetes inadequately controlled with metformin plus glyburide
Exclusion criteria	• Severe heart failure • Respiratory failure • Uncontrolled hypertension • Coronary heart disease • Arrhythmias • Hepatic and renal dysfunctions • Endocrine and gastrointestinal disorders • Malignancy

	• Alcohol abuse • Use of insulin • Beta blockers or calcium channel antagonists • Type 1 DM
Recruitment / selection of participants	NR
Intervention(s)	Sitagliptin 100 mg daily
Cointervention	All medications were kept constant during the study
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Exclusion criteria for severe heart failure but unclear about other forms
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Note that there is exclusion criteria for coronary heart disease
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Exclusion criteria for renal dysfunction but not explicitly 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

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	Bedtime NPH-insulin (final dose 11.0 ± 6.7 IU)
Number of participants	35 participants: 18 allocated to sitagliptin and 17 allocated to NHP insulin. No information around attrition
Duration of follow-up	24 weeks
Indirectness	Directly applicable
Method of analysis	Not stated/unclear Methods state that differences were assessed with two-way ANOVA models
Additional comments	

348.2. Study arms

348.2.1. Sitagliptin (N = 18)

348.2.2. Insulin NPH (N = 17)

348.3. Characteristics

348.3.1. Arm-level characteristics

Characteristic	Sitagliptin (N = 18)	Insulin NPH (N = 17)
% Male Sample size	n = 9 ; % = 50	n = 6 ; % = 35.3
Mean age (SD) Mean (SD)	55.1 (6.7)	58.4 (6.9)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed Mean (SD)	10.9 (5.8)	10.9 (7.5)
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 (mg/day)	NA (NA)	NA (NA)

Characteristic	Sitagliptin (N = 18)	Insulin NPH (N = 17)
Mean (SD)		
Metformin dose Mean (SD)	2.4 (0.3)	2.3 (0.6)
Glyburide Mean (SD)	17.6 (3)	18.1 (4.1)
Blood pressure-lowering medication used IECA or diuretics Sample size	n = 14 ; % = 77.8	n = 17 ; % = 100
Statins/lipid-lowering medication used Sample size	n = 14 ; % = 77.8	n = 11 ; % = 64.7
Other treatment being received Nominal	NR	NR

349. Nowicki, 2011

Bibliographic Reference	Nowicki, M.; Rychlik, I.; Haller, H.; Warren, M.; Suchower, L.; Gause-Nilsson, I.; Schützer, K. M.; Long-term treatment with the dipeptidyl peptidase-4 inhibitor saxagliptin in patients with type 2 diabetes mellitus and renal impairment: a randomised controlled 52-week efficacy and safety study; Int J Clin Pract; 2011; vol. 65 (no. 12); 1230-9

349.1. Study details

Secondary publication of another included study- see primary study for details	Not applicable
Other publications associated with this study included in review	Nowicki M, Rychlik I, Haller H, Warren ML, Suchower L, Gause-Nilsson I; D1680C00007 Investigators. Saxagliptin improves glycaemic control and is well tolerated in patients with type 2 diabetes mellitus and renal impairment. Diabetes Obes Metab. 2011 Jun;13(6):523-32. doi: 10.1111/j.1463-1326.2011.01382.x. PMID: 21332627.
Trial name / registration number	NCT00614939
Study type	Randomised controlled trial (RCT)
Study location	Multi-centre - Belarus, Croatia, Czech Republic, Estonia, Germany, Hungary, Latvia, Lithuania, Poland, Romania, Russia, Ukraine, USA
Study setting	Not reported
Study dates	January 2008 to March 2010
Sources of funding	Bristol-Myers Squibb and AstraZeneca
Inclusion criteria	• Adult patients with type 2 diabetes and CrCl <50 ml/min within the past 3 months • C-peptide ≥ 0.33 nmol/l • HbA1c ≥7.0% and ≤11.0%
Exclusion criteria	• Current or anticipated need for peritoneal dialysis or expected kidney transplant within 3 months after enrolment • Aspartate aminotransferase, alanine aminotransferase and/or total bilirubin > 1.5 times the upper limit of normal

	• Creatine kinase ≥ 3 times the upper limit of normal • Treatment with metformin within 4 weeks before enrolment • Previous or current treatment with any DPP-4 inhibitor or GLP-1 agonist
Recruitment / selection of participants	Not reported
Intervention(s)	Saxagliptin 2.5 mg once daily
Cointervention	• Other antidiabetic drugs in use at enrolment were continued, subject to adjustment as needed to prevent hypoglycaemia throughout the 52-week study or to improve glycaemic control during the 40-week extension • Addition of new drugs except thiazolidinediones, glucagon-like peptide-1 (GLP-1) agonists, metformin and other DPP-4 inhibitors was allowed
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	People with chronic kidney disease People with renal impairment entering the study (creatinine clearance <50mL/min within the past 3 months)
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	• Moderate baseline renal impairment (CrCl ≥ 30 and < 50 nml/min) • Severe baseline renal impairment (CrCl < 30 ml/min and not receiving dialysis) • End-stage renal disease on haemodialysis at baseline
Comparator	Placebo
Number of participants	170 participants
Duration of follow-up	• 12 weeks • 52 weeks
Indirectness	Directly applicable
Method of analysis	ACA Extracted data - absolute changes in HbA1c from baseline to week 52 were assessed using observed data only. Per protocol Sensitivity analysis was reported with per-protocol analysis set (i.e. those without significant protocol deviations) using LOCF methodology

	ITT Absolute changes in HbA1c were compared using an ANCOVA model with treatment group and baseline renal impairment as fixed effects and baseline value as covariate. Data were included up to completion, discontinuation, or change in insulin or OAD dose. Missing efficacy data were imputed using last observed data carried forward.
Additional comments	• Patients were stratified based on degree of renal impairment were and randomized (1 : 1) via an interactive voice response system in balanced blocks within each renal impairment category. • Study-specific discontinuation criteria were FPG > 15.0 mmol/l at weeks 2 or 4, > 13.3 mmol/l at weeks 6 or 9, > 12.2 mmol/l at week 12 or > 11.1 mmol/l at week 20; and HbA1c > 8% (> 7.5% at sites in Germany) at weeks 28, 36 or 44.

349.2. Study arms

349.2.1. Saxagliptin (N = 85)

349.2.2. Placebo (N = 85)

349.3. Characteristics

349.3.1. Arm-level characteristics

Characteristic	Saxagliptin (N = 85)	Placebo (N = 85)
% Male Sample size	n = 32 ; % = 37.6	n = 41 ; % = 48.2
Mean age (SD) Mean (SD)	66.8 (8.3)	66.2 (9.1)
White Sample size	n = 85 ; % = 100	n = 85 ; % = 100
Presence of frailty Nominal	NR	NR

Characteristic	Saxagliptin (N = 85)	Placebo (N = 85)
Time since type 2 diabetes diagnosed Mean (SD)	15.1 (7.5)	18.2 (8.5)
HbA1c (%) Sample size	n = 85 ; % = 100	n = 84 ; % = 98.8
HbA1c (%) Mean (SD)	8.5 (1.2)	8.1 (1.1)
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)	83.6 (15.7)	82.2 (14.4)
BMI (kg/m²) Mean (SD)	31.2 (6.1)	30.2 (6.8)
Number of people with obesity Nominal	NR	NR
Other antidiabetic medication used Sample size	n = 83 ; % = 97.6	n = 84 ; % = 98.8
Insulin Sample size	n = 71 ; % = 83.5	n = 57 ; % = 67.1
Oral blood glucose-lowering drug Sample size	n = 23 ; % = 27.1	n = 30 ; % = 35.3

Characteristic	Saxagliptin (N = 85)	Placebo (N = 85)
Oral blood glucose-lowering drug - alpha-Glucosidase inhibitor Sample size	n = 2 ; % = 2.4	n = 2 ; % = 2.4
Oral blood glucose-lowering drug - Sulphonylurea Sample size	n = 17 ; % = 20	n = 26 ; % = 30.6
Oral blood glucose-lowering drug - Gilnide Sample size	n = 5 ; % = 5.9	n = 3 ; % = 3.5
Oral blood glucose-lowering drug - Thiazolidinedione Sample size	n = 0 ; % = 0	n = 1 ; % = 1.2
Oral blood glucose-lowering drug and insulin Sample size	n = 11 ; % = 12.9	n = 3 ; % = 3.5
Blood pressure-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

350. Nowicki, 2011

Bibliographic Reference	Nowicki, M; Rychlik, I; Haller, H; Warren, M L; Suchower, L; Gause-Nilsson, I; Saxagliptin improves glycaemic control and is well tolerated in patients with type 2 diabetes mellitus and renal impairment.; Diabetes, obesity & metabolism; 2011; vol. 13 (no. 6); 523-32

350.1. Study details

Secondary publication of another included study- see primary study for details	Nowicki M, Rychlik I, Haller H, Warren M, Suchower L, Gause-Nilsson I, Schützer KM. Long-term treatment with the dipeptidyl peptidase-4 inhibitor saxagliptin in patients with type 2 diabetes mellitus and renal impairment: a randomised controlled 52-week efficacy and safety study. Int J Clin Pract. 2011 Dec;65(12):1230-9. doi: 10.1111/j.1742-1241.2011.02812.x. Epub 2011 Oct 7. PMID: 21977965.
Other publications associated with this study included in review	

350.2. Study arms

350.2.1. Saxagliptin (N = 85)

350.2.2. Placebo (N = 85)

351. Oh, 2021

Bibliographic Reference	Oh, M.; Choi, J. H.; Kim, S. O.; Lee, P. H.; Ahn, J. M.; Lee, S. W.; Moon, D. H.; Lee, C. W.; Comparison of empagliflozin and sitagliptin therapy on myocardial perfusion reserve in diabetic patients with coronary artery disease; Nuclear Medicine Communications; 2021; vol. 42 (no. 9); 972-978

351.1. Study details

Secondary publication of another included study- see primary study for details	No information available.
Other publications associated with this study included in review	No information available.
Trial name / registration number	ELITE trial NCT03208465
Study type	Randomised controlled trial (RCT)
Study location	South Korea
Study setting	University, medical centre
Study dates	August 2017 - August 2019
Sources of funding	No information available.
Inclusion criteria	Adults (≥18years of age) with type 2 diabetes with stable coronary artery disease, global myocardial perfusion reserve (MPR) <2.5 and a glycated hemoglobin level < 10.0%.
Exclusion criteria	Patients were excluded if they had • Contraindications to empagliflozin or sitagliptin; had received SGLT2 inhibitors or dipeptidyl peptidase-4 inhibitors within the previous 4weeks;

	• Had insulin-requiring diabetes; acute coronary syndrome; stent placement or coronary artery bypass graft surgery within the previous 6months; planned revascularisation within 6 months; • Heart failure requiring loop diuretics; chronic kidney disease; hepatic disease or biliary tract obstruction; • Were pregnant, breast-feeding, or had child-bearing potential or if they had an expected life expectancy <1year.
Recruitment / selection of participants	Eligible patients who met all the inclusion criteria and non of the exclusion criteria were included and randomly assigned to empagliflozin group or sitagliptin group using a computer generated randomisation program.
Intervention(s)	Empagliflozin 10 mg, administered orally once daily
Cointervention	Other conventional oral antidiabetic drugs, including metformin, sulfonylurea and pioglitazone were used to control the glucose levels in both groups.
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Heart failure requiring loop diuretics as an exclusion criteria - likely a large proportion of people with heart failure
Strata 2: People with atherosclerotic cardiovascular disease	People with atherosclerotic cardiovascular diseases People with coronary artery disease
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	People without chronic kidney disease Exclusion criteria
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	Not stated/unclear
Population subgroups	
Comparator	Sitagliptin 100 mg, administered orally once daily.
Number of participants	N=100
Duration of follow-up	6 months
Indirectness	
Method of analysis	ITT
Additional comments	

351.2. Study arms

351.2.1. Empagliflozin 10 mg (N = 48)

Administered orally, once daily

351.2.2. Sitagliptin 100 mg (N = 49)

Administered orally, once daily

351.3. Characteristics

351.3.1. Arm-level characteristics

Characteristic	Empagliflozin 10 mg (N = 48)	Sitagliptin 100 mg (N = 49)
% Male No of events	n = 41 ; % = 85.4	n = 44 ; % = 89.8
Mean age (SD) (years) Mean (SD)	63.6 (9.2)	66.3 (7.6)
Ethnicity Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed (Months) Mean (SD)	75.2 (75)	73.2 (64.7)
Smokers No of events	n = 11 ; % = 23.4	n = 8 ; % = 17
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

Characteristic	Empagliflozin 10 mg (N = 48)	Sitagliptin 100 mg (N = 49)
Metformin No of events	n = 31 ; % = 64.6	n = 34 ; % = 69.4
Sulfonylurea No of events	n = 17 ; % = 35.4	n = 15 ; % = 30.6
Pioglitazone No of events	n = 1 ; % = 2.1	n = 2 ; % = 4.1
Statin No of events	n = 48 ; % = 100	n = 49 ; % = 100
Beta-blocker No of events	n = 25 ; % = 52.1	n = 31 ; % = 63.3
ACEI or ARB No of events	n = 16 ; % = 33.3	n = 20 ; % = 40.8
Calcium-channel blocker No of events	n = 26 ; % = 54.2	n = 28 ; % = 57.1
Antiplatelet agents No of events	n = 48 ; % = 100	n = 49 ; % = 100
Previous MI (myocardial infarction) No of events	n = 22 ; % = 45.8	n = 19 ; % = 38.8
Previous PCI (percutaneous coronary intervention) No of events	n = 45 ; % = 93.8	n = 47 ; % = 95.9
Previous CABG (coronary artery bypass graft surgery) No of events	n = 1 ; % = 2.1	n = 2 ; % = 4.1

352. Ohira, 2014

Bibliographic Reference	Ohira, M.; Yamaguchi, T.; Saiki, A.; Ban, N.; Kawana, H.; Nagayama, D.; Nagumo, A.; Murano, T.; Shirai, K.; Tatsuno, I.; Metformin reduces circulating malondialdehyde-modified low-density lipoprotein in type 2 diabetes mellitus; Clin Invest Med; 2014; vol. 37 (no. 4); E243-51

352.1. Study details

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	NA
Trial name / registration number	NR
Study type	Randomised controlled trial (RCT)
Study location	Japan
Study setting	NR
Study dates	NR
Sources of funding	NR
Inclusion criteria	Patients with type 2 diabetes that was inadequately controlled despite ongoing treatment with metformin 500 mg/day
Exclusion criteria	NR
Recruitment / selection of participants	Before participation, the purpose of this study was explained to each participant, and consent was obtained for both participation in the study and for release of the study data.

Intervention(s)	Sitagliptin 50 mg/day
Cointervention	Participants continued to take metformin 500 mg/day. All participants maintained their same diet and exercise therapies and did not change medications including statins. Participants received nutritional guidance from a dietitian every month.
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 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	Additional 500 mg/day metformin (total metformin dose 1000 mg/day)
Number of participants	70 participants were randomised, 35 participants were allocated to the sitagliptin arm, and 35 participants were allocated to the additional metformin arm. No information was provided about treatment or study completion.
Duration of follow-up	6 months
Indirectness	Directly applicable
Method of analysis	Not stated/unclear
Additional comments	NA

352.2. Study arms

352.2.1. Sitagliptin + metformin (N = 35)

352.2.2. Metformin (N = 35)

352.3. Characteristics

352.3.1. Arm-level characteristics

Characteristic	Sitagliptin + metformin (N = 35)	Metformin (N = 35)
% Male Sample size	n = 21 ; % = 60	n = 15 ; % = 42.9
Mean age (SD) (years) Mean (SD)	60.03 (12.35)	60.71 (11.01)
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 Nominal	NR	NR
Blood pressure 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	Sitagliptin + metformin (N = 35)	Metformin (N = 35)
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 Sample size	n = 7 ; % = 20	n = 12 ; % = 34.2
Other treatment being received Nominal	NR	NR

353. Ohira, 2014

Bibliographic Reference	Ohira, M.; Yamaguchi, T.; Saiki, A.; Ban, N.; Kawana, H.; Nagumo, A.; Murano, T.; Shirai, K.; Tatsuno, I.; Pioglitazone improves the cardio-ankle vascular index in patients with type 2 diabetes mellitus treated with metformin; Diabetes Metab Syndr Obes; 2014; vol. 7; 313-319

353.1. Study details

Secondary publication of another included study- see primary study for details	NR
Other publications associated with this study included in review	NA
Trial name / registration number	NR
Study type	Randomised controlled trial (RCT)
Study setting	NR
Study dates	NR
Sources of funding	NR
Inclusion criteria	• Participants with type 2 diabetes (HbA1c > 7.0%) • All participants treated solely with 500 mg/day of metformin
Exclusion criteria	NR
Recruitment / selection of participants	Before participation, the purpose of the study was explained to each subject, and consent was obtained for both participation in this study and for release of the study data.
Intervention(s)	• Pioglitazone 15 mg/day

	• Glimepiride 1 mg/day
Cointervention	• 500 mg/day metformin • All patients maintained the same diet and exercise therapies and did not change medications during this study • A dietician provided nutritional guidance to all subjects on a monthly basis
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 non-alcoholic	Not stated/unclear

fatty liver disease	
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	NA
Comparator	NA
Number of participants	60 participants were randomised - 30 participants were allocated to pioglitazone and 30 participants were allocated to glimepiride
Duration of follow-up	6 months
Indirectness	Directly applicable
Method of analysis	Not stated/unclear
Additional comments	NA

353.2. Study arms

353.2.1. Pioglitazone (N = 30)

353.2.2. Glimepiride (N = 30)

353.3. Characteristics

353.3.1. Arm-level characteristics

Characteristic	Pioglitazone (N = 30)	Glimepiride (N = 30)
% Male Sample size	n = 19 ; % = 63.3	n = 15 ; % = 50
Mean age (SD) Mean (SD)	63.7 (7.94)	62.23 (12.26)
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 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

Characteristic	Pioglitazone (N = 30)	Glimepiride (N = 30)
Other antidiabetic medication used Nominal	NR	NR
Blood pressure-lowering medication used Nominal	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

354. Owens, 2011

Bibliographic Reference	Owens, D. R.; Swallow, R.; Dugi, K. A.; Woerle, H. J.; Efficacy and safety of linagliptin in persons with type 2 diabetes inadequately controlled by a combination of metformin and sulphonylurea: a 24-week randomized study; Diabetic Med; 2011; vol. 28 (no. 11); 1352-61

354.1. 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	NCT00602472
Study type	Randomised controlled trial (RCT)
Study location	100 trial centres in 11 countries: Argentina, Belgium, Canada, China, Germany, Korea, the Philippines, Russia, Taiwan, Turkey and the UK
Study setting	NR
Study dates	NR
Sources of funding	Boehringer Ingelheim
Inclusion criteria	• Type 2 diabetes aged ≥18 and ≤80 years • BMI ≤ 40 kg/m2 • HbA1c ≥ 7.0% and ≤10% despite receiving a total daily dose of ≥1500 mg metformin (or the maximum tolerated dose, if lower) and the maximum tolerated dose of sulfonylurea. The dose and regimen of metformin and the sulfonylurea were unchanged for ≥ 10 weeks before enrolment

Exclusion criteria	• Clinical conditions that would, in the investigator's opinion, interfere with participation and safety. • Myocardial infarction, stroke or transient ischaemic attack within 6 months before enrolment • Impaired hepatic function • Renal failure or renal impairment • Current acute or chronic metabolic acidosis • Hereditary galactose intolerance • Being unable or unwilling to avoid nursing or pregnancy • Patients treated with rosiglitazone, pioglitazone, GLP-1 analogues, insulin or anti-obesity drugs (e.g. sibutramine, rimonabant, orlistat) within 3 months
Recruitment / selection of participants	NR
Intervention(s)	Linagliptin 5 mg once daily
Cointervention	Participants received established background therapy of metformin in combination with a sulfonylurea
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Exclusion criteria for myocardial infarction, stroke or TIA within 6 months of enrolment
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 non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Mixed population
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	NA
Comparator	Placebo
Number of participants	1,058 participants were randomised. Of 793 participants allocated to linagliptin, 792 received the intervention, and of these 58 participants discontinued. Of 265 participants allocated to placebo, 263 received the intervention, of these 21 discontinued.
Duration of follow-up	24 weeks
Indirectness	Directly applicable
Method of analysis	Per protocol For HbA1c change, sensitivity analyses were performed to assess the impact of important protocol violations and premature discontinuation, and to assess missing data assumptions i.e. mixed-model repeated measures Not stated/unclear

	Described as full analysis set - all randomised participants who were treated with at least one dose of study medication, had a baseline HbA1c measurement and at least on on-treatment HbA1c measurement. ANCOVA analysis performed. A last observation carried forward approach was taken to replace missing data.
Additional comments	Patients who changed their dose of background therapy remained in the trial to provide safety data. During the first 12 weeks of treatment, rescue medication (pioglitazone and, in Canada only, insulin) was initiated if a patient had a confirmed fasting glucose level of >13.3 mmol/l. During the last 12 weeks of randomized treatment, rescue medication was initiated if a patient had a confirmed fasting glucose level of > 11.1 mmol/l or a random glucose level of >22.2 mmol/l. Patients discontinued if the fasting glucose levels remained >13.3 mmol/l during the first 12 weeks or >11.1 mmol/l during the last 12 weeks despite rescue medication, and if the investigator anticipated no further glucose-lowering effect.

354.2. Study arms

354.2.1. Linagliptin (N = 793)

354.2.2. Placebo (N = 265)

354.3. Characteristics

354.3.1. Arm-level characteristics

Characteristic	Linagliptin (N = 793)	Placebo (N = 265)
% Male Sample size	n = 371 ; % = 46.8	n = 127 ; % = 48.3
Mean age (SD) Mean (SD)	58.3 (9.9)	57.6 (9.7)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
American Indian/Alaska Native Sample size	n = 6 ; % = 0.8	n = 4 ; % = 1.5

Characteristic	Linagliptin (N = 793)	Placebo (N = 265)
Asian Sample size	n = 404 ; % = 51	n = 141 ; % = 53.6
Black or African American Sample size	n = 6 ; % = 0.8	n = 2 ; % = 0.8
White Sample size	n = 376 ; % = 47.5	n = 116 ; % = 44.1
Not Hispanic/Latino Sample size	n = 611 ; % = 77.1	n = 204 ; % = 77.6
Hispanic/Latino Sample size	n = 180 ; % = 22.7	n = 58 ; % = 22.1
MIssing Sample size	n = 1 ; % = 0.1	n = 1 ; % = 0.4
Comorbidities Sample size	n = NA ; % = NA	n = NA ; % = NA
Macrovascular diseases Sample size	n = 643 ; % = 81.2	n = 262 ; % = 80.2
Metabolic syndrome Sample size	n = 547 ; % = 69.1	n = 172 ; % = 65.4
Microvascular complications Sample size	n = 361 ; % = 45.6	n = 124 ; % = 47.1
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed Sample size	n = NA ; % = NA	n = NA ; % = NA
Up to 1 year Sample size	n = 24 ; % = 3.1	n = 5 ; % = 1.9
>1 to 5 years Sample size	n = 185 ; % = 23.8	n = 64 ; % = 24.4
5+ years Sample size	n = 569 ; % = 73.1	n = 193 ; % = 73.3

Characteristic	Linagliptin (N = 793)	Placebo (N = 265)
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
BMI (kg/m2) Mean (SD)	28.4 (4.8)	28.2 (4.5)
Number of people with obesity BMI >=30 Sample size	n = 260 ; % = 32.8	n = 78 ; % = 29.7
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

355. Pan, 2012

Bibliographic Reference	Pan, C.; Xing, X.; Han, P.; Zheng, S.; Ma, J.; Liu, J.; Lv, X.; Lu, J.; Bader, G.; Efficacy and tolerability of vildagliptin as add-on therapy to metformin in Chinese patients with type 2 diabetes mellitus; Diabetes Obes Metab; 2012; vol. 14 (no. 8); 737-44

355.1. Study details

Secondary publication of another included study- see primary study for details	NR
Other publications associated with this study included in review	NA
Trial name / registration number	NR
Study type	Randomised controlled trial (RCT)
Study location	Multicentre trial in China
Study setting	NR
Study dates	NR
Sources of funding	Novartis Beijing
Inclusion criteria	• Patients with T2DM (aged 18–78) who were inadequately controlled by metformin monotherapy with HbA1c of 7.0–10.0% at week -2. • Patients were required to have been treated with metformin for at least 8 weeks and be on a stable dose of at least 1500 mg daily for a minimum of 4 weeks prior to the screening visit 1 (week -2). • Men, non-fertile women or women of childbearing potential using a medically approved contraceptive method, whose body mass index (BMI) of 20–40 kg/m2 and fasting plasma glucose (FPG) level was <270 mg/dl (15 mmol/l) were included.

Exclusion criteria	• History of type 1 diabetes mellitus or diabetes due to pancreatic injury or secondary forms of diabetes • Any acute metabolic diabetic complications such as ketoacidosis or hyperosmolar state (coma) within past 6 months • Myocardial infarction, unstable angina or coronary artery bypass surgery within past 6 months. • Patients with congestive heart failure, liver disease such as cirrhosis or chronic active hepatitis • Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2 times the upper limit of normal (ULN), total bilirubin >2 times ULN, serum creatinine levels [men: ≥1.5 mg/dl (132 µmol/l); women: ≥1.4 mg/dl (123 µmol/l)] or thyroid-stimulating hormone beyond the normal range, fasting triglycerides ≥500 mg/dl (5.64 mmol/l) at Visit 1
Recruitment / selection of participants	Patients were screened for eligibility at Visit 1 and were randomised at Visit 2
Intervention(s)	• Vildagliptin 50 mg BID • Vildagliptin 50 mg QD
Cointervention	Metformin
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Congestive heart failure was 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. People with the following serum creatinine results based on lab test at visit 1 were excluded: men: ≥1.5mg/dl; women: 132µmol/l. No information in baseline characteristics.
Strata 4: People with type 2 diabetes	Not stated/unclear

mellitus and high cardiovascular risk	
Subgroup 4: People with obesity	Mixed population
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	Pre-specified subgroup analysis of <30 kg/m2 (without obesity) and ≥30 kg/m2 (with obesity)
Comparator	Placebo
Number of participants	774 participants were assessed for eligibility and 438 were randomised. 148 participants were allocated to vildagliptin 50 mg qd, and of these 13 discontinued and 135 completed (91.2%). 146 participants were allocated to Vildagliptin 50 mg bid, of these 9 discontinued and 137 completed (93.8%). 144 participants were allocated to placebo, of these 13 discontinued and 131 completed (91%).
Duration of follow-up	24 weeks
Indirectness	Directly applicable
Method of analysis	Per protocol Methods describe that robustness of data were assessed in the per-protocol set, however, the results of this analysis were not reported Other 'Full analysis set' used for efficacy analysis - no definition provided Safety population - All patients who received at least one dose of the study drug
Additional comments	NA

355.2. Study arms

355.2.1. Vildagliptin 50 mg qd (N = 148)

355.2.2. Vildagliptin 50 mg bid (N = 146)

355.2.3. Placebo (N = 144)

355.3. Characteristics

355.3.1. Arm-level characteristics

Characteristic	Vildagliptin 50 mg qd (N = 148)	Vildagliptin 50 mg bid (N = 146)	Placebo (N = 144)
Mean age (SD) Mean (SD)	53.7 (10)	54.2 (9.62)	54.5 (9.68)
Ethnicity Nominal	NR	NR	NR
Comorbidities Nominal	NR	NR	NR
Presence of frailty Nominal	NR	NR	NR
Time since type 2 diabetes diagnosed Mean (SD)	5.02 (4.42)	4.92 (4.8)	5.15 (4.58)
Cardiovascular risk factors Nominal	NR	NR	NR
Smoking status Nominal	NR	NR	NR
Alcohol consumption Nominal	NR	NR	NR

Characteristic	Vildagliptin 50 mg qd (N = 148)	Vildagliptin 50 mg bid (N = 146)	Placebo (N = 144)
Presence of severe mental illness Nominal	NR	NR	NR
People with significant cognitive impairment Nominal	NR	NR	NR
People with a learning disability Nominal	NR	NR	NR
Weight Mean (SD)	68.36 (11.1)	71.58 (11.93)	69.83 (11.18)
BMI Mean (SD)	25.03 (3.09)	26.01 (3.26)	25.46 (3.09)
Number of people with obesity Sample size	n = 10 ; % = 6.8	n = 16 ; % = 11	n = 13 ; % = 9
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
% Female Sample size	n = 82 ; % = 55.4	n = 73 ; % = 50	n = 78 ; % = 54.2

356. Pan, 2014

Bibliographic Reference	Pan, C.Y.; Han, P.; Liu, X.; Yan, S.; Feng, P.; Zhou, Z.; Lv, X.; Tian, H.; Jin Kui, Y.; Su, B.; Shang, S.; Niemoeller, E.; Lixisenatide treatment improves glycaemic control in Asian patients with type 2 diabetes mellitus inadequately controlled on metformin with or without sulfonylurea: a randomized, double-blind, placebo-controlled, 24-week trial (GetGoal-M-Asia); Diabetes Metab Res Rev; 2014; vol. 30 (no. 8); 726-35

356.1. 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	GetGoal-M-Asia/NCT01169779
Study type	Randomised controlled trial (RCT) Double-blind placebo-controlled randomised trial
Study location	International (37 centres in 3 countries: China, Hong Kong, Malaysia, Thailand)
Study setting	Outpatient
Study dates	07/2010 to 12/2011
Sources of funding	Funded by Sanofi, France.

Inclusion criteria	• Diagnosis of type 2 diabetes for at least 1 year
	• Inadequately controlled on metformin with or without sulphonylurea
	  ○ HbA1c 7-10% inclusive
	  ○ FPG ≤13.9 mmol/L
	• Stable metformin dose 1000-1500 mg daily for 3 months before screening

	• Maximum effective sulphonylurea dose and stable for 3 months before screening

Exclusion criteria	• Treatment with oral antidiabetic drug other than metformin and sulphonylurea for 3 months or more prior to screening
	• History of:
	  ○ Hypoglycaemia unawareness
	  ○ Unexplained pancreatitis
	  ○ Chronic pancreatitis
	  ○ Pancreatectomy
	  ○ Stomach/gastric surgery
	  ○ Inflammatory bowel disease or patients considered by investigator to be at high risk for acute pancreatitis
	• Personal or family history of medullary thyroid cancer
	• History of metabolic acidosis, including diabetic ketoacidosis within 1 year prior to screening
	• Renal impairment
	• History of gastrointestinal disease associated with prolonged nausea and vomiting within 6 months prior to screening

Recruitment / selection of participants	Three-week screening period (screening phase of 2 weeks, 1 week blinded placebo run-in period), followed by randomisation 1:1 using interactive voice response system/interactive web-based system, stratified by HbA1c level (<8%, ≥8%) and sulphonylurea use, to 24-week treatment period.
Intervention(s)	• Lixisenatide 20 mcg daily Subcutaneous injection of lixisenatide 20 mcg daily 1 hour before breakfast for 24 weeks, in addition to metformin with or without sulphonylurea. Starting dose of 10 mcg for 2 weeks, then maintenance dose of 20 mcg for remainder of trial. Study drug (but not study drug dose) blinded
Cointervention	• Metformin All participants received background metformin 1000-1500 mg daily. In participants receiving sulphonylurea, dose was reduced 25-50% at randomisation in those with screening HbA1c<8%; in participants with HbA1c ≥8%, dose was kept stable at baseline dose of at least maximal effective dose (equating to half maximum recommended dose acc. to local labelling). For participants whose sulphonylurea dose was reduced at screening, sulphonylurea dose was increased to baseline dose between weeks 4 and 12 acc. to FPG values. Treatment period followed by 3 day follow up safety 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	People without chronic kidney disease Exclusion criteria included renal impairment.
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	
Comparator	• Placebo Volume-matched subcutaneous placebo injection for 24 weeks, in addition to metformin with or without sulphonylurea.
Number of participants	N=390 randomised
Duration of follow-up	24 weeks
Indirectness	None
Method of analysis	Modified ITT mITT LOCF analysis (all randomised participants who received at least one double-blind study dose and had both baseline and post-baseline efficacy assessment) for all efficacy outcomes. Safety population was all randomised participants who received at least one dose of double-blind treatment.

356.2. Study arms

356.2.1. Lixisenatide 20 mcg daily (N = 196)

Subcutaneous injection of lixisenatide 20 mcg once daily for 24 weeks, in addition to metformin with or without sulphonylurea.

356.2.2. Placebo (N = 195)

Volume-matched placebo for 24 weeks, in addition to metformin with or without sulphonylurea.

356.3. Characteristics

356.3.1. Arm-level characteristics

Characteristic	Lixisenatide 20 mcg daily (N = 196)	Placebo (N = 195)
% Male Sample size	n = 101 ; % = 51.5	n = 91 ; % = 46.9

Characteristic	Lixisenatide 20 mcg daily (N = 196)	Placebo (N = 195)
Mean age (SD) (years) Mean (SD)	54.5 (10.3)	55.1 (10.5)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Asian/Oriental Sample size	n = 196 ; % = 100	n = 194 ; % = 100
Comorbidities Nominal	NR	NR
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed Mean (SD)	6.5 (4.6)	6.8 (4.8)
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 (years) Mean (SD)	NA (NA)	NA (NA)

Characteristic	Lixisenatide 20 mcg daily (N = 196)	Placebo (N = 195)
Duration of metformin treatment Mean (SD)	4 (4)	3.5 (3.1)
Duration of sulphonylurea treatment Mean (SD)	3.1 (4.3)	2.8 (3)
Blood pressure-lowering medication used Nominal	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

Data for placebo arm is for N=194.

357. Papathanassiou, 2009

Bibliographic Reference	Papathanassiou, Katerina; Naka, Katerina K; Kazakos, Nikolaos; Kanioglou, Chryssanthi; Makriyiannis, Demetrios; Pappas, Konstantinos; Katsouras, Christos S; Liveris, Konstantinos; Kolettis, Theofilos; Tsatsoulis, Agathocles; Michalis, Lampros K; Pioglitazone vs glimepiride: Differential effects on vascular endothelial function in patients with type 2 diabetes.; Atherosclerosis; 2009; vol. 205 (no. 1); 221-6

357.1. 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 RCT
Study location	Ioannina, Greece
Study setting	Outpatient
Study dates	Not reported
Sources of funding	Funded in part by Michaelidion Cardiac Center, University of Ioannina, Ioannina, Greece
Inclusion criteria	• Type 2 diabetes diagnosis • Treated with metformin only for 6-mo prior to screening • HbA1c>6.5% • Normal liver enzymes and renal function
Exclusion criteria	• History of coronary artery, cerebrovascular, or peripheral vascular disease, chronic heart failure, liver or renal disease, anemia,

	thyroid dysfunction, and new onset of any medications within previous 8 weeks
Recruitment / selection of participants	Recruited at endocrinology outpatient clinic of University and Hatzikosta General Hospital of Ioannina, Greece. Eligible participants randomly assigned 1:1, using block randomisation, on basis of order of presentation to outpatient clinic. Participants maintained same diet and physical activity level, as well as other antihyptensive/hypolipidaemic/antiplatelet medications, for duration of trial.
Intervention(s)	• Pioglitazone 30 mg daily Oral pioglitazone 30 mg daily for 26 weeks, in addition to metformin.
Cointervention	• Metformin All participants continued with metformin for duration of trial.
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Heart failure an exclusion criterion.
Strata 2: People with atherosclerotic cardiovascular disease	People without atherosclerotic cardiovascular diseases Coronary artery, cerebrovascular, or peripheral vascular disease were exclusion criteria.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	People without chronic kidney disease Normal renal function stated in the inclusion criteria. Renal disease stated in the exclusion criteria.
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	
Comparator	• Glimepiride 4 mg daily Oral glimepiride 4 mg daily for 26 weeks, in addition to metformin.
Number of participants	N=28 randomised
Duration of follow-up	26 weeks
Indirectness	None
Method of analysis	ITT Appears to be ITT completer population Not stated/unclear
Additional comments	Method of analysis not explicitly reported but reports all randomised participants completed study and data reported for this number

357.2. Study arms

357.2.1. Pioglitazone 30 mg daily (N = 14)

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

357.2.2. Glimepiride 4 mg daily (N = 14)

Oral glimepiride 4 mg daily for 26 weeks, in addition to metformin.

357.3. Characteristics

357.3.1. Arm-level characteristics

Characteristic	Pioglitazone 30 mg daily (N = 14)	Glimepiride 4 mg daily (N = 14)
% Male Sample size	n = 3 ; % = 21.4	n = 3 ; % = 21.4
Mean age (SD) (years) Mean (SD)	62.8 (7.2)	63.6 (7.3)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	5.3 (3.6)	5.3 (6.5)
Cardiovascular risk factors Nominal	NR	NR
Smoking status Smoker Sample size	n = 3 ; % = 21.4	n = 3 ; % = 21.4
Alcohol consumption Nominal	NR	NR
Presence of severe mental illness Nominal	NR	NR

Characteristic	Pioglitazone 30 mg daily (N = 14)	Glimepiride 4 mg daily (N = 14)
People with significant cognitive impairment Nominal	NR	NR
People with a learning disability Nominal	NR	NR
Other antidiabetic medication used Nominal	NR	NR
Blood pressure-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Antihypertensives Sample size	n = 9 ; % = 64.3	n = 13 ; % = 92.9
ACE or Angiotensin II receptor blockers Sample size	n = 5 ; % = 35.7	n = 9 ; % = 64.3
Calcium channel blockers Sample size	n = 5 ; % = 35.7	n = 6 ; % = 42.9
Statins/lipid-lowering medication used Statins Sample size	n = 3 ; % = 21.4	n = 6 ; % = 42.9
Other treatment being received Sample size	n = NA ; % = NA	n = NA ; % = NA
Antiplatelets Sample size	n = 2 ; % = 14.3	n = 3 ; % = 21.4
Beta-blockers Sample size	n = 0 ; % = 0	n = 3 ; % = 21.4

358. Park, 2014

Bibliographic Reference	Park, C. Y.; Kang, J. G.; Chon, S.; Noh, J.; Oh, S. J.; Lee, C. B.; Park, S. W.; Comparison between the therapeutic effect of metformin, glimepiride and their combination as an add-on treatment to insulin glargine in uncontrolled patients with type 2 diabetes; PLoS ONE; 2014; vol. 9 (no. 3); e88779

358.1. 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	NCT00708578
Study type	Randomised controlled trial (RCT)
Study location	Multicentre trial in Korea
Study setting	Participants were enrolled from outpatient clinics of 5 centres
Study dates	20 June 2008 to 18 December 2009
Sources of funding	Sanofi-Korea
Inclusion criteria	• Men and women 18 to 80 years old who had had type 2 diabetes for at least 6 months • BMI of <30 kg/m2 • HbA1c levels ≥7.0% to ≤11.0% despite ≥3 months of treatment with a stable dose of both a sulfonylurea (more than daily 4 mg glimepiride or equivalent to dose of other sulfonylureas) and metformin (at least 1000 mg/day) up to the maximum tolerated dose) • Fasting serum C-peptide >0.99 ng/mL

	• Patients were also required to have a demonstrated ability and willingness to inject insulin and to perform self-monitoring of blood glucose (SMBG) with use of a plasma-referenced glucose meter
Exclusion criteria	• Type 1 diabetes • Insulin treated type 2 diabetes or having previously received long-term insulin • History of hypersensitivity to the investigational product or to drugs with similar chemical structures • Levels of alanine aminotransferase or aspartate aminotransferase greater than twice the upper limit of the normal range • A creatinine level greater than 1.5 mg/dL in men and 1.4 mg/dL in women • Pregnancy or lactation • Systemic treatment with corticosteroids within 3 months • Patients unable to perform SMBG or inject insulin on their own
Recruitment / selection of participants	There was a 4-week screening/titration phase, and patients who did not achieve good metabolic control while receiving nearly maximal dose of oral anti-diabetic drugs, were subsequently randomised to assigned treatment.
Intervention(s)	• Glimepiride 4 mg/day • Metformin 1500 mg/day • Glimepiride 4 mg/day plus metformin 1500 mg/day
Cointervention	Insulin glargine administered as a single daily subcutaneous injection in the morning at a starting dose of 0.2 U/kg, sometimes 10 IU for 3 days, which was titrated every third day to achieve a target FPG value of 5.0 to 7.2 mmol/l. Study medication accountability logs for insulin glargine, glimepiride and metformin were collected and evaluated for compliance.
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 occlusion/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: "a creatinine level greater than1.5mg/dL in man and 1.4mg/dL in woman."

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	NA
Number of participants	122 patients were screened and 99 were randomised. Of 33 participants allocated to metformin, 33 were included in the safety analysis, 32 were included in the ITT analysis and 26 were included in the PP analysis. Of 34 participants allocated to glimepiride, 34 were included in the safety analysis, 32 were included in the ITT analysis, and 27 were included in the PP analysis. Of 32 participants allocated to metformin + glimepiride, 32 were included in the safety analysis, 32 were included in the ITT analysis, and 24 were included in the PP analysis.
Duration of follow-up	24 weeks
Indirectness	Directly applicable
Method of analysis	Per protocol Described in the methods, but results were not reported

	ITT Used ANCOVA with last observation carried forward principle for participants who dropped out The safety population included all randomised participants who received the study product
Additional comments	NA

358.2. Study arms

358.2.1. Metformin (N = 33)

358.2.2. Glimepiride (N = 34)

358.2.3. Metformin + Glimepiride (N = 32)

358.3. Characteristics

358.3.1. Arm-level characteristics

Characteristic	Metformin (N = 33)	Glimepiride (N = 34)	Metformin + Glimepiride (N = 32)
% Male Sample size	n = 20 ; % = 60.61	n = 20 ; % = 58.82	n = 23 ; % = 71.88
Mean age (SD) (years) Mean (SD)	55.8 (10.5)	57.3 (9.2)	56.8 (10.9)
Ethnicity Nominal	NR	NR	NR
Comorbidities Chronic diabetes complications Sample size	n = 15 ; % = 45.45	n = 16 ; % = 37.06	n = 11 ; % = 34.38
Presence of frailty	NR	NR	NR

Characteristic	Metformin (N = 33)	Glimepiride (N = 34)	Metformin + Glimepiride (N = 32)
Nominal			
Time since type 2 diabetes diagnosed (years) Mean (SD)	11.3 (6.4)	13 (8)	11.7 (5)
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
Weight Nominal	NR	NR	NR
BMI (kg/m2) Mean (SD)	25.1 (3.6)	25.6 (2.7)	25.2 (2.7)
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

Characteristic	Metformin (N = 33)	Glimepiride (N = 34)	Metformin + Glimepiride (N = 32)
Statins/lipid-lowering medication used Nominal	NR	NR	NR
Other treatment being received Nominal	NR	NR	NR

359. Park, 2023

Bibliographic Reference	Park, Hyeong Kyu; Kim, Kyoung-Ah; Min, Kyung-Wan; Sohn, Tae-Seo; Jeong, In Kyung; Ahn, Chul Woo; Kim, Nan-Hee; Park, Ie Byung; Cho, Ho Chan; Chung, Choon Hee; Choi, Sung Hee; Park, Kang Seo; Yang, Seoung-Oh; Lee, Kwan Woo; Effects of dapagliflozin compared with glimepiride on body composition in Asian patients with type 2 diabetes inadequately controlled with metformin: The BEYOND study.; Diabetes, obesity & metabolism; 2023

359.1. 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	BEYOND study [(NCT02564926]
Study type	Randomised controlled trial (RCT)
Study location	14 centres in Korea
Study setting	NR
Study dates	Between January 2016 and January 2018
Sources of funding	AstraZeneca
Inclusion criteria	Adults aged 19-75 years with T2D and inadequately controlled glycated haemoglobin (HbA1c) of 7.0 to <10.0% on stable metformin monotherapy (≥1000 mg/day) for at least 8 weeks before randomization
Exclusion criteria	NR

Recruitment / selection of participants	NR
Intervention(s)	• Dapagliflozin 10 mg orally once daily • Glimepiride 1 mg orally, 1 or 2 tablets at a dose of 1 to 2 mg/day
Cointervention	• ≥100 mg metformin • Rescue therapy was prescribed for participants who met the following criteria: weeks 4-8, fasting blood glucose (FBG) >240 mg/dl; weeks 8-24, FBG >200 mg/dl; and weeks 24-56, HbA1c >8%. Sitagliptin was provided as rescue therapy.
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 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	NA
Number of participants	178 participants were enrolled and 124 were randomised. Of 62 participants allocated to dapagliflozin, 2 participants were not treated, 56 participants were analysed at week 52, and 52 completed. Of 62 participants allocated to glimepiride, 1 participant was not treated, 56 participants were analysed at week 52. and 54 completed.
Duration of follow-up	52 weeks
Indirectness	Directly applicable
Method of analysis	Not stated/unclear Efficacy analyses were performed on the full analysis set, which was defined as all randomised participants who received at least one dose of study medication during the treatment period with no missing baseline values and at least one post-baseline value for primary efficacy variables. Analysis were performed using a mixed model repeated measures or analysis of covariance for continuous variables. Safety analysis set included participant who received at least one dose of study medication.
Additional comments	NA

359.2. Study arms

359.2.1. Dapagliflozin (N = 62)

359.2.2. Glimepiride (N = 62)

359.3. Characteristics

359.3.1. Arm-level characteristics

Characteristic	Dapagliflozin (N = 62)	Glimepiride (N = 62)
% Male Sample size	n = 36 ; % = 64.3	n = 26 ; % = 46.4
Mean age (SD) (years) Mean (SD)	54.8 (9)	55.5 (9.3)
Ethnicity Korean Sample size	n = 60 ; % = 100	n = 61 ; % = 100
Comorbidities Sample size	n = NA ; % = NA	n = NA ; % = NA
Neuropathy Sample size	n = 8 ; % = 14.3	n = 8 ; % = 14.3
Retinopathy Sample size	n = 2 ; % = 3.6	n = 4 ; % = 7.1
Nephropathy Sample size	n = 1 ; % = 1.8	n = 1 ; % = 1.8
Vascular disorder Sample size	n = 1 ; % = 1.8	n = 1 ; % = 1.8
Hypertension Sample size	n = 24 ; % = 42.9	n = 25 ; % = 44.6
Dyslipidaemia Sample size	n = 28 ; % = 50	n = 27 ; % = 48.2

Characteristic	Dapagliflozin (N = 62)	Glimepiride (N = 62)
Patients with cardiac disorders Sample size	n = 2 ; % = 3.3	n = 5 ; % = 8.2
Renal and urinary disorders Sample size	n = 7 ; % = 11.7	n = 6 ; % = 9.8
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	6 (4.8)	6.5 (4.9)
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
Blood pressure-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Amlopidine + valsartan Sample size	n = 4 ; % = 6.7	n = 2 ; % = 3.3
Losartan potassium Sample size	n = 3 ; % = 5	n = 2 ; % = 3.3

Characteristic	Dapagliflozin (N = 62)	Glimepiride (N = 62)
Statins/lipid-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Atorvastatin Sample size	n = 9 ; % = 15	n = 6 ; % = 9.8
Other treatment being received Sample size	n = NA ; % = NA	n = NA ; % = NA
Paracetamol Sample size	n = 3 ; % = 5	n = 0 ; % = 0
Acetylcysteine Sample size	n = 4 ; % = 6.7	n = 1 ; % = 1.6
Almagate Sample size	n = 3 ; % = 5	n = 0 ; % = 0
Acetylsalicylic acid - Aspirin Sample size	n = 4 ; % = 6.7	n = 1 ; % = 1.6
Acetysalicylic acid - Aspirin Protect Sample size	n = 3 ; % = 5	n = 3 ; % = 4.9
Clopidogrel Sample size	n = 7 ; % = 11.7	n = 8 ; % = 13.1
Dexibruprofen Sample size	n = 3 ; % = 5	n = 0 ; % = 0
Erdosteine Sample size	n = 3 ; % = 5	n = 1 ; % = 1.6
Gamolenic acid Sample size	n = 5 ; % = 8.3	n = 2 ; % = 3.3
Herbal NOS Sample size	n = 5 ; % = 8.3	n = 3 ; % = 4.9
Pregabalin Sample size	n = 3 ; % = 5	n = 1 ; % = 1.6

360. Park, 2011

Bibliographic Reference	Park, J. S.; Cho, M. H.; Nam, J. S.; Yoo, J. S.; Ahn, C. W.; Cha, B. S.; Kim, K. R.; Lee, H. C.; Effect of pioglitazone on serum concentrations of osteoprotegerin in patients with type 2 diabetes mellitus; Eur J Endocrinol; 2011; vol. 164 (no. 1); 69-74

360.1. 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, RCT
Study location	Seoul, South Korea
Study setting	Outpatient
Study dates	Not reported
Sources of funding	Supported by Faculty research grant of Yonsei University College of Medicine for 2007 and Yonsei University College of Medicine, Internal Medicine Research Grant 2007.
Inclusion criteria	• Type 2 diabetes diagnosis with stable or worsening glycaemic control on glimepiride≥2 mg or equivalent dose of other sulphonylurea (e.g. gliclazide MR 30 mg) for≥3 months before screening • Aged 40-70 years • HbA1c 7-10% inclusive at screening • Fasting C-peptide≥1.5 ng/ml at screening

Exclusion criteria	• Type 1 diabetes • Diabetic ketoacidosis • Symptomatic heart failure • Malignant disease in the previous 10 years • Renal failure
Recruitment / selection of participants	Eligible participants recruited from Diabetes Clinic, Kangnam Severance Hospital, South Korea and randomised to pioglitazone or metformin.
Intervention(s)	• Pioglitazone 15 mg daily Oral pioglitazone 15 mg daily for 24 weeks, in addition to glimepiride or equivalent dose of other sulphonylurea.
Cointervention	• Glimepiride≥2 mg daily or equivalent dose of other sulphonylurea It is not explicit in article whether participants continued with existing blood-glucose lowering drugs but likely that they did.
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure People with symptomatic heart failure were excluded.
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. Renal failure is an 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	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
Comparator	• Metformin 1000 mg daily Oral metformin 1000 mg daily for 24 weeks, (probably) in addition to glimepiride or equivalent dose of other sulphonylurea.
Number of participants	N=67 randomised
Duration of follow-up	24 weeks
Indirectness	Not explicitly stated whether study is an add-on trial or switching trial.
Method of analysis	ITT Appears to be ITT analysis for all outcomes Other Not explicitly reported, appears to be for all randomised participants

360.2. Study arms

360.2.1. Pioglitazone 15 mg daily (N = 34)

Oral pioglitazone 15 mg daily for 24 weeks, in addition to glimepiride or other sulphonylurea.

360.2.2. Metformin 1000 mg daily (N = 33)

Oral metformin 1000 mg daily for 24 weeks, in addition to glimepiride or other sulphonylurea.

360.3. Characteristics

360.3.1. Arm-level characteristics

Characteristic	Pioglitazone 15 mg daily (N = 34)	Metformin 1000 mg daily (N = 33)
% Male Sample size	n = 18 ; % = 52.9	n = 17 ; % = 51.5
Mean age (SD) (years) Mean (SD)	62.3 (8)	63.1 (8.4)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	5.1 (5)	4.9 (5.3)
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	Pioglitazone 15 mg daily (N = 34)	Metformin 1000 mg daily (N = 33)
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

361. Pasquel, 2021

Bibliographic Reference	Pasquel, F. J.; Urrutia, M. A.; Cardona, S.; Coronado, K. W. Z.; Albury, B.; Perez-Guzman, M. C.; Galindo, R. J.; Chaudhuri, A.; Iacobellis, G.; Palacios, J.; Farias, J. M.; Gomez, P.; Anzola, I.; Vellanki, P.; Fayfman, M.; Davis, G. M.; Migdal, A. L.; Peng, L.; Umpierrez, G. E.; Liraglutide hospital discharge trial: A randomized controlled trial comparing the safety and efficacy of liraglutide versus insulin glargine for the management of patients with type 2 diabetes after hospital discharge; Diabetes, Obesity & Metabolism; 2021; vol. 23 (no. 6); 1351-1360

361.1. 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	NCT01919489
Study type	Randomised controlled trial (RCT)
Study location	United States
Study setting	Multicentre trial carried out at four academic institutions
Study dates	NR
Sources of funding	Novo Nordisk
Inclusion criteria	• Glucose levels between 7.8 and 22.2 mmol/L and HbA1c levels >7% to 10% • Aged 18 to 80 years • Home diabetes regimen included diet and/or OADs including sulfonylureas, repaglinide, nateglinide, or metformin, either as

	monotherapy or in combination therapy, or taking a low total daily dose of insulin (≤0.4 unit/kg/d)
Exclusion criteria	• History of diabetic ketoacidosis or hyperosmolar hyperglycaemic state or with laboratory evidence of ketoacidosis • Patients with history of type 1 diabetes, medullary thyroid cancer or multiple endocrine neoplasia, acute or chronic pancreatitis, pancreatic cancer or gallbladder disease • Previous treatment with GLP-1RAs during the past 3 months prior to admission • Patients admitted to or expected to require admission to an intensive care unit • Corticosteroid therapy >5 mg/d of prednisone equivalent • Clinically relevant hepatic disease or impaired renal function (estimated glomerular filtration rate <30 mL/min per 1.73 m2) • Body mass index (BMI) <25 and > 45 kg/m2 • Pregnancy • Parenteral nutrition • Immunosuppressive treatment • Mental condition rendering the participant unable to understand the nature, scope and possible consequences of the study.
Recruitment / selection of participants	Patients with T2D were screened during their hospital admission from medical or general surgical services. During the hospital stay, patients were managed with a standard basal or basal-bolus regimen according to hospital protocol.
Intervention(s)	Liraglutide beginning at 0.6 mg once daily by subcutaneous injections, with dose escalation every 2 weeks by increments of 0.6 mg until the maintenance dose of 1.8 mg was reached. Injections were given at any time of the day and irrespective of meals; however, it was recommended that the time of injection be consistent throughout the trial. Dose escalation was extended over 4 weeks at the discretion of the investigator in case of adverse events. Treatment-naïve patients with HbA1c < 8% (<64 mmol/mol) received liraglutide as monotherapy or in combination with metformin if HbA1c was > 8% (> 64 mmol/mol). Dipeptidyl peptidase-4 inhibitors were not used in combination with liraglutide during the study period.
Cointervention	Treatment was given as add-on to the participant's preadmission OAD regimen. The dose of insulin secretagogues (sulfonylureas, nateglinide and repaglinide) was reduced by 50% or stopped at the discretion of the investigator, otherwise, the dose of OAD remained unchanged throughout the 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	Not stated/unclear

atherosclerotic cardiovascular disease	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 People with "impaired renal function (estimated glomerular filtration rate <30 mL/min per 1.73 m2)" 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	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
Population subgroups	NA

Comparator	Insulin glargine U-100/mL was provided in 3-mL pen cartridges. Treatment-naïve patients with HbA1c <8% received glargine as monotherapy or in combination with metformin if HbA1c was >8%). Patients who were treated with OADs prior to admission with HbA1c between 7% and 9% were discharged on their preadmission OADs in combination with glargine at 50% of the hospital daily dose. Patients with HbA1c > 9% were discharged on 80% of the hospital glargine dose.
Number of participants	306 gave consent to participate and 19 participants were not included at screening. 140 participants were allocated to liraglutide: 136 were included in the intention-to-treat analysis and there were HbA1c data for 80 participants at week 26. 147 participants were allocated to insulin glargine: 137 were included in the intention-to-treat analysis. and there were HbA1c data for 93 participants at week 26.
Duration of follow-up	12 and 26 weeks
Indirectness	Partially applicable - 16% of participants in the liraglutide arm and 18% of participants in the insulin arm had not received previous treatment for diabetes.
Method of analysis	ITT Report states that data were from the intention-to-treat population
Additional comments	The paper reports acute myocardial infarction in the liraglutide group, however, it was not possible to ascertain whether this resulted in death or was non-fatal as two deaths occurred in the liraglutide group. Therefore, this was not extracted. Among patients treated with OADs prior to admission, 140 (77%) were discharged on metformin, 17 (9%) were discharged on sulfonylureas, and no patients were discharged on thiazolidinediones. During follow-up, nine patients in the liraglutide group received additional insulin therapy as basal insulin (n = 5), pre-mixed insulin (n = 1) or prandial insulin (n = 3).

361.2. Study arms

361.2.1. Liraglutide (N = 140)

361.2.2. Insulin glargine (N = 147)

361.3. Characteristics

361.3.1. Arm-level characteristics

Characteristic	Liraglutide (N = 140)	Insulin glargine (N = 147)
% Male Based on ITT population Sample size	n = 89 ; % = 65	n = 76 ; % = 55
Mean age (SD) Mean (SD)	56.1 (9.5)	55.9 (11.2)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Black Sample size	n = 97	*empty data*
White Sample size	n = 23 ; % = 17	n = 27 ; % = 20
Other Sample size	n = 16 ; % = 12	n = 15 ; % = 11
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	9.5 (7.8)	9.8 (9.1)
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	Liraglutide (N = 140)	Insulin glargine (N = 147)
People with significant cognitive impairment Nominal	NR	NR
People with a learning disability Nominal	NR	NR
BMI (years) Mean (SD)	33.5 (5.3)	33.3 (5.3)
Number of people with obesity Nominal	NR	NR
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
No diabetes medication Sample size	n = 22 ; % = 16	n = 24 ; % = 18
Oral agents Sample size	n = 61 ; % = 45	n = 69 ; % = 51
Insulin Sample size	n = 22 ; % = 16	n = 19 ; % = 14
Oral agents + insulin Sample size	n = 30 ; % = 22	n = 23 ; % = 17
Blood pressure-lowering medication used Nominal	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

362. Patel, 2019

Bibliographic Reference	Patel, Sapna; Abreu, Marconi; Tumyan, Anna; Adams-Huet, Beverley; Li, Xilong; Lingvay, Ildiko; Effect of medication adherence on clinical outcomes in type 2 diabetes: analysis of the SIMPLE study.; BMJ open diabetes research & care; 2019; vol. 7 (no. 1); e000761

362.1. Study details

Secondary publication of another included study- see primary study for details	Abreu 2019

363. Pei, 2021

Bibliographic Reference	Pei, Yu; Agner, Bue R; Luo, Bin; Dong, Xiaolin; Li, Dongmei; Liu, Jun; Liu, Lei; Liu, Ming; Lu, Yibing; Nishida, Tomoyuki; Xu, Xiangjin; Mu, Yiming; DUAL II China: Superior HbA1c reductions and weight loss with insulin degludec/liraglutide (IDegLira) versus insulin degludec in a randomized trial of Chinese people with type 2 diabetes inadequately controlled on basal insulin.; Diabetes, obesity & metabolism; 2021; vol. 23 (no. 12); 2687-2696

363.1. 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	DUAL II China [NCT03175120]
Study type	Randomised controlled trial (RCT)
Study location	40 sites across mainland China and Hong Kong
Study setting	
Study dates	May 2017 to July 2019
Sources of funding	Novo Nordisk
Inclusion criteria	• Participants aged 18 years or older with clinically diagnosed T2D • BMI of 24 kg/m2 or higher • HbA1c of 7.5% or more • Treated for 90 days or longer prior to screening with basal insulin and metformin, with or without one other of the following OADs: AGIs, sulphonylureas, glinides, or thiazolidinediones. Additionally, participants had received stable doses for 60 days or longer of

	1500 mg or more of metformin (or maximum tolerated dose), and 20 to 50 U/day of a basal insulin.
Exclusion criteria	• Known or suspected hypersensitivity to trial product(s) or related products. • Previous participation in this trial. Participation is defined as informed consent. • Female who is pregnant, breast-feeding or intends to become pregnant or is of child-bearing potential and not using adequate contraceptive methods (sterilization, intrauterine device, oral contraceptives or barrier methods). • Receipt of any investigational medicinal product within 30 calendar days before Visit 1. • Current use of any antidiabetic drug (except for basal insulin, AGI, SU, glinides and TZD) or anticipated change in concomitant medication that, in the investigator's opinion, could interfere with glucose level (e.g. systemic corticosteroids). • Use of non-herbal Chinese medicine or other non-herbal local medicine with unknown/unspecified content within 90 calendar days prior to screening. Herbal traditional Chinese medicine or other local herbal medicines may, at the investigator's discretion, be continued throughout the trial. • Treatment with GLP-1 RAs or DPP-4is or insulin (except for basal insulin) within 90 days prior to Visit 1. • Impaired liver function defined as alanine aminotransferase ≥2.5 times the upper normal range. • Impaired renal function defined as serum-creatinine ≥133 µmol/L for males and ≥125 µmol/L for females, or as defined according to local contraindications for metformin. • Screening calcitonin ≥50 ng/L. • Personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2. • Cardiac disorder defined as: congestive heart failure (New York Heart Association class III-IV), diagnosis of unstable angina pectoris, cerebral stroke and/or myocardial infarction within the last 12 months period to screening and/or planned coronary, carotid or peripheral artery revascularization procedures. • Severe uncontrolled treated or untreated hypertension (systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥100 mmHg). • Proliferative retinopathy or maculopathy (macular oedema) requiring acute treatment. • Subject with a clinically significant, active (during the past 12 months) disease of the gastrointestinal, pulmonary, neurological, genito-urinary or haematological system (except for conditions associated with T2D) that, in the opinion of the investigator, may confound compliance and the results of the trial or pose additional risk in administering trial drug. • Mental incapacity, unwillingness or language barrier precluding adequate understanding of the trial procedure or cooperation with the trial site personnel. • Known or suspected abuse of alcohol or narcotics. • History of pancreatitis (acute or chronic).

	• Suffer from a life-threatening disease, including malignant neoplasms, and medical history of malignant neoplasms and medical history of malignant neoplasms within the last 5 years (except basal and squamous cell skin cancer).
Recruitment / selection of participants	555 participants were screened for eligibility over a 2-week period. 102 participants were excluded at screening and 453 participants were randomised.
Intervention(s)	Subcutaneous IDegLira received once daily. The recommended starting doses were 16 dose steps for IDegLira (16 units degludec/0.6 mg liraglutide).
Cointervention	Treatment received in combination with metformin. Other OADs were discontinued at randomisation. Doses were titrated twice weekly for both treatments to a target fasting plasma glucose (FPG) of 4 to 5 mmol/L.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Exclusion criteria: "Cardiac disorder defined as: congestive heart failure (New York Heart Association class III-IV), diagnosis of unstable angina pectoris, cerebral stroke and/or myocardial infarction within the last 12 months period to screening and/or planned coronary, carotid or peripheral artery revascularization procedures."
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 Exclusion criteria: "Impaired renal function defined as serum-creatinine ≥133 μmol/L for males and ≥125 μmol/L for females, or as defined according to local contraindications for metformin."
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	Subcutaneous insulin degludec once daily. The recommended starting dose was 16 units.
Number of participants	Of 302 participants allocated to IDegLira, 301 received treatment, and 290 (96%) completed treatment. Of 151 participants allocated to insulin degludec, 151 received treatment, and 92.1% completed treatment.
Duration of follow-up	26 weeks at end of treatment with follow-up at 27 and 30 weeks.
Indirectness	Directly applicable
Method of analysis	Per protocol Per-protocol and completer analysis were assessed for HbA1c outcome. Other Full analysis set with missing values after 26 weeks of treatment imputed by last observation carried forward with ANCOVA analysis.
Additional comments	Double-blind study

363.2. Study arms

363.2.1. IDegLira (N = 302)

363.2.2. Insulin degludec (N = 151)

363.3. Characteristics

363.3.1. Arm-level characteristics

Characteristic	IDegLira (N = 302)	Insulin degludec (N = 151)
% Male Sample size	n = 183 ; % = 60.6	n = 91 ; % = 60.3
Mean age (SD) Mean (SD)	54.5 (9.8)	55.3 (10)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	11.52 (5.9)	11.33 (6.3)
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	IDegLira (N = 302)	Insulin degludec (N = 151)
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 = NR ; % = NR	n = NR ; % = NR
Metformin only Sample size	n = 141 ; % = 46.7	n = 74 ; % = 49
Metformin + sulphonylurea Sample size	n = 44 ; % = 14.6	n = 22 ; % = 14.6
Metformin + glinide Sample size	n = 20 ; % = 6.6	n = 10 ; % = 6.6
Metformin + alpha-glucosidase inhibitors Sample size	n = 89 ; % = 29.5	n = 44 ; % = 29.1
metformin + TZD Sample size	n = 8 ; % = 2.6	n = 1 ; % = 0.7
Statins/lipid-lowering medication used Nominal	NR	NR
Basal insulin use during screening period Sample size	n = NR ; % = NR	n = NR ; % = NR
Insulin detemir Sample size	n = 33 ; % = 10.9	n = 17 ; % = 11.3
Insulin glargine Sample size	n = 218 ; % = 72.2	n = 111 ; % = 73.5
Insulin isophane Sample size	n = 46 ; % = 15.2	n = 23 ; % = 15.2

Characteristic	IDegLira (N = 302)	Insulin degludec (N = 151)
Insulin zinc protamine Sample size	n = 5 ; % = 1.7	n = 0 ; % = 0

364. Perkovic, 2019

Bibliographic Reference	Perkovic, V.; Jardine, M. J.; Neal, B.; Bompoint, S.; Heerspink, H. J. L.; Charytan, D. M.; Edwards, R.; Agarwal, R.; Bakris, G.; Bull, S.; Cannon, CP; Capuano, G; Chu, P-L; De Zeeuw, D.; Greene, T.; VLevin, A; Pollock, C.; Wheeler, DC; Yavin, Y.; Zhang, H; Zinman, B; Mieininger, G; Brenner, BM; Mahaffey, KW; for the CREDENCE Trial, Investigators; Canagliflozin and renal outcomes in type 2 diabetes and nephropathy; N Engl J Med; 2019; vol. 380 (no. 24); 2295-2306

364.1. Study details

Secondary publication of another included study- see primary study for details	Parent study CREDENCE trial
Other publications associated with this study included in review	Sarraju, Ashish, Li, JingWei, Cannon, Christopher P et al. (2021) Effects of canagliflozin on cardiovascular, renal, and safety outcomes in participants with type 2 diabetes and chronic kidney disease according to history of heart failure: Results from the CREDENCE trial. American heart journal 233: 141-148 Jardine, Meg J, Mahaffey, Kenneth W, Neal, Bruce et al. (2017) The Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) Study Rationale, Design, and Baseline Characteristics. American journal of nephrology 46(6): 462-472
Trial name / registration number	CREDENCE trial. NCT02065791
Study type	Randomised controlled trial (RCT)
Study location	690 sites in 34 countries
Study setting	Unspecified clinical setting
Study dates	February 17, 2014 - October 30, 2018
Sources of funding	Janssen Research & Development, LLC

Inclusion criteria	• Type 2 diabetes mellitus with a hemoglobin A1c (HbA1c) greater than or equal to (>=) 6.5 percent (%) and less than or equal to (<=) 12.0%, with an estimated glomerular filtration rate (eGFR) of >= 30 millilitre (mL)/minute (min)/1.73meter (m)^2 and less than (<) 90 mL/min/1.73 m^2 • Participants need to be on a stable maximum tolerated labelled daily dose of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) for at least 4 weeks prior to randomization • Must have a urine albumin to creatinine ratio (UACR) of greater than (>) 300 milligram (mg)/gram (g) and <= 5000 mg/g • 30 years or older
Exclusion criteria	• History of diabetic ketoacidosis or type 1 diabetes mellitus • History of hereditary glucose-galactose malabsorption or primary renal glucosuria • Renal disease that required treatment with immunosuppressive therapy • Known significant liver disease • Current or history of New York Heart Association (NYHA) Class IV heart failure • Blood potassium level >5.5 millimole (mmol)/litre (L) during Screening
Recruitment / selection of participants	No information
Intervention(s)	Drug: Canagliflozin. One 100 mg over-encapsulated tablet orally once daily
Cointervention	angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure 14.8% had HF
Strata 2: People with atherosclerotic cardiovascular disease	Mixed population 50.4% had CVD
Strata 3: People with type 2 diabetes mellitus and	People with chronic kidney disease Included "chronic kidney disease, defined as an estimated glomerular filtration rate (GFR, as calculated by the Chronic Kidney Disease Epidemiology Collaboration formula) of 30 to <90 ml per minute per 1.73 m2 of body-surface area and albuminuria (urinary albumin-to-creatinine

chronic kidney disease	ratio, >300 to 5000, with albumin measured in milligrams and creatinine in grams), as measured in a central laboratory. "
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)
Population subgroups	None
Comparator	Placebo
Number of participants	A total of 4401 participants were randomized, with 2199 and 2202 participants assigned to placebo and canagliflozin 100 milligrams (mg), respectively.
Duration of follow-up	Median 31.44 months

Indirectness	None
Method of analysis	ITT
Additional comments	Post-hoc analysis by

364.2. Study arms

364.2.1. Canagliflozin (N = 2202)

Participants received canagliflozin 100 milligram (mg) orally once daily.

364.2.2. Placebo (N = 2199)

Participants received matching placebo orally once daily

364.3. Characteristics

364.3.1. Arm-level characteristics

Characteristic	Canagliflozin (N = 2202)	Placebo (N = 2199)
% Male Nominal	65.4	66.6
Mean age (SD) Mean (SD)	62.9 (9.2)	63.2 (9.2)
White Nominal	67.5	65.7
Black Nominal	5.1	5.1
Asian Nominal	19.3	20.6
Other Nominal	8.1	8.7

Characteristic	Canagliflozin (N = 2202)	Placebo (N = 2199)
Hypertension Nominal	96.8	96.8
Heart failure Nominal	14.9	14.7
Cardiovascular disease Nominal	50.5	50.3
Time since type 2 diabetes diagnosed (years) Mean (SD)	15.5 (8.7)	16 (8.6)
HbA1c (%) Nominal	*empty data*	8.3
HbA1c (%) Mean (SD)	8.3 (1.3)	8.3 (1.3)
Systolic Mean (SD)	139.8 (15.6)	140.2 (15.6)
Diastolic Mean (SD)	78.2 (9.4)	78.4 (9.4)
Smoking status (% smokers) Nominal	15.5	13.6
BMI Mean (SD)	31.4 (6.2)	31.3 (6.2)
Albumin creatinine ratio Median (IQR)	923 (459 to 1794)	931 (473 to 1868)
eGFR mL/min/1.73m2 Mean (SD)	56.3 (18.2)	56 (18.3)

365. Perkovic, 2020

Bibliographic Reference	Perkovic, V; Toto, R; Cooper M, E; Mann J, F.E; Rosenstock, J; McGuire D, K; Kahn S, E; Marx, N; Alexander J, H; Zinman, B; Pfarr, E; Schnaidt, S; Meinicke, T; Eynatten M, V; George J, T; Johansen O, E; Wanner, C; Effects of linagliptin on cardiovascular and kidney outcomes in people with normal and reduced kidney function: Secondary analysis of the carmelina randomized trial; Diabetes Care; 2020; vol. 43 (no. 8); 1803-1812

365.1. Study details

Secondary publication of another included study- see primary study for details	Perkovic 2020A. This study is a part of the CARMELINA trial. For the full data extraction please see the primary study. Rosenstock, Julio, Perkovic, Vlado, Johansen Odd, Erik et al. (2019) Effect of Linagliptin vs Placebo on Major Cardiovascular Events in Adults With Type 2 Diabetes and High Cardiovascular and Renal Risk: The CARMELINA Randomized Clinical Trial. JAMA 321(1): 69-79
Other publications associated with this study included in review	Rosenstock, Julio, Perkovic, Vlado, Alexander John, H et al. (2018) Rationale, design, and baseline characteristics of the CArdiovascular safety and Renal Microvascular outcomE study with LINAgliptin (CARMELINA R): a randomized, double-blind, placebo-controlled clinical trial in patients with type 2 diabetes and high cardio-renal risk. Cardiovascular diabetology 17(1): 39 McGuire Darren, K, Alexander John, H, Johansen Odd, Erik et al. (2019) Linagliptin Effects on Heart Failure and Related Outcomes in Individuals With Type 2 Diabetes Mellitus at High Cardiovascular and Renal Risk in CARMELINA. Circulation 139(3): 351-361
Trial name / registration number	CARMELINA. ClinicalTrials.gov = NCT01897531

365.2. Study arms

365.2.1. Linagliptin - eGFR ≥60 (N = 1294)

Linagliptin 5mg once daily initially for 12 weeks, then 24 week periods until the study end, median end follow up of 2.2 years. Concomitant therapy: Majority received at least 1 background glucose-lowering therapy in addition to the new therapy, as well as a large number of people receiving antihypertensive medication, aspirin and statins (see characteristics table).

365.2.2. Linagliptin - eGFR ≥45-<60 (N = 690)

Linagliptin 5mg once daily initially for 12 weeks, then 24 week periods until the study end, median end follow up of 2.2 years. Concomitant therapy: Majority received at least 1 background glucose-lowering therapy in addition to the new therapy, as well as a large number of people receiving antihypertensive medication, aspirin and statins (see characteristics table).

365.2.3. Linagliptin - eGFR ≥30 to <45 (N = 994)

Linagliptin 5mg once daily initially for 12 weeks, then 24 week periods until the study end, median end follow up of 2.2 years. Concomitant therapy: Majority received at least 1 background glucose-lowering therapy in addition to the new therapy, as well as a large number of people receiving antihypertensive medication, aspirin and statins (see characteristics table).

365.2.4. Linagliptin - eGFR <30 (N = 516)

Linagliptin 5mg once daily initially for 12 weeks, then 24 week periods until the study end, median end follow up of 2.2 years. Concomitant therapy: Majority received at least 1 background glucose-lowering therapy in addition to the new therapy, as well as a large number of people receiving antihypertensive medication, aspirin and statins (see characteristics table).

365.2.5. Placebo - eGFR ≥60 (N = 1337)

Placebo once daily initially for 12 weeks, then 24 weeks periods until the study end, median end follow up of 2.2 years. Concomitant therapy: Majority received at least 1 background glucose-lowering therapy in addition to the new therapy, as well as a large number of people receiving antihypertensive medication, aspirin and statins (see characteristics table).

365.2.6. Placebo - eGFR ≥45-<60 (N = 658)

Placebo once daily initially for 12 weeks, then 24 weeks periods until the study end, median end follow up of 2.2 years. Concomitant therapy: Majority received at least 1 background glucose-lowering therapy in addition to the new therapy, as well as a large number of people receiving antihypertensive medication, aspirin and statins (see characteristics table).

365.2.7. Placebo - eGFR ≥30 to <45 (N = 944)

Placebo once daily initially for 12 weeks, then 24 weeks periods until the study end, median end follow up of 2.2 years. Concomitant therapy: Majority received at least 1 background glucose-lowering therapy in addition to the new therapy, as well as a

large number of people receiving antihypertensive medication, aspirin and statins (see characteristics table).

365.2.8. Placebo - eGFR <30 (N = 546)

Placebo once daily initially for 12 weeks, then 24 weeks periods until the study end, median end follow up of 2.2 years. Concomitant therapy: Majority received at least 1 background glucose-lowering therapy in addition to the new therapy, as well as a large number of people receiving antihypertensive medication, aspirin and statins (see characteristics table).

366. Perkovic, 2024

Bibliographic Reference	Perkovic V, Tuttle KR, Rossing P, Mahaffey KW, Mann JFE, Bakris G, Baeres FMM, Idorn T, Bosch-Traberg H, Lausvig NL PR; FLOW Trial Committees and Investigators.; Effects of Semaglutide on Chronic Kidney Disease in Patients with Type 2 Diabetes; N Engl J Med; 2024; vol. 391 (no. 2); 109-121

366.1. 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	FLOW [NCT03819153]
Study type	Randomised controlled trial (RCT)
Study location	International multicentre trial: Argentina, Australia, Belgium, Bulgaria, Brazil, Canada, China, France, Germany, Greece, Hungary, India, Israel, Italy, Japan, Mexico, Malaysia, Netherlands, Poland, Russia, Slovakia, Spain, Thailand, Turkey, Ukraine, United Kingdom, United States, South Africa
Study setting	Not reported
Study dates	Participants were recruited between June 2019 and May 2021. The prespecified single interim analysis was triggered on October 2023, and the final trial visit was in January 2024.
Sources of funding	Novo Nordisk
Inclusion criteria	• Adults with T2DM and HbA1c ≤10% • With high-risk chronic kidney disease (renal impairment defined either by serum creatinine-based eGFR ≥ 50 and ≤ 75 mL/min/1.73 m2 (CKD-EPI), and UACR > 300 and < 5000 mg/g or serum creatinine-based eGFR ≥ 25 and < 50 mL/min/1.73 m2 (CKD-EPI) and UACR > 100 and < 5000 mg/g) • Receiving stable maximal labelled dose (or the maximal dose without unacceptable side effects) of RAS inhibitors

Exclusion criteria	• Known or suspected hypersensitivity to trial product(s) or related products. • Female who is pregnant, breast-feeding or intends to become pregnant or is of child-bearing potential and not using a highly effective contraceptive method. • Any disorder, which in the investigator's opinion might have jeopardized the subject's safety or compliance with the protocol. • Congenital or hereditary kidney diseases including polycystic kidney disease, autoimmune kidney diseases including glomerulonephritis or congenital urinary tract malformations. • Use of any GLP-1 receptor agonist within 30 days prior to screening. • Personal or first-degree relative(s) history of multiple endocrine neoplasia type 2 (MEN2) or medullary thyroid carcinoma (MTC). • Myocardial infarction, stroke, hospitalisation for unstable angina pectoris or transient ischemic attack within 60 days prior to the day of screening. • Presently classified as being in New York Heart Association (NYHA) Class IV heart failure. • Planned coronary, carotid or peripheral artery revascularization. • Current (or within 90 days) chronic or intermittent haemodialysis or peritoneal dialysis. • Uncontrolled and potentially unstable diabetic retinopathy or maculopathy. Verified by a fundus examination performed within the past 90 days prior to screening or in the period between screening and randomization. Pharmacological pupil-dilation is a requirement unless using a digital fundus photography camera specified for non-dilated examination. • Presence or history of malignant neoplasm within 5 years prior to the day of screening. Basal and squamous cell skin cancer and any carcinoma in-situ are allowed. • prior solid organ transplant or awaiting solid organ transplant. • Combination use of an angiotensin converting enzyme (ACE) inhibitor and an angiotensin II receptor blocker (ARB).
Recruitment / selection of participants	Not reported
Intervention(s)	Subcutaneous semaglutide with 8-week dose escalation regimen from 0.25 mg per week for 4 weeks and and 0.5 mg per week for another 4 weeks followed by a maintenance dose of 1.0 mg per week for the remainder of the treatment period. If unacceptable adverse events occurred, the dose-escalation intervals could be extended, treatment could be paused, or lower maintenance doses could be used.
Cointervention	The use of SGLT2 inhibitors was permitted
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Exclusion criteria state people with NHYA class IV were excluded

Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	People with chronic kidney disease
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	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
Subgroup 6: Albuminuria category at baseline	Mixed population
Population subgroups	Not applicable - subgroup analyses were reported, however, these were only for a composite renal outcome that wasn't eligible for extraction
Comparator	Matching placebo
Number of participants	5581 participants were screened and 3533 were randomised. Of 1767 participants randomised to semaglutide, 43 (2.4%) did not complete the trial and 439 (24.8%) did not complete treatment. Of 1766 participant

	randomised to placebo. 58 (3.3%) did not complete the trial, and 480 (27.2%) did not complete treatment.
Duration of follow-up	Median follow-up was 3.4 years
Indirectness	Directly applicable
Method of analysis	ITT Included all unique participants who underwent randomisation irrespective of adherence or changes to background medication
Additional comments	Trial included people had controlled and uncontrolled HbA1c

366.2. Study arms

366.2.1. Semaglutide. s.c. (N = 1767)

366.2.2. Placebo (N = 1766)

367. Characteristics

367.1. Arm-level characteristics

Characteristic	Semaglutide. s.c. (N = 1767)	Placebo (N = 1766)
% Male Sample size	n = 1248 ; % = 70.6	n = 1216 ; % = 68.9
Mean age (SD) Mean (SD)	66.6 (9)	66.7 (9)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 1155 ; % = 65.4	n = 1168 ; % = 66.1
Asian Sample size	n = 439 ; % = 24.8	n = 407 ; % = 23
Black Sample size	n = 78 ; % = 4.4	n = 82 ; % = 4.6
Other Sample size	n = 95 ; % = 5.4	n = 109 ; % = 6.2
Hispanic or Latinx ethnic group Sample size	n = 273 ; % = 15.4	n = 283 ; % = 16
Comorbidities Sample size	n = NA ; % = NA	n = NA ; % = NA
Previous MI or stroke Sample size	n = 405 ; % = 22.9	n = 403 ; % = 22.8
Chronic heart failure Sample size	n = 342 ; % = 19.4	n = 336 ; % = 19
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed Sample size	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Semaglutide. s.c. (N = 1767)	Placebo (N = 1766)
Less than 15 years Sample size	n = 774 ; % = 43.8	n = 753 ; % = 42.6
15 years and greater Sample size	n = 992 ; % = 56.1	n = 1013 ; % = 57.4
HbA1c Mean (SD)	7.8 (1.3)	7.8 (1.3)
Cardiovascular risk factors Nominal	NR	NR
Blood pressure (mmHg) Systolic blood pressure Mean (SD)	138.9 (16.1)	138.4 (15.4)
Heart rate Nominal	NA	NA
Smoking status Sample size	n = NA ; % = NA	n = NA ; % = NA
Current smoker Sample size	n = 223 ; % = 12.6	n = 206 ; % = 11.7
Previous smoker Sample size	n = 661 ; % = 37.4	n = 696 ; % = 39.4
Never smoked Sample size	n = 883 ; % = 50	n = 864 ; % = 48.9
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	Semaglutide. s.c. (N = 1767)	Placebo (N = 1766)
Weight (kg) Mean (SD)	89.5 (19.8)	89.8 (21.2)
BMI (kg/m2) Mean (SD)	31.9 (6.1)	32 (6.5)
Number of people with obesity BMI>30 kg/m2 Sample size	n = 1031 ; % = 58.5	n = 1029 ; % = 58.3
Cholesterol and lipid levels Nominal	NR	NR
Albumin creatinine ratio (ratio) Nominal	582.3	557.8
eGFR mL/min/1.73m2 (ml/min/1.73 m²) Mean (SD)	46.9 (15.6)	47.1 (14.7)
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
SGLT2 inhibitor Sample size	n = 277 ; % = 15.7	n = 273 ; % = 15.5
Metformin Sample size	n = 908 ; % = 51.4	n = 924 ; % = 52.3
Insulin Sample size	n = 1083 ; % = 61.3	n = 1085 ; % = 61.4
Blood pressure-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
ACE-inhibitor Sample size	n = 625 ; % = 35.4	n = 615 ; % = 34.8
ARB Sample size	n = 1066 ; % = 60.3	n = 1061 ; % = 60.1
Diuretic agent Sample size	n = 870 ; % = 49.2	n = 910 ; % = 51.5

Characteristic	Semaglutide. s.c. (N = 1767)	Placebo (N = 1766)
Statins/lipid-lowering medication used Sample size	n = 1418 ; % = 80.2	n = 1416 ; % = 80.2
Other treatment being received Nominal	NR	NR

368. Petrica, 2011

Bibliographic Reference	Petrica, L.; Vlad, A.; Petrica, M.; Jianu, C. D.; Gluhovschi, G.; Gadalean, F.; Dumitrascu, V.; Ianculescu, C.; Firescu, C.; Giju, S.; Gluhovschi, C.; Bob, F.; Velciov, S.; Bozdog, G.; Milas, O.; Marian, R.; Ursoniu, S.; Pioglitazone delays proximal tubule dysfunction and improves cerebral vessel endothelial dysfunction in normoalbuminuric people with type 2 diabetes mellitus; Diabetes Res Clin Pract; 2011; vol. 94 (no. 1); 22-32

368.1. Study details

Trial name / registration number	NR
Study type	Randomised controlled trial (RCT)
Study location	Department of Diabetes and Metabolic Diseases, Romania
Study setting	No additional information
Study dates	NR
Sources of funding	NR
Inclusion criteria	Inclusion criteria consisted of long-standing DM (>5 years), normoalbuminuria at the time of enrolment, absence of microangiopathic complications, no chronic kidney disease of non-diabetic origin, and poor glycaemic control (HbA1c > 7%) with previous medication (stable therapy with metformin for at least 6 months), a fact which required association of other antidiabetic agents.
Exclusion criteria	Symptoms and/or history of cerebrovascular disease (transient ischaemic attack, stroke), and micro/macroalbuminuria.
Recruitment / selection of participants	No additional information
Intervention(s)	Pioglitazone (n=39) Patients received 30 mg / day pioglitazone for 12 months
Cointervention	Metformin Patients received 1700 mg/day metformin for 12 months
Strata 1: People with type 2	Not stated/unclear Not an inclusion /exclusion criteria. No information in baseline characteristics.

diabetes mellitus and heart failure	
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Exclusion criteria were symptoms and/or history of cerebrovascular disease (transient ischaemic attack, stroke). No information about other types of CVD. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	People without chronic kidney disease CKD not an inclusion/exclusion criteria. Inclusion criteria state: normoalbuminuria at time of enrolment, absence of microangiopathic complications, no chronic kidney disease of non-diabetic origin.
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	Not stated/unclear

category at baseline	
Population subgroups	NA
Comparator	Glimepiride (n = 39) Patients were treated with 4 mg/ day glimepiride plus 1700 mg/ day metformin for 12 months
Number of participants	78
Duration of follow-up	12 months
Indirectness	NA
Method of analysis	Per protocol

368.2. Study arms

368.2.1. Pioglitazone (N = 39)

Patients received 30 mg / day pioglitazone plus 1700 mg / day metformin for 12 months

368.2.2. Glimepiride (N = 39)

Patients received 4 mg / day glimepiride plus 1700 mg / day metformin for 12 months

368.3. Characteristics

368.3.1. Arm-level characteristics

Characteristic	Pioglitazone (N = 39)	Glimepiride (N = 39)
% Male Pioglitazone n = 34, Glimepiride n = 34 Sample size	n = 12 ; % = 35.3	n = 13 ; % = 38.2
Mean age (SD) Pioglitazone n = 34, Glimepiride n = 34	56.88 (6.44)	58.82 (7.78)

Characteristic	Pioglitazone (N = 39)	Glimepiride (N = 39)
Mean (SD)		
Ethnicity Pioglitazone n = 34, Glimepiride n = 34 Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed (Years (mean, SD)) Pioglitazone n = 34, Glimepiride n = 34 Mean (SD)	10 (3.48)	10.17 (5.26)
Smoking status Pioglitazone n = 34, Glimepiride n = 34 Sample size	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Pioglitazone n = 34, Glimepiride n = 34 Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Pioglitazone n = 34, Glimepiride n = 34 Sample size	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Pioglitazone n = 34, Glimepiride n = 34 Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Pioglitazone n = 34, Glimepiride n = 34 Sample size	n = NR ; % = NR	n = NR ; % = NR
Other antidiabetic medication used Pioglitazone n = 34, Glimepiride n = 34 Sample size	n = NA ; % = NA	n = NA ; % = NA
Metformin Sample size	n = 34 ; % = 100	n = 34 ; % = 100
Blood pressure-lowering medication used Pioglitazone n = 34, Glimepiride n = 34 Sample size	n = NA ; % = NA	n = NA ; % = NA
Statins/lipid-lowering medication used Pioglitazone n = 34, Glimepiride n = 34 Sample size	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Pioglitazone (N = 39)	Glimepiride (N = 39)
Other treatment being received Pioglitazone n = 34, Glimepiride n = 34 Sample size	n = NA ; % = NA	n = NA ; % = NA