National Institute for Health and Care Excellence

1

Final

Type 2 diabetes in adults: management (medicines update)

[F2.9] Evidence reviews for subsequent pharmacological management of type 2 diabetes – Appendix D8

NICE guideline

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

February 2026

Final

This evidence review was developed by NICE

Disclaimer

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

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

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 All NICE guidance is subject to regular review and may be updated or withdrawn.

Copyright

ISBN: 978-1-4731-9262-1

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.

488. Wanner, 2018

Bibliographic Reference	Wanner, Christoph; Lachin John, M; Inzucchi Silvio, E; Fitchett, David; Mattheus, Michaela; George, Jyothis; Woerle Hans, J; Broedl Uli, C; von Eynatten, Maximilian; Zinman, Bernard; EMPA-REG, OUTCOME; Investigators; Empagliflozin and Clinical Outcomes in Patients With Type 2 Diabetes Mellitus, Established Cardiovascular Disease, and Chronic Kidney Disease.; Circulation; 2018; vol. 137 (no. 2); 119-129

488.1. Study details

Secondary publication of another included study- see primary study for details	This paper is Wanner 2018A EMPA-REG OUTCOME trial. Zinman, Bernard, Wanner, Christoph, Lachin John, M et al. (2015) Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. The New England journal of medicine 373(22): 2117-28
Other publications associated with this study included in review	Zinman, Bernard, Inzucchi, Silvio E, Lachin, John M et al. (2014) Rationale, design, and baseline characteristics of a randomized, placebo-controlled cardiovascular outcome trial of empagliflozin (EMPA-REG OUTCOME TM). Cardiovascular diabetology 13: 102 Butler, Javed, Zannad, Faiez, Fitchett, David et al. (2019) Empagliflozin Improves Kidney Outcomes in Patients With or Without Heart Failure. Circulation. Heart failure 12(6): e005875
Trial name / registration number	EMPA-REG OUTCOME. ClinicalTrials.gov number, NCT01131676

488.2. Study arms

488.2.1. Empagliflozin - eGFR <45 (N = 381)

488.2.2. Placebo - eGFR <45 (N = 189)

488.2.3. Empagliflozin - eGFR 45 to <60 (N = 831)

488.2.4. Placebo - eGFR 45 to <60 (N = 418)

488.2.5. Empagliflozin - eGFR 60 to <90 (N = 2423)

488.2.6. Placebo - eGFR 60 to <90 (N = 1238)

488.2.7. Empagliflozin - eGFR >90 (N = 1050)

488.2.8. Placebo - eGFR >90 (N = 488)

489. Watada, 2019

Bibliographic Reference	Watada, Hirotaka; Kaneko, Shizuka; Komatsu, Mitsuhisa; Agner, Bue Ross; Nishida, Tomoyuki; Ranthe, Mattis; Nakamura, Jiro; Superior HbA1c control with the fixed-ratio combination of insulin degludec and liraglutide (IDegLira) compared with a maximum dose of 50 units of insulin degludec in Japanese individuals with type 2 diabetes in a phase 3, double-blind, randomized trial.; Diabetes, obesity & metabolism; 2019; vol. 21 (no. 12); 2694-2703

489.1. 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	DUAL II Japan/NCT02911948
Study type	Randomised controlled trial (RCT) Double-blind, treat-to-target, RCT
Study location	Japan (Multicentre trial, 38 sites)
Study setting	Outpatient
Study dates	09/2016 to 11/2017
Sources of funding	Funded by Novo Nordisk A/S
Inclusion criteria	• Aged≥20 years at time of informed consent • Type 2 diabetes diagnosis≥6-mo prior to screening • HbA1c 7.5-11% inclusive • Stable daily insulin dose≥60 days prior to screening either as basal insulin (e.g. insulin degludec, insulin detemir, NPH insulin) or pre-mixed/combination insulin (e.g. biphasic insulin aspart) with total

	insulin dose in previous 60 days prior to screening within 20-50 units (fluctuation +/- 20 U permissible) • Stable metformin dose≥60 days prior to screening • BMI≥23 kg/m2
Exclusion criteria	• Receipt of any investigational medicinal product (IMP) within 30 days before screening • Use of any anti-diabetic drug in a period of 60 days before screening (except premix/ combination or basal insulin, metformin, SU, glinides, α-GI, SGLT2i, or TZD) or anticipated change in concomitant medication, which in the investigators opinion could interfere with glucose metabolism (e.g. systemic corticosteroids or bolus insulin) • Treatment with GLP-1 receptor agonist during the last 60 days prior to screening (discontinuation of GLP-1 RA at any point in time must not have been due to safety concerns, tolerability issues or lack of efficacy, as judged by the investigator) • Treatment with DPP-4 inhibitors during the last 60 days prior to screening • Impaired liver function (ALT or AST equal or above 2.5 times upper limit of normal) • Renal impairment (eGFR<60 mL/min/1.73m2, CKD-EPI) • Screening calcitonin equal or above 50 ng/L • History of pancreatitis (acute or chronic) • Personal or family history of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia type 2 (MEN 2) • Classified as NYHA Class IV
Recruitment / selection of participants	Eligible participants recruited from sites across Japan entered 2-wk screening period and were randomised 1:1 to IDegLira or insulin degludec arms using central interactive voice-/web- response system, stratified by pre-trial glucose-lowering treatment (metformin + basal insulin; metformin + basal insulin + one other oral anti-diabetic drug; metformin + pre-mix/combination insulin; metformin + pre-mix/combination insulin + one other oral anti-diabetic drug). All participants discontinued all other anti-diabetic drugs other than metformin at randomisation.
Intervention(s)	• IDegLira titrated twice weekly Subcutaneous daily injection of IDegLira titrated twice weekly for 26 weeks, in addition to metformin. Recommended starting dose of 10 dose steps (10 U degludec/0.36 mg liraglutide) with option at investigator discretion of higher starting dose (up to 16 dose step). Twice weekly titration based on mean of 3 consecutive pre-breakfast self-measured blood glucose values using calibrated glucose monitor. Maximum dose was 50 dose steps (50 U degludec/1.8 mg liraglutide).
Cointervention	• Metformin All participants continued on their pre-trial metformin dose although could be reduced at investigator discretion or if safety concerns.
Strata 1: People with	Not stated/unclear

type 2 diabetes mellitus and heart failure	Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Mixed population
Subgroup 5: eGFR category at baseline	eGFR ≥30mL/min/1.73m2 Exclusion criteria: eGFR<60 mL/min/1.73 m2

Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Comparator	• Insulin degludec Subcutaneous daily injection of insulin degludec titrated twice weekly for 26 weeks, in addition to metformin. Recommended starting dose of 10 dose steps (10 U degludec) with option at investigator discretion of higher starting dose (up to 16 dose step). Twice weekly titration based on mean of 3 consecutive pre-breakfast self-measured blood glucose values using calibrated glucose monitor. Maximum dose was 50 dose steps (50 U degludec).
Number of participants	N=210 randomised (full analysis set/safety analysis set); N=203 completers
Duration of follow-up	26 weeks
Indirectness	None
Method of analysis	ITT ITT LOCF analysis (full analysis set, all randomised participants) for primary analysis. Sensitivity analysis using pattern mixture model (ITT analysis) and mixed model for repeated measurements (treatment and trial policy estimands).

489.2. Study arms

489.2.1. IDegLira titrated twice weekly (N = 105)

Subcutaneous fixed-ratio combination of insulin degludec and liraglutide (IDegLira) titrated twice weekly to maximum of 50 U degludec/1.8 mg liraglutide, in addition to metformin.

489.2.2. Insulin degludec titrated twice weekly (N = 105)

Subcutaneous injection of insulin degludec titrated twice weekly to maximum of 50 U degludec/1.8 mg liraglutide, in addition to metformin.

489.3. Characteristics

489.3.1. Arm-level characteristics

Characteristic	IDegLira titrated twice weekly (N = 105)	Insulin degludec titrated twice weekly (N = 105)
% Male Sample size	n = 70 ; % = 66.7	n = 63 ; % = 60
Mean age (SD) (years) Mean (SD)	56.6 (10.4)	55.5 (10)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	14.33 (7.79)	13.77 (7.46)
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	NR	NR

Characteristic	IDegLira titrated twice weekly (N = 105)	Insulin degludec titrated twice weekly (N = 105)
Nominal		
Other antidiabetic medication used At screening Sample size	n = NA ; % = NA	n = NA ; % = NA
Metformin and basal insulin Sample size	n = 46 ; % = 43.8	n = 46 ; % = 43.8
Metformin, basal insulin and 1 other oral antidiabetic Sample size	n = 20 ; % = 19	n = 21 ; % = 20
Metformin and pre-mix/combination insulin Sample size	n = 26 ; % = 24.8	n = 25 ; % = 23.8
Metformin, pre-mix/combination insulin and 1 other oral antidiabetic Sample size	n = 13 ; % = 12.4	n = 12 ; % = 12.4
Blood pressure-lowering medication used Nominal	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

490. Webb, 2020

Bibliographic Reference	Webb, D. R.; Htike, Z. Z.; Swarbrick, D. J.; Brady, E. M.; Gray, L. J.; Biglands, J.; Gulsin, G. S.; Henson, J.; Khunti, K.; McCann, G. P.; et, al.; A randomized, open-label, active comparator trial assessing the effects of 26 weeks of liraglutide or sitagliptin on cardiovascular function in young obese adults with type 2 diabetes; Diabetes Obes Metab; 2020; vol. 22; 1187-1196

490.1. 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	Liraglutide in Young adults with type 2 DIAbetes (LYDIA)/NCT02043054, EudraCT 2012-002422-78
Study type	Randomised controlled trial (RCT) Open-label, active-controlled RCT
Study location	Diabetes Research Centre, University of Leicester, Leicester, UK
Study setting	Outpatient
Study dates	01/2014 to 09/2018
Sources of funding	Funded by Novo Nordisk and supported by NIHR Leicester Biomedical Research Center, the NIHR CLAHRC-East Midlands, the NIHR Leicester Clinical Research Facility and The NIHR Leicester Clinical Trial Unit.
Inclusion criteria	• Aged 18-50 years (revised to 18-60 years in 2017) • Type 2 diabetes diagnosis • HbA1c ≥6.5 and <10% • Obesity (BMI≥27 kg/m2 if of South Asian ethnicity or other BME populations, otherwise ≥30 mg/m2)

	• Current treatment with oral glucose-lowering drug (metformin and/or a sulphonylurea)≥3-mo
Exclusion criteria	• Current treatment with insulin, SGLT-2 inhibitors, GLP-1 receptor agonists or DPP-4 inhibitors • Treatment with a thiazolidinedione in past 3-mo • Type 1 diabetes • Contraindication to MRI scan • Females of child bearing potential who are pregnant, breast-feeding or intend to become pregnant or are not using adequate contraceptive methods • Suffer from terminal illness • Impaired renal function (eGFR < 30 ml/min/1.73m2)) • Impaired liver function (ALAT≥2.5 times upper limit of normal) • Hepatitis B antigen or Hepatitis C antibody positive • Clinically significant active cardiovascular disease including history of myocardial infarction within the past 6 months and/or heart failure (NYHA class III and IV) at the discretion of the investigator • Recurrent major hypoglycaemia as judged by the investigator • Known or suspected allergy to the trial products • Known or suspected thyroid disease • Receipt of any investigational drug within four weeks prior to this trial • Have severe and enduring mental health problems • Are not primarily responsible for their own care • Any contraindication to Sitagliptin or Liraglutide • Have severe irritable bowel disorder • Have pancreatitis or a previous history of pancreatitis
Recruitment / selection of participants	Eligible participants recruited from primary and secondary care diabetes clinics and were randomised and allocated using independent online assignment system after consent and baseline assessments. Glycaemic control managed in accordance with national clinical practice guidelines (NICE NG28 (2015)). Rescue therapy (addition of non-incretin-based medication) considered if FPG>11 mmol/L at visit 4 (12 weeks).
Intervention(s)	• Liraglutide 0.6-1.8 mg daily Subcutaneous injection of liraglutide 0.6 mg-1.8 mg daily using pre-filled pen (Victoza 6 mg/mL) for 26 weeks, in addition to background metformin and/or sulphonylurea. Starting dose of 0.6 mg daily with weekly increase of 0.6 mg at investigator discretion.
Cointervention	• Metformin and/or a sulphonylurea All participants continued with background metformin and/or sulphonylurea for duration of trial. Sulphonylurea dose was halved if baseline HbA1c<7% or in case of severe hypoglycaemia.
Strata 1: People with type 2 diabetes	Not stated/unclear Exclusion criteria: Clinically significant active cardiovascular disease including heart failure (NYHA class III and IV) at the discretion of the investigator

mellitus and heart failure	
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Exclusion criteria: Clinically significant active cardiovascular disease including history of myocardial infarction within the past 6 months at the discretion of the investigator
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	People at higher risk of developing cardiovascular disease Trial describes participants as 'younger asymptomatic adults with type 2 diabetes who have a significant lifetime risk of developing heart failure'.
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	People with obesity Inclusion criteria: BMI≥27 kg/m2 if of South Asian descent or if of other BME population, otherwise BMI≥30 kg/m2
Subgroup 5: eGFR category at baseline	eGFR ≥30mL/min/1.73m2 Exclusion criteria: eGFR<30 ml/min/1.73 m2
Subgroup 6: Albuminuria	Not stated/unclear

category at baseline	
Comparator	• Sitagliptin 100 mg daily Oral sitagliptin tablet 100 mg daily for 26 weeks, in addition to background metformin and/or sulphonylurea. There was no titration protocol in this arm.
Number of participants	N=76 randomised
Duration of follow-up	26 weeks
Indirectness	
Method of analysis	ITT ITT complete case analysis for efficacy and safety outcomes; sensitivity analysis for primary outcome with multiple imputation for missing data

490.2. Study arms

490.2.1. Liraglutide 0.6-1.8 mg weekly (N = 38)

Subcutaneous injection of liraglutide 0.6-1.8 mg daily for 26 weeks, in addition to metformin and/or a sulphonylurea.

490.2.2. Sitagliptin 100 mg daily (N = 38)

Oral sitagliptin tablet 100 mg daily for 26 weeks, in addition to metformin and/or a sulphonylurea.

490.3. Characteristics

490.3.1. Arm-level characteristics

Characteristic	Liraglutide 0.6-1.8 mg weekly (N = 38)	Sitagliptin 100 mg daily (N = 38)
% Male Sample size	n = 20 ; % = 52.6	n = 15 ; % = 39.5
Mean age (SD) (years) Mean (SD)	43.4 (7)	44.8 (5.9)

Characteristic	Liraglutide 0.6-1.8 mg weekly (N = 38)	Sitagliptin 100 mg daily (N = 38)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	4.5 (4.5)	4.4 (4.4)
Cardiovascular risk factors Nominal	NR	NR
Smoking status Current smoker Sample size	n = 11 ; % = 29	n = 8 ; % = 21.1
Alcohol consumption Nominal	NR	NR
Presence of severe mental illness Sample size	n = 0 ; % = 0	n = 0 ; % = 0
People with significant cognitive impairment Sample size	n = 0 ; % = 0	n = 0 ; % = 0
People with a learning disability Nominal	NR	NR
Number of people with obesity Sample size	n = 38 ; % = 100	n = 38 ; % = 100
Other antidiabetic medication used Nominal	NR	NR
Blood pressure-lowering medication used Nominal	NR	NR

Characteristic	Liraglutide 0.6-1.8 mg weekly (N = 38)	Sitagliptin 100 mg daily (N = 38)
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

491. Weinstock, 2015

Bibliographic Reference	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

491.1. Study details

Secondary publication of another included study- see primary study for details	Nauck, M.; Weinstock, R. S.; Umpierrez, G. E.; Guerci, B.; Skrivanek, Z.; Milicevic, Z. Efficacy and safety of dulaglutide versus sitagliptin after 52 weeks in type 2 diabetes in a randomized controlled trial (AWARD-5). Diabetes Care; 2014; vol. 37 (no. 8); 2149-2158.
Other publications associated with this study included in review	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 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 dates	
Inclusion criteria	

491.2. Study arms

491.2.1. Dulaglutide 1.5 mg weekly (N = 304)

Administered subcutaneously

491.2.2. Dulaglutide 0.75 mg weekly (N = 302)

Administered subcutaneously

491.2.3. Sitagliptin 100 mg daily (N = 315)

Administered orally

491.2.4. Placebo daily (N = 177)

Administered orally

492. White William, 2013

Bibliographic Reference	White William, B; Cannon Christopher, P; Heller Simon, R; Nissen Steven, E; Bergenstal Richard, M; Bakris George, L; Perez Alfonso, T; Fleck Penny, R; Mehta Cyrus, R; Kupfer, Stuart; Wilson, Craig; Cushman William, C; Zannad, Faiez; EXAMINE, Investigators; Alogliptin after acute coronary syndrome in patients with type 2 diabetes.; The New England journal of medicine; 2013; vol. 369 (no. 14); 1327-35

492.1. Study details

Secondary publication of another included study- see primary study for details	This is the parent study of the EXAMINE trial - any information from the primary study is extracted in this record
Other publications associated with this study included in review	Zannad, Faiez, Cannon Christopher, P, Cushman William, C et al. (2015) Heart failure and mortality outcomes in patients with type 2 diabetes taking alogliptin versus placebo in EXAMINE: a multicentre, randomised, double-blind trial. Lancet (London, England) 385(9982): 2067-76
Trial name / registration number	EXAMINE trial. ClinicalTrials.gov number, NCT00968708
Study type	Randomised controlled trial (RCT)
Study location	49 countries; United States and Canada; Western Europe, Australia, New Zealand, and Middle East; Central and South America and Mexico; Eastern Europe and Africa; Asia and Pacific Islands
Study setting	898 centres; Described as multicentre; reference made to outpatient visits - no further details
Study dates	Recruitment undertaken from October 2009 to March 2013; last patient visit June 18, 2013
Sources of funding	Takeda Development Center Americas
Inclusion criteria	People with a diagnosis of type 2 diabetes mellitus receiving antidiabetic therapy (other than a DPP-4 inhibitor or GLP-1 analogue) and had had an acute coronary syndrome within 15 to 90 days before randomisation. Further criteria for the diagnosis of type 2 diabetes included a glycates haemoglobin level of 6.5 to 11.0% at screening, or if the antidiabetic regimen included insulin, a glycated haemoglobin level of 7.0 to 11.0%.

	Acute coronary syndromes included acute myocardial infarction and unstable angina requiring hospitalisation.
Exclusion criteria	Diagnosis of type 1 diabetes; unstable cardiac disorders (e.g. New York Heart Association class IV heart failure, refractory angina, uncontrolled arrhythmias, critical valvular heart disease or severe uncontrolled hypertension); dialysis within 14 days before screening.
Recruitment / selection of participants	No additional information.
Intervention(s)	Alogliptin N=2701 Oral alogliptin with dose adjusted to eGFR from 6.25mg (if eGFR <30) to 12.5mg (if eGFR 30-60) or 25mg (if eGFR >60) daily. Concomitant therapy: Throughout the study, people were required to received standard-of-care treatment for type 2 diabetes and cardiovascular risk factors according to regional guidelines.
Strata 1: People with type 2 diabetes mellitus and heart failure	Mixed population Excluded "New York Heart Association class IV heart failure". Around 28% of people had heart failure
Strata 2: People with atherosclerotic cardiovascular disease	People with atherosclerotic cardiovascular diseases Inclusion criteria was "had an acute coronary syndrome within 15 to 90 days before randomization (included acute myocardial infarction and unstable angina requiring hospitalization)". 87.5% of people had a myocardial infarction, 7.2% of people had a stroke, 9.4% of people had peripheral arterial disease, 62.8% of people had had a percutaneous coronary intervention.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Not an inclusion/exclusion criteria. Baseline characteristics divide by baseline kidney function based on eGFR but not by CKD status.
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 Based on mean age and median duration of diabetes
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Mixed population Based on BMI range
Subgroup 5: eGFR category at baseline	eGFR ≥30mL/min/1.73m2 Baseline eGFR category data taken from related renal study. 2.9% participants had baseline eGFR <30mL/min/1.73m2
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	Subgroups by eGFR category for comparing eGFR change. Subgroups for 3-point MACE outcome.
Comparator	Placebo N=2679 In addition to standard care. Concomitant therapy: Throughout the study, people were required to received standard-of-care treatment for type 2 diabetes and cardiovascular risk factors according to regional guidelines.
Number of participants	5380
Duration of follow-up	18 months (median follow-up)
Indirectness	No additional information

Method of analysis	ITT
Additional comments	Cox proportional-hazards models were used to analyse the time to the first occurrence of a primary or secondary end-point event among all randomly assigned patients, with stratification according to geographic region and renal function at baseline.

492.2. Study arms

492.2.1. Alogliptin (N = 2701)

Oral alogliptin with dose adjusted to eGFR from 6.25mg (if eGFR <30) to 12.5mg (if eGFR 30-60) or 25mg (if eGFR >60) daily. Concomitant therapy: Throughout the study, people were required to received standard-of-care treatment for type 2 diabetes and cardiovascular risk factors according to regional guidelines.

492.2.2. Placebo (N = 2679)

In addition to standard care. Concomitant therapy: Throughout the study, people were required to received standard-of-care treatment for type 2 diabetes and cardiovascular risk factors according to regional guidelines.

492.3. Characteristics

492.3.1. Arm-level characteristics

Characteristic	Alogliptin (N = 2701)	Placebo (N = 2679)
% Male Sample size	n = 1828 ; % = 67.7	n = 1823 ; % = 68
Mean age (SD) (years) Median (IQR)	61 (NR to NR)	61 (NR to NR)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 1966 ; % = 72.8	n = 1943 ; % = 72.5
Black Sample size	n = 101 ; % = 3.7	n = 115 ; % = 4.3

Characteristic	Alogliptin (N = 2701)	Placebo (N = 2679)
Asian Sample size	n = 547 ; % = 20.3	n = 542 ; % = 20.2
Native American Sample size	n = 56 ; % = 2.1	n = 54 ; % = 2
Other Sample size	n = 31 ; % = 1.1	n = 25 ; % = 0.9
Comorbidities Sample size	n = NA ; % = NA	n = NA ; % = NA
Hypertension Sample size	n = 2229 ; % = 82.5	n = 2240 ; % = 83.6
Myocardial infarction Sample size	n = 2389 ; % = 88.4	n = 2345 ; % = 87.5
Congestive heart failure Sample size	n = 757 ; % = 28	n = 744 ; % = 27.8
Stroke Sample size	n = 195 ; % = 7.2	n = 193 ; % = 7.2
Peripheral arterial disease Sample size	n = 262 ; % = 9.7	n = 252 ; % = 9.4
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed (years) Range	2.6 to 13.8	2.8 to 13.7
Time since type 2 diabetes diagnosed (years) Median (IQR)	7.1 (NR to NR)	7.3 (NR to NR)
HbA1c (%) Mean (SD)	8 (1.1)	8 (1.1)
Cardiovascular risk factors Sample size	n = NA ; % = NA	n = NA ; % = NA
Percutaneous coronary intervention Sample size	n = 1689 ; % = 62.5	n = 1683 ; % = 62.8

Characteristic	Alogliptin (N = 2701)	Placebo (N = 2679)
Coronary-artery bypass grafting Sample size	n = 347 ; % = 12.8	n = 341 ; % = 12.7
Blood pressure Mean (SD)	NR (NR)	NR (NR)
Heart rate Mean (SD)	NR (NR)	NR (NR)
Smoking status Sample size	n = 351 ; % = 13	n = 383 ; % = 14.3
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR
Weight (kg) Range	36 to 185	35.5 to 196.3
Weight (kg) Median (IQR)	80.2 (NR to NR)	80 (NR to NR)
BMI (kg/m2) Range	2.6 to 13.8	2.8 to 13.7
BMI (kg/m2) Median (IQR)	7.1 (NR to NR)	7.3 (NR to NR)
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR
Cholesterol and lipid levels See below (Lipids) Mean (SD)	NA (NA)	NA (NA)
Albumin creatinine ratio	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Alogliptin (N = 2701)	Placebo (N = 2679)
Sample size		
eGFR mL/min/1.73m2 Median (IQR)	71.1 (NR to NR)	71.2 (NR to NR)
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Insulin Sample size	n = 793 ; % = 29.4	n = 812 ; % = 30.3
Metformin Sample size	n = 1757 ; % = 65	n = 1805 ; % = 67.4
Thiazolidinediones Sample size	n = 67 ; % = 2.5	n = 64 ; % = 2.4
Sulfonylureas Sample size	n = 1266 ; % = 46.9	n = 1237 ; % = 46.2
Blood pressure-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Beta-blockers Sample size	n = 2208 ; % = 81.7	n = 2203 ; % = 82.2
Calcium-channel blockers Sample size	n = 586 ; % = 21.7	n = 611 ; % = 22.8
Diuretics Sample size	n = 1005 ; % = 37.2	n = 1009 ; % = 37.7
Renin-angiotensin system-blocking agents Sample size	n = 2201 ; % = 81.5	n = 2210 ; % = 82.5
Statins/lipid-lowering medication used Statins Sample size	n = 2446 ; % = 90.6	n = 2420 ; % = 90.3
Other treatment being received Sample size	n = NA ; % = NA	n = NA ; % = NA
Aspirin Sample size	n = 2448 ; % = 90.6	n = 2433 ; % = 90.8

Characteristic	Alogliptin (N = 2701)	Placebo (N = 2679)
Thienopyridine Sample size	n = 2155 ; % = 79.8	n = 2165 ; % = 80.8
Lipids (mg/dL) Mean (SD)	NA (NA)	NA (NA)
Total cholesterol Mean (SD)	153.9 (44.2)	154.8 (43.5)
HDL cholesterol Mean (SD)	43.2 (10.8)	43.1 (10.3)
LDL cholesterol Mean (SD)	78.4 (34.9)	78.9 (34.6)
Triglycerides Mean (SD)	162.7 (101.9)	166.4 (106)

493. Wilcox, 2008

Bibliographic Reference	Wilcox, Robert; Kupfer, Stuart; Erdmann, Erland; PROactive, Study; investigators; Effects of pioglitazone on major adverse cardiovascular events in high-risk patients with type 2 diabetes: results from PROspective pioglitAzone Clinical Trial In macro Vascular Events (PROactive 10).; American heart journal; 2008; vol. 155 (no. 4); 712-7

493.1. Study details

Secondary publication of another included study- see primary study for details	This is the primary record for the PROactive trial. All study details are included in this record.
Other publications associated with this study included in review	Dormandy John, A, Charbonnel, Bernard, Eckland David J, A et al. (2005) Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. Lancet (London, England) 366(9493): 1279-89
Trial name / registration number	PROactive trial. Clinicaltrial.gov = NCT00174993
Study type	Randomised controlled trial (RCT)
Study location	19 European countries
Study setting	321 clinical sites
Study dates	28 May 2001 to 31 January 2005
Sources of funding	Takeda Europe R&D Centre Ltd, London, United Kingdom, and Eli Lilly and Company, Indianapolis, IN.
Inclusion criteria	Adults (aged 35-75, inclusive) with type 2 diabetes and with an established history of macrovascular disease; Type 2 diabetes was defined as: haemoglobin A1c level above the upper limit of normal; i.e., the local equivalent of 6.5% for a DCCT traceable assay; An established history of macrovascular disease was defined as having one or more of the following: MI, stroke, percutaneous coronary intervention (PCI), or coronary artery bypass graft (CABG) ≥6 months before entering the study; ACS ≥3 months before entering the study; Objective evidence of coronary artery disease (positive exercise test or scintigraphy, or angiography showing at least one lesion >50% stenosis); Peripheral arterial obstructive

	disease of the leg (previous leg amputation above the ankle, or intermittent claudication with an ankle or toe brachial pressure index >0.9).
Exclusion criteria	People with type 1 diabetes, including any history of ketoacidosis or requirement for insulin therapy within 1 year of diagnosis; haemodialysis; or significantly impaired hepatic function (defined as serum alanine aminotransferase >2.5 times the upper limit of normal); insulin as sole therapy for diabetes; symptomatic heart failure (New York Heart Association class II or above); planned coronary revascularization procedure within 90 days after screening; planned revascularization - no time frame; leg ulcers, gangrene, or pain at rest.
Recruitment / selection of participants	Not specified; patents were recruited to the PROspective pioglitAzone Clinical Trial In macro Vascular Events (PROactive) trial
Intervention(s)	Pioglitazone (Dose was force-titrated from 15 to 45 mg/d during the first 2 months, depending upon tolerability)
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Excluded symptomatic HF class II and above.
Strata 2: People with atherosclerotic cardiovascular disease	People with atherosclerotic cardiovascular diseases Recruited people with "an established history of macrovascular disease (defined as one of the following: MI, stroke, percutaneous coronary intervention (PCI), or coronary artery bypass graft (CABG) ≥6 months before entering the study; ACS ≥3 months before entering the study; objective evidence of coronary artery disease (positive exercise test or scintigraphy, or angiography showing at least one lesion >50% stenosis); peripheral arterial obstructive disease of the leg (previous leg amputation above the ankle, or intermittent claudication with an ankle or toe brachial pressure index >0.9).
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristic
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	People at higher risk of developing cardiovascular disease

Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	All study participants are relevant to subgroup of interest (people with T2DM and high cardiovascular risk)
Comparator	Placebo
Number of participants	5238
Duration of follow-up	34.5 months (mean)
Indirectness	None - Study population, intervention, and comparator meets review protocol
Method of analysis	ITT
Additional comments	Kaplan-Meier estimates of the 3-year event rates were calculated; Time-to-event analyses were carried out by fitting proportional hazards survival models with “treatment” as the only covariate, and estimated hazard ratios (HRs) and 95% CIs were calculated.

493.2. Study arms

493.2.1. Pioglitazone (N = 2605)

493.2.2. Placebo (N = 2633)

493.3. Characteristics

493.3.1. Arm-level characteristics

Characteristic	Pioglitazone (N = 2605)	Placebo (N = 2633)
% Male Taken from Dormandy 2005 Sample size	n = 1735 ; % = 67	n = 1726 ; % = 66
Mean age (SD) (years) Taken from Dormandy 2005 Mean (SD)	61.9 (7.6)	61.6 (7.8)
Ethnicity Males Sample size	n = 2564 ; % = 98	n = 2600 ; % = 99
Time since type 2 diabetes diagnosed (years) Median (IQR)	8 (4 to 13)	8 (4 to 14)
Systolic blood pressure Standardised Mean (SD)	144 (18)	143 (18)
Diastolic blood pressure Standardised Mean (SD)	83 (10)	83 (9)
Current smoker Sample size	n = 340 ; % = 13	n = 381 ; % = 14
Past smoker Sample size	n = 1199 ; % = 46	n = 1159 ; % = 44
BMI (kg/m2) Taken from Dormandy 2005	30.7 (4.7)	31 (4.8)

Characteristic	Pioglitazone (N = 2605)	Placebo (N = 2633)
Mean (SD)		
Other antidiabetic medication used Taken from Dormandy 2005 Sample size	n = 2496 ; % = 96	n = 2528 ; % = 96
Metfomin Sample size	n = 253 ; % = 10	n = 261 ; % = 10
Sulphonylureas only Sample size	n = 508 ; % = 20	n = 493 ; % = 19
Metformin + sulphonylureas Sample size	n = 654 ; % = 25	n = 660 ; % = 25
Insulin Sample size	n = 5 ; % = 0.2	n = 8 ; % = 0.3
Insulin + metformin Sample size	n = 456 ; % = 18	n = 475 ; % = 18
Insulin + sulphonylureas Sample size	n = 209 ; % = 8	n = 219 ; % = 8
Insulin + metformin + sulphonylureas Sample size	n = 105 ; % = 4	n = 107 ; % = 4
Other combination Sample size	n = 306 ; % = 12	n = 305 ; % = 12
Beta-blockers Sample size	n = 1423 ; % = 55	n = 1434 ; % = 54
ACE inhibitor Sample size	n = 1630 ; % = 63	n = 1658 ; % = 63
Angiotensin II antagonists Sample size	n = 170 ; % = 7	n = 184 ; % = 7
Calcium channel blockers Sample size	n = 892 ; % = 34	n = 964 ; % = 37
Nitrates Sample size	n = 1018 ; % = 39	n = 1045 ; % = 40

Characteristic	Pioglitazone (N = 2605)	Placebo (N = 2633)
Thiazides Sample size	n = 401 ; % = 15	n = 430 ; % = 16
Loop diuretics Sample size	n = 372 ; % = 14	n = 378 ; % = 14
Statins Sample size	n = 1108 ; % = 43	n = 1137 ; % = 43
Fibrates Sample size	n = 264 ; % = 10	n = 294 ; % = 11
Antiplatelet medications does not reports the names Sample size	n = 2221 ; % = 85	n = 2175 ; % = 83
Aspirin Sample size	n = 1942 ; % = 75	n = 1888 ; % = 72
LDL-cholesterol Median (IQR)	2.9 (2.3 to 3.5)	2.9 (2.3 to 0.35)
HDL cholesterol Median (IQR)	1.1 (0.9 to 1.3)	1.1 (0.9 to 1.3)
Triglycerides Median (IQR)	79 (68 to 92)	79 (68 to 92.5)
History of hypertension Taken from Dormandy 2005 Sample size	n = 1947 ; % = 75	n = 2005 ; % = 76
History of microvascular diseases Taken from Dormandy 2005 Sample size	n = 1113 ; % = 43	n = 1076 ; % = 41
HbA1c (Percentage) Taken from Dormandy 2005 Median (IQR)	7.8 (7 to 8.9)	7.9 (7.1 to 8.9)
Creatinine (micromol/L) Taken from Dormandy 2005 Median (IQR)	79 (68 to 92)	79 (68 to 92.5)

494. Wilding, 2013

Bibliographic Reference	Wilding, J P H; Leonsson-Zachrisson, M; Wessman, C; Johnsson, E; Dose-ranging study with the glucokinase activator AZD1656 in patients with type 2 diabetes mellitus on metformin.; Diabetes, obesity & metabolism; 2013; vol. 15 (no. 8); 750-9

494.1. 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	NCT01020123
Study type	Randomised controlled trial (RCT)
Study location	92 sites in: Germany, Hungary , Latvia, Lithuania, Poland, Romania, Sweden, UK, Chile, Mexico and Peru
Study setting	Clinic
Study dates	10/2009 - 02/2011
Sources of funding	Astra Zeneca
Inclusion criteria	Male and female (of non-childbearing potential) patients could participate if they were aged ≥18 years with body mass index of ≥19 to ≤42 kg/m2, HbA1c of ≥7.5 to ≤12% and receiving metformin (≥1500 mg/day) as sole glucose-lowering medication for at least 10 weeks before enrolment.
Exclusion criteria	Any significant cardiovascular event within 6 months, ALT or AST>3× upper limit of normal, or the use of warfarin, amiodarone, anabolic steroids and systemic glucocorticosteroid treatment or known potent CYP450 inhibitors.

Recruitment / selection of participants	Patients with uncontrolled type 2 diabetes on metformin were recruited from 92 sites across Europe and Latin America. Patients were randomised to placebo/AZD1656/glipizide. Only data for the placebo and glipizide arms meet the inclusion criteria and have been extracted for the purpose of this review.
Intervention(s)	Glipizide 5-20 mg daily Administered orally.
Cointervention	Metformin ≥1500 mg/day - started at least 10 weeks before enrolment. Two weeks before the start of study treatment, patients were switched to commercially available metformin, supplied by the study sponsor, remaining on their original dose throughout the study.
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 People with "significant cardiovascular events within 6 months" stated in the exclusion criteria. No information about cardiovascular events prior to the 6 months. 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	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
Comparator	Placebo daily. Administered orally.
Number of participants	N=182 The study included and randomised a total number of 458 patients however only n=182 were considered relevant for inclusion (glipizide and placebo arms)
Duration of follow-up	6-month (4-month + 2-month extension)
Indirectness	
Method of analysis	Modified ITT
Additional comments	Patients with at least one dose of study medication, who had both a baseline measurement and a minimum of one postbaseline measurement were included in the efficacy analysis.

	The safety analysis included all patients who received at least one dose of study treatment and for whom post-dose data were available regardless of whether hyperglycaemia rescue medicine was required.

494.2. Study arms

494.2.1. Glipizide 5-20 mg (N = 94)

Administered orally

494.2.2. Placebo (N = 88)

Administered orally

494.3. Characteristics

494.3.1. Arm-level characteristics

Characteristic	Glipizide 5-20 mg (N = 94)	Placebo (N = 88)
% Male No of events	n = 46 ; % = 49	n = 45 ; % = 51
Mean age (SD) (year) Mean (SD)	57.1 (9.1)	56.9 (9.6)
Hispanic or Latino No of events	n = 57 ; % = 60.6	n = 45 ; % = 51.1
Other No of events	n = 37 ; % = 39.4	n = 43 ; % = 48.9
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	6.4 (5.6)	5.5 (4)
HbA1c (%) Mean (SD)	8.3 (0.8)	8.3 (0.8)

Characteristic	Glipizide 5-20 mg (N = 94)	Placebo (N = 88)
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
Albumin creatinine ratio Nominal	NR	NR
Metformin No of events	n = 94 ; % = 100	n = 88 ; % = 100
Rescue insulin No of events	n = 5 ; % = 5.4	n = 8 ; % = 9.2
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

495. Wilding, 2014

Bibliographic Reference	Wilding, J P H; Woo, V; Rohwedder, K; Sugg, J; Parikh, S; Dapagliflozin in patients with type 2 diabetes receiving high doses of insulin: efficacy and safety over 2 years.; Diabetes, obesity & metabolism; 2014; vol. 16 (no. 2); 124-36

495.1. Study details

Secondary publication of another included study- see primary study for details	Yes, see primary article for further details: • Wilding, J. P., Woo, V., Soler, N. G., Pahor, A., Sugg, J., Rohwedder, K., ... & Dapagliflozin 006 Study Group*. (2012). Long-term efficacy of dapagliflozin in patients with type 2 diabetes mellitus receiving high doses of insulin: a randomized trial. *Annals of internal medicine*, *156*(6), 405-415.
Other publications associated with this study included in review	Wilding, J. P., Woo, V., Soler, N. G., Pahor, A., Sugg, J., Rohwedder, K., ... & Dapagliflozin 006 Study Group*. (2012). Long-term efficacy of dapagliflozin in patients with type 2 diabetes mellitus receiving high doses of insulin: a randomized trial. *Annals of internal medicine*, *156*(6), 405-415.
Trial name / registration number	NCT00673231)
Study type	Randomised controlled trial (RCT) Double-blind, double-dummy, placebo-controlled, parallel-group RCT

495.2. Study arms

495.2.1. Dapagliflozin 10 mg daily (N = 194)

Oral dapagliflozin 10 mg daily for 104 weeks (48 weeks + 56 weeks), in addition to insulin.

495.2.2. Dapagliflozin 5/10 mg daily (N = 211)

Oral dapagliflozin 5 mg daily for 48 weeks then 10 mg daily for 56 weeks, in addition to insulin.

495.2.3. Dapagliflozin 2.5 mg daily (N = 202)

Oral dapagliflozin 2.5 mg daily for 104 weeks (48 weeks + 56 weeks), in addition to insulin.

495.2.4. Placebo (N = 193)

Matching placebo daily for 104 weeks, in addition to insulin.

496. Wilding, 2013

Bibliographic Reference	Wilding, J. P. H.; Charpentier, G.; Hollander, P.; Gonzalez-Galvez, G.; Mathieu, C.; Vercruysse, F.; Usiskin, K.; Law, G.; Black, S.; Canovatchel, W.; Meininger, G.; Efficacy and safety of canagliflozin in patients with type 2 diabetes mellitus inadequately controlled with metformin and sulphonylurea: A randomised trial; Int J Clin Pract; 2013; vol. 67 (no. 12); 1267-1282

496.1. 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	NCT01106625. **CANTATA-MSU Trial**
Study type	Randomised controlled trial (RCT)
Study location	85 study centres in 11 countries
Study setting	Unspecified clinical setting
Study dates	between April 2010 and April 2012
Sources of funding	Janssen Research & Development, LLC
Inclusion criteria	• All patients must have a diagnosis of T2DM and be currently treated with metformin and sulphonylurea • Patients in the study must have a HbA1c between >=7 and <=10.5% • Patients must have a fasting plasma glucose (FPG) <270 mg/dL (15 mmol/L) • 18 Years to 80 Years

Exclusion criteria	• History of diabetic ketoacidosis, type 1 diabetes mellitus (T1DM), pancreas or beta cell transplantation, or diabetes secondary to pancreatitis or pancreatectomy, or a severe hypoglycemic episode within 6 months before screening
Recruitment / selection of participants	Eligible patients were men and women aged 18– 80 years with T2DM who had inadequate glycaemic control (HbA1c ≥ 7.0% to ≤ 10.5%) on metformin plus sulphonylurea, with both agents at maximally or near-maximally effective doses. Patients taking below protocolspecified doses of metformin and/or sulphonylurea underwent an OAD adjustment period
Intervention(s)	• Canagliflozin 100 mg: Each patient will receive 100 mg of canagliflozin once daily for 52 weeks with protocol-specified doses of metformin and sulphonylurea. • Canagliflozin 300 mg: Each patient will receive 300 mg of canagliflozin once daily for 52 weeks with protocol-specified doses of metformin and sulphonylurea.
Cointervention	• Drug: Metformin. The patient's stable dose of background metformin therapy should be continued throughout the study. • Drug: Sulphonylurea. The patient's stable dose of background sulphonylurea therapy should be continued throughout the study.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and high	Not stated/unclear

cardiovascular risk	
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	eGFR ≥30mL/min/1.73m2 Excluded: estimated glomerular filtration rate (eGFR) < 55 ml/min/1.73 m2 (or < 60 ml/min/1.73 m2 based upon restriction of metformin use in the local label)
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	subgroups of patients with baseline HbA1c of < 8.0%, ≥ 8.0% to < 9.0%, and ≥ 9.0%
Comparator	Placebo
Number of participants	A total of 469 patients were randomised into the core treatment period and received ≥ 1 dose of study medication, comprising the mITT analysis set; of 381 patients who completed the core period, 374 entered the extension period and 310 completed 52 weeks of treatment. Canagliflozin 100mg (n=157), Canagliflozin 300mg (n=156), Placebo (n=156)
Duration of follow-up	52 weeks
Indirectness	none
Method of analysis	Modified ITT

Additional comments	Primary efficacy analyses were conducted using the modified intent-to-treat (mITT) population (all randomised patients who took ≥ 1 dose of double-blind study drug). Efficacy data were analysed according to randomised treatment with the last observation carried forward (LOCF) approach used to impute missing values. For patients who received rescue therapy, the last postbaseline value prior to initiation of rescue therapy was used for analyses. Safety analyses were conducted in all randomised patients who took ≥ 1 dose of study drug and were analysed according to the predominant treatment received. In this study, the efficacy and safety analysis sets were identical.

496.2. Study arms

496.2.1. Canagliflozin 100 mg (N = 157)

100 mg of canagliflozin once daily for 52 weeks with protocol-specified doses of metformin and sulphonylurea.

496.2.2. Canagliflozin 300 mg (N = 156)

300 mg of canagliflozin once daily for 52 weeks with protocol-specified doses of metformin and sulphonylurea.

496.2.3. Placebo (N = 156)

matching placebo once daily for 52 weeks with protocol-specified doses of metformin and sulphonylurea.

496.3. Characteristics

496.3.1. Arm-level characteristics

Characteristic	Canagliflozin 100 mg (N = 157)	Canagliflozin 300 mg (N = 156)	Placebo (N = 156)
% Male Nominal	48.8	55.8	48.7
Mean age (SD) Mean (SD)	57.4 (10.5)	56.1 (8.9)	56.8 (8.3)
White Nominal	84.1	81.4	82.1

Characteristic	Canagliflozin 100 mg (N = 157)	Canagliflozin 300 mg (N = 156)	Placebo (N = 156)
Black Nominal	3.2	7.1	6.4
Asian Nominal	1.3	0	1.3
Other Nominal	11.5	11.5	10.3
Comorbidities Nominal	NR	NR	NR
Presence of frailty Nominal	NR	NR	NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	9 (5.7)	9.4 (6.4)	10.3 (6.7)
HbA1c (%) Mean (SD)	8.1 (0.9)	8.1 (0.9)	8.1 (0.9)
Cardiovascular risk factors Nominal	NR	NR	NR
Smoking status Nominal	NR	NR	NR
Alcohol consumption Mean (SD)	NR (NR)	NR (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

Characteristic	Canagliflozin 100 mg (N = 157)	Canagliflozin 300 mg (N = 156)	Placebo (N = 156)
Weight Mean (SD)	93.8 (22.6)	93.5 (22)	91.2 (22.6)
BMI Mean (SD)	33.3 (6.3)	33.2 (6.3)	32.7 (6.8)
Number of people with obesity Nominal	NR	NR	NR
Other antidiabetic medication used Nominal	NR	NR	NR
Blood pressure-lowering medication used Nominal	NR	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR	NR
Other treatment being received Nominal	NR	NR	NR

497. Wilding, 2012

Bibliographic Reference	Wilding, J. P.; Woo, V.; Soler, N. G.; Pahor, A.; Sugg, J.; Rohwedder, K.; Parikh, S.; Long-term efficacy of dapagliflozin in patients with type 2 diabetes mellitus receiving high doses of insulin: a randomized trial; Ann Intern Med; 2012; vol. 156 (no. 6); 405-15

497.1. Study details

Secondary publication of another included study- see primary study for details	No
Other publications associated with this study included in review	For 104-week data, see: • Wilding, J. P. H., Woo, V., Rohwedder, K., Sugg, J., Parikh, S., & Dapagliflozin 006 Study Group. (2014). Dapagliflozin in patients with type 2 diabetes receiving high doses of insulin: efficacy and safety over 2 years. *Diabetes, Obesity and Metabolism*, *16*(2), 124-136.
Trial name / registration number	NCT00673231
Study type	Randomised controlled trial (RCT) Double-blinded, placebo-controlled, parallel-group RCT
Study location	International (126 centres in 13 countries: Austria, Bulgaria, Canada, Finland, Germany, Hungary, Netherlands, Romania, Russian Federation, Slovakia, Spain, UK, USA)
Study setting	Outpatient
Study dates	04/2008 to 01/2011
Sources of funding	Sponsored by Bristol-Myers Squibb and AstraZeneca.
Inclusion criteria	• Aged 18-80 years inclusive • Type 2 diabetes diagnosis • BMI≤45 kg/m2 • HbA1c 7.5-10.5% inclusive • Receiving stable insulin dose (mean daily dose ≥30 U with daily insulin requirements varying >10% on no more than 1 occasion in 7 days before randomisation) for more than 8 weeks

	• If receiving additional oral anti-diabetic drugs then if metformin, receiving at least 1500 mg daily metformin (or at least 1/2 max tolerated dose); otherwise for other oral anti-diabetes drugs, receiving at least half daily max dose
Exclusion criteria	• Type 1 diabetes mellitus diagnosis • Symptoms of poorly-controlled diabetes • Calculated creatinine clearance less than 50 mL/min per 1.73 m2 or a measured serum creatinine level greater than 177miu-mol/Lor, if receiving metformin, greater than 133 miu-mol/L for men and at least 124 miu-mol/L for women
Recruitment / selection of participants	Computer-generated block randomisation schedule containing stratum, randomisation code and treatment provided by AstraZeneca, with participants randomly assigned in 2 strata (insulin with or without oral anti-diabetic drugs) in balanced blocks of 4 (goal to have at least 4% participants in insulin-only stratum). Trial personnel, participants, investigators etc. had no access to randomisation schedule except in case of emergency (Sponsor personnel had access at 24 weeks since this was primary outcome timepoint). Participants on other oral anti-diabetic drugs remained on baseline dose with no modifications permitted during trial except when hypoglycaemia concerns despite cessation of insulin therapy.
Intervention(s)	• Dapagliflozin 10 mg daily • Dapagliflozin 5/10 mg daily • Dapagliflozin 2.5 mg daily Oral dapagliflozin 2.5 mg, 5 mg or 10 mg daily, with double dummy (10 mg tablet slightly larger than other doses), for 48 weeks, in addition to insulin with or without other oral anti-diabetic drugs. After 48-wks treatment, participants in 5 mg group, switched to 10 mg daily for 56 weeks, whilst those in 2.5 mg and 10 mg daily groups remained on these doses for 56 weeks.
Cointervention	• Insulin All participants remained on the baseline insulin dose/regimen, with dose kept ±10% unless up-titration clinically indicated (3 fasting self-monitored blood glucose readings from 7 days prior to study visit).
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	Mixed population Not an inclusion/exclusion criteria. Baseline characteristics table reports the percentage of participants with history of cardiovascular disease (≥ condition other than hypertension) as between 31.8 - 42.8% across the four groups.

Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	eGFR ≥30mL/min/1.73m2 Exclusion criteria: calculated creatinine clearance<50 ml/min/1.73 m2
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Comparator	• Placebo Matching placebo daily with double dummy for 104 weeks, in addition to insulin with or without other oral anti-diabetic drugs.
Number of participants	N=808 randomised (N=711 completed 24-wks treatment; N=676 completed 48-wks treatment; N=513 completed 104 weeks treatment)

Duration of follow-up	24, 48 and 104 weeks
Indirectness	None
Method of analysis	Modified ITT mITT analysis for efficacy outcomes (all randomised participants who received at least one dose study medication and non-missing baseline efficacy value for at least one efficacy variable) and safety outcomes (all randomised participants with at least one study drug dose). Participants with missing data included.

497.2. Study arms

497.2.1. Dapagliflozin 10 mg daily (N = 196)

Oral dapagliflozin 10 mg for 104 weeks (48-wks + 56 week extension period), in addition to open-label insulin.

497.2.2. Dapagliflozin 5/10 mg daily (N = 212)

Oral dapagliflozin 5 mg for 48 weeks then 10 mg for 56 weeks, in addition to open-label insulin.

497.2.3. Dapagliflozin 2.5 mg daily (N = 202)

Oral dapagliflozin 2.5 mg for 104 weeks (48-wks + 56 week extension period), in addition to open-label insulin.

497.2.4. Placebo (N = 197)

Matching placebo for 104 weeks, in addition to open-label insulin.

497.3. Characteristics

497.3.1. Arm-level characteristics

Characteristic	Dapagliflozin 10 mg daily (N = 196)	Dapagliflozin 5/10 mg daily (N = 212)	Dapagliflozin 2.5 mg daily (N = 202)	Placebo (N = 197)
% Male	n = 87 ; % = 44.8	n = 100 ; % = 47.4	n = 100 ; % = 49.5	n = 95 ; % = 49.2

Characteristic	Dapagliflozin 10 mg daily (N = 196)	Dapagliflozin 5/10 mg daily (N = 212)	Dapagliflozin 2.5 mg daily (N = 202)	Placebo (N = 197)
Sample size				
Mean age (SD) (years) Mean (SD)	59.3 (8.8)	59.3 (7.9)	59.8 (7.6)	58.8 (8.6)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Asian Sample size	n = 3 ; % = 1.5	n = 3 ; % = 1.4	n = 7 ; % = 3.5	n = 0 ; % = 0
Black/African American Sample size	n = 5 ; % = 2.6	n = 5 ; % = 2.4	n = 3 ; % = 1.5	n = 6 ; % = 3.1
Other Sample size	n = 2 ; % = 1	n = 3 ; % = 1.4	n = 2 ; % = 1	n = 1 ; % = 0.5
White Sample size	n = 184 ; % = 94.8	n = 200 ; % = 94.8	n = 190 ; % = 94.1	n = 186 ; % = 96.4
Comorbidities Nominal	NR	NR	NR	NR
Presence of frailty Nominal	NR	NR	NR	NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	14.2 (7.3)	13.1 (7.8)	13.6 (6.6)	13.5 (7.3)
Cardiovascular risk factors Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
History of hypertension only Sample size	n = 92 ; % = 47.4	n = 110 ; % = 52.1	n = 99 ; % = 49	n = 107 ; % = 55.4
History of one or more cardiovascular diseases (excluding hypertension) Sample size	n = 83 ; % = 42.8	n = 67 ; % = 31.8	n = 82 ; % = 40.6	n = 64 ; % = 33.2

Characteristic	Dapagliflozin 10 mg daily (N = 196)	Dapagliflozin 5/10 mg daily (N = 212)	Dapagliflozin 2.5 mg daily (N = 202)	Placebo (N = 197)
Smoking status Nominal	NR	NR	NR	NR
Alcohol consumption Nominal	NR	NR	NR	NR
Presence of severe mental illness Nominal	NR	NR	NR	NR
People with significant cognitive impairment Nominal	NR	NR	NR	NR
People with a learning disability Nominal	NR	NR	NR	NR
Number of people with obesity Nominal	NR	NR	NR	NR
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Basal insulin Sample size	n = 32 ; % = 16.5	n = 31 ; % = 14.7	n = 29 ; % = 14.4	n = 44 ; % = 22.8
Bolus insulin only Sample size	n = 65 ; % = 33.5	n = 76 ; % = 36	n = 81 ; % = 40.1	n = 60 ; % = 31.1
Basal-bolus insulin Sample size	n = 97 ; % = 50	n = 104 ; % = 49.3	n = 92 ; % = 45.5	n = 89 ; % = 46.1
No oral anti-diabetic drug Sample size	n = 96 ; % = 49.5	n = 104 ; % = 49.3	n = 104 ; % = 51.5	n = 96 ; % = 49.7
Metformin only Sample size	n = 83 ; % = 42.8	n = 78 ; % = 37	n = 80 ; % = 39.6	n = 78 ; % = 40.4

Characteristic	Dapagliflozin 10 mg daily (N = 196)	Dapagliflozin 5/10 mg daily (N = 212)	Dapagliflozin 2.5 mg daily (N = 202)	Placebo (N = 197)
Metformin + a sulphonylurea Sample size	n = 8 ; % = 4.1	n = 12 ; % = 5.7	n = 13 ; % = 6.4	n = 13 ; % = 6.7
Metformin + a thiazolidinedione Sample size	n = 0 ; % = 0	n = 2 ; % = 0.9	n = 1 ; % = 0.5	n = 1 ; % = 0.5
Metformin + other oral anti-diabetic drug Sample size	n = 1 ; % = 0.5	n = 2 ; % = 0.9	n = 1 ; % = 0.5	n = 1 ; % = 0.5
Other drugs or drug combinations Sample size	n = 6 ; % = 3.1	n = 13 ; % = 6.2	n = 3 ; % = 1.5	n = 4 ; % = 2.1
Blood pressure-lowering medication used Sample size	n = 163 ; % = 83.2	n = 170 ; % = 80.2	n = 170 ; % = 84.2	n = 154 ; % = 78.2
Statins/lipid-lowering medication used Sample size	n = 134 ; % = 68.4	n = 141 ; % = 66.5	n = 141 ; % = 69.8	n = 122 ; % = 61.9
Other treatment being received Acetylsalicylic acid Sample size	n = 108 ; % = 55.1	n = 104 ; % = 49.1	n = 104 ; % = 51.5	n = 90 ; % = 45.7

Baseline data is for the following number of participants: DAPA 10 mg, N=194; DAPA 5/10 mg, N=211; DAPA 2.5 mg, N=202; Placebo, N=193.

498. Wiviott, 2018

Bibliographic Reference	Wiviott, Stephen D; Raz, Itamar; Bonaca, Marc P; Mosenzon, Ofri; Kato, Eri T; Cahn, Avivit; Silverman, Michael G; Bansilal, Sameer; Bhatt, Deepak L; Leiter, Lawrence A; McGuire, Darren K; Wilding, John Ph; Gause-Nilsson, Ingrid Am; Langkilde, Anna Maria; Johansson, Peter A; Sabatine, Marc S; The design and rationale for the Dapagliflozin Effect on Cardiovascular Events (DECLARE)-TIMI 58 Trial.; American heart journal; 2018; vol. 200; 83-89

498.1. Study details

Secondary publication of another included study- see primary study for details	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	Mosenzon, Ofri, Wiviott Stephen, D, Cahn, Avivit et al. (2019) 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 7(8): 606-617 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

499. Wiviott, 2019

Bibliographic Reference	Wiviott, Stephen, D.; Raz, Itamar; Bonaca, Marc, P.; Mosenzon, Ofri; Kato, Eri, T.; Cahn, Avivit; Silverman, Michael, G.; Zelniker, Thomas, A.; Kuder, Julia, F.; Murphy, Sabina, A.; Bhatt, Deepak, L.; Leiter, Lawrence, A.; McGuire, Darren, K.; Wilding, John, P. H.; Ruff, Christian, T.; Gause-Nilsson, Ingrid, A.M.; Fredriksson, Martin; Johansson, Peter, A.; Langkilde, Anna-Maria; Sabatine, Marc, S.; DECLARE-TIMI 58 Investigators, 58; Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes.; The New England journal of medicine; 2019; vol. 380 (no. 4); 347-357

499.1. Study details

Secondary publication of another included study- see primary study for details	No additional information. This study is the parent trial of the DECLARE-TIMI trial and so all primary data is reported in this record.
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 • Mosenzon, Ofri, Wiviott Stephen, D, Cahn, Avivit et al. (2019) 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 7(8): 606-617 • 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/NCT01730534
Study type	Randomised controlled trial (RCT)
Study location	33 countries (regions: N. America; Europe; Latin America; Asia-Pacific)

Study setting	882 sites (not specified)
Study dates	Not reported
Sources of funding	Funded by AstraZeneca
Inclusion criteria	Provision of informed consent prior to any study specific procedures (including run-in); female or male aged at least 40 years; diagnosed with type 2 diabetes mellitus, defined as: prior documentation of type 2 diabetes and/or treatment with anti-hyperglycaemic medication and/or diet and/or ADA criteria: fasting >126 mg/dL (7.0 mmol/L) or HbA1c at least 6.5% or 2-h plasma glucose at least 200mg/dL (11.1 mmol/L) during an oral glucose tolerance test, or a random plasma glucose at least 200 mg/dL (11.1 mmol/L) in people with classic symptoms of hyperglycaemia or hyperglycaemic crisis. In the absence of inequivalve hyperglycaemia, results should be confirmed by repeat testing; high risk for cardiovascular event defined as having either established cardiovascular disease and/or multiple risk factors: established cardiovascular disease defined as any of the following: ischaemic heart disease (any of the following): documented myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, objective findings of coronary stenosis (at least 50%) in at least 2 coronary artery territories) (ie, left anterior descending, ramus intermedius, left circumflex, right coronary artery) involving main vessel, a major branch or a bypass graft); cerebrovascular disease (any of the following); documented ischaemic stroke (known transient ischaemic attack, primary intracerebral haemorrhage or subarachnoid haemorrhage do not qualify), carotid stenting or endarterectomy; peripheral arterial disease (any of the following): peripheral arterial intervention, stenting or surgical revascularisation, lower extremity amputation as a result of peripheral arterial obstructive disease, current symptoms of intermittent claudication AND ankle/brachial index (ABI) <0.90 documented within last 12 months; OR no known cardiovascular disease AND at least two cardiovascular risk factors in addition to T2DM, defined as: age at least 55 years in men and at least 60 in women AND presence of at least 1 of the following additional risk factors: dyslipidaemia (at least one of the following): LDL-cholesterol >130mg/dL (3.36 mmol?L) within last 12 months), on lipid lowering therapy prescribed by a physician for hypercholesterolaemia for greater than 12 months. This should be veriied by a previous documentation of a lab value of LDL-C >130mg/dL; hypertension (at least one of the following): BP >140/90 mmHg at enrollment visit. The person may have both an elevated systolic and diastolic BP on both measurements, on anti-hypertensive therapy prescribed by a physician for blood pressure lowering; current tobacco use (5 cigarettes/day or more for at least 1 year at randomisation); women of child bearing potential must take precautions to avoid pregnancy throughout the study and for 4 weeks after the intake of the last dose: they must have a negative urine pregnancy test, they must be wiling to use a medically accepted method of contraception that is considered reliable in the judgement of the investigator.
Exclusion criteria	Current or recent (within 24 months) treatment with pioglitazone and/or use of pioglitazone for a total of 2 years or more during lifetime; current or recent (within 12 month) treatment with rosiglitazone); previous treatment

	with any SGLT2 inhibitor; any patient currently receiving chronic (>30 consecutive days) treatment with an oral steroid at a dose equivalent to oral prednisolone at least 10mg (e.g. betamethasone at least 1.2mg, dexamethasone at least 1.5mg, hydrocortisone at least 40mg) per day; acute cardiovascular event (for example: acute coronary syndrome, transient ischaemic attack, stroke, any revascularisation, decompensated heart failure, sustained ventricular tachycardia <8 weeks prior to randomisation. People with acute cardiovascular events can be enrolled in the run-in period as long as randomisation does not occur within 8 weeks of the event; systolic blood pressure >180 or diastolic blood pressure >100mmHg at randomisation. The person should be excluded if either the systolic or diastolic blood pressure is elevated on both measurements. Diagnosis of type 1 diabetes mellitus, MODY or secondary diabetes mellitus; history of bladder cancer or history of radiation therapy to the lower abdomen or pelvis at any time; history of any other malignancy within 5 years (with the exception of successfully treated non-melanoma skin cancers); chronic cystitis and/or recurrent urinary tract infections (3 or more in the last year); any conditions that, in the opinion of the investigator, may render the person unable to complete the study including but not limited to cardiovascular (NYHA class IV CHF, recurrent ventricular arrhythmias) or non-cardiovascular disease (e.g., active malignancy with the exception of basal cell carcinoma, cirrhosis, chronic lung disease, severe autoimmune disease) and/or a likely fatal outcome within 5 years; pregnant or breast-feeding patients; involvement in the planning and/or conduct of the study or other dapagliflozin studies (applies to AZ, BMS, Hadassah and Thombolysis in Myocardial Infarction or representative staff and/or staff at the study site); previous enrolment or randomisation in the present study; active participation in another clinical study with IP and/or investigational device; individuals at risk from poor protocol or medication compliance during run-in period (reasonable compliance defined as 80-120%, unless a reason for non-compliance is judged acceptable by the investigator). If for any reason, the investigator believes the person will not tolerate or be compliant with the procedures, the person should not be randomised and considered a run-in failure; HbA1c greater than 12 and less than 6.5 from the central laboratory; AST or ALT >3x the upper limit of normal or total bilirubin >2.5 x upper limit of normal; haematuria (confirmed by microscopy at visit 1) with no explanation as judged by the investigator up to randomisation. If bladder cancer is identified, the person is not eligible to participate; any reason the investigator believes the person is not likely to be compliant with the study medication and protocol.
Recruitment / selection of participants	Multinational, phase 3 trial. People recruited across 882 sites in 33 countries.
Intervention(s)	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.

Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Around 10% of people had heart failure
Strata 2: People with atherosclerotic cardiovascular disease	Mixed population Eligible patients had multiple risk factors for atherosclerotic cardiovascular disease (without CVD) or had established atherosclerotic cardiovascular disease (defined as clinically evident ischemic heart disease, ischemic cerebrovascular disease, or peripheral artery disease). 6974 patients (40.6%) with established atherosclerotic cardiovascular disease and 10,186 (59.4%) with multiple risk factors for atherosclerotic cardiovascular disease
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Included people with "a creatinine clearance of 60 ml or more per minute", otherwise unclear. Baseline characteristics give eGFR categories but CKD unclear.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	People at higher risk of developing cardiovascular disease Either with cardiovascular disease or at least 2 risk factors
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear

Subgroup 4: People with obesity	Mixed population
Subgroup 5: eGFR category at baseline	eGFR ≥30mL/min/1.73m2 Baseline characteristics show that only 7% were <60ml/min/1.73m2 (protocol states cut-off of 20%)
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	In main study: For MACE and cardiovascular death or hospitalisation for heart failure: atherosclerotic cardiovascular disease, multiple risk factors with no evidence of atherosclerotic cardiovascular disease, history of heart failure, eGFR values.
Comparator	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.
Number of participants	17157
Duration of follow-up	Median: 4.2 years
Indirectness	No additional information.
Method of analysis	ITT
Additional comments	Hazard ratios, 95% confidence intervals, and P values for time-to-event analyses are reported for the primary outcomes and were derived from a Cox proportional hazards model in the overall population

499.2. Study arms

499.2.1. 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.

499.2.2. 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.

499.3. Characteristics

499.3.1. Arm-level characteristics

Characteristic	Dapagliflozin (N = 8582)	Placebo (N = 8578)
% Male Sample size	n = 5411 ; % = 63.1	n = 5324 ; % = 62.1
Mean age (SD) (years) Mean (SD)	63.9 (6.8)	64 (6.8)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 6843 ; % = 79.7	n = 6810 ; % = 79.4
Black Sample size	n = 295 ; % = 3.4	n = 308 ; % = 3.6
Asian Sample size	n = 1148 ; % = 13.4	n = 1155 ; % = 13.5
Other Sample size	n = 296 ; % = 3.4	n = 305 ; % = 3.6
Comorbidities Sample size	n = NA ; % = NA	n = NA ; % = NA
Established atherosclerotic cardiovascular disease Sample size	n = 3474 ; % = 40.5	n = 3500 ; % = 40.8
History of coronary artery disease Sample size	n = 2824 ; % = 32.9	n = 2834 ; % = 33
History of peripheral artery disease	n = 522 ; % = 6.1	n = 503 ; % = 5.9

Characteristic	Dapagliflozin (N = 8582)	Placebo (N = 8578)
Sample size		
History of cerebrovascular disease Sample size	n = 653 ; % = 7.6	n = 648 ; % = 7.6
History of heart failure Sample size	n = 852 ; % = 9.9	n = 872 ; % = 10.2
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed (years) Median (IQR)	11 (6 to 16)	10 (6 to 16)
HbA1c (%) Mean (SD)	8.3 (1.2)	8.3 (1.2)
Cardiovascular risk factors Mean (SD)	NA (NA)	NA (NA)
Blood pressure (mmHg) Mean (SD)	NA (NA)	NA (NA)
Systolic blood pressure Mean (SD)	135.1 (15.3)	134.8 (15.5)
Heart rate Mean (SD)	NR (NR)	NR (NR)
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Dapagliflozin (N = 8582)	Placebo (N = 8578)
Weight Mean (SD)	NR (NR)	NR (NR)
BMI (kg/m2) Mean (SD)	32.1 (6)	32 (6.1)
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR
Cholesterol and lipid levels Mean (SD)	NR (NR)	NR (NR)
Albumin creatinine ratio Sample size	n = NR ; % = NR	n = NR ; % = NR
eGFR mL/min/1.73m2 Mean (SD)	85.4 (15.8)	85.1 (16)
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Insulin Sample size	n = 3567 ; % = 41.6	n = 3446 ; % = 40.2
Metformin Sample size	n = 7020 ; % = 81.8	n = 7048 ; % = 82.2
Sulfonylurea Sample size	n = 3615 ; % = 42.1	n = 3707 ; % = 43.2
DPP-4 Sample size	n = 1418 ; % = 16.5	n = 1470 ; % = 17.1
GLP-1 receptor agonist Sample size	n = 397 ; % = 4.6	n = 353 ; % = 4.1
Antiplatelet agents Sample size	n = 5245 ; % = 61.1	n = 5242 ; % = 61.1
ACE inhibitors or ARB Sample size	n = 6977 ; % = 81.3	n = 6973 ; % = 81.3

Characteristic	Dapagliflozin (N = 8582)	Placebo (N = 8578)
Beta-blocker Sample size	n = 4498 ; % = 52.4	n = 4532 ; % = 52.8
Statin or ezetimibe Sample size	n = 6432 ; % = 74.9	n = 6436 ; % = 75
Diuretics Sample size	n = 3488 ; % = 40.6	n = 3479 ; % = 40.6
Blood pressure-lowering medication used See Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Statins/lipid-lowering medication used See Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Other treatment being received See Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA

500. Wu, 2014

Bibliographic Reference	Wu, S.; Li, X.; Zhang, H.; Effects of metformin on endothelial function in type 2 diabetes; Exp Ther Med; 2014; vol. 7 (no. 5); 1349-1353

500.1. Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.
Trial name / registration number	No additional information.
Study location	China
Study setting	Hospital
Study dates	Study dates not specified but authors state that patients admitted to hospital between September 2010 and August 2012 were recruited into the study.
Sources of funding	No additional information.
Inclusion criteria	Patients treated with a diabetes diet, exercise and hypoglycemic drugs (without the use of biguanides and thiazolidinediones) and had fasting blood glucose levels of >7.8 mmol/l and/or 2 h postprandial blood glucose (2hPBG) levels of >10.0 mmol/l.
Exclusion criteria	Patients with Type 1 diabetes mellitus, hypertension, hyperlipidemia, kidney disease, infection, heart failure, thyroid dysfunction, diabetic ketoacidosis and those who smoked.
Recruitment / selection of participants	Patients with type 2 diabetes were recruited and randomly allocated to metformin (300 mg 3 times/day) and pioglitazone 15 mg once daily.
Intervention(s)	Metformin 500 mg three times daily

	Administered orally.
Cointervention	Hypoglycemic drugs (without the use of biguanides and thiazolidinediones) • Sulphonylureas • Non-sulfonylurea insulin secretagogues • Glucosidase inhibitors • Insulin
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure People with heart failure were excluded from the study.
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 People with kidney disease were excluded from the study.
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
Comparator	Pioglitazone 15 mg once daily
Number of participants	N=93
Duration of follow-up	12-month
Indirectness	No additional information.
Method of analysis	Not stated/unclear

500.2. Study arms

500.2.1. Metformin 1500 mg daily (N = 47)

Administered orally.

500.2.2. Pioglitazone 15 mg daily (N = 46)

Administered orally.

500.3. Characteristics

500.3.1. Arm-level characteristics

Characteristic	Metformin 1500 mg daily (N = 47)	Pioglitazone 15 mg daily (N = 46)
% Male No of events	n = 17 ; % = 50	n = 17 ; % = 51.5
Mean age (SD) (years) Mean (SD)	60.1 (9.6)	60.3 (9.7)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed Nominal	NR	NR
Smoking status Nominal	NR	NR
Alcohol consumption Nominal	NR	NR
Presence of severe mental illness Nominal	NR	NR
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 No of events	n = 12 ; % = 25.53	n = 11 ; % = 23.91

Characteristic	Metformin 1500 mg daily (N = 47)	Pioglitazone 15 mg daily (N = 46)
Non-sulfonylurea insulin secretagogues No of events	n = 10 ; % = 21.28	n = 9 ; % = 19.57
Glucosidase inhibitors No of events	n = 26 ; % = 55.32	n = 25 ; % = 54.35
Insulin No of events	n = 13 ; % = 27.66	n = 12 ; % = 26.09
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

501. Wulffele, 2002

Bibliographic Reference	Wulffele, Michiel G; Kooy, Adriaan; Lehert, Philippe; Bets, Daniel; Ogterop, Jeles C; Borger van der Burg, Bob; Donker, Ab J M; Stehouwer, Coen D A; Combination of insulin and metformin in the treatment of type 2 diabetes.; Diabetes care; 2002; vol. 25 (no. 12); 2133-40

501.1. Study details

Secondary publication of another included study- see primary study for details	Kooy A, de Jager J, Lehert P, Bets D, Wulffelé MG, Donker AJ, Stehouwer CD. Long-term effects of metformin on metabolism and microvascular and macrovascular disease in patients with type 2 diabetes mellitus. Arch Intern Med. 2009 Mar 23;169(6):616-25. doi: 10.1001/archinternmed.2009.20. PMID: 19307526.
Strata 1: People with type 2 diabetes mellitus and heart failure	People without 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

502. Wysham, 2014

Bibliographic Reference	Wysham, C.; Blevins, T.; Arakaki, R.; Colon, G.; Garcia, P.; Atisso, C.; Kuhstoss, D.; Lakshmanan, M.; Efficacy and safety of dulaglutide added onto pioglitazone and metformin versus exenatide in type 2 diabetes in a randomized controlled trial (AWARD-1); Diabetes Care; 2014; vol. 37 (no. 8); 2159-2167

502.1. 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	AWARD-1/NCT01064687
Study type	Randomised controlled trial (RCT)
Study location	USA
Study setting	Clinic and hospital
Study dates	02/2010 - 05/2012
Sources of funding	Eli Lilly and company
Inclusion criteria	Eligible patients at screening were $18 years of age with a BMI between 23 and 45 kg/m2 and HbA1c between 7.0% and 11.0% (53–97 mmol/mol) on oral antihyperglycemic medication (OAM) monotherapy or between 7.0% and 10.0% (53–86 mmol/mol) on combination oral antihyperglycaemic therapy.
Exclusion criteria	Taking GLP-1 receptor agonists during the 3 months before screening or were on long-term insulin therapy.

Recruitment / selection of participants	Participants aged ≥18 years of age with a BMI between 23 and 45 kg/m2 and HbA1c between 7.0% and 11.0% (53–97 mmol/mol) on oral antihyperglycaemic medication monotherapy or between 7.0% and 10.0% (53–86 mmol/mol) on combination oral antihyperglycaemic therapy.
Intervention(s)	Exenatide 10 µg twice daily Administered subcutaneously.
Cointervention	Pioglitazone (30 - 45 mg/day) + metformin (1,500 - 3,000 mg/day) Administered orally.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear

Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	
Comparator	Dulaglutide 1.5 mg Dulaglutide 0.75 mg Administered subcutaneously.
Number of participants	N=976
Duration of follow-up	52-week
Indirectness	No additional information.
Method of analysis	Modified ITT
Additional comments	Safety and efficacy analysis included all patients randomised who received at least one dose of study medication.

502.2. Study arms

502.2.1. Dulaglutide 1.5 mg once weekly (N = 279)

Administered subcutaneously

502.2.2. Dulaglutide 0.75 mg once weekly (N = 280)

Administered subcutaneously

502.2.3. Exenatide 10 µg twice daily (N = 276)

Administered subcutaneously

502.2.4. Placebo twice daily (N = 141)

Administered subcutaneously

502.3. Characteristics

502.3.1. Arm-level characteristics

Characteristic	Dulaglutide 1.5 mg once weekly (N = 279)	Dulaglutide 0.75 mg once weekly (N = 280)	Exenatide 10 µg twice daily (N = 276)	Placebo twice daily (N = 141)
% Male No of events	n = 163 ; % = 58	n = 168 ; % = 60	n = 156 ; % = 57	n = 83 ; % = 59
Mean age (SD) (year) Mean (SD)	56 (10)	56 (9)	55 (10)	55 (10)
Hispanic or Latino No of events	n = 93 ; % = 33	n = 102 ; % = 36	n = 91 ; % = 33	n = 45 ; % = 32
American Indian No of events	n = 40 ; % = 14	n = 37 ; % = 13	n = 38 ; % = 14	n = 20 ; % = 14
Asian No of events	n = 6 ; % = 2	n = 8 ; % = 3	n = 4 ; % = 1	n = 6 ; % = 4
Black No of events	n = 24 ; % = 9	n = 24 ; % = 9	n = 18 ; % = 7	n = 10 ; % = 7
Multiple No of events	n = 3 ; % = 1	n = 3 ; % = 1	n = 3 ; % = 1	n = 2 ; % = 1
Native Hawaiian No of events	n = 1 ; % = 1	n = 1 ; % = 1	n = 1 ; % = 1	n = 0 ; % = 0

Characteristic	Dulaglutide 1.5 mg once weekly (N = 279)	Dulaglutide 0.75 mg once weekly (N = 280)	Exenatide 10 µg twice daily (N = 276)	Placebo twice daily (N = 141)
White No of events	n = 205 ; % = 74	n = 207 ; % = 74	n = 211 ; % = 76	n = 103 ; % = 73
Presence of frailty Nominal	NR	NR	NR	NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	9 (6)	9 (5)	9 (6)	9 (6)
Smoking status Nominal	NR	NR	NR	NR
Alcohol consumption Nominal	NR	NR	NR	NR
Presence of severe mental illness Nominal	NR	NR	NR	NR
People with significant cognitive impairment Nominal	NR	NR	NR	NR
People with a learning disability Nominal	NR	NR	NR	NR
Number of people with obesity Nominal	NR	NR	NR	NR
Blood pressure-lowering medication used Nominal	NR	NR	NR	NR

503. Xiao, 2015

Bibliographic Reference	Xiao, C. C.; Ren, A.; Yang, J.; Ye, S. D.; Xing, X. N.; Li, S. M.; Chen, C.; Chen, R. P.; Effects of pioglitazone and glipizide on platelet function in patients with type 2 diabetes; Eur Rev Med Pharmacol Sci; 2015; vol. 19 (no. 6); 963-70

503.1. 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	Anhui, China
Study setting	Outpatient
Study dates	03/2008 to 12/2011
Sources of funding	Financially supported by the Natural Science Foundation of Anhui Province (09B117)
Inclusion criteria	• Diagnosed with type 2 diabetes for less than 12 months • HbA1c>7% • Receiving metformin monotherapy
Exclusion criteria	• History of diabetic ketoacidosis • Family history of cancer • Heart failure • Impaired kidney function (CCR<80 mL/min)

	• Impaired liver function (baseline aminotransferase more than 2 x upper limit of normal) • Pregnant women or those of childbearing potential • Anemia • Treatment using aspirin, clopidogrel, heparin, glucocorticoid, nonsteroidal anti-inflammatory drugs, fibrates, ACE inhibitors or angiotension II receptor agonist during last 2 weeks before study entry.
Recruitment / selection of participants	Participants recruited from Anhui Provincal Hospital and entered 4-week run-in period in which metformin monotherapy (at least 1500 mg/daily) was continued. Participants assessed after run-in period and only those with HbA1c≥7% were randomised using computer-generated table and sequentially numbered envelopes. Results for insulin arm not reported.
Intervention(s)	• Pioglitazone 15-45 mg daily Oral pioglitazone 15-45 mg daily for 24 weeks in addition to metformin monotherapy.
Cointervention	• Metformin All participants received metformin (at least 1500 mg daily) for 24 weeks.
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Heart failure stated in exclusion criteria.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Not an inclusion/exclusion criteria.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Exclusion criteria state "impaired kidney function (Ccr<80ml/min)." No further information. No information in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear

Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Comparator	• Glipizide 5-10 mg daily Oral glipizide 5-10 mg daily for 24 weeks in addition to metformin monotherapy.
Number of participants	N=120
Duration of follow-up	24 weeks
Indirectness	None
Method of analysis	Modified ITT Appears to be mITT completer analysis (randomised participants who completed trial, excludes those lost to follow up)
Additional comments	Data for insulin arm is not reported in this article.

503.2. Study arms

503.2.1. Pioglitazone 15-45 mg daily (N = 40)

Oral pioglitazone 15-45 mg daily, for 24 weeks, in addition to metformin 1500 mg/day.

503.2.2. Glipizide 5-10 mg daily (N = 40)

Oral glipizide 5-10 mg daily, for 24 weeks, in addition to metformin 1500 mg/day.

503.2.3. Insulin (N = 40)

Up-titrated prandial insulin for 24 weeks, in addition to metformin 1500 mg/day.

503.3. Characteristics

503.3.1. Arm-level characteristics

Characteristic	Pioglitazone 15-45 mg daily (N = 40)	Glipizide 5-10 mg daily (N = 40)	Insulin (N = 40)
% Male Sample size	n = 20 ; % = 58.8	n = 21 ; % = 58.3	n = NR ; % = NR
Mean age (SD) Mean (SD)	54.15 (4.91)	53.56 (3.61)	NR (NR)
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)	NR (NR)	NR (NR)	NR (NR)
Cardiovascular risk factors Nominal	NR	NR	NR

Characteristic	Pioglitazone 15-45 mg daily (N = 40)	Glipizide 5-10 mg daily (N = 40)	Insulin (N = 40)
Smoking status Number of participants who smoke Sample size	n = 24 ; % = 70.6	n = 22 ; % = 61.1	n = NR ; % = NR
Alcohol consumption Nominal	NR	NR	NR
Presence of severe mental illness Nominal	NR	NR	NR
People with significant cognitive impairment Nominal	NR	NR	NR
People with a learning disability Nominal	NR	NR	NR
Number of people with obesity Nominal	NR	NR	NR
Other antidiabetic medication used Nominal	NR	NR	NR
Blood pressure-lowering medication used Nominal	NR	NR	NR
Statins/lipid-lowering medication used Sample size	n = 12 ; % = 35.3	n = 15 ; % = 41.7	n = NR ; % = NR
Other treatment being received Nominal	NR	NR	NR

Baseline characteristics data for pioglitazone group, N=34 and glipizide group, N=36.

504. Xiao, 2016

Bibliographic Reference	Xiao, X.; Cui, X.; Zhang, J.; Han, Z.; Xiao, Y.; Chen, N.; Li, B.; Cheng, M.; Gao, H.; Tang, K.; Effects of sitagliptin as initial therapy in newly diagnosed elderly type 2 diabetics: A randomized controlled study; Exp Ther Med; 2016; vol. 12 (no. 5); 3002-3008

504.1. 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) Parallel-group RCT (not reported whether open-label or blinded)
Study location	Qilu Hospital, Shandong University, Jinan, China
Study setting	Outpatient
Study dates	03/2012 to 08/2013
Sources of funding	Supported by grants from special funds for scientific research projects of clinical medicine of the Chinese Medical Association (grant no. 13060990484), the Medicine Health Care Science and Technology Development Project Program of Shandong Province (grant no. 2013WSC02036), Science Foundation of Qilu Hospital of Shandong University (grant no. 2015QLMS11) and Fundamental Research Funds of Shandong University (26010175616012).
Inclusion criteria	• Newly diagnosed with type 2 diabetes • Aged 45-80 years inclusive • Results from oral glucose tolerance test in accordance with WHO 1999 guidance • Negative plasma glutamic acid decarboxylase antibody, islet cell antibody and insulin autoantibody test results

	• No previous sue of hypoglycaemic drugs
Exclusion criteria	• Fasting blood glucose >16.7 mmol/l or HbA1c >10% • Acute diabetic complications such as ketoacidosis • Severe hepatic, renal, cerebral-cardiovascular or gastrointestinal co-morbidities • Allergies to metformin hydrochloride, sitagliptin phosphate or glimepiride.
Recruitment / selection of participants	Trial part of larger case control study of 129 newly diagnosed type 2 diabetes patients in Jinan, China. Reports that 86 participants ≥65 years-old were assigned to randomised trial but results only reported for 41 participants who used a continuous blood glucose monitoring system.
Intervention(s)	• Glimepiride 4 mg daily Oral glimepiride started at 1 mg daily and increased to 4 mg daily according to glucose level for 24 weeks in addition to metformin 1500 mg daily.
Cointervention	• Metformin 1500 mg daily All participants received oral metformin 750 mg (250 mg three times) daily, increased to 1500 mg (500 mg three times) daily.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear The exclusion criteria state: "severe hepatic, renal, cerebral-cardiovascular or gastrointestinal co-morbidities". No further information. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear The exclusion criteria state: "severe hepatic, renal, cerebral-cardiovascular or gastrointestinal co-morbidities". No further information. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear The exclusion criteria state: "severe hepatic, renal, cerebral-cardiovascular or gastrointestinal co-morbidities". No further information. No information in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear

Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Comparator	• Sitagliptin 100 mg daily Oral sitagliptin 100 mg daily for 24 weeks, in addition to metformin 1500 mg daily.
Number of participants	N=41 (article reports N=86 randomised but not clear how many were assigned to each group)
Duration of follow-up	24 weeks
Indirectness	None
Method of analysis	Not stated/unclear Not reported. N=86 participants reported as being randomised but results only reported for N=41 participants who had continuous glucose monitoring.

504.2. Study arms

504.2.1. Glimepiride 4 mg daily (N = 18)

Oral glimepiride 4 mg daily for 24 weeks, in addition to metformin 1500 mg daily.

504.2.2. Sitagliptin 100 mg daily (N = 23)

Oral sitagliptin 100 mg daily for 24 weeks, in addition to metformin 1500 mg daily.

504.3. Characteristics

504.3.1. Arm-level characteristics

Characteristic	Glimepiride 4 mg daily (N = 18)	Sitagliptin 100 mg daily (N = 23)
% Male Sample size	n = 10 ; % = 55.6	n = 13 ; % = 56.5
Mean age (SD) (years) Mean (SD)	69.1 (6.5)	68.7 (6.3)
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

Characteristic	Glimepiride 4 mg daily (N = 18)	Sitagliptin 100 mg daily (N = 23)
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

505. Xu, 2017

Bibliographic Reference	Xu, W.; Mu, Y.; Zhao, J.; Zhu, D.; Ji, Q.; Zhou, Z.; Yao, B.; Mao, A.; Engel, S. S.; Zhao, B.; Bi, Y.; Zeng, L.; Ran, X.; Lu, J.; Ji, L.; Yang, W.; Jia, W.; Weng, J.; Efficacy and safety of metformin and sitagliptin based triple antihyperglycemic therapy (STRATEGY): a multicenter, randomized, controlled, non-inferiority clinical trial; Sci China Life Sci; 2017; vol. 60 (no. 3); 225-238

505.1. 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	STRATEGY [NCT 01709305]
Study type	Randomised controlled trial (RCT)
Study location	237 centres across 25 provinces in China
Study setting	NR
Study dates	November 2012 to April 2015
Sources of funding	Merck & Co., Inc.
Inclusion criteria	• Eligibility for metformin monotherapy run-in: People with an HbA1c ≥7 % and ≤10% who either were on metformin monotherapy, metformin dual therapy or other OHAs (AGI or SUs, but not TZD). • Eligibility for stage 2 following dual therapy with stable metformin/sitagliptin: Participants with HbA1c ≥7.0% and ≤10.0% at week 16 and a FFSG ≥7.2 and ≤15.6 mmol L-1 at week 20.

Exclusion criteria	NR
Recruitment / selection of participants	• Run-in period: Participants on metformin monotherapy ≥1,500 mg per day for at least 10 weeks entered a 2-week metformin ≥1,500 mg per day run-in, after which metformin/sitagliptin dual therapy was initiated. • Run-in period: Participant on low dose metformin monotherapy (<1,500 mg/day), other OHAs, or low-dose (<1,500 mg per day) dual therapy entered a metformin monotherapy titration/dose-stabilization period for 6 to 8 weeks. After 6 to 8 weeks on metformin ≥1,500 mg per day, participants with an HbA1c ≥7 % and ≤10% continued with a 2-week metformin run-in before metformin/sitagliptin dual therapy was initiated. • Stage 1 (dual therapy): Participants received metformin ≥1,500 mg per day + sitagliptin 100 mg per day for 20 weeks. Participants with HbA1c ≥7.0% and ≤10.0% at week 16 and a FFSG ≥7.2 and ≤15.6 mmol L-1 at week 20 were eligible for randomisation for the triple-therapy study.
Intervention(s)	Glimepiride at initial dose of 1 mg per day up-titrated to a maximal dose of 6 mg per day
Cointervention	Metformin ≥1,500 mg per day + sitagliptin 100 mg
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and high	Not stated/unclear

cardiovascular risk	
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	NA
Comparator	Gliclazide at initial does of 30 mg per day up-titrated to 120 mg per day based on the degree of glycaemic control
Number of participants	7880 participants were assessed for eligibility and 5535 enrolled into metformin/sitagliptin dual therapy. 2577 completed the dual therapy and did not achieve the HbA1c goal. 2202 participants were randomised. Of 551 participants allocated to glimepiride, 51 discontinued treatment and 500 completed the study. Of 552 participants allocated to gliclazide, 47 discontinued treatment and 505 completed the study.
Duration of follow-up	24 weeks
Indirectness	Directly applicable
Method of analysis	Per protocol Analysis used for the primary efficacy outcome of HbA1c. Defined as excluding participants with major protocol violations that could potentially affect or confound measures of efficacy based on clinical assessment.

	Analysis was based on a constrained longitudinal data analysis (cLDA) model and no missing data were imputed. Other Full analysis set: Used for secondary efficacy measures including weight change. Defined as participants who had received at least one study dose post-randomisation, and at least one outcome measurement, either at baseline or after baseline. Missing data were imputed with LOCF. All patients as treated (APaT) population: Used for safety analysis. Defined as all participants enrolled that received at least one dose of the study treatment where participants were included in the treatment group corresponding to the study treatment they received.
Additional comments	NA

505.2. Study arms

505.2.1. Glimepiride (N = 551)

505.2.2. Gliclazide (N = 552)

505.3. Characteristics

505.3.1. Arm-level characteristics

Characteristic	Glimepiride (N = 551)	Gliclazide (N = 552)
% Male Sample size	n = 296 ; % = 53.9	n = 303 ; % = 55.1
Mean age (SD) Mean (SD)	53.5 (9.8)	53.3 (9.9)
Ethnicity Nominal	NR	NR
Comorbidities	NR	NR

Characteristic	Glimepiride (N = 551)	Gliclazide (N = 552)
Nominal		
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed Mean (SD)	5.8 (4.4)	5.5 (4.2)
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 (mg/k2) Mean (SD)	25.9 (3.3)	25.8 (3.5)
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

506. Yabe, 2020

Bibliographic Reference	Yabe, Daisuke; Nakamura, Jiro; Kaneto, Hideaki; Deenadayalan, Srikanth; Navarria, Andrea; Gislum, Mette; Inagaki, Nobuya; Safety and efficacy of oral semaglutide versus dulaglutide in Japanese patients with type 2 diabetes (PIONEER 10): an open-label, randomised, active-controlled, phase 3a trial.; The lancet. Diabetes & endocrinology; 2020; vol. 8 (no. 5); 392-406

506.1. Study details

Secondary publication of another included study- see primary study for details	No
Trial name / registration number	PIONEER 10/NCT03015220
Study type	Randomised controlled trial (RCT) Open-label active-controlled, parallel group randomised trial.
Study location	Japan (36 clinics and hospitals)
Study setting	Outpatient
Study dates	01/2017 to 05/2017
Sources of funding	Funded by Novo Nordisk, Denmark.
Inclusion criteria	• Aged 20 years or more • Type 2 diabetes diagnosis at least 60 days before screening • HbA1c 7-10.5% inclusive • Receiving oral antidiabetic monotherapy (sulphonylurea, glinide, thiazolidinedione, AG-inhibitor, SGLT-inhibitor) at stable dose for at least 60 days before screening
Exclusion criteria	• Known or suspected hypersensitivity to trial product(s) or related products • Previous participation (i.e. signed informed consent) in this trial • Female who is pregnant, breast-feeding, intends to become pregnant, or is of child-bearing potential and not using an adequate contraceptive method (abstinence (not having sex), diaphragm,

	condom (by the partner), intrauterine device, sponge, spermicide, or oral contraceptives) • Receipt of any investigational medicinal product within 90 days before screening • Any disorder, which in the investigator's opinion might jeopardise subject's safety or compliance with the protocol • Family or personal history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma • History of pancreatitis (acute or chronic). • History of major surgical procedures involving the stomach potentially affecting absorption of trial product (e.g. subtotal and total gastrectomy, sleeve gastrectomy, gastric bypass surgery) • Any of the following: myocardial infarction, stroke, or hospitalisation for unstable angina or transient ischaemic attack within the past 180 days prior to the day of screening and randomisation • New York Heart Association Class IV classification • Planned coronary, carotid, or peripheral artery revascularisation known on the day of screening • Alanine aminotransferase >2·5 x upper limit of normal • Renal impairment (estimated glomerular filtration rate <30 mL/min/1·73 m2,as per Chronic Kidney Disease Epidemiology collaboration) • Treatment with once-weekly glucagon-like peptide-1 receptor agonist or once-weekly dipeptidyl peptidase-4 inhibitor in a period of 90 days before the day of screening • For subjects treated with a glucose-lowering medication other than TZD as background medication at screening: treatment with TZD in a period of 90 days before the day of screening • Treatment with any medication for the indication of diabetes or obesity in addition to background glucose-lowering medication (sulphonylurea, glinide, TZD, α-GI,or SGLT2 inhibitor) in a period of 60 days before the day of screening, with the exception of short-term insulin treatment for acute illness for a total of ≤14 days • Proliferative retinopathy or maculopathy requiring acute treatment. Verified by fundus photography or dilated fundoscopy performed within 90 days prior to randomisation • History or presence of malignant neoplasms within the last 5 years (except basal and squamous cell skin cancer and in situ carcinomas) • History of diabetic ketoacidosis.
Recruitment / selection of participants	Participants recruited from 36 sites in Japan, and after 2-wk screening period, were randomised, using interactive web response system, 2:2:2:1 to semaglutide 3, 7, and 14 mg arms or dulaglutide arm. Randomisation was stratified on basis of background medication (sulphonylurea, glinide, thiazolidinedione, AG-inhibitor, SGLT inhibitor). All participants continued trial regardless of whether rescue medication received or study drug prematurely discontinued.

Intervention(s)	• Semaglutide 3 mg daily • Semaglutide 7 mg daily • Semaglutide 14 mg daily Open-label subcutaneous semaglutide injection 3, 7 or 14 mg once daily in morning (in fasting state) for 52 weeks, in addition to background glucose-lowering medication. Semaglutide dose was blinded (the three doses of semaglutide were visually identical tablets). For all participants in semaglutide groups, semaglutide was started at 3 mg daily, with the higher dose arms escalated 7 mg at 4-wk intervals. Tablets were taken with water and at least 30 min before food/drink/other oral medicine.
Cointervention	• Background glucose-lowering drugs
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Exclusion criteria state: "Subjects presently classified as being in New York Heart Association Class IV" (see supplement). No information in baseline characteristics. Unclear regarding class II and III.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Exclusion criteria state: "Any of the following: myocardial infarction, stroke, or hospitalisation for unstable angina or transient ischaemic attack within the past 180 days prior to the day of screening and randomisation" (see supplement). No information in baseline characteristics. Unclear about events preceding the 180 days and unclear about PAD/stable angina.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear CKD not an inclusion/exclusion criteria. Exclusion criteria state: "Renal impairment defined as estimated glomerular filtration rate <30 mL/min/1·73 m2, as per Chronic Kidney Disease Epidemiology collaboration".
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear

Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	eGFR ≥30mL/min/1.73m2 Exclusion criteria: eGFR<30 mL/min.1.73m2
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Comparator	• Dulaglutide 0.75 mg weekly Open label subcutaneous dulaglutide injection 0.75 mg once weekly on same day of week. independently of meals, for 52 weeks, in addition to background glucose-lowering medication. No dose escalation permitted.
Number of participants	N=458
Duration of follow-up	52 weeks
Indirectness	None
Method of analysis	ITT Results reported for all continuous outcomes reported using all randomised participants regardless of discontinuation or use of rescue medication (treatment policy estimand) as well as all randomised participants under assumption all participants remained on drug (trial product estimand). Safety analysis set=ITT set.
Additional comments	Additional HR-QoL data (Diabetes Therapy-Related Quality of Life questionnaire) available in Ishii 2021: • Ishii, H., Hansen, B. B., Langer, J., & Horio, H. (2021). Effect of orally administered semaglutide versus dulaglutide on diabetes-related quality of life in japanese patients with type 2 diabetes: the

	PIONEER 10 randomized, active-controlled trial. *Diabetes Therapy*, *12*, 613-623.

506.2. Study arms

506.2.1. Semaglutide 3 mg weekly (N = 131)

Subcutaneous semaglutide injection 3 mg once daily for 52 weeks, in addition to stable background glucose-lowering medication.

506.2.2. Semaglutide 7 mg daily (N = 132)

Subcutaneous semaglutide injection 7 mg once daily for 52 weeks, in addition to stable background glucose-lowering medication.

506.2.3. Semaglutide 14 mg daily (N = 130)

Subcutaneous semaglutide injection 14 mg once daily for 52 weeks, in addition to stable background glucose-lowering medication.

506.2.4. Dulaglutide 0.75 mg weekly (N = 65)

Subcutaneous dulaglutide injection 0.75 mg once weekly for 52 weeks, in addition to stable background glucose-lowering medication.

506.3. Characteristics

506.3.1. Arm-level characteristics

Characteristic	Semaglutide 3 mg weekly (N = 131)	Semaglutide 7 mg daily (N = 132)	Semaglutide 14 mg daily (N = 130)	Dulaglutide 0.75 mg weekly (N = 65)
% Male Sample size	n = 100 ; % = 76	n = 90 ; % = 68	n = 100 ; % = 77	n = 51 ; % = 78
Mean age (SD) Mean (SD)	59 (10)	58 (11)	57 (10)	61 (9)
Ethnicity	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Semaglutide 3 mg weekly (N = 131)	Semaglutide 7 mg daily (N = 132)	Semaglutide 14 mg daily (N = 130)	Dulaglutide 0.75 mg weekly (N = 65)
Sample size				
Japanese Sample size	n = 131 ; % = 100	n = 132 ; % = 100	n = 130 ; % = 100	n = 65 ; % = 100
Comorbidities Nominal	NR	NR	NR	NR
Presence of frailty Nominal	NR	NR	NR	NR
Time since type 2 diabetes diagnosed Mean (SD)	9.4 (6.3)	9.3 (6.3)	9.1 (6.4)	9.9 (6.3)
Cardiovascular risk factors Nominal	NR	NR	NR	NR
Smoking status Nominal	NR	NR	NR	NR
Alcohol consumption Nominal	NR	NR	NR	NR
Presence of severe mental illness Nominal	NR	NR	NR	NR
People with significant cognitive impairment Nominal	NR	NR	NR	NR
People with a learning disability Nominal	NR	NR	NR	NR
Number of people with obesity Nominal	NR	NR	NR	NR

Characteristic	Semaglutide 3 mg weekly (N = 131)	Semaglutide 7 mg daily (N = 132)	Semaglutide 14 mg daily (N = 130)	Dulaglutide 0.75 mg weekly (N = 65)
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Sulphonylurea Sample size	n = 42 ; % = 32	n = 42 ; % = 32	n = 42 ; % = 32	n = 21 ; % = 32
Glinide Sample size	n = 22 ; % = 17	n = 22 ; % = 17	n = 22 ; % = 17	n = 11 ; % = 17
Thiazolidinedione Sample size	n = 23 ; % = 18	n = 23 ; % = 17	n = 22 ; % = 17	n = 11 ; % = 17
Alpha-glucosidase inhibitor Sample size	n = 22 ; % = 17	n = 22 ; % = 17	n = 22 ; % = 17	n = 11 ; % = 17
SGLT2 inhibitor Sample size	n = 22 ; % = 17	n = 23 ; % = 17	n = 22 ; % = 17	n = 11 ; % = 17
Blood pressure-lowering medication used Nominal	NR	NR	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR	NR	NR
Other treatment being received Nominal	NR	NR	NR	NR

507. Yabe, 2023

Bibliographic Reference	Yabe, Daisuke; Shiki, Kosuke; Homma, Gosuke; Meinicke, Thomas; Ogura, Yuji; Seino, Yutaka; Efficacy and safety of the sodium-glucose co-transporter-2 inhibitor empagliflozin in elderly Japanese adults (>=65 years) with type 2 diabetes: A randomized, double-blind, placebo-controlled, 52-week clinical trial (EMPA-ELDERLY).; Diabetes, obesity & metabolism; 2023

507.1. 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	EMPA-ELDERLY. NCT04531462.
Study type	Randomised controlled trial (RCT)
Study location	Japan.
Study setting	Outpatient follow-up.
Study dates	No additional information.
Sources of funding	Sponsored by Nippon Boehringer Ingelheim Co. Ltd and Eli Lilly K.K.
Inclusion criteria	People with type 2 diabetes aged at least 65 years if they had BMI at least 22 kg/m2 and insufficient glycaemic control (HbA1c 7.0-10%) from diet/exercise alone or treatment with oral glucose-lowering drugs; people receiving glucose-lowering drugs who were at risk for severe hypoglycaemia (e.g. those receiving sulphonylureas or glinides) had to have HbA1c at least 7.5% if aged <75 years and at least 8.0% if at least 75 years.

Exclusion criteria	Fasting plasma glucose >200 mg/dL (>11.1 mmol/L); treatment in the previous 12 weeks with SGLT-2 inhibitors, insulin, GLP-1 receptor agonists or anti-obesity drugs; impaired cognitive ability on the Japanese version of the MMSE-J (<23 points); acute coronary syndrome; stroke or TIA in the previous 12 weeks; impaired kidney function (eGFR <45 mL/min/1.73m2); liver disease (serum ALT, AST or ALP >3x the upper limit of normal); history of diabetic ketoacidosis or cancer; previous or planned bariatric surgery; sarcopenia diagnosis; low handgrip strength (<28 kg for men, <18 kg for women); low calf circumference (<34 cm for men, <33 cm for women); could not perform the five times sit-to-stand test (5 x SST) in <12 s.
Recruitment / selection of participants	No additional information.
Intervention(s)	Empagliflozin N=64 Empagliflozin 10mg once a day for 52 weeks.
Cointervention	The majority of people received concomitant glucose-lowering therapy (77.2%). This included DPP-4 inhibitors, biguanides, sulphonylureas, thiazolidinediones, alpha-glucosidase inhibitors and meglitinides.
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	No additional information.
Comparator	Placebo N=63 Matching placebo for 52 weeks.
Number of participants	127
Duration of follow-up	52 weeks.
Indirectness	No additional information.
Method of analysis	ACA Full analysis set - all randomised people receiving at least 1 dose of study drug with a baseline HbA1c measurement and at least 1 on-treatment HbA1c measurement
Additional comments	No additional information.

507.2. Study arms

507.2.1. Empagliflozin (N = 64)

Empagliflozin 10mg once a day for 52 weeks. Concomitant therapy: The majority of people received concomitant glucose-lowering therapy (77.2%). This included DPP-4 inhibitors, biguanides, sulphonylureas, thiazolidinediones, alpha-glucosidase inhibitors and meglitinides.

507.2.2. Placebo (N = 63)

Matching placebo for 52 weeks. Concomitant therapy: The majority of people received concomitant glucose-lowering therapy (77.2%). This included DPP-4 inhibitors, biguanides, sulphonylureas, thiazolidinediones, alpha-glucosidase inhibitors and meglitinides.

507.3. Characteristics

507.3.1. Arm-level characteristics

Characteristic	Empagliflozin (N = 64)	Placebo (N = 63)
% Male Sample size	n = 48 ; % = 75	n = 44 ; % = 69.8
Mean age (SD) (years) Mean (SD)	74.2 (4.9)	74 (5.1)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	12.4 (8.2)	11.8 (7.6)
Cardiovascular risk factors Sample size	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Empagliflozin (N = 64)	Placebo (N = 63)
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 = 52 ; % = 81.3	n = 46 ; % = 73
DPP4 inhibitors Sample size	n = 45 ; % = 70.3	n = 41 ; % = 65.1
Biguanides (including metformin) Sample size	n = 34 ; % = 53.1	n = 31 ; % = 49.2
Sulphonylureas Sample size	n = 5 ; % = 7.8	n = 5 ; % = 7.9
Thiazolidinediones Sample size	n = 3 ; % = 4.7	n = 4 ; % = 6.3
Alpha-glucosidase inhibitors Sample size	n = 3 ; % = 4.7	n = 5 ; % = 7.9
Meglitinides Sample size	n = 2 ; % = 3.1	n = 2 ; % = 3.2
Blood pressure-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Statins/lipid-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Empagliflozin (N = 64)	Placebo (N = 63)
Other treatment being received Sample size	n = NA ; % = NA	n = NA ; % = NA

508. Yabiku, 2017

Bibliographic Reference	Yabiku, K.; Mutoh, A.; Miyagi, K.; Takasu, N.; Effects of Oral Antidiabetic Drugs on Changes in the Liver-to-Spleen Ratio on Computed Tomography and Inflammatory Biomarkers in Patients With Type 2 Diabetes and Nonalcoholic Fatty Liver Disease; Clin Ther; 2017; vol. 39 (no. 3); 558-566

508.1. Study details

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 " Subjects with serious renal dysfunction" stated in the exclusion criteria; no definition of serious renal dysfunction provided. No information in baseline characteristics.

509. Yale, 2014

Bibliographic Reference	Yale, J. F.; Bakris, G.; Cariou, B.; Nieto, J.; David-Neto, E.; Yue, D.; Wajs, E.; Figueroa, K.; Jiang, J.; Law, G.; Usiskin, K.; Meininger, G.; Group, D. I. A. Study; Efficacy and safety of canagliflozin over 52 weeks in patients with type 2 diabetes mellitus and chronic kidney disease; Diabetes Obes Metab; 2014; vol. 16 (no. 10); 1016-27

509.1. Study details

Secondary publication of another included study- see primary study for details	Parent study Yale 2013
Trial name / registration number	
Study type	Randomised controlled trial (RCT)
Study location	89 centres in 19 countries
Study setting	Unspecified clinical setting
Study dates	Not provided
Sources of funding	Janssen Research & Development, LLC.
Inclusion criteria	Eligible subjects were men and women aged ≥25 years with T2DM who had inadequate glycaemic control (HbA1c ≥7.0 and ≤10.5%) and stage 3 CKD (eGFR ≥30 and <50 ml/min/1.73 m2), and were either not on AHA therapy or were on a stable AHA regimen (monotherapy or combination therapy with any approved agent including metformin, sulphonylurea, dipeptidyl peptidase-4 (DPP-4) inhibitor, αglucosidase inhibitor, GLP-1 analogue, pioglitazone or insulin) for ≥8 weeks (≥12 weeks with pioglitazone) prior to the week –2 visit. Subjects were required to have generally stable renal function, as determined by a ≤25% decrease in eGFR from the screening to the week –2 visits.
Exclusion criteria	Subjects were excluded if they had repeated fasting plasma glucose (FPG) >15.0 mmol/l (270 mg/dl) during the pretreatment phase; a history of T1DM; renal disease that required immunosuppressive therapy, dialysis or transplant; nephrotic syndrome or inflammatory renal disease; New York Heart Association Class III-IV cardiovascular disease; myocardial infarction, unstable angina, revascularization procedure or cerebrovascular

	accident within 3 months prior to screening; or haemoglobin concentration <100 g/l (10 g/dl) at screening.
Recruitment / selection of participants	Not provided
Intervention(s)	once-daily oral doses of canagliflozin 100 or 300 mg
Cointervention	During the double-blind, core treatment period, glycaemic rescue therapy (up-titration of current AHAs or step-wise addition of oral or non-oral AHAs) was initiated if FPG >15.0 mmol/l (270 mg/dl) after day 1 to week 6, >13.3 mmol/l (240 mg/dl) after week 6 to week 12, and >11.1 mmol/l (200 mg/dl) after week 12 to week 26
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 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	eGFR ≥30mL/min/1.73m2
Subgroup 6: Albuminuria category at baseline	Mixed population median baseline ACR was 30.0 µg/mg, so population must straddle A1 and A2
Population subgroups	None
Comparator	once-daily oral doses of placebo
Number of participants	Of the 272 randomized subjects, 269 received ≥1 dose of study drug and were included in the mITT analysis population. Canagliflozin 100mg n=90; Canagliflozin 300mg n=89; Placebo n=90
Duration of follow-up	52-week study
Indirectness	None
Method of analysis	Modified ITT
Additional comments	Analysis was prespecified for 26 weeks, but not for 52 weeks. Baseline characteristics are identical to parent study Yale 2013.

509.2. Study arms

509.2.1. Canagliflozin 100 (N = 90)

Canagliflozin 100mg once daily

509.2.2. Canagliflozin 300 (N = 89)

Canagliflozin 100mg once daily

509.2.3. Placebo (N = 90)

Placebo once daily

510. Yale, 2013

Bibliographic Reference	Yale, J. F.; Bakris, G.; Cariou, B.; Yue, D.; David-Neto, E.; Xi, L.; Figueroa, K.; Wajs, E.; Usiskin, K.; Meininger, G.; Efficacy and safety of canagliflozin in subjects with type 2 diabetes and chronic kidney disease; Diabetes Obes Metab; 2013; vol. 15 (no. 5); 463-73

510.1. Study details

Secondary publication of another included study- see primary study for details	
Other publications associated with this study included in review	Yale 2014 follow up data
Trial name / registration number	DIA3004 trial; NCT01064414
Study type	Randomised controlled trial (RCT)
Study location	89 centres in 19 countries
Study setting	Unspecified clinical setting
Study dates	Not provided
Sources of funding	Janssen Research & Development, LLC.
Inclusion criteria	Eligible subjects were men and women aged ≥25 years with T2DM who had inadequate glycaemic control (HbA1c ≥7.0 and ≤10.5%) and stage 3 CKD (eGFR ≥30 and <50 ml/min/1.73 m2), and were either not on AHA therapy or were on a stable AHA regimen (monotherapy or combination therapy with any approved agent including metformin, sulphonylurea, dipeptidyl peptidase-4 (DPP-4) inhibitor, αglucosidase inhibitor, GLP-1 analogue, pioglitazone or insulin) for ≥8 weeks (≥12 weeks with pioglitazone) prior to the week –2 visit. Subjects were required to have generally stable renal function, as determined by a ≤25% decrease in eGFR from the screening to the week –2 visits.

Exclusion criteria	Subjects were excluded if they had repeated fasting plasma glucose (FPG) >15.0 mmol/l (270 mg/dl) during the pretreatment phase; a history of T1DM; renal disease that required immunosuppressive therapy, dialysis or transplant; nephrotic syndrome or inflammatory renal disease; New York Heart Association Class III-IV cardiovascular disease; myocardial infarction, unstable angina, revascularization procedure or cerebrovascular accident within 3 months prior to screening; or haemoglobin concentration <100 g/l (10 g/dl) at screening.
Recruitment / selection of participants	Not provided
Intervention(s)	once-daily oral doses of canagliflozin 100 or 300 mg
Cointervention	During the double-blind, core treatment period, glycaemic rescue therapy (up-titration of current AHAs or step-wise addition of oral or non-oral AHAs) was initiated if FPG >15.0 mmol/l (270 mg/dl) after day 1 to week 6, >13.3 mmol/l (240 mg/dl) after week 6 to week 12, and >11.1 mmol/l (200 mg/dl) after week 12 to week 26
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear "New York Heart Association Class III-IV cardiovascular disease" stated in the exclusion criteria. Therefore people with class II might have been included. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Mixed population "Myocardial infarction, unstable angina, revascularization procedure or cerebrovascular accident within 3 months prior to screening" stated in the exclusion criteria. Baseline characteristics table reports that 54.6% participants had a history of atherosclerotic cardiovascular disease.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	People with chronic kidney disease "Stage 3 CKD (eGFR ≥30 and <50 ml/min/1.73m2)" stated as an inclusion criteria. Baseline characteristics table reports 72% with nephropathy.
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	eGFR ≥30mL/min/1.73m2
Subgroup 6: Albuminuria category at baseline	Mixed population median baseline ACR was 30.0 µg/mg, so population must straddle A1 and A2
Population subgroups	None
Comparator	once-daily oral doses of placebo
Number of participants	Of the 272 randomized subjects, 269 received ≥1 dose of study drug and were included in the mITT analysis population. Canagliflozin 100mg n=90; Canagliflozin 300mg n=89; Placebo n=90
Duration of follow-up	52-week study. Outcomes reported at 26 weeks.
Indirectness	None
Method of analysis	Modified ITT

510.2. Study arms

510.2.1. Canagliflozin 100 (N = 90)

Canagliflozin 100mg once daily

510.2.2. Canagliflozin 300 (N = 89)

Canagliflozin 300mg once daily

510.2.3. Placebo (N = 90)

Placebo once daily

510.3. Characteristics

510.3.1. Arm-level characteristics

Characteristic	Canagliflozin 100 (N = 90)	Canagliflozin 300 (N = 89)	Placebo (N = 90)
% Male Nominal	64.4	53.9	63.3
Mean age (SD) Mean (SD)	69.5 (8.2)	67.9 (8.2)	68.2 (8.4)
Ethnicity Nominal	NA	NA	NA
White % Nominal	78.9	74.2	86.7
Black Nominal	3.3	2.2	0
Asian Nominal	10	12.4	7.8
Other Nominal	7.8	11.2	5.6
Comorbidities (%) Nominal	NA	NA	NA
Neuropathy Nominal	40	42.7	50
Retinopathy Nominal	30	40.4	27.8

Characteristic	Canagliflozin 100 (N = 90)	Canagliflozin 300 (N = 89)	Placebo (N = 90)
Nephropathy Nominal	55.6	51.7	56.7
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	15.6 (7.4)	17 (7.8)	16.4 (10.1)
HbA1c Mean (SD)	7.9 (0.9)	8 (0.8)	8 (0.9)
Cardiovascular risk factors Nominal	NA	NA	NA
History of atherosclerotic cardiovascular disease % Nominal	55.6	51.7	56.7
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Mean (SD)	NR (NR)	NR (NR)	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
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
eGFR mL/min/1.73m2 Mean (SD)	39.7 (6.9)	38.5 (6.9)	40.1 (6.8)

Characteristic	Canagliflozin 100 (N = 90)	Canagliflozin 300 (N = 89)	Placebo (N = 90)
Other antidiabetic medication used Sample size	n = 87 ; % = 96.7	n = 88 ; % = 98.9	n = 88 ; % = 97.8
Sulfonylureas Sample size	n = 24 ; % = 26.7	n = 27 ; % = 30.3	n = 33 ; % = 36.7
Thiazolidinediones Sample size	n = 3 ; % = 3.3	n = 7 ; % = 7.9	n = 7 ; % = 7.8
DPP4 inhibitors Sample size	n = 7 ; % = 7.8	n = 8 ; % = 9	n = 5 ; % = 5.6
Biguanide Sample size	n = 1 ; % = 1.1	n = 2 ; % = 2.2	n = 1 ; % = 1.1
Other Sample size	n = 6 ; % = 6.7	n = 10 ; % = 11.2	n = 7 ; % = 7.8
Insulin Sample size	n = 67 ; % = 74.4	n = 66 ; % = 74.2	n = 66 ; % = 73.3
Blood pressure-lowering medication used (%) Nominal	NA	NA	NA
Agents acting on the renin-angiotensin system Nominal	87.8	88.8	85.6
Diuretics Nominal	72.2	78.7	68.9
β-blocking agents Nominal	56.7	56.2	55.6
Calcium channel blockers Nominal	44.4	43.8	36.7
Statins/lipid-lowering medication used (%) Nominal	82.2	76.4	77.8

511. Yan, 2019

Bibliographic Reference	Yan, J.; Yao, B.; Kuang, H.; Yang, X.; Huang, Q.; Hong, T.; Li, Y.; Dou, J.; Yang, W.; Qin, G.; Yuan, H.; Xiao, X.; Luo, S.; Shan, Z.; Deng, H.; Tan, Y.; Xu, F.; Xu, W.; Zeng, L.; Kang, Z.; Weng, J.; Liraglutide, Sitagliptin, and Insulin Glargine Added to Metformin: The Effect on Body Weight and Intrahepatic Lipid in Patients With Type 2 Diabetes Mellitus and Nonalcoholic Fatty Liver Disease; Hepatology; 2019; vol. 69 (no. 6); 2414-2426

511.1. 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	Light-On/NCT02147925
Study type	Randomised controlled trial (RCT) Open-label active-controlled randomised trial
Study location	China (10 centres)
Study setting	Outpatient
Study dates	08/2014 to 12/2016
Sources of funding	Supported by investigator-initiated trial research funds from Novo Nordisk, National Natural Science Foundation of China (81770821), Pearl River S&T Nova Program of Guangzhou (201610010175) and Guangdong High-Level Talents Special Support Program (2016TQ03R590)
Inclusion criteria	• Aged 30-75 years • Diagnosis of type 2 diabetes • HbA1c level 6.5% to 10% inclusive • Treated with metformin monotherapy at stable dose (≥1500 mg/day) for at least 3 month • Clinical diagnosis of non-alcoholic fatty disease

	• MRI-PDFF>10% • BMI 20-35 kg/m2 inclusive • Stable body weight (≤10% variation for at least 3 months)
Exclusion criteria	• Diagnosis of type 1 diabetes • Treatment with any antidiabetic agent other than metformin, or treatment with any other drugs associated with hepatic steatosis (including but not limited to glucocorticoids, tamoxifen, amiodarone, or methotrexate) within 3 months of screening • History or current episode of pancreatitis or other pancreatic diseases • Plasma alanine trans-aminase level >2.5 times the upper limit of normal • eGFR<60 mL/min/1.73 m2 • Diagnosis of congestive heart failure (New York Heart Association Functional Classification III-IV) • Any history of liver disease, including autoimmune liver diseases or viral hepatitis • Weekly alcohol intake of >14 units for women or >21 units for men • Pregnancy or plans to become pregnant
Recruitment / selection of participants	After 2-wk screening, eligible participants randomised 1:1:1 using randomisation list (SAS) and allocated using interactive-web-based response system. Drugs were titrated and dosages maintained during trial. All participants received diabetes education (including dietary and exercise suggestions acc. to Chinese guidelines) throughout trial.
Intervention(s)	• Liraglutide 1.8 mg daily Subcutaneous injection of liraglutide 1.8 mg daily at bedtime, initiated at 0.6 mg/day increased by weekly forced titration to 1.8 mg /day or maximum tolerated dose (at least 1.2 mg/day).
Cointervention	• Metformin All participants received stable metformin dose (≥1500 mg/day) for duration of trial.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear "A diagnosis of congestive heart failure (New York Heart Association Functional Classification III-IV)" stated in the exclusion criteria. Therefore the study might include people with class II heart failure.
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	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	People with non-alcoholic fatty liver disease Inclusion criteria: clinical diagnosis of NAFLD
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	eGFR ≥30mL/min/1.73m2 Exclusion criteria: eGFR<60 mL/min/1.73 m2.
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Comparator	• Sitagliptin 100 mg daily • Insulin glargine Oral sitagliptin 100 mg daily for 26 weeks, in addition to metformin. Subcutaneous injection of insulin glargine for 26 weeks, started at 0.2 IU/kg/day, titrated by 2 to 6 IU/kg/day to achieve FPG <7 mmol/L, in addition to metformin.

Number of participants	N=75
Duration of follow-up	26 weeks
Indirectness	None
Method of analysis	Per protocol Sensitivity analysis conducted with PP population ITT All outcomes use ITT (all randomised participants) population regardless of whether they had end of treatment evaluation

511.2. Study arms

511.2.1. Liraglutide 1.8 mg daily (N = 24)

Subcutaneous injection of liraglutide 1.8 mg daily, for 26 weeks, in addition to metformin.

511.2.2. Sitagliptin 100 mg daily (N = 27)

Oral sitagliptin 100 mg daily, for 26 weeks, in addition to metformin.

511.2.3. Insulin glargine (N = 24)

Subcutaneous injection of insulin glargine, for 26 weeks, in addition to metformin.

511.3. Characteristics

511.3.1. Arm-level characteristics

Characteristic	Liraglutide 1.8 mg daily (N = 24)	Sitagliptin 100 mg daily (N = 27)	Insulin glargine (N = 24)
% Male Sample size	n = 17 ; % = 70.8	n = 21 ; % = 77.8	n = 14 ; % = 58.3
Mean age (SD)	43.1 (9.7)	45.7 (9.2)	45.6 (7.6)

Characteristic	Liraglutide 1.8 mg daily (N = 24)	Sitagliptin 100 mg daily (N = 27)	Insulin glargine (N = 24)
Mean (SD)			
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Chinese Sample size	n = 24 ; % = 100	n = 27 ; % = 100	n = 24 ; % = 100
Comorbidities Nominal	NR	NR	NR
Presence of frailty Nominal	NR	NR	NR
Time since type 2 diabetes diagnosed Mean (SD)	3.3 (3.5)	4.3 (3.8)	5.8 (4.5)
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
Number of people with obesity Nominal	NR	NR	NR

Characteristic	Liraglutide 1.8 mg daily (N = 24)	Sitagliptin 100 mg daily (N = 27)	Insulin glargine (N = 24)
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

512. Yang, 2012

Bibliographic Reference	Yang, W.; Guan, Y.; Shentu, Y.; Li, Z.; Johnson-Levonas, A. O.; Engel, S. S.; Kaufman, K. D.; Goldstein, B. J.; Alba, M.; The addition of sitagliptin to ongoing metformin therapy significantly improves glycemic control in Chinese patients with type 2 diabetes; J Diabetes; 2012; vol. 4 (no. 3); 227-37

512.1. 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	NCT00813995; Merck Protocol MK-0431 P074
Study type	Randomised controlled trial (RCT) Double-blind, placebo-controlled RCT
Study location	China (17 sites)
Study setting	Outpatient
Study dates	01/2009 to 08/2010
Sources of funding	Funded by Merck Sharp & Dohme Corp., subsidiary of Merck & Co, Inc.
Inclusion criteria	• Aged 18-78 years • Type 2 diabetes diagnosis • Receiving stable metformin (1000 or 1700 mg daily) at enrolment (at least 10-wks before screening) or after dose stabilisation/anti-hyperglycaemic agent washout/ run-in period • HbA1c 7.5-11% inclusive for those on metformin monotherapy or HbA1c 7-9% inclusive for those on metformin combination therapy

Exclusion criteria	• Taking peroxisome proliferator-activated receptor (PPAE) gamma agent • Type 1 diabetes diagnosis • History of diabetic ketoacidosis • Active liver or gallbladder disease • Congestive heart failure • Unstable coronary heart disease • Elevated liver enzymes (>2 times upper limit of normal) • Pregnancy or breastfeeding • Any contraindication for the use of metformin
Recruitment / selection of participants	Participants enrolled after 2 week screening period, followed by up to 9 week metformin up-titration/dose stabilisation/diet and exercise period, a 2 week single-blind placebo run-in period, followed by 24 weeks treatment period. Participants on stable metformin dose and who had HbA1c 7.5-11% inclusive continued with their dose and entered 2 week placebo run-in period; those on other metformin doses entered up to 9 week dose up-titration/stabilisation/diet and exercise period. Participants on metformin combination therapy entered up-titration/stabilisation period before run-in period after discontinuing second oral anti-hyperglycaemic agent. Randomisation 1:1 using computer-generated schedule, stratified by metformin dose. Throughout trial, participants received exercise counselling and weight management in line with ADA recommendations. Rescue therapy using open-label glipizide used when progressively stricter glycaemic goals not met.
Intervention(s)	• Sitagliptin
Cointervention	• Metformin 1000 mg or 1700 mg daily All participants continued to receive stable metformin dose for duration of trial.
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure History of congestive heart failure stated in the exclusion criteria.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear "History of unstable coronary heart disease" stated as an exclusion criteria. It is not clear which specific conditions this includes. Some types of atherosclerotic heart disease may not be covered by this (e.g. stable angina, stroke, TIA, PAD, revascularisation procedures).
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	• Placebo Matching placebo for 24 weeks, in addition to stable metformin dose.
Number of participants	N=395 randomised (N=356 completers)
Duration of follow-up	24 weeks
Indirectness	None
Method of analysis	Modified ITT

	mITT LOCF analysis (full analysis set: all randomised participants who received at least one study drug dose, and had both baseline at least one post-baseline measurement prior to any rescue therapy) for efficacy outcomes. Safety outcomes analysed using 'as treated' population (all participants who took at least one study drug dose) Other Safety outcomes analysed using 'as treated' population (all participants who took at least one study drug dose)

512.2. Study arms

512.2.1. Sitagliptin 100 mg daily (N = 197)

Oral sitagliptin 100 mg daily for 24 weeks, in addition to metformin (1000-1700 mg daily).

512.2.2. Placebo (N = 198)

Matching oral placebo daily for 24 weeks, in addition to metformin (1000-1700 mg daily).

512.3. Characteristics

512.3.1. Arm-level characteristics

Characteristic	Sitagliptin 100 mg daily (N = 197)	Placebo (N = 198)
% Male Sample size	n = 92 ; % = 47	n = 108 ; % = 55
Mean age (SD) (years) Mean (SD)	54.1 (9)	55.1 (9.8)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR

Characteristic	Sitagliptin 100 mg daily (N = 197)	Placebo (N = 198)
Time since type 2 diabetes diagnosed (years) Mean (SD)	6.4 (4.4)	7.3 (4.6)
Cardiovascular risk factors Nominal	NR	NR
Smoking status Nominal	*empty data*	NR
Alcohol consumption Nominal	NR	NR
Presence of severe mental illness Nominal	NR	NR
People with significant cognitive impairment Nominal	NR	NR
People with a learning disability Nominal	NR	NR
Number of people with obesity Nominal	NR	NR
Other antidiabetic medication used Nominal	NR	NR
Blood pressure-lowering medication used Nominal	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

513. Yang, 2016

Bibliographic Reference	Yang, W.; Han, P.; Min, K. W.; Wang, B.; Mansfield, T.; T'Joen, C.; Iqbal, N.; Johnsson, E.; Ptaszynska, A.; Efficacy and safety of dapagliflozin in Asian patients with type 2 diabetes after metformin failure: A randomized controlled trial; J Diabetes; 2016; vol. 8 (no. 6); 796-808

513.1. 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	NCT01095666
Study type	Randomised controlled trial (RCT) Double-blind, placebo-controlled, parallel-group RCT
Study location	International (32 sites in China, India and South Korea)
Study setting	Outpatient
Study dates	06/2010 to 03/2013
Sources of funding	Funded by Bristol-Myers Squibb, NJ, USA, and AstraZeneca, MD, USA
Inclusion criteria	• Aged 18 and over • HbA1c 7.5-10.5% inclusive • Receiving stable metformin treatment≥1500 mg daily for more than 8 weeks
Exclusion criteria	Main exclusion criteria include: • Serum creatinine≥133μmol/L for men and≥124μmol/L for women • ALT or AST >3 times upper limit of normal (ULN)

	• Serum total bilirubin>34.2μmol/L • Creatinine kinase >3 times ULN • Any of the following cardiovascular diseases in past 6 months: Myocardial infarction, cardiac surgery or revascularization (coronary artery bypass graft/percutaneous transluminal coronary angioplasty), unstable angina or congestive heart failure, transient ischemic attack or significant cerebrovascular disease; and symptoms of poorly controlled diabetes including, but not limited to, marked polyuria and polydipsia with>10% weight loss during 3 months prior to enrolment, or other signs and symptoms.
Recruitment / selection of participants	Eligible participants entered 6-wk single-blind placebo lead-in period in which open-label metformin was maintained at pre-trial dose (≥1500 mg daily), followed by randomisation 1:1:1 to dapagliflozin 10 mg or 5 mg or placebo using computer-generated randomisation scheme produced by interactive voice response system. All participants received diet and exercise counselling throughout trial in line with Chinese Diabetes Association. Rescue medication (open-label pioglitazone) permitted with inadequate glycaemic control with rescued participants continuing study.
Intervention(s)	• Dapagliflozin 10 mg daily • Dapagliflozin 5 mg daily Oral dapagliflozin 10 mg or 5 mg daily in addition to stable dose of metformin.
Cointervention	• Metformin≥1500 mg daily All participants continued receiving their pre-trial dose of metformin for duration of trial.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Exclusion criteria state: "Any of the following cardiovascular/vascular diseases within 6 months of the enrolment visit: Myocardial infarction, Cardiac surgery or revascularization (coronary artery bypass graft/percutaneous transluminal coronary angioplasty, Unstable angina, Unstable congestive heart failure, Congestive heart failure New York Heart Association Class III or IV, Transient ischemic attack or significant cerebrovascular disease, Unstable or previously undiagnosed arrhythmia." No information about cardiovascular diseases preceding the 6 months. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Exclusion criteria state: "Any of the following cardiovascular/vascular diseases within 6 months of the enrolment visit: Myocardial infarction, Cardiac surgery or revascularization (coronary artery bypass graft/percutaneous transluminal coronary angioplasty, Unstable angina, Unstable congestive heart failure, Congestive heart failure New York Heart Association Class III or IV, Transient ischemic attack or significant cerebrovascular disease, Unstable or previously undiagnosed arrhythmia." No information about cardiovascular diseases preceding the 6 months. No information in baseline characteristics.

Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Exclusion criteria state: "History of unstable or rapidly progressing renal disease", but no definition provided. No information in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Mixed population ~24% baseline BMI≥28 kg/m2
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Comparator	• Placebo Matching daily placebo for 24 weeks in addition to stable metformin dose.
Number of participants	N=445 randomised (N=444 received treatment; N=409 completers)

Duration of follow-up	24 weeks + 4-wk follow up
Indirectness	None
Method of analysis	Modified ITT mITT analysis for both efficacy (LOCF) and safety outcomes: for efficacy, all randomised participants who received at least one study drug dose, excluding data after rescue therapy; for safety, all randomised participants who received at least one study drug dose.

513.2. Study arms

513.2.1. Dapagliflozin 10 mg daily (N = 152)

Oral dapagliflozin 10 mg daily for 24 weeks, in addition to metformin.

513.2.2. Dapagliflozin 5 mg daily (N = 147)

Oral dapagliflozin 10 mg daily for 24 weeks, in addition to metformin.

513.2.3. Placebo (N = 145)

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

513.3. Characteristics

513.3.1. Arm-level characteristics

Characteristic	Dapagliflozin 10 mg daily (N = 152)	Dapagliflozin 5 mg daily (N = 147)	Placebo (N = 145)
% Male Sample size	n = 88 ; % = 57.9	n = 67 ; % = 45.6	n = 86 ; % = 59.3
Mean age (SD) (years) Mean (SD)	54.6 (9.5)	53.1 (9.1)	53.5 (9.2)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Asian Indian Sample size	n = 13 ; % = 8.6	n = 11 ; % = 7.5	n = 10 ; % = 6.9

Characteristic	Dapagliflozin 10 mg daily (N = 152)	Dapagliflozin 5 mg daily (N = 147)	Placebo (N = 145)
Chinese Sample size	n = 129 ; % = 84.9	n = 127 ; % = 86.4	n = 126 ; % = 86.9
Korean Sample size	n = 10 ; % = 6.6	n = 9 ; % = 6.1	n = 9 ; % = 6.2
Comorbidities Nominal	NR	NR	NR
Presence of frailty Nominal	NR	NR	NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	5.3 (4.6)	4.2 (3.8)	5.3 (4.4)
Cardiovascular risk factors Nominal	NR	NR	NR
Smoking status Nominal	NR	NR	NR
Alcohol consumption Nominal	NR	NR	NR
Presence of severe mental illness Nominal	NR	NR	NR
People with significant cognitive impairment Nominal	NR	NR	NR
People with a learning disability Nominal	NR	NR	NR
Number of people with obesity Participants>=28 kg/m2 Sample size	n = 38 ; % = 25	n = 40 ; % = 27.2	n = 30 ; % = 20.7
Other antidiabetic medication used	NR	NR	NR

Characteristic	Dapagliflozin 10 mg daily (N = 152)	Dapagliflozin 5 mg daily (N = 147)	Placebo (N = 145)
Nominal			
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

514. Yang, 2018

Bibliographic Reference	Yang, W.; Ma, J.; Li, Y.; Li, Y.; Zhou, Z.; Kim, J. H.; Zhao, J.; Ptaszynska, A.; Dapagliflozin as add-on therapy in Asian patients with type 2 diabetes inadequately controlled on insulin with or without oral antihyperglycemic drugs: A randomized controlled trial; J Diabetes; 2018; vol. 10 (no. 7); 589-599

514.1. 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	NCT02096705
Study type	Randomised controlled trial (RCT) Double-blind, placebo-controlled, parallel-group RCT
Study location	International (28 sites in China, Singapore and South Korea)
Study setting	Outpatient
Study dates	03/2014 to 02/2016
Sources of funding	Funded by AstraZeneca
Inclusion criteria	• Aged≥18 years • Type 2 diabetes diagnosis • HbA1c 7.5-11% • On stable dose of injectable insulin≥20 IU for ≥8-wks prior to enrolment • BMI≤45 kg/m2

Exclusion criteria	• Receiving more than two OADs within 6 weeks before enrolment • Symptoms of poorly controlled diabetes • Conditions of congenital renal glucosuria • History of type 1 diabetes mellitus, diabetes insipidus or diabetic ketoacidosis • Cardiovascular event within 3 months prior to screening • Unstable or rapidly progressing renal disease • NHYA class III and IV
Recruitment / selection of participants	Eligible participants entered 6-wk single-blind placebo lead-in period during which they were given diet and exercise instruction according to local guidelines. Insulin dose kept stable as possible (≤20% mean total daily dose). After lead-in period, participants randomised 1:1, stratified by insulin status (insulin only, insulin + other drug), using interactive voice response system. No more than 60% in each group were to be taking insulin combination therapy. No dose titration of study drug or insulin type was permitted during trial. Down titration of insulin permitted to prevent hypoglycaemia. Open-label rescue insulin permitted.
Intervention(s)	• Dapagliflozin 10 mg daily Oral dapagliflozin 10 mg daily for 24 weeks, in addition to insulin with or without oral anti-hyperglycaemic drugs.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear "Congestive heart failure defined as NYHA stage III and IV" stated in exclusion criteria. Therefore might include people with class II. No information in baseline table.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear "Cardiovascular disease within 3 months of the screening visit" stated in the exclusion criteria. No information about cardiovascular disease preceding the 3 months. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear "History of unstable or rapidly progressing renal disease" stated in the exclusion criteria. No definition provided. No information in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear

Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Mixed population ~29.5% baseline BMI≥28 kg/m2
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Comparator	• Placebo Matching placebo daily for 24 weeks, in addition to insulin with or without oral anti-hyperglycaemic drugs.
Number of participants	N=272 randomised (N=258 completers)
Duration of follow-up	24 weeks
Indirectness	None
Method of analysis	Modified ITT Appears to be mITT analysis (all randomised participants with at least one study drug dose and baseline/post-baseline HbA1c measurement) for efficacy outcomes using observed cases only; safety outcomes for all randomised participants.

514.2. Study arms

514.2.1. Dapagliflozin 10 mg daily (N = 139)

Oral dapagliflozin 10 mg daily for 24 weeks, in addition to insulin with or without oral anti-hyperglycaemic drugs.

514.2.2. Placebo (N = 133)

Matching daily placebo for 24 weeks, in addition to insulin with or without oral anti-hyperglycaemic drugs.

514.3. Characteristics

514.3.1. Arm-level characteristics

Characteristic	Dapagliflozin 10 mg daily (N = 139)	Placebo (N = 133)
% Male Sample size	n = 66 ; % = 47.5	n = 64 ; % = 48.1
Mean age (SD) (years) Mean (SD)	56.5 (8.4)	58.6 (8.9)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Asian Indian Sample size	n = 0 ; % = 0	n = 1 ; % = 0.8
Chinese Sample size	n = 114 ; % = 82	n = 108 ; % = 81.2
Japanese Sample size	n = 0 ; % = 0	n = 1 ; % = 0.8
Korean Sample size	n = 23 ; % = 16.5	n = 23 ; % = 17.3
Asian (other) Sample size	n = 2 ; % = 1.4	n = 0 ; % = 0
Comorbidities Nominal	NR	NR

Characteristic	Dapagliflozin 10 mg daily (N = 139)	Placebo (N = 133)
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	12.7 (7.2)	12.2 (6.7)
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 Participants with BMI>=28 kg/m2 Sample size	n = 39 ; % = 28.1	n = 41 ; % = 30.8
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Aldose reductase inhibitors Sample size	n = 0 ; % = 0	n = 2 ; % = 1.5
Alpha-glucosidase inhibitors Sample size	n = 18 ; % = 12.9	n = 18 ; % = 13.5
Metformin Sample size	n = 64 ; % = 46	n = 59 ; % = 44.4
Combination drug with metformin	n = 3 ; % = 2.2	n = 5 ; % = 3.8

Characteristic	Dapagliflozin 10 mg daily (N = 139)	Placebo (N = 133)
Sample size		
DPP4 inhibitors Sample size	n = 7 ; % = 5	n = 8 ; % = 6
Meglitinides Sample size	n = 6 ; % = 4.3	n = 3 ; % = 2.3
Sulphonylureas Sample size	n = 16 ; % = 11.5	n = 14 ; % = 10.5
Thiazolidinediones Sample size	n = 6 ; % = 4.3	n = 5 ; % = 3.8
Insulin only Sample size	n = 54 ; % = 38.8	n = 54 ; % = 40.6
Insulin + oral anti-hyperglycaemic drug(s) Sample size	n = 85 ; % = 61.2	n = 79 ; % = 59.4
Blood pressure-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Antihypertensive agent Sample size	n = 69 ; % = 49.6	n = 71 ; % = 53.4
Calcium channel blockers Sample size	n = 33 ; % = 23.7	n = 32 ; % = 24.1
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Sample size	n = NA ; % = NA	n = NA ; % = NA
Beta blocker Sample size	n = 20 ; % = 14.4	n = 17 ; % = 12.8
Diuretics Sample size	n = 5 ; % = 3.6	n = 9 ; % = 6.8

Characteristic	Dapagliflozin 10 mg daily (N = 139)	Placebo (N = 133)
Hyperuricemic medication (allopurinol) Sample size	n = 2 ; % = 1.4	n = 0 ; % = 0

515. Yang, 2018

Bibliographic Reference	Yang, W.; Min, K.; Zhou, Z.; Li, L.; Xu, X.; Zhu, D.; Venkateshwar Rao, A.; Murthy, L. S.; Zhang, N.; Li, I.; et, al.; Efficacy and safety of lixisenatide in a predominantly Asian population with type 2 diabetes insufficiently controlled with basal insulin: the GetGoal-L-C randomized trial; Diab Obes Metab; 2018; vol. 20 (no. 2); 335-343

515.1. 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-L-C/NCT01632163
Study type	Randomised controlled trial (RCT) Double-blind, placebo-controlled, parallel-group RCT.
Study location	International (51 centres in China, India, South Korea and Russian Federation)
Study setting	Outpatient
Study dates	10/2012 to 05/2015
Sources of funding	Funded by Sanofi
Inclusion criteria	• Adults with type 2 diabetes diagnosis≥1 year • HbA1c 7-10.5% inclusive • Receiving basal insulin with or without metformin
Exclusion criteria	• Not on stable basal insulin regimenfor≥3 months and/or not at a stable dose (±20%) of≥15 U/d for≥2 months prior to screening visit • Not at a stable metformin dose of≥1.0 g/d for≥3 months prior to screening visit

	• HbA1c <7% or >9.5% at visit 9 (week−1) or mean fasting self-monitored plasma glucose (SMPG) calculated for week prior to randomization visit >7.8 mmol/L
Recruitment / selection of participants	After screening, eligible participants entered 8-2k run-in phase in which existing basal insulin was optimally titrated to self-monitored blood glucose target 4.4-5.6 mmol/L, then were randomised 1:1 using interactive voice/web response system, stratified by HbA1c and metformin use at screening. No rescue therapy was used.
Intervention(s)	• Lixisenatide 20 mcg daily Subcutaneous injection of lixisenatide 20 mcg daily for 24 weeks, initiated at 10 mcg once daily for 2 weeks, increased to maintenance dose of 20 mcg once daily. If target dose not tolerated, reduction to 10 mcg permitted with attempted increase to target within 4 weeks. If still not tolerated participant remained on 10 mcg.
Cointervention	• Basal insulin All participants continued to receive stable dose/regimen of basal insulin for duration of trial, with adjustments within ±20%. Metformin, if taken, remained unchanged in dose and more than 1000 mg daily.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear

Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Comparator	• Placebo Volume-matched daily placebo for 24 weeks, in addition to basal insulin.
Number of participants	N=448 randomised
Duration of follow-up	24 weeks
Indirectness	None
Method of analysis	Modified ITT Efficacy outcomes analysed using mITT population (all randomised participants who received at least one study drug dose, and had both baseline and at least one post-baseline assessment of any outcome) with LOCF for missing data; safety outcomes using all randomised participants who received at least one study drug dose.

515.2. Study arms

515.2.1. Lixisenatide 20 mcg daily (N = 224)

Subcutaneous injection 20 mcg daily for 24 weeks, in addition to basal insulin.

515.2.2. Placebo (N = 224)

Volume-matched placebo for 24 weeks, in addition to basal insulin.

515.3. Characteristics

515.3.1. Arm-level characteristics

Characteristic	Lixisenatide 20 mcg daily (N = 224)	Placebo (N = 224)
% Male Sample size	n = 105 ; % = 46.9	n = 98 ; % = 43.8
Mean age (SD) Mean (SD)	53.9 (9.9)	56.3 (9.1)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Asian Sample size	n = 195 ; % = 87.1	n = 190 ; % = 84.8
White Sample size	n = 29 ; % = 12.9	n = 34 ; % = 15.2
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	10.3 (6.1)	10.2 (6.2)
Cardiovascular risk factors Nominal	NR	NR

Characteristic	Lixisenatide 20 mcg daily (N = 224)	Placebo (N = 224)
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 at screening Sample size	n = 198 ; % = 88.4	n = 199 ; % = 88.8
Insulin glargine Sample size	n = 182 ; % = 81.3	n = 189 ; % = 84.4
NPH insulin Sample size	n = 27 ; % = 12.1	n = 23 ; % = 10.3
Insulin detemir Sample size	n = 15 ; % = 6.7	n = 12 ; % = 5.4
Blood pressure-lowering medication used Nominal	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

516. Yang, 2011

Bibliographic Reference	Yang, W.; Pan, C. Y.; Tou, C.; Zhao, J.; Gause-Nilsson, I.; Efficacy and safety of saxagliptin added to metformin in Asian people with type 2 diabetes mellitus: a randomized controlled trial; Diabetes Res Clin Pract; 2011; vol. 94 (no. 2); 217-24

516.1. 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	NCT00661362
Study type	Randomised controlled trial (RCT) Double-blind, placebo-controlled, parallel-group RCT
Study location	International (40 sites in China, India, South Korea)
Study setting	Outpatient
Study dates	06/2008 to 09/2009
Sources of funding	Funded by AstraZeneca LP and Bristol-Myers Squibb.
Inclusion criteria	• Aged≥18 years • Type 2 diabetes diagnosis • HbA1c 7-10% inclusive at enrolment • Treatment with stable metformin dose (≥1500 mg daily for ≥8 weeks) • C-peptide level≥0.33 nmol/L
Exclusion criteria	• Type 1 diabetes, history of diabetic ketoacidosis or hyperosmolar nonketotic coma, or symptoms of poorly controlled diabetes

	• Insulin therapy within 1 year of enrolment (except during hospitalisation or for gestational diabetes) • Previous treatment with any DPP-4 inhibitor • Treatment with anti-hyperglycaemic agent (other than metformin) in past 98 weeks of enrolment (12 weeks for thiazolidinediones) • Current use of systemic glucocorticoids or cytochrome P450 3A4 inducers • NYHA class 3 or 4 congestive heart failure and/or a left ventricular ejection fraction of≤40% • Significant cardiovascular illness within 6 month of enrolment • Active liver disease and/or significant abnormal liver function • History of haemoglobinopathies, unstable or rapidly progressing renal disease, or autoimmune skin disorder • Gastrointestinal surgery that could affect drug absorption • History of alcohol or illegal drug abuse within past 12 month • Immunocompromised patients, pregnant or breast-feeding women, or patients with any clinically significant abnormality identified on physical examination, ECG, or lab tests that, in investigator's view would compromise patients' safety or successful participation in trial. • Other limits for lab parameters (e.g. serum creatinine, AST, ALT)
Recruitment / selection of participants	Eligible participants entered 2 week screening period in which they continued taking prescribed metformin dose. Participants who met inclusion criteria after this received single-blind placebo and open-label metformin (1500, 2000, 2500 or 3000 mg daily [max 2500 mg daily in China]), in addition to dietary and lifestyle counselling (continued for duration of trial), for 2 weeks, then randomised 1:1 to saxagliptin or placebo using computer-generated sequence, stratified by country. Rescue therapy not permitted during trial; participants withdrawn if FPG, after repeat measurement, above specific decreasing thresholds (e.g. >15 mmol/L at visits 4 and 5; >12.2 mmol/L at visit 8-10).
Intervention(s)	• Saxagliptin 5 mg daily Double-blind oral saxagliptin 5 mg daily for 24 weeks.
Cointervention	• Metformin All participants received open-label stable metformin dose for duration of trial
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Exclusion criteria state that patients were excluded "if they had New York Heart Association class III or IV congestive heart failure and/or a left ventricular ejection fraction of 40%". No information in baseline characteristics. Therefore people with class II heart failure might be included.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Exclusion criteria state that patients were excluded if there is "a significant cardiovascular illness within 6 months of enrolment". No information about cardiovascular illness in the preceding 6 months. No information in baseline characteristics.

Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear "Unstable or rapidly progressing renal disease" stated as an exclusion criteria. No definition given. 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
Comparator	• Placebo Double-blind placebo for 24 weeks
Number of participants	N=570 randomised (N=501 completers)

Duration of follow-up	24 weeks
Indirectness	None
Method of analysis	ITT ITT analysis (all randomised participants) for safety outcomes Modified ITT mITT analysis (full analysis set: all randomised participants who received at least one study drug dose and had baseline and at least one post-baseline efficacy measurement) with LOCF for efficacy outcomes.

516.2. Study arms

516.2.1. Saxagliptin 5 mg daily (N = 283)

Oral saxagliptin 5 mg daily for 24 weeks, in addition to stable metformin dose.

516.2.2. Placebo (N = 287)

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

516.3. Characteristics

516.3.1. Arm-level characteristics

Characteristic	Saxagliptin 5 mg daily (N = 283)	Placebo (N = 287)
% Male Sample size	n = 136 ; % = 48.1	n = 139 ; % = 48.4
Mean age (SD) (years) Mean (SD)	53.8 (10.4)	54.4 (10.1)
Ethnicity Participant country Sample size	n = NA ; % = NA	n = NA ; % = NA
China Sample size	n = 165 ; % = 58.3	n = 161 ; % = 56.1

Characteristic	Saxagliptin 5 mg daily (N = 283)	Placebo (N = 287)
India Sample size	n = 73 ; % = 25.8	n = 74 ; % = 25.8
South Korea Sample size	n = 45 ; % = 15.9	n = 52 ; % = 18.1
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	5.1 (5)	5.1 (4)
Cardiovascular risk factors Nominal	NR	NR
Smoking status Nominal	NR	NR
Alcohol consumption Nominal	NR	NR
Presence of severe mental illness Nominal	NR	NR
People with significant cognitive impairment Nominal	NR	NR
People with a learning disability Nominal	NR	NR
Number of people with obesity Nominal	NR	NR
Other antidiabetic medication used Dose at randomisation Sample size	n = NA ; % = NA	n = NA ; % = NA
Metformin 1500 to <2000 mg daily	n = 224 ; % = 79.2	n = 227 ; % = 79.1

Characteristic	Saxagliptin 5 mg daily (N = 283)	Placebo (N = 287)
Sample size		
Metformin 2000 to <2500 mg daily Sample size	n = 52 ; % = 18.4	n = 59 ; % = 20.6
Metformin 2500 to <3000 mg daily Sample size	n = 5 ; % = 1.8	n = 1 ; % = 0.3
Metformin >=3000 mg daily Sample size	n = 2 ; % = 0.7	n = 0 ; % = 0
Blood pressure-lowering medication used Nominal	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

517. Yang, 2015

Bibliographic Reference	Yang, W.; Xing, X.; Lv, X.; Li, Y.; Ma, J.; Yuan, G.; Sun, F.; Wang, W.; Woloschak, M.; Lukashevich, V.; Kozlovski, P.; Kothny, W.; Vildagliptin added to sulfonylurea improves glycemic control without hypoglycemia and weight gain in Chinese patients with type 2 diabetes mellitus; J Diabetes; 2015; vol. 7 (no. 2); 174-81

517.1. 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	NCT01357252
Study type	Randomised controlled trial (RCT) Double-blind, placebo-controlled RCT
Study location	China (multisite trial)
Study setting	Outpatient
Study dates	04/2011 to 01/2013
Sources of funding	Novartis Pharmaceuticals
Inclusion criteria	• Aged 18-80 years • BMI 20-40 kg/m2 inclusive • Inadequately controlled with diet, exercise and a sulphonylurea monotherapy • HbA1c 7.5-11% inclusive • Stable dose of a sulphonylurea≥12 weeks

Exclusion criteria	• History of type 1 diabetes mellitus or diabetes due to pancreatic injury or secondary forms • Congestive heart failure (New York Heart Association Class III or IV) • Liver disease (e.g. cirrhosis or hepatitis) • Any acute metabolic diabetic complications (e.g. ketoacidosis, lactic acidosis, or hyperosmolar state [coma]) • Myocardial infarction, unstable angina, or coronary artery bypass surgery in the past 6 months • ALT, AST or total bilirubin>2 times upper limit of normal (ULN) • FPG≥15.0 mmol/L • Fasting triglycerides>5.65 mmol/L
Recruitment / selection of participants	Eligible participants entered 2-week screening period, followed by 9 week run-in period in which participants switched from pre-trial glimepiride or other sulphonylureas to glimepiride (Amaryl; Sanofi-Aventis). or maintained/reduced dose. Participants who were taking ≥half maximal recommended dose of sulphonylurea other than glimepiride for at least 12 weeks were switched to glimepiride 4 mg daily; those who were taking less than half maximal recommended dose switched to glimepiride 2 mg daily. Participants already on glimepiride dose of 2, 4, 6 and 8 mg daily maintained dose; those on 3, 5 or 7 mg daily decreased dose by 1 mg. After this 9 week run-in period, participants still eligible for trial randomised 1:1, stratified by glimepiride dose at randomisation to vildagliptin or placebo. Rescue therapy permitted using metformin, pioglitazone or insulin if loss of glycaemic control at investigator discretion.
Intervention(s)	• Vildagliptin 50 mg daily Oral vildagliptin 50 mg daily in addition to glimepiride.
Cointervention	• Glimepiride All participants received oral glimepiride 2-8 mg daily for duration of trial.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Exclusion criteria: heart failure NYHA 3 and 4 only
Strata 2: People with atherosclerotic cardiovascular disease	People without atherosclerotic cardiovascular diseases Exclusion criteria for myocardial infarction, unstable angina and coronary artery bypass surgery in the past 6 month
Strata 3: People with type 2 diabetes mellitus and	Not stated/unclear

chronic kidney disease	
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	People without non-alcoholic fatty liver disease Exclusion criteria: liver disease
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	
Comparator	• Placebo Matching placebo for 24 weeks, in addition to glimepiride.
Number of participants	N=279 randomised (N=260 completers)
Duration of follow-up	24 weeks
Indirectness	None

Method of analysis	Modified ITT mITT analysis (full analysis set: all randomised participants who received at least one dose of study drug and had at least one post-baseline efficacy assessment for efficacy outcomes, except for HbA1c which only includes data before or at start of rescue medication and used LOCF for missing data) for HbA1c outcomes. Safety outcomes assessed in 'as-treated' population (all participants who received at least one study drug dose).

517.2. Study arms

517.2.1. Vildagliptin 50 mg daily (N = 143)

Oral vildagliptin 50 mg daily for 24 weeks, in addition to glimepiride.

517.2.2. Placebo (N = 136)

Matching placebo for 24 weeks, in addition to glimepiride.

517.3. Characteristics

517.3.1. Arm-level characteristics

Characteristic	Vildagliptin 50 mg daily (N = 143)	Placebo (N = 136)
% Male Sample size	n = 79 ; % = 55.2	n = 79 ; % = 58.1
Mean age (SD) (years) Mean (SD)	58.3 (9.8)	58.7 (9.3)
Ethnicity Chinese Sample size	n = 143 ; % = 100	n = 136 ; % = 100
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed (years)	6.9 (4.6)	6.9 (4.1)

Characteristic	Vildagliptin 50 mg daily (N = 143)	Placebo (N = 136)
Mean (SD)		
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 Nominal	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

518. Yang, 2021

Bibliographic Reference	Yang, W.; Xu, X.; Lei, T.; Ma, J.; Li, L.; Shen, J.; Ye, B.; Zhu, S.; Meinicke, T.; Efficacy and safety of linagliptin as add-on therapy to insulin in Chinese patients with type 2 diabetes mellitus: A randomized, double-blind, placebo-controlled trial; Diabetes, Obesity & Metabolism; 2021; vol. 23 (no. 2); 642-647

518.1. 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	NCT02897349
Study type	Randomised controlled trial (RCT)
Study location	China (25 sites)
Study dates	09/2016 to 01/2019
Sources of funding	Funded by Boehringer Ingelheim
Inclusion criteria	• Aged ≥18 years • HbA1c 7.5-10% inclusive • Current treatment with basal (insulin glargine, insulin detemir, NPH insulin) or pre-mixed (25/75 or 30/70 ratio) insulin with or without metformin for at least 12 weeks
Exclusion criteria	• FPG levels >13.3mmol/L (>240 mg/dL) • Received any other antidiabetic or anti-obesity drug within 3 months preceding informed consent • History of cardiovascular events in the 3 months prior to informed consent • Liver disease

	• Bariatric surgery in the past 2 years • Any medical history of cancer within 5 years prior to informed consent.
Recruitment / selection of participants	Eligible participants entered 2-week placebo run-in period before randomisation 1:1 by study sponsor (Boehringer Ingelheim) using computer-generated random sequence via interactive voice response system, stratified by HbA1c level (<8.5%, ≥8.5%) and type of background insulin (basal, premix; at least 90 participants in each group). All participants, staff etc blinded to allocation until database unlocked. Rescue therapy was insulin adjustment at investigator discretion, with in rare cases, adjustment of metformin or other oral anti-diabetic medication.
Intervention(s)	• Linagliptin 5 mg daily Oral linagliptin 5 mg daily for 24 weeks, in addition to insulin with or without metformin.
Cointervention	• Insulin All participants continued to receive stable insulin dose (basal or premix; ≤10% change in baseline insulin dose) for duration of trial.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear "History of cardiovascular events in the 3 months prior to informed consent" stated as an exclusion criteria in the supplementary information. No information about cardiovascular events preceding the 3 months. 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. Baseline characteristics reports renal function according to the EGFR categories (MDRD).
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear

Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	People without non-alcoholic fatty liver disease Exclusion criteria: liver disease
Subgroup 4: People with obesity	Mixed population
Subgroup 5: eGFR category at baseline	eGFR ≥30mL/min/1.73m2 All participants had eGFR≥30 mL/min/1.73 m2 at baseline.
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	• eGFR≥30 mL/min/1.73 m2 Predefined subgroup analysis by eGFR category (30-<60, 60 to <90, ≥90) for change in HbA1c level. Since all participants had eGFR≥30 mL/min/1.73 m2, results for this subgroup are same as for main primary analysis.
Comparator	• Placebo Matching placebo for 24 weeks in addition to insulin with or without metformin.
Number of participants	N=206 randomised (N=195 completers)
Duration of follow-up	24 weeks
Indirectness	None
Method of analysis	Modified ITT mITT analysis (all randomised participants who had baseline and at least one post-baseline HbA1c measurement) for efficacy outcomes. As treated (randomised participants who received at least one study drug dose)

	population used for safety outcomes. Unclear what missing data strategy is.

518.2. Study arms

518.2.1. Linagliptin 5 mg daily (N = 104)

Oral linagliptin 5 mg daily for 24 weeks, in addition to basal or premix insulin with or without metformin.

518.2.2. Placebo (N = 102)

Matching placebo daily for 24 weeks, in addition to basal or premix insulin with or without metformin.

518.3. Characteristics

518.3.1. Arm-level characteristics

Characteristic	Linagliptin 5 mg daily (N = 104)	Placebo (N = 102)
% Male Sample size	n = 52 ; % = 50	n = 54 ; % = 52.9
Mean age (SD) (years) Mean (SD)	60.1 (9.5)	57.1 (10.6)
Ethnicity Asian race Sample size	n = 104 ; % = 100	n = 102 ; % = 100
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed (years) Data for this characteristic is for Linagliptin, N=101, and Placebo, N=101. Sample size	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Linagliptin 5 mg daily (N = 104)	Placebo (N = 102)
Less than or equal to 5 years Sample size	n = 8 ; % = 7.9	n = 11 ; % = 10.9
5-10 years Sample size	n = 30 ; % = 29.7	n = 33 ; % = 32.7
More than 10 years Sample size	n = 63 ; % = 62.4	n = 57 ; % = 56.4
Cardiovascular risk factors Nominal	NR	NR
Smoking status Nominal	NR	NR
Alcohol consumption Nominal	NR	NR
Presence of severe mental illness Nominal	NR	NR
People with significant cognitive impairment Nominal	NR	NR
People with a learning disability Nominal	NR	NR
Number of people with obesity Nominal	NR	NR
Other antidiabetic medication used Data for this baseline characteristic is for Linagliptin, N=101, and Placebo, N=101. Sample size	n = NA ; % = NA	n = NA ; % = NA
Insulin only Sample size	n = 29 ; % = 28.7	n = 32 ; % = 31.7
Insulin + metformin Sample size	n = 72 ; % = 71.3	n = 69 ; % = 68.3
Basal insulin Sample size	n = 57 ; % = 56.4	n = 56 ; % = 55.4

Characteristic	Linagliptin 5 mg daily (N = 104)	Placebo (N = 102)
Premixed insulin Sample size	n = 44 ; % = 43.6	n = 44 ; % = 43.6
Blood pressure-lowering medication used Nominal	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

519. Yang, 2022

Bibliographic Reference	Yang, Wenying; Dong, Xiaolin; Li, Qingju; Cheng, Zhifeng; Yuan, Guoyue; Liu, Ming; Xiao, Jianzhong; Gu, Shenghong; Niemoeller, Elisabeth; Chen, Lijuan; Ping, Lin; Souhami, Elisabeth; Efficacy and safety benefits of iGlarLixi versus insulin glargine 100 U/mL or lixisenatide in Asian Pacific people with suboptimally controlled type 2 diabetes on oral agents: The LixiLan-O-AP randomized controlled trial.; Diabetes, obesity & metabolism; 2022; vol. 24 (no. 8); 1522-1533

519.1. Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	LixiLan-O-AP NCT03798054
Study type	Randomised controlled trial (RCT)
Study location	China
Study setting	Hospital
Study dates	February 2019 to March 2021
Sources of funding	Sanofi
Inclusion criteria	Inclusion criteria were screening glycated haemoglobin (HbA1c) ≥58 and ≤97 mmol/mol (≥7.5% and ≤11%) for participants previously treated with metformin, with or without an SGLT2 inhibitor, or ≥53 and ≤86 mmol/mol (≥7.0% and ≤10%) for participants previously treated with metformin and a second non-SGLT2 inhibitor oral antidiabetic.
Exclusion criteria	No additional information.

Recruitment / selection of participants	Participants were randomized 2:2:1 to once-daily iGlarLixi , iGlar or Lixi. The study comprised a 4-week run-in phase during which treatments other than metformin and SGLT2 inhibitors were discontinued, metformin was optimized to a dose of ≥1500 mg/d and SGLT2 inhibitors were kept at a stable dose, a 24-week treatment period, and a 3-day post-treatment safety follow-up period.
Intervention(s)	iGlarLixi Self-administered by subcutaneous injection once daily during the hour before the first meal of the day and doses were titrated once weekly to target once daily self-monitored plasma glucose (SMPG) of 80 to 100 mg/dL (4.4-5.6 mmol/L).
Cointervention	All patients in the trial had suboptimally controlled type 2 diabetes with or without a second oral antihyperglycaemic drug (sulfonylureas, glinides, DPP-4 inhibitor, SGLT2-inhibitors)
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with	Not stated/unclear

moderate or severe frailty	
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	No additional information.
Comparator	Lixisenatide Self-administered once daily in the hour prior to a meal (preferably breakfast, and the chosen meal was to remain the same throughout treatment). Lixisenatide was initiated at a dose of 10 µg for 2 weeks, then continued with the maintenance dose of 20 µg until treatment conclusion. Insulin glargine Self-administered by subcutaneous injection daily at any time. The starting dose was 5 to 10 U and doses were titrated once weekly to target once daily self-monitored plasma glucose (SMPG) of 80 to 100 mg/dL (4.4-5.6 mmol/L).
Number of participants	N=878
Duration of follow-up	24-week
Indirectness	No additional information.

Method of analysis	Modified ITT
Additional comments	mITT population defined as all randomised patients who had both a baseline assessment and at least one post-baseline assessment of any primary or secondary efficacy variables. The safety endpoints were analysed in the safety population, defined as all randomized participants who received ≥1 dose of investigational product, regardless of the amount of treatment administered.

519.2. Study arms

519.2.1. iGlarLixi (N = 351)

Self-administered by subcutaneous injection once daily during the hour before the first meal of the day and doses were titrated once weekly to target once daily self-monitored plasma glucose (SMPG) of 80 to 100 mg/dL (4.4-5.6 mmol/L).

519.2.2. Insulin glargine (N = 350)

Self-administered by subcutaneous injection daily at any time. The starting dose was 5 to 10 U and doses were titrated once weekly to target once daily self-monitored plasma glucose (SMPG) of 80 to 100 mg/dL (4.4-5.6 mmol/L).

519.2.3. Lixisenatide (N = 177)

Self-administered once daily in the hour prior to a meal (preferably breakfast, and the chosen meal was to remain the same throughout treatment). Lixisenatide was initiated at a dose of 10 µg for 2 weeks, then continued with the maintenance dose of 20 µg until treatment conclusion.

519.3. Characteristics

519.3.1. Arm-level characteristics

Characteristic	iGlarLixi (N = 351)	Insulin glargine (N = 350)	Lixisenatide (N = 177)
% Male No of events	n = 180 ; % = 51	n = 186 ; % = 53	n = 96 ; % = 54
Mean age (SD) (years)	55.4 (9.1)	56.5 (9.8)	56.3 (10)

Characteristic	iGlarLixi (N = 351)	Insulin glargine (N = 350)	Lixisenatide (N = 177)
Mean (SD)			
Ethnicity Nominal	NR	NR	NR
Comorbidities Nominal	NR	NR	NR
Presence of frailty Nominal	NR	NR	NR
Time since type 2 diabetes diagnosed Nominal	NR	NR	NR
Smoking status Nominal	NR	NR	NR
Alcohol consumption Nominal	NR	NR	NR
Presence of severe mental illness Nominal	NR	NR	NR
People with significant cognitive impairment Nominal	NR	NR	NR
People with a learning disability Nominal	NR	NR	NR
Number of people with obesity Nominal	NR	NR	NR
Metformin No of events	n = 351 ; % = 100	n = 350 ; % = 100	n = 177 ; % = 100
Sulfonylureas No of events	n = 160 ; % = 45.6	n = 142 ; % = 40.6	n = 73 ; % = 41.2
Glinides No of events	n = 14 ; % = 4	n = 22 ; % = 6.3	n = 11 ; % = 6.2

Characteristic	iGlarLixi (N = 351)	Insulin glargine (N = 350)	Lixisenatide (N = 177)
DPP4-inhibitors No of events	n = 33 ; % = 9.4	n = 34 ; % = 9.7	n = 24 ; % = 13.6
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

520. Yki-Järvinen, 2013

Bibliographic Reference	Yki-Järvinen, H.; Rosenstock, J.; Durán-Garcia, S.; Pinnetti, S.; Bhattacharya, S.; Thiemann, S.; Patel, S.; Woerle, H. J.; Effects of adding linagliptin to basal insulin regimen for inadequately controlled type 2 diabetes: a ≥52-week randomized, double-blind study; Diabetes Care; 2013; vol. 36 (no. 12); 3875-81

520.1. 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	NCT00954447
Study type	Randomised controlled trial (RCT) Double-blind, placebo-controlled, parallel-group, RCT
Study location	International (167 diabetes centers in 19 countries: Argentina, Belgium, Brazil, Canada, Czech Republic, Finland, Germany, Greece, Italy, Korea, Mexico, the Netherlands, Norway, Peru, Russia, Slovakia, Spain, Taiwan, USA).
Study setting	Outpatient
Study dates	08/209 to 09/2011
Sources of funding	Sponsored by Boehringer Ingelheim.
Inclusion criteria	• Aged 18 years or more • Type 2 diabetes diagnosis • HbA1c 7-10% inclusive • BMI≤45 kg/m2

	• Receiving basal insulin (glargine, detemir, npH insulin) with or without metformin and/or pioglitazone for more than 12 weeks
Exclusion criteria	• Uncontrolled fasting hyperglycemia (glu-cose.13.3 mmol/L during placebo run-in) • Myocardial infarction, stroke, or transient ischemic attack within 6 months before informed consent • Impaired hepatic function (either alanine transaminase, aspartate transaminase, or alkalinephosphate≥3 times times the upper limit of normal) • Previous gastric bypass surgery • Any medical history of cancer (except basal cell carcinoma) in 5 years before screening • Hypersensitivity or allergy to the investigational products • Contraindications to metformin or pioglitazone • Treat-ment with rosiglitazone, sulfonylureas, GLP-1 RAs, DPP-4 inhibitors, or anti-obesity drugs within 3 months before informed consent • History of alcohol or drug abuse in previous 3 months • Current treatment with systemic steroids or change in dosage of thyroid hormones within 6 weeks before informed consent • Premenopausal women who were nursing, pregnant, or not practicing an acceptable method of birth control
Recruitment / selection of participants	Eligible participants underwent screening and 2-wk open-label placebo run-in period to confirm eligibility, then randomised 1:1 using computer-generated random sequence via interactive voice-response system (stratified by HbA1c, eGFR, and use of other oral anti-diabetic drugs) to linagliptin or placebo for at least 52 weeks. Participants on other oral anti-diabetic drugs continued doses were unchanged for duration for trial.
Intervention(s)	• Linagliptin 5 mg daily Oral linagliptin 5 mg daily for 52 weeks, in addition to basal insulin.
Cointervention	• Basal insulin All participants continued to receive baseline basal insulin dose for first 24 weeks, after which dose could be adjusted at investigator discretion (FPG target 6.1 mmol/L). Other oral-antidiabetics taken at baseline were continued unchanged for duration of trial.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Exclusion criteria states "Patients were ineligible if they had a myocardial infarction, stroke, or transient ischemic attack within 6 months before

	informed consent." No information about CV events preceding 6 months prior to study entry. 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. Baseline characteristics states 43% had normal renal function. Unclear what percentage would meet the definition CKD, as categorisation is based on eGFR (MDRD)
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Comparator	• Placebo Matching placebo for at least 52 weeks, in addition to basal insulin.

Number of participants	N=1261 randomised (N=1235 full analysis set; N=1063 completers)
Duration of follow-up	52 weeks or more
Indirectness	None
Method of analysis	Modified ITT As treated population (all participants with at least one study drug dose) for safety outcomes. Full analysis set (all randomised participants with at least one dose study drug, and baseline and at least one post-baseline HbA1c measurement at week 24) for HbA1c outcome with LOCF.

520.2. Study arms

520.2.1. Linagliptin 5 mg daily (N = 631)

Oral linagliptin 5 mg daily for 52 weeks, in addition to insulin with or without metformin and/or pioglitazone.

520.2.2. Placebo (N = 630)

Matching placebo for 52 weeks, in addition to insulin with or without metformin and/or pioglitazone.

520.3. Characteristics

520.3.1. Arm-level characteristics

Characteristic	Linagliptin 5 mg daily (N = 631)	Placebo (N = 630)
% Male Sample size	n = 329 ; % = 52.1	n = 329 ; % = 52.2
Mean age (SD) (years) Mean (SD)	59.7 (9.9)	60.4 (10)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
American/Indian/Alaskan Native Sample size	n = 4 ; % = 0.6	n = 6 ; % = 1

Characteristic	Linagliptin 5 mg daily (N = 631)	Placebo (N = 630)
Asian Sample size	n = 80 ; % = 12.7	n = 74 ; % = 11.7
Black/African American Sample size	n = 41 ; % = 6.5	n = 39 ; % = 6.2
Hawaiian/Pacific Islander Sample size	n = 2 ; % = 0.3	n = 3 ; % = 0.5
White Sample size	n = 504 ; % = 79.9	n = 508 ; % = 80.6
Time since type 2 diabetes diagnosed (years) Sample size	n = NA ; % = NA	n = NA ; % = NA
Less than 1 year Sample size	n = 14 ; % = 2.3	n = 12 ; % = 1.9
>1 up to 5 years Sample size	n = 86 ; % = 13.9	n = 66 ; % = 10.7
More than 5 years Sample size	n = 518 ; % = 83.8	n = 539 ; % = 87.4
Cardiovascular risk factors Nominal	NR	NR
Smoking status Nominal	NR	NR
Alcohol consumption Nominal	NR	NR
Presence of severe mental illness Nominal	NR	NR
People with significant cognitive impairment Nominal	NR	NR
People with a learning disability Nominal	NR	NR

Characteristic	Linagliptin 5 mg daily (N = 631)	Placebo (N = 630)
Number of people with obesity Nominal	NR	NR
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
None Sample size	n = 96 ; % = 15.5	n = 102 ; % = 16.5
Metformin only Sample size	n = 470 ; % = 76.1	n = 464 ; % = 75.2
Pioglitazone only Sample size	n = 6 ; % = 1	n = 6 ; % = 1
Metformin + Pioglitazone Sample size	n = 46 ; % = 7.4	n = 45 ; % = 7.3
Blood pressure-lowering medication used Nominal	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

521. Yokoyama, 2014

Bibliographic Reference	Yokoyama, Hiroki; Hirao, Koichi; Yamaguchi, Kohei; Oishi, Mariko; Lee, Gendai; Yagi, Noriharu; Takamura, Hiroshi; Kashiwagi, Atsunori; Liraglutide Versus Sitagliptin in a 24-week, Multicenter, Open-label, Randomized, Parallel-group Study in Japanese Type 2 Diabetes Mellitus Patients Responding Inadequately to a Sulfonylurea and/or One or Two Other Oral Antidiabetic Drugs (JDDM 33).; Japanese clinical medicine; 2014; vol. 5; 33-41

521.1. 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	JDMM 33/UMIN000004970
Study type	Randomised controlled trial (RCT) Open-label, active-controlled, parallel-group, RCT
Study location	Japan (21 primary care centres)
Study setting	Outpatient
Study dates	07/2010 to 10/2012
Sources of funding	Supported by Japan Diabetes Foundation.
Inclusion criteria	• Aged 18 to <80 years • Receiving diet and exercise therapy education • Current treatment with a sulphonylurea (stable dose: glimepiride 2-6 mg; glibenclamide 2.5-10 mg; gliclazide 60-160 mg) with or without up to 2 other oral anti-diabetic drug for ≥8 weeks before screening

Exclusion criteria	• Repeated hypoglycemia unawareness or clinically significant hypoglycemia in past • Maculopathy requiring urgent treatment • Proliferative retinopathy • Hepatic dysfunction (aspartate aminotransferase>80 IU/L or alanine aminotransferase >80 IU/L) or a past history of liver fibrosis/cirrhosis • Renal impairment (eGFR<60 mL/minute/1.73 m2) • Known allergy to the test drugs or related products • Current or history of malignant tumor with recurrence strongly suspected • Women who were pregnant, breast-feeding (within one year after delivery), or intended to become pregnant • Participation in another clinical trial within 12 weeks of Visit 1 • Treatment with liraglutide or sitagliptin within 12 weeks of Visit 1 • Treatment with insulin within 12 weeks of Visit 1 (patients who had used insulin for less than or equal to seven days in the last 12 weeks were eligible) • Current or planned systemic steroid treatment • Patients who were considered to be unsuitable for this study at the attending physician's discretion
Recruitment / selection of participants	Eligible participants recruited from 21 primary care centres in Japan and randomised 1:1 using internet-based case management system to liraglutide or sitagliptin. Participants using non-sulphonylurea-based oral anti-diabetic drugs discontinued these at randomisation. Participants instructed to continue diet and exercise therapy for duration of trial. Use of oral anti-diabetic drugs other than sulphonylurea and insulin not permitted. Follow up every month for 24 weeks.
Intervention(s)	• Liraglutide 0.9 mg daily Subcutaneous liraglutide 0.9 mg daily for 24 weeks. Liraglutide started at 0.3 mg, increased 0.3 mg at week 1 and 2 to 0.9 mg. Dose increase could be delayed due to tolerability issues.
Cointervention	• Sulphonylurea All participants received a stable dose of a sulphonylurea, at investigator's discretion, for duration of trial.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.

Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	People without chronic kidney disease "Renal impairment (estimated glomerular filtration rate □60 mL/minute/ 1.73 m2)" stated as an 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 Exclusion criteria: eGFR<=60 ml/min/1.73 m2
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Comparator	• Sitagliptin 50-100 mg daily Oral sitagliptin 50-100 mg daily for 24 weeks, starting at 50 mg daily and increased to 100 mg daily at investigator discretion.
Number of participants	N=99 randomised (N=82 completer

Duration of follow-up	24 weeks
Indirectness	None
Method of analysis	Per protocol Efficacy outcomes evaluated using per protocol set (all participants who complied with study protocol). Missing data not substituted ITT Safety outcomes analysed using all randomised participants.

521.2. Study arms

521.2.1. Liraglutide 0.9 mg daily (N = 50)

Subcutaneous injection of liraglutide 0.9 mg daily for 24 weeks, in addition to a sulphonylurea.

521.2.2. Sitagliptin 50-100 mg daily (N = 49)

Oral sitagliptin 50-100 mg daily for 24 weeks, in addition to a sulphonylurea.

521.3. Characteristics

521.3.1. Arm-level characteristics

Characteristic	Liraglutide 0.9 mg daily (N = 50)	Sitagliptin 50-100 mg daily (N = 49)
% Male Sample size	n = 33 ; % = 66	n = 32 ; % = 65.3
Mean age (SD) (years) Mean (SD)	61.1 (8.6)	61.5 (9.7)
Ethnicity Japanese Sample size	n = 50 ; % = 100	n = 49 ; % = 100
Comorbidities Nominal	NR	NR

Characteristic	Liraglutide 0.9 mg daily (N = 50)	Sitagliptin 50-100 mg daily (N = 49)
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	11.68 (7.2)	10.99 (6.69)
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	*empty data*
People with a learning disability Nominal	NR	NR
Number of people with obesity Nominal	NR	NR
Other antidiabetic medication used Prior therapy Sample size	n = NA ; % = NA	n = NA ; % = NA
Sulphonylurea only Sample size	n = 25 ; % = 50	n = 21 ; % = 42.9
Sulphonylurea + 1 other drug Sample size	n = 13 ; % = 26	n = 15 ; % = 30.6
Sulphonylurea + 2 other drugs Sample size	n = 6 ; % = 12	n = 8 ; % = 16.3

Characteristic	Liraglutide 0.9 mg daily (N = 50)	Sitagliptin 50-100 mg daily (N = 49)
Other Sample size	n = 6 ; % = 12	n = 5 ; % = 10.2
Blood pressure-lowering medication used Nominal	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

522. Yu, 2017

Bibliographic Reference	Yu, Maria; Brunt, Kate Van; Milicevic, Zvonko; Varnado, Oralee; Boye, Kristina S; Patient-reported Outcomes in Patients with Type 2 Diabetes Treated with Dulaglutide Added to Titrated Insulin Glargine (AWARD-9).; Clinical therapeutics; 2017; vol. 39 (no. 11); 2284-2295

522.1. Study details

Secondary publication of another included study- see primary study for details	Parent study Pozzilli 2017: • Pozzilli, P., Norwood, P., Jódar, E., Davies, M. J., Ivanyi, T., Jiang, H., ... & Milicevic, Z. (2017). Placebo-controlled, randomized trial of the addition of once-weekly glucagon-like peptide-1 receptor agonist dulaglutide to titrated daily insulin glargine in patients with type 2 diabetes (AWARD-9). *Diabetes, Obesity and Metabolism*, *19*(7), 1024-1031.
Other publications associated with this study included in review	See above
Trial name / registration number	AWARD-9/NCT02152371
Study type	Randomised controlled trial (RCT)

522.2. Study arms

522.2.1. Dulaglutide 1.5 mg weekly (N = 150)

Subcutaneous injection of dulaglutide 1.5 mg weekly for 28 weeks, in addition to titrated daily insulin glargine with or without metformin.

522.2.2. Placebo (N = 150)

Matched placebo for 28 weeks, in addition to titrated daily insulin glargine with or without metformin.

523. Yuan, 2022

Bibliographic Reference	Yuan, X.; Guo, X.; Zhang, J.; Dong, X.; Lu, Y.; Pang, W.; Gu, S.; Niemoeller, E.; Ping, L.; Nian, G.; Souhami, E.; Improved glycaemic control and weight benefit with iGlarLixi versus insulin glargine 100 U/mL in Chinese people with type 2 diabetes advancing their therapy from basal insulin plus oral antihyperglycaemic drugs: Results from the LixiLan-L-CN randomized controlled trial; Diabetes, Obesity and Metabolism; 2022; vol. 24 (no. 11); 2182-2191

523.1. 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	LixiLan-L-CN/NCT03798080
Study type	Randomised controlled trial (RCT) Open-label, active-controlled, parallel-group RCT
Study location	China (44 centres)
Study setting	Outpatient
Study dates	02/2019 to 12/2020
Sources of funding	Funded by Sanofi, Paris, France.
Inclusion criteria	• Aged 18 years • Type 2 diabetes diagnosis • HbA1c level 7-10.5% inclusive whilst on basal insulin with or without stable dose of ≤2 oral antidiabetic agents (metformin, sulphonylureas, glinides, alpha-glucosidase/SGHLT2/DPP4 inhibitors permitted if on stable dose for 3 months before screening)

	• Treated with basal insulin for at least 6 months before screening • Stable dose (+/-20%) of 10-25 U/day for at least 2 months before screening • FPG≤160 mg/dl at screening
Exclusion criteria	• Use of any oral antidiabetic agent other than those permitted during 3 months before screening • Use of any insulin regimen besides basal insulin during year before screening (except for short-term treatment (≤10 days) because of intercurrent illness) • Mean fasting self-measured plasma glucose>160 mg/dl during the 7 days before randomization (mean of at least four measurements)
Recruitment / selection of participants	After 2-wk screening period, participants entered 30-wk treatment period, randomised 1:1 using central interactive response technology, and 3-day post-treatment safety follow up. Treatments titrated once weekly to target mean fasting self-measured plasma glucose 80-100 mg/dl inclusive whilst avoiding hypoglycaemia. Titration conducted using algorithm up to max permitted dose of 40 dose steps for iGlarLixi or 40 U for insulin glargine. Previous metformin therapy continued at stable dose but all other oral antidiabetic agents were stopped at randomisation. Rescue therapy administered if HbA1c level>8%. at week 12 or later, if daily dose>40 dose steps or if >40 U necessary, or if safety concerns prevents up-titration to 40 dose steps/40U. Recommended rescue therapy was addition of rapid-acting insulin at main meal (additional GLP_1 RA, DPP-4 inhibitor, basal insulin, not permitted as rescue therapy).
Intervention(s)	• iGlarLixi once daily Fixed-rate combination IGlarLixi (Soliqua®/Suliqua®, Sanofi; 2 U iGlar to 1 mcg lixisenatide) once daily, within 1 hour of first meal of day, using SoloStar® pen. Starting dose between 10-20 dose steps (from 10 U iGlar/5 mcg lixi to 20 U iGlar/10 mcg lixi, inclusive) based on insulin dose on day before randomisation. Participants with previous basal insulin dose of <20U, initial iGlarLizi dose same as day before randomisation; if prior basal insulin administered twice daily then iGlarLixi starting dose was 80% of previous dose. If previous basal insulin dose was ≥20 U, starting dose was 20 dose steps.
Cointervention	• Basal insulin All participants continued to receive their background insulin therapy
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 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	• Insulin glargine once daily Subcutaneous injection of insulin glargine (Lantus, Sanofi), once daily, using SoloStar® pen. Injection time determined at randomisation and

	remained same throughout trial period. Insulin glargine dose between 10 and 20 dose steps (from 10 U glargine to 20 U glargine) based on insulin dose day before randomisation; if participants with previous basal insulin dose <20U, initial dose same as basal insulin dose on day before randomisation; if glargine dose administered twice daily, initial glargine dose 80% of previous dose. If previous basal insulin dose was ≥20 U, starting dose was 20 dose steps.
Number of participants	N=426 randomised (N=404 completers)
Duration of follow-up	30 weeks
Indirectness	None
Method of analysis	ITT ITT analysis for safety outcomes Modified ITT mITT analysis (all randomised participants who had baseline and at least one post-baseline primary or secondary efficacy variable measurement) including data regardless of compliance or rescue therapy use.

523.2. Study arms

523.2.1. iGlarLixi (N = 212)

IGlarLixi (2U insulin glargine to 1 mcg lixisenatide) for 30 weeks, in addition to basal insulin with or without other oral antidiabetic drugs.

523.2.2. Insulin glargine (N = 214)

Subcutaneous injection of insulin glargine for 30 weeks, in addition to basal insulin with or without other oral antidiabetic drugs.

523.3. Characteristics

523.3.1. Arm-level characteristics

Characteristic	iGlarLixi (N = 212)	Insulin glargine (N = 214)
% Male Sample size	n = 126 ; % = 59.4	n = 122 ; % = 57
Mean age (SD) (years) Mean (SD)	58.2 (8.7)	56.7 (9.3)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Chinese Sample size	n = 212 ; % = 100	n = 214 ; % = 100
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	13.3 (6.2)	11.4 (6)
Cardiovascular risk factors Nominal	NR	NR
Smoking status Nominal	NR	NR
Alcohol consumption Nominal	NR	NR
Presence of severe mental illness Nominal	NR	NR
People with significant cognitive impairment Nominal	NR	NR
People with a learning disability Nominal	NR	NR

Characteristic	iGlarLixi (N = 212)	Insulin glargine (N = 214)
Number of people with obesity Nominal	NR	NR
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Metformin Sample size	n = 166 ; % = 78.3	n = 167 ; % = 78
Using 2 oral antidiabetic at screening Sample size	n = 131 ; % = 61.8	n = 118 ; % = 55.1
Using 1 oral antidiabetic at screening Sample size	n = 66 ; % = 31.1	n = 80 ; % = 37.4
Not using oral antidiabetic at screening Sample size	n = 15 ; % = 7.1	n = 16 ; % = 7.5
Insulin glargine Sample size	n = 187 ; % = 88.2	n = 175 ; % = 81.8
Insulin detemir Sample size	n = 16 ; % = 7.5	n = 33 ; % = 15.4
NPH Sample size	n = 9 ; % = 4.2	n = 5 ; % = 2.3
Insulin degludec Sample size	n = 0 ; % = 0	n = 1 ; % = 0.5
Other oral antidiabetics at screening Sample size	n = 147 ; % = 69.3	n = 137 ; % = 64
Blood pressure-lowering medication used Nominal	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

524. Zang, 2016

Bibliographic Reference	Zang, L.; Liu, Y.; Geng, J.; Luo, Y.; Bian, F.; Lv, X.; Yang, J.; Liu, J.; Peng, Y.; Li, Y.; Sun, Y.; Bosch-Traberg, H.; Mu, Y.; Efficacy and safety of liraglutide versus sitagliptin, both in combination with metformin, in Chinese patients with type 2 diabetes: a 26-week, open-label, randomized, active comparator clinical trial; Diabetes Obes Metab; 2016; vol. 18 (no. 8); 803-11

524.1. 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	NCT02008682
Study type	Randomised controlled trial (RCT) Open-label, active-comparator, parallel-group randomised trial
Study location	China (25 sites)
Study setting	Outpatient
Study dates	12/2013 to 11/2014
Sources of funding	Funded by Novo Nordisk
Inclusion criteria	• Aged 18-80 years • Type 2 diabetes diagnosis • HbA1c level 7-10% inclusive • Treated with stable metformin monotherapy (≥1500 mg/day or maximum tolerated dose ≥1000 mg/day) for 60 days before screening • BMI≤45 kg/m2

Exclusion criteria	• Treatment with any antihyperglycaemic agent other than metformin within 60 days before screening • History of pancreatitis • Screening calcitonin value≥50 ng/l • History of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2 • Cancer diagnosis in previous 5 years • Impaired renal or hepatic function
Recruitment / selection of participants	Participants randomised 1:1 using interactive voice/web response system, stratified by baseline HbA1c level (≤8%, >8%). Participants unable after randomisation to tolerate minimum dose liraglutide 1.2 mg/day; sitagliptin 100 mg; metformin, unchanged dose) were discontinued from trial product.
Intervention(s)	• Liraglutide 1.8 mg daily Subcutaneous injection of liraglutide 1.8 mg daily for 26 weeks, at any (but consistent) time of day, in addition to stable metformin. Starting dose of 0.6 mg/day, escalated weekly by 0.6 mg/day, until maintenance 1.8 mg/day dose reached. If 1.8 mg/day not tolerated during maintenance period, dose could be reduced to 1.2 mg/day.
Cointervention	• Metformin Oral metformin remained stable throughout trial with dose/frequency remaining unchanged.
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 Key exclusion criteria included "impaired renal function".
Strata 4: People with type 2 diabetes mellitus and	Not stated/unclear

high cardiovascular risk	
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Comparator	• Sitagliptin 100 mg daily Oral sitagliptin 100 mg daily for 26 weeks, in addition to stable metformin.
Number of participants	N=368
Duration of follow-up	26 weeks
Indirectness	None
Method of analysis	Modified ITT mITT analysis (all randomised participants exposed to trial product and had post-randomisation data) for all efficacy outcomes, appears to assume everyone continued using trial medication.; safety analysis conducted for all randomised participants exposed to trial products
Additional comments	

524.2. Study arms

524.2.1. Liraglutide 1.8 mg daily (N = 184)

Subcutaneous injection of liraglutide 1.8 mg daily for 26 weeks, in addition to metformin.

524.2.2. Sitagliptin 100 mg daily (N = 184)

Oral sitagliptin 100 mg daily for 26 weeks, in addition to metformin.

524.3. Characteristics

524.3.1. Arm-level characteristics

Characteristic	Liraglutide 1.8 mg daily (N = 184)	Sitagliptin 100 mg daily (N = 184)
% Male Sample size	n = 102 ; % = 55.7	n = 117 ; % = 63.6
Mean age (SD) (years) Mean (SD)	51.7 (10.7)	51.4 (11)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Chinese Sample size	n = 183 ; % = 100	n = 184 ; % = 100
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	5.3 (4.4)	5.2 (5.4)
Cardiovascular risk factors Nominal	NR	NR

Characteristic	Liraglutide 1.8 mg daily (N = 184)	Sitagliptin 100 mg daily (N = 184)
Smoking status Nominal	NR	NR
Alcohol consumption Nominal	NR	NR
Presence of severe mental illness Nominal	NR	NR
People with significant cognitive impairment Nominal	NR	NR
People with a learning disability Nominal	NR	NR
Number of people with obesity Nominal	NR	NR
Other antidiabetic medication used Nominal	NR	NR
Blood pressure-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Angiotensin-converting enzyme inhibitors Sample size	n = 12 ; % = 6.6	n = 10 ; % = 5.4
Angiotensin II-antagonists Sample size	n = 1 ; % = 0.5	n = 1 ; % = 0.5
Beta-blockers Sample size	n = 12 ; % = 6.6	n = 10 ; % = 5.4
Statins/lipid-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Statins Sample size	n = 26 ; % = 14.2	n = 18 ; % = 9.8

Characteristic	Liraglutide 1.8 mg daily (N = 184)	Sitagliptin 100 mg daily (N = 184)
Other treatment being received Nominal	NR	NR

Baseline data for liraglutide arm is for N=183 because 1 participant withdrew before exposure to trial product.

525. Zannad, 2015

Bibliographic Reference	Zannad, Faiez; Cannon Christopher, P; Cushman William, C; Bakris George, L; Menon, Venu; Perez Alfonso, T; Fleck Penny, R; Mehta Cyrus, R; Kupfer, Stuart; Wilson, Craig; Lam, Hung; White William, B; EXAMINE, Investigators; Heart failure and mortality outcomes in patients with type 2 diabetes taking alogliptin versus placebo in EXAMINE: a multicentre, randomised, double-blind trial.; Lancet (London, England); 2015; vol. 385 (no. 9982); 2067-76

525.1. Study details

Secondary publication of another included study- see primary study for details	EXAMINE trial. Parent paper: White William, B, Cannon Christopher, P, Heller Simon, R et al. (2013) Alogliptin after acute coronary syndrome in patients with type 2 diabetes. The New England journal of medicine 369(14): 1327-35
Other publications associated with this study included in review	NA
Trial name / registration number	EXAMINE trial. NCT00968708

525.2. Study arms

525.2.1. Alogliptin - history of heart failure (N = 771)

525.2.2. Placebo - history of heart failure (N = 762)

525.2.3. Alogliptin - no history of heart failure (N = 1930)

525.2.4. Placebo - no history of heart failure (N = 1917)

526. Zelniker T, 2020

Bibliographic Reference	Zelniker T, A; Bonaca M, P; Furtado R, H.M; Mosenzon, O; Kuder J, F; Murphy S, A; Bhatt D, L; Leiter L, A; McGuire D, K; Wilding J, P.H; Budaj, A; Kiss R, G; Padilla, F; Gause-Nilsson, I; Langkilde A, M; Raz, I; Sabatine M, S; Wiviott S, D; Effect of dapagliflozin on atrial fibrillation in patients with type 2 diabetes mellitus: Insights from the DECLARE-TIMI 58 Trial; Circulation; 2020; 1227-1234

526.1. Study details

Secondary publication of another included study- see primary study for details	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 Mosenzon, Ofri, Wiviott Stephen, D, Cahn, Avivit et al. (2019) 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 7(8): 606-617 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

526.2. Study arms

526.2.1. 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.

526.2.2. 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.

527. Zelniker, 2021

Bibliographic Reference	Zelniker, Thomas A; Raz, Itamar; Mosenzon, Ofri; Dwyer, Jamie P; Heerspink, Hiddo H J L; Cahn, Avivit; Goodrich, Erica L; Im, Kyungah; Bhatt, Deepak L; Leiter, Lawrence A; McGuire, Darren K; Wilding, John P H; Gause-Nilsson, Ingrid; Langkilde, Anna Maria; Sabatine, Marc S; Wiviott, Stephen D; 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; 2021; vol. 6 (no. 7); 801-810

527.1. Study details

Secondary publication of another included study- see primary study for details	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 Mosenzon, Ofri, Wiviott Stephen, D, Cahn, Avivit et al. (2019) 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 7(8): 606-617 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 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

528. Zhang, 2020

Bibliographic Reference	Zhang, J.; Xian, T. Z.; Wu, M. X.; Li, C.; Pan, Q.; Guo, L. X.; Comparison of the effects of twice-daily exenatide and insulin on carotid intima-media thickness in type 2 diabetes mellitus patients: a 52-week randomized, open-label, controlled trial; Cardiovascular Diabetology; 2020; vol. 19 (no. 1); 48

528.1. Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.
Trial name / registration number	ChiCTR-1800015658
Study type	Randomised controlled trial (RCT)
Study location	China
Study setting	Hospital
Study dates	03/2015 - 06/2017
Sources of funding	Astra Zeneca and 3SBioInc.
Inclusion criteria	Diagnosed with T2DM according to the 1999 WHO criteria; aged between 20 and 75 years; glucose control was not satisfactory with HbA1c level between 7.5 and 11%; had taken at least two oral hypoglycemic drugs with higher than 1/2 of the maximum dose for at least 3 months.
Exclusion criteria	Type 1 diabetes; >75% stenosis of any segment of the carotid artery by high frequency B mode ultrasound; an acute cardiovascular event within 30 days prior to randomization; currently planned cardiovascular, carotid or peripheral artery revascularisation or cardiac valvular surgery; previous use of insulin or exenatide more than 1 month; an ALT or AST level >2.5 times the upper limit of normal range; serum creatinine concentration

	≥133 μmol/L for males or ≥106 μmol/L for females; history of pancreatitis; currently participating in or having completed another clinical trial within 3 months; or positive for human urinary chorionic gonadotropin or could not adopt a contraceptive method during the study.
Recruitment / selection of participants	Patients with uncontrolled type 2 diabetes on at least two oral antihyperglycaemic drugs were recruited from Chinese hospitals and randomised 1:1 to receive exenatide or insulin aspart administered subcutaneously.
Intervention(s)	Exenatide 5-10 μg twice daily 5 μg twice daily and increased to 10 μg twice daily after 4 weeks. Administered subcutaneously 1 hour before breakfast and dinner.
Cointervention	Patients were free to take antihyperglycaemic treatments except for sulfonylureas and nateglinide drugs. All patients were educated on suitable diet and exercise.
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 People were excluded if they had "an acute cardiovascular event within 30 days prior to randomization; currently planned cardiovascular, carotid or peripheral artery revascularization or cardiac valvular surgery". No information about events more than 30 days prior to randomisation. 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	Insulin initially 0.2 - 0.4 IU/Kg daily and then titrated. Administered subcutaneously.
Number of participants	N=80
Duration of follow-up	52-week
Indirectness	
Method of analysis	Modified ITT
Additional comments	Full analysis set

528.2. Study arms

528.2.1. Exenatide 5-10 µg twice daily (N = 27)

Administered subcutaneously 1 hour before breakfast and dinner.

528.2.2. Insulin (initially 0.2-0.4 IU/Kg then titrated) daily (N = 32)

Administered subcutaneously.

528.3. Characteristics

528.3.1. Arm-level characteristics

Characteristic	Exenatide 5-10 µg twice daily (N = 27)	Insulin (initially 0.2-0.4 IU/Kg then titrated) daily (N = 32)
% Male No of events	n = 19 ; % = 70	n = 14 ; % = 44
Mean age (SD) (years) Mean (SD)	58.85 (12.54)	58.03 (13.32)
Ethnicity Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	6.95 (5.32)	7.81 (6.02)
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	Exenatide 5-10 µg twice daily (N = 27)	Insulin (initially 0.2-0.4 IU/Kg then titrated) daily (N = 32)
ARB or ACE inhibitor No of events	n = 9 ; % = 33	n = 11 ; % = 34
Statins No of events	n = 4 ; % = 15	n = 11 ; % = 34
Aspirin No of events	n = 5 ; % = 19	n = 9 ; % = 28

529. Zhao, 2017

Bibliographic Reference	Zhao, Lijie; Sun, Tingli; Wang, Lina; Chitosan oligosaccharide improves the therapeutic efficacy of sitagliptin for the therapy of Chinese elderly patients with type 2 diabetes mellitus.; Therapeutics and clinical risk management; 2017; vol. 13; 739-750

529.1. Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.
Trial name / registration number	No additional information.
Study type	Randomised controlled trial (RCT)
Study location	China.
Study setting	Outpatient follow-up.
Study dates	May 2013 to August 2014.
Sources of funding	None declared.
Inclusion criteria	Type 2 diabetes mellitus for >5 years; HbA1c <10.5%; BMI >25-<39 kg/m2; stable weight for >3 months before the present experiment; no other serious diseases; fasting plasma glucose >130-<240 mg/dL.
Exclusion criteria	Type 1 diabetes mellitus; renal function impairment; FPG >270mg/dL; achieved weight loss by using medicines within 3 months before the present experiment; family history of type 2 diabetes mellitus; it was hard to chat with them.
Recruitment / selection of participants	No additional information.

Intervention(s)	Sitagliptin N=50 Sitagliptin 100 mg/day for 42 weeks.
Cointervention	No additional information.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Inclusion criteria states that patients were included if "they had no other serious diseases", but no definition of serious diseases is given. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Inclusion criteria states that patients were included if "they had no other serious diseases", but no definition of serious diseases is given. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	People without chronic kidney disease Exclusion criteria states "patients were excluded if they had renal function impairment". No information in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear

Subgroup 4: People with obesity	People with obesity
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	No additional information.
Comparator	Placebo N=50 Matching placebo for 42 weeks. Two other arms are included in the two (one receives chitosan oligosaccharide, one receives chitosan oligosaccharide and sitagliptin) - both of these were not extracted as they do not match the protocol criteria for this review.
Number of participants	100 (200 if you include the chitosan oligosaccharide arms).
Duration of follow-up	42 weeks.
Indirectness	No additional information.
Method of analysis	Not stated/unclear
Additional comments	No additional information.

529.2. Study arms

529.2.1. Sitagliptin (N = 50)

Sitagliptin 100 mg/day for 42 weeks. Concomitant therapy: No additional information.

529.2.2. Placebo (N = 50)

Matching placebo for 42 weeks. Concomitant therapy: No additional information.

529.3. Characteristics

529.3.1. Arm-level characteristics

Characteristic	Sitagliptin (N = 50)	Placebo (N = 50)
% Male Sample size	n = 29 ; % = 58	n = 31 ; % = 62
Mean age (SD) (years) Mean (SD)	69.1 (8.4)	67.8 (7.5)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Han zhu Sample size	n = 44 ; % = 88	n = 43 ; % = 86
Manchu Sample size	n = 4 ; % = 8	n = 5 ; % = 10
Mongolians Sample size	n = 1 ; % = 2	n = 1 ; % = 2
Tibetans Sample size	n = 1 ; % = 2	n = 1 ; % = 2
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	5.8 (4.6)	5.5 (4.2)
Cardiovascular risk factors Sample size	n = NR ; % = NR	n = NR ; % = NR
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Sitagliptin (N = 50)	Placebo (N = 50)
Sample size		
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR
Other antidiabetic medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Blood pressure-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Statins/lipid-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR

530. Zhou, 2019

Bibliographic Reference	Zhou, Z; Lindley R, I; Radholm, K; Jenkins, B; Watson, J; Perkovic, V; Mahaffey K, W; De Zeeuw, D; Fulcher, G; Shaw, W; Oh, R; Desai, M; Matthews D, R; Neal, B; Canagliflozin and Stroke in Type 2 Diabetes Mellitus: Results from the Randomized CANVAS Program Trials; Stroke; 2019; vol. 50 (no. 2); 396-404

530.1. 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 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
Trial name / registration number	CANVAS Program combines the CANVAS trial (NCT01032629) and the CANVAS-R trial (NCT01989754)
Study type	Randomised controlled trial (RCT)

531. Zinman, 2019

Bibliographic Reference	Zinman, B.; Aroda, V. R.; Buse, J. B.; Cariou, B.; Harris, S. B.; Hoff, S. T.; Pedersen, K. B.; Tarp-Johansen, M. J.; Araki, E.; Investigators, Pioneer; Efficacy, Safety, and Tolerability of Oral Semaglutide Versus Placebo Added to Insulin With or Without Metformin in Patients With Type 2 Diabetes: The PIONEER 8 Trial; Diabetes Care; 2019; vol. 42 (no. 12); 2262-2271

531.1. Study details

Secondary publication of another included study- see primary study for details	N/A
Other publications associated with this study included in review	N/A
Trial name / registration number	PIONEER 8 / NCT03021187
Study type	Randomised controlled trial (RCT)
Study location	Multinational study which took place in the following countries: Canada, France, Greece, India, Japan, Mexico, Poland, Russian Federation, United States of America.
Study setting	No additional information.
Study dates	Study conducted between 2 February 2017 and 18 January 2018
Sources of funding	PIONEER 8 was funded by Novo Nordisk A/S Denmark.
Inclusion criteria	• Male or female aged ≥18 years at tie of signing informed consent (aged ≥20 years in Japan). • Diagnosed with type 2 diabetes ≥90 days prior to screening. • HbA1c 7.0 to 9.5% (53-80 mmol/mol) inclusive. • Stable treatment with one of the following insulin regimens (minimum 10 U/day) ≥90 days prior to the day of screening: basal insulin alone, basal-bolus insulin in any combination, pre-mixed insulin including combinations of soluble insulins. Maximum 20%

	change in total daily dose was acceptable. Concomitant treatment with stable dose of metformin (≥1500 mg or maximum tolerated dose) ≥90 days prior to screening was permitted (in Japan concomitant metformin treatment was permitted only with a basal insulin regimen).
Exclusion criteria	• Pregnancy, breastfeeding, intention to become pregnant, or of child-bearing potential and not using contraception. • Receipt of any investigational medicinal product within 90 days prior to screening. • Any disorder which in the investigator's opinion might jeopardise patient safety or compliance with the protocol. • Family or personal history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma. • History of pancreatitis (acute or chronic). • History of major surgery of the stomach potentially affecting absorption of trial product. • Myocardial infarction, stroke, or hospitalisation for unstable angina and/or transient ischaemic attack within the past 180 days prior to screening. • Patients presently classified as New York Heart Association Class IV. • Planned coronary, carotid or peripheral artery revascularisation known at screening. • Renal impairment defined as estimated glomerular filtration rate <60 mL/min/1.73m2. • Treatment with any medication for diabetes or obesity, other than stated in the inclusion criteria within 90 days prior to screening. Short term insulin for acute illness for ≤14 days was allowed. • Known hypoglycaemia unawareness. • Proliferative retinopathy or maculopathy requiring acute treatment. Verified by fundus photography or dilated fundoscopy within 90 days prior to randomisation. • History or presence of malignant neoplasms within the last 5 years (except basal and squamous cell skin cancer, and in-situ carcinoma). • Patients with alanine aminotransferase >2.5 times upper limit of normal.
Recruitment / selection of participants	No further information.
Intervention(s)	1) Semaglutide 3 mg once daily administered via oral tablet. 2) Semaglutide 7 mg once daily administered via oral tablet. Treatment initiated at 3 mg dose with dose escalation to 7 mg after 4 weeks .

	3) Semaglutide 14 mg once daily administered via oral tablet. Treatment initiated at 3 mg dose with dose escalation to 7 mg after 4 weeks and to 14 mg after a further 4 weeks. Patients were instructed to take semaglutide in the morning in a fasting state with ≤120 mL water, and to wait for 30 minutes before eating or taking any other medication
Cointervention	Pre-existing insulin regimen, with or without metformin. Any of the following insulin regimens were permitted: basal alone, basal-bolus or pre-mixed insulin. Total daily insulin dose was reduced by 20% at randomisation and maintained until week 8 (unless an increase was required to prevent acute metabolic deterioration). During weeks 8 to 26, insulin dose could be adjusted without exceeding pre-randomisation dosage. During weeks 26 to 52, insulin dose could be freely adjusted at the investigator's discretion. Throughout the trial, insulin dose could be reduced as needed (it was recommended that any dose reduction be made based on the lowest of three self-monitored blood glucose values measured on three consecutive days). Metformin at ≥1500 mg or maximum tolerated dose.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear NY class IV excluded. No other information reported in methods or baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Any of the following were excluded: myocardial infarction, stroke, or hospitalisation for unstable angina and/or transient ischemic attack within the past 180 days prior to the day of screening. No further information in the methods or baseline characteristic about events pre-dating 180 days prior to the study.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Exclusion criteria state people with "renal impairment defined as estimated glomerular filtration rate <60 mL/min/1.73 m2 as per Chronic Kidney Disease Epidemiology Collaboration" were excluded. No further information in methods or baseline characteristics about CKD.

Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear Only mean duration of diabetes reported in baseline characteristics
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear Alanine aminotransferase >2.5 times upper limit of normal an exclusion criteria. No further information.
Subgroup 4: People with obesity	Not stated/unclear Only mean BMI reported in baseline characteristics
Subgroup 5: eGFR category at baseline	eGFR ≥30mL/min/1.73m2 eGFR >60 mL/min/1.73m2 an exclusion criterion
Subgroup 6: Albuminuria category at baseline	Not stated/unclear No information in inclusion/exclusion criteria or baseline characteristics
Population subgroups	
Comparator	Placebo once daily oral tablet identical in appearance to semaglutide tablets.
Number of participants	N=731
Duration of follow-up	52 week treatment period and 5 week follow-up period
Method of analysis	ITT

	Treatment policy estimand analysis correlates to ITT (included all randomised patients, irrespective of treatment discontinuation or initiation of rescue therapy). Modified ITT Safety endpoints were analysed using the safety analysis set (all participants who were exposed to at least one dose of trial medication).
Additional comments	

531.2. Study arms

531.2.1. Semaglutide 3 mg (N = 184)

3 mg semaglutide once daily tablet via oral administration.

531.2.2. Semaglutide 7 mg (N = 181)

7 mg semaglutide once daily tablet via oral administration.

531.2.3. Semaglutide 14 mg (N = 181)

14 mg semaglutide once daily tablet via oral administration.

531.2.4. Placebo (N = 184)

Matched placebo tablet once daily via oral administration.

531.3. Characteristics

531.3.1. Arm-level characteristics

Characteristic	Semaglutide 3 mg (N = 184)	Semaglutide 7 mg (N = 181)	Semaglutide 14 mg (N = 181)	Placebo (N = 184)
% Male Sample size	n = 102 ; % = 55.4	n = 103 ; % = 56.6	n = 85 ; % = 47	n = 105 ; % = 57.1
Mean age (SD) (years) Mean (SD)	61 (9)	60 (10)	61 (10)	60 (10)

Characteristic	Semaglutide 3 mg (N = 184)	Semaglutide 7 mg (N = 181)	Semaglutide 14 mg (N = 181)	Placebo (N = 184)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Hispanic or Latino Sample size	n = 18 ; % = 9.8	n = 24 ; % = 13.2	n = 30 ; % = 16.6	n = 25 ; % = 13.6
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	15.1 (7.9)	16.2 (8.6)	14.1 (8)	14.8 (7.9)
HbA1c (%) Mean (SD)	8.2 (0.7)	8.2 (0.7)	8.2 (0.7)	8.2 (0.7)
Cardiovascular risk factors Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Blood pressure Mean (SD)	NR (NR)	NR (NR)	NR (NR)	NR (NR)
Heart rate Mean (SD)	NR (NR)	NR (NR)	NR (NR)	NR (NR)
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Mean (SD)	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
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Semaglutide 3 mg (N = 184)	Semaglutide 7 mg (N = 181)	Semaglutide 14 mg (N = 181)	Placebo (N = 184)
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Weight (kg) Mean (SD)	85.9 (21.5)	87.1 (23.6)	84.6 (21)	86 (21.4)
BMI (kg/m²) Mean (SD)	31 (6.8)	31.1 (7)	30.8 (6.3)	31 (6.5)
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Cholesterol and lipid levels Mean (SD)	NR (NR)	NR (NR)	NR (NR)	NR (NR)
Albumin creatinine ratio Mean (SD)	NR (NR)	NR (NR)	NR (NR)	NR (NR)
eGFR mL/min/1.73m2 Mean (SD)	NR (NR)	NR (NR)	NR (NR)	NR (NR)
Other antidiabetic medication used Insulin regimen at screening Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Basal Sample size	n = 76 ; % = 41.3	n = 76 ; % = 41.8	n = 75 ; % = 41.4	n = 79 ; % = 42.9
Basal-bolus Sample size	n = 71 ; % = 38.6	n = 72	n = 70 ; % = 38.7	n = 71 ; % = 38.6
Premixed Sample size	n = 35 ; % = 19	n = 28 ; % = 15.4	n = 34 ; % = 18.8	n = 32 ; % = 17.4
Bolus Sample size	n = 1 ; % = 0.5	n = 2 ; % = 1.1	n = 1 ; % = 0.6	n = 1 ; % = 0.5
Basal and premixed Sample size	n = 0 ; % = 0	n = 2 ; % = 1.1	n = 0 ; % = 0	n = 1 ; % = 0.5

Characteristic	Semaglutide 3 mg (N = 184)	Semaglutide 7 mg (N = 181)	Semaglutide 14 mg (N = 181)	Placebo (N = 184)
Bolus and premixed Sample size	n = 1 ; % = 0.5	n = 2 ; % = 1.1	n = 1 ; % = 0.6	n = 0 ; % = 0
Blood pressure-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Statins/lipid-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Other treatment being received Insulin regimen at screening Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Race Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 89 ; % = 48.4	n = 95 ; % = 52.2	n = 94 ; % = 51.9	n = 98 ; % = 53.3
Black or African American Sample size	n = 15 ; % = 8.2	n = 10 ; % = 5.5	n = 11 ; % = 6.1	n = 13 ; % = 17.1
Asian Sample size	n = 66 ; % = 35.9	n = 66 ; % = 36.3	n = 66 ; % = 36.5	n = 65 ; % = 35.3
Other Includes American Indian or Alaska Native, Native Hawaiian or Pacific Islander, Other and Not Applicable (race not recorded in France only) Sample size	n = 14 ; % = 7.6	n = 11 ; % = 6	n = 10 ; % = 5.5	n = 8 ; % = 4.3

532. Zinman, 2019

Bibliographic Reference	Zinman, B.; Bhosekar, V.; Busch, R.; Holst, I.; Ludvik, B.; Thielke, D.; Thrasher, J.; Woo, V.; Philis-Tsimikas, A.; Semaglutide once weekly as add-on to SGLT-2 inhibitor therapy in type 2 diabetes (SUSTAIN 9): a randomised, placebo-controlled trial; Lancet Diabetes Endocrinol; 2019; vol. 7 (no. 5); 356-367

532.1. Study details

Secondary publication of another included study- see primary study for details	N/A
Other publications associated with this study included in review	N/A
Trial name / registration number	SUSTAIN 9 / NCT03086330
Study type	Randomised controlled trial (RCT) Full analysis set used for analysis of HbA1c and weight change. Full analysis set = all randomised patients.
Study location	Study conducted in six countries: Austria, Canada, Japan, Norway, Russia, and in the USA.
Study setting	61 centres including hospitals, clinical research units, and private offices.
Study dates	Enrolment and treatment assignment took place between 15 March and 4 December 2017.
Sources of funding	Novo Nordisk
Inclusion criteria	• Patients with type 2 diabetes aged ≤18 years (≥20 years in Japan) • HbA1c level of 7.0 - 10.0 % (53-86 mmol/mol) at the time of screening • On stable treatment with an SGLT-2 inhibitor (as monotherapy, or in combination with a sulfonylurea or metformin [≥1500 mg/day or

	maximum tolerated dose]), and to have started the SGLT-2 inhibitor treatment at least 90 days before screening
Exclusion criteria	• Estimated glomerular filtration rate of <60 mL/min per 1.73m2 • Present New York Heart Association class IV heart failure • Proliferative retinopathy or maculopathy requiring acute treatment, verified by fundus photography or dilated fundoscopy within 90 days before randomisation • Pregnancy, breastfeeding, intention to become pregnant or potential to become pregnant • Alanine aminotransferase levels >2.5 times upper limit of normal • Family (first degree relative) or personal history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma • History or presence of acute or chronic pancreatitis • History of diabetic ketoacidosis • Myocardial infarction, stroke, hospitalisation for unstable angina, or transient ischaemic attack within 180 days prior to screening • Planned coronary, carotid or peripheral artery revascularisation known on day of screening • Treatment with any medication for diabetes or obesity other than those stated in the inclusion criteria. Short term (maximum 14 days) insulin therapy prior to screening was permitted • Presence or history of malignant neoplasms within 5 years prior to screening. Basal and squamous skin cancer and any carcinoma in situ were allowed.
Recruitment / selection of participants	
Intervention(s)	Semaglutide 1.0 mg administered via once weekly subcutaneous injection using a prefilled pen injector. Injections were given at the same day each week at any time of day (irrespective of meals) at the thigh, abdomen or upper arm. For the first 8 weeks, patients followed a fixed dose-escalation schedule, in which the maintenance dose of semaglutide (1.0 mg) was reached after 4 weeks of semaglutide 0.25 mg followed by 4 weeks of semaglutide 0.5 mg.
Cointervention	Existing antidiabetic medications, including SGLT-2 inhibitors, were continued for the trial duration. Rescue medication was defined as intensification of background treatment or initiation of new glucose-lowering medications. Rescue medication was administered at the discretion of the investigator and was consistent with ADA/EASD guidelines. GLP-1 agonists, DPP-4 inhibitors and amylin analogues were not permitted.

Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Study excluded people with NY class IV heart failure. No further information.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Not an inclusion/exclusion criteria. No information reported in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	People without chronic kidney disease Not an inclusion/exclusion criteria. Baseline characteristics table reports that 8.3% of participants had diabetic nephropathy.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear Mean duration only reported in baseline characteristics
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear Alanine aminotransferase levels >2.5 times upper limit of normal an exclusion criterion. No information in baseline characteristics.
Subgroup 4: People with obesity	Not stated/unclear Not an inclusion or exclusion criteria. Mean BMI only in baseline characteristics.

Subgroup 5: eGFR category at baseline	eGFR ≥30mL/min/1.73m2 eGFR <60 mL/min/1.73m2 an exclusion criterion.
Subgroup 6: Albuminuria category at baseline	Not stated/unclear No information in the inclusion/exclusion criteria and not reported in baseline characteristics
Population subgroups	
Comparator	Placebo 1.0 mg administered via once weekly subcutaneous injection using a prefilled pen injector. Injections were given at the same day each week at any time of day (irrespective of meals) at the thigh, abdomen or upper arm. Dose escalation schedules per the intervention (4 weeks of semaglutide 0.25 mg, followed by 4 weeks of semaglutide 0.5 mg and then 1.0,mg maintenance dose thereafter).
Number of participants	N = 302
Duration of follow-up	30 week treatment period plus 5 week follow up
Method of analysis	ITT Full analysis set used for analysis of primary, confirmatory secondary and secondary efficacy endpoints. Full analysis set = all randomised patients. Modified ITT
Additional comments	Safety outcomes analysed using the safety analysis set (all patients who received at least one dose of trial medication).

532.2. Study arms

532.2.1. Semaglutide 1.0 mg (N = 151)

Semaglutide 1.0 mg administered via once weekly subcutaneous injection

532.2.2. Placebo (N = 151)

Volume matched placebo administered via once weekly subcutaneous injection

532.3. Characteristics

532.3.1. Arm-level characteristics

Characteristic	Semaglutide 1.0 mg (N = 151)	Placebo (N = 151)
% Male Sample size	n = 89 ; % = 58.9	n = 87 ; % = 57.6
Mean age (SD) (years) Mean (SD)	57.5 (8.9)	56.6 (10.1)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Hispanic or Latino Sample size	n = 9 ; % = 6	n = 13 ; % = 8.6
Not Hispanic or Latino Sample size	n = 142 ; % = 94	n = 138 ; % = 91.4
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)	9.8 (6.3)	9.6 (5.9)
HbA1c (%) Mean (SD)	8 (0.8)	8.1 (0.8)
Cardiovascular risk factors Sample size	n = NR ; % = NR	n = NR ; % = NR
Blood pressure (mmHg) Mean (SD)	NA (NA)	NA (NA)
Systolic blood pressure Mean (SD)	127.2 (14)	128.6 (15)
Diastolic blood pressure Mean (SD)	77.8 (8)	79.9 (9.5)

Characteristic	Semaglutide 1.0 mg (N = 151)	Placebo (N = 151)
Heart rate (beats per minute) Pulse rate Mean (SD)	73.7 (11.1)	74.6 (9.6)
Smoking status Sample size	n = NA ; % = NA	n = NA ; % = NA
Current Sample size	n = 23 ; % = 15.2	n = 22 ; % = 14.6
Never Sample size	n = 89 ; % = 58.9	n = 82 ; % = 54.3
Previous Sample size	n = 39 ; % = 25.8	n = 47 ; % = 31.1
Alcohol consumption Mean (SD)	NR (NR)	NR (NR)
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR
Weight Mean (SD)	89.6 (19.5)	93.8 (22.3)
BMI Mean (SD)	31.1 (6.2)	32.7 (6.9)
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR
Cholesterol and lipid levels Mean (SD)	NA (NA)	NA (NA)
Total cholesterol Mean (SD)	4.4 (25.7)	4.5 (25.5)

Characteristic	Semaglutide 1.0 mg (N = 151)	Placebo (N = 151)
HDL cholesterol Mean (SD)	1.1 (28.6)	1.2 (23.3)
LDL cholesterol Mean (SD)	2.3 (40.6)	2.3 (45.7)
Triglycerides Mean (SD)	1.7 (60.8)	1.9 (51.4)
Albumin creatinine ratio Mean (SD)	NR (NR)	NR (NR)
eGFR mL/min/1.73m2 (ml/min/1.73 m²) Mean (SD)	94.5 (15.3)	96 (15.1)
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
SGLT2 inhibitors Sample size	n = 150 ; % = 99.3	n = 151 ; % = 100
Metformin Sample size	n = 106 ; % = 70.2	n = 110 ; % = 72.8
Sulfonylurea Sample size	n = 19 ; % = 12.6	n = 20 ; % = 13.2
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
Race Sample size	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 100 ; % = 66.2	n = 109 ; % = 72.2

Characteristic	Semaglutide 1.0 mg (N = 151)	Placebo (N = 151)
Asian Sample size	n = 36 ; % = 23.8	n = 35 ; % = 23.2
Black or African American Sample size	n = 9 ; % = 6	n = 4 ; % = 2.6
American Indian or Alaska Native Sample size	n = 2 ; % = 1.3	n = 0
Other Includes Guyanese, Indian, Latino, Metis, Turkish and West Indian Sample size	n = 4 ; % = 2.6	n = 3 ; % = 2

533. Zinman, 2009

Bibliographic Reference	Zinman, B.; Gerich, J.; Buse, J. B.; Lewin, A.; Schwartz, S.; Raskin, P.; Hale, P. M.; Zdravkovic, M.; Blonde, L.; Efficacy and safety of the human glucagon-like peptide-1 analog liraglutide in combination with metformin and thiazolidinedione in patients with type 2 diabetes (LEAD-4 Met+TZD); Diabetes Care; 2009; vol. 32 (no. 7); 1224-30

533.1. Study details

Secondary publication of another included study- see primary study for details	N/A
Other publications associated with this study included in review	N/A
Trial name / registration number	LEAD-4 Met+TZD / NCT00333151
Study type	Randomised controlled trial (RCT)
Study location	Multi-centre (96 sites) study conducted in the USA and Canada.
Study setting	No further information
Study dates	Study dates not stated.
Sources of funding	Funding source not clearly stated. Statistical and writing assistance was provided by staff from Novo Nordisk.
Inclusion criteria	• People with type 2 diabetes aged between 18 and 80 years • HbA1c between 7 and 11% (pre-study oral anti-diabetic monotherapy for ≥3 months) or between 7 to 10% (if pre-study combination oral anti-diabetic therapy for ≥3 months) • BMI ≤45 kg/m2
Exclusion criteria	• Use of insulin during the previous 3 months (except short-term treatment) were excluded

Recruitment / selection of participants	Patients who tolerated the final doses of metformin and rosiglitazone and had fasting plasma glucose (FPG) values 135-230 mg/dL after 6 weeks of treatment at titrated doses were eligible for randomisation.
Intervention(s)	1) 1.2 mg liraglutide once daily, administered via subcutaneous injection. Liraglutide initiated with100 µL injection corresponding to 0.6 mg dose, increased to 1.2 mg/day after 1 week (200 µL injection). The titration period was followed by a 24 week maintenance period. Liraglutide was administered via subcutaneous injection once daily at any time of day in the upper arm, thigh or abdomen using a pre-filled pen device. 2) 1.8 mg liraglutide once daily, administered via subcutaneous injection Liraglutide initiated with 100 µL injection corresponding to 0.6 mg dose, increased to 1.2 mg/day after 1 week (200 µL injection) and then to 1.8 mg/day (300 µL injection) after an additional week. The titration period was followed by a 24 week maintenance period. Liraglutide was administered via subcutaneous injection once daily at any time of day in the upper arm, thigh or abdomen using a pre-filled pen device.
Cointervention	Metformin and rosiglitazone. 6 to 9 week run in and dose titration period took place prior to randomisation. Prior treatment with other oral antidiabetic medicines other than metformin and rosiglitazone was discontinued. Patients previously treated with pioglitazone underwent rosiglitazone dose titration (by transferring to rosiglitazone at the corresponding dose) or went straight to the maximum dose of rosiglitazone if they were previously taking the maximum dose of pioglitazone. Metformin was started at 500 mg at breakfast and increased weekly by increments of 500 mg to a final dose of 2,000 mg/day (1,000 mg at breakfast and 1,000 mg at evening meal time). Rosiglitazone was started at 4 mg in the morning and increased to 8 mg/day (4 mg in the morning and 4 mg in the evening).
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.

Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear Only average duration of diabetes reported in baseline characteristics
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear BMI ≤45 kg/m2 in the inclusion criteria. Only mean BMI reported in baseline characteristics.
Subgroup 5: eGFR category at baseline	Not stated/unclear No information in inclusion/exclusion or baseline characteristics.
Subgroup 6: Albuminuria category at baseline	Not stated/unclear

Population subgroups	No information in inclusion/exclusion or baseline characteristics.
Comparator	Placebo once daily administered via subcutaneous injection. Placebo initiated with 100 µL injection corresponding to 0.6 mg dose, increased to 1.2 mg/day after 1 week (200 µL injection). The titration period was followed by a 24 week maintenance period. Placebo was administered via subcutaneous injection once daily at any time of day in the upper arm, thigh or abdomen using a pre-filled pen device.
Number of participants	N = 533
Duration of follow-up	26 weeks
Method of analysis	Modified ITT Authors state that efficacy end points were analysed based on the intent-to-treat population, defined as participants who were exposed to at least one dose of trial product and had one post baseline measurement of the parameter.

533.2. Study arms

533.2.1. Liraglutide 1.2 mg (N = 178)

100 µL subcutaneous injection corresponding to 0.6 mg dose, increased to 1.2 mg/day after 1 week (200 µL injection). The titration period was followed by a 24 week maintenance period.

533.2.2. Liraglutide 1.8 mg (N = 178)

100 µL subcutaneous injection corresponding to 0.6 mg dose, increased to 1.2 mg/day after 1 week (200 µL injection) and then to 1.8 mg/day (300 µL injection) after an additional week. The titration period was followed by a 24 week maintenance period.

533.2.3. Placebo (N = 177)

Initial 100 µL subcutaneous injection (corresponding to 0.6 mg/ day, increased to 1.2 mg/day (200 µL injection) after 1 week.

533.3. Characteristics

533.3.1. Arm-level characteristics

Characteristic	Liraglutide 1.2 mg (N = 178)	Liraglutide 1.8 mg (N = 178)	Placebo (N = 177)
% Male Sample size	n = 101 ; % = 57	n = 91 ; % = 51	n = 110 ; % = 62
Mean age (SD) (years) Mean (SD)	55 (10)	51 (49)	55 (10)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Hispanic or Latino Sample size	n = 23 ; % = 13	n = 28 ; % = 16	n = 28 ; % = 16
Not hispanic or latino Sample size	n = 155 ; % = 87	n = 150 ; % = 84	n = 149 ; % = 84
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	9 (6)	9 (6)	9 (6)
HbA1c Mean (SD)	8.5 (1.2)	8.6 (1.2)	8.4 (1.2)
Cardiovascular risk factors Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Blood pressure (mmHg) Mean (SD)	NA (NA)	NA (NA)	NA (NA)
Systolic blood pressure Mean (SD)	129 (14.8)	126 (14.2)	128 (14.5)
Diastolic blood pressure Mean (SD)	75.8 (9)	75.2 (8.4)	76.2 (9.2)

Characteristic	Liraglutide 1.2 mg (N = 178)	Liraglutide 1.8 mg (N = 178)	Placebo (N = 177)
Heart rate Mean (SD)	NR (NR)	NR (NR)	NR (NR)
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Mean (SD)	NR (NR)	NR (NR)	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	% = NR	n = NR ; % = NR	n = NR ; % = NR
Weight Mean (SD)	NR (NR)	NR (NR)	NR (NR)
BMI (kg/m²) Mean (SD)	33.2 (5.4)	33.5 (5.1)	33.9 (5.2)
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Cholesterol and lipid levels (mmol/L) Mean (SD)	NA (NA)	NA (NA)	NA (NA)
Total cholesterol Mean (SD)	5.01 (1.33)	5.17 (1.43)	4.99 (1.34)
LDL cholesterol Mean (SD)	2.82 (0.95)	2.96 (1.08)	2.77 (0.95)
VLDL cholesterol Mean (SD)	0.74 (0.38)	0.76 (0.38)	0.71 (0.36)

Characteristic	Liraglutide 1.2 mg (N = 178)	Liraglutide 1.8 mg (N = 178)	Placebo (N = 177)
HDL cholesterol Mean (SD)	1.26 (0.32)	1.27 (0.31)	1.25 (0.28)
Triglycerides Mean (SD)	2.41 (2.24)	2.39 (1.88)	2.74 (2.8)
Free Fatty Acids Mean (SD)	0.51 (0.22)	0.55 (0.27)	0.52 (0.34)
Albumin creatinine ratio Mean (SD)	NR (NR)	NR (NR)	NR (NR)
eGFR mL/min/1.73m2 Mean (SD)	NR (NR)	NR (NR)	NR (NR)
Other antidiabetic medication used Pre-study oral anti-diabetes treatment Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Monotherapy Sample size	n = 29 ; % = 16	n = 29 ; % = 16	n = 32 ; % = 18
Combination therapy Sample size	n = 149 ; % = 84	n = 149 ; % = 84	n = 145 ; % = 82
Blood pressure-lowering medication used Mean (SD)	NR (NR)	NR (NR)	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
Race Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Caucasian Sample size	n = 144 ; % = 81	n = 148 ; % = 83	n = 149 ; % = 84

Characteristic	Liraglutide 1.2 mg (N = 178)	Liraglutide 1.8 mg (N = 178)	Placebo (N = 177)
Black Sample size	n = 27 ; % = 15	n = 18 ; % = 10	n = 18 ; % = 10
Asian Sample size	n = 2 ; % = 1	n = 5 ; % = 3	n = 3 ; % = 2
American Indian Sample size	n = 2 ; % = 1	n = 2 ; % = 1	n = 2 ; % = 1
Other Sample size	n = 3 ; % = 2	n = 5 ; % = 3	n = 5 ; % = 3

534. Zinman, 2014

Bibliographic Reference	Zinman, Bernard; Inzucchi, Silvio E; Lachin, John M; Wanner, Christoph; Ferrari, Roberto; Fitchett, David; Bluhmki, Erich; Hantel, Stefan; Kempthorne-Rawson, Joan; Newman, Jennifer; Johansen, Odd Erik; Woerle, Hans-Juergen; Broedl, Uli C; Rationale, design, and baseline characteristics of a randomized, placebo-controlled cardiovascular outcome trial of empagliflozin (EMPA-REG OUTCOME TM).; Cardiovascular diabetology; 2014; vol. 13; 102

534.1. Study details

Secondary publication of another included study- see primary study for details	EMPA-REG OUTCOME trial. Zinman, Bernard, Wanner, Christoph, Lachin John, M et al. (2015) Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. The New England journal of medicine 373(22): 2117-28
Other publications associated with this study included in review	Butler, Javed, Zannad, Faiez, Fitchett, David et al. (2019) Empagliflozin Improves Kidney Outcomes in Patients With or Without Heart Failure. Circulation. Heart failure 12(6): e005875 Wanner, Christoph, Lachin John, M, Inzucchi Silvio, E et al. (2018) Empagliflozin and Clinical Outcomes in Patients With Type 2 Diabetes Mellitus, Established Cardiovascular Disease, and Chronic Kidney Disease. Circulation 137(2): 119-129
Trial name / registration number	EMPA-REG OUTCOME. ClinicalTrials.gov number, NCT01131676

535. Zinman, 2015

Bibliographic Reference	Zinman, Bernard; Wanner, Christoph; Lachin John, M; Fitchett, David; Bluhmki, Erich; Hantel, Stefan; Mattheus, Michaela; Devins, Theresa; Johansen Odd, Erik; Woerle Hans, J; Broedl Uli, C; Inzucchi Silvio, E; EMPA-REG, OUTCOME; Investigators; Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes.; The New England journal of medicine; 2015; vol. 373 (no. 22); 2117-28

535.1. Study details

Secondary publication of another included study- see primary study for details	This is the primary study of the EMPA-REG trial. The information for the data extraction from this trial is included in this record.
Other publications associated with this study included in review	Wanner, Christoph, Lachin John, M, Inzucchi Silvio, E et al. (2018) Empagliflozin and Clinical Outcomes in Patients With Type 2 Diabetes Mellitus, Established Cardiovascular Disease, and Chronic Kidney Disease. Circulation 137(2): 119-129 Zinman, Bernard, Inzucchi, Silvio E, Lachin, John M et al. (2014) Rationale, design, and baseline characteristics of a randomized, placebo-controlled cardiovascular outcome trial of empagliflozin (EMPA-REG OUTCOME TM). Cardiovascular diabetology 13: 102 Butler, Javed, Zannad, Faiez, Fitchett, David et al. (2019) Empagliflozin Improves Kidney Outcomes in Patients With or Without Heart Failure. Circulation. Heart failure 12(6): e005875
Trial name / registration number	EMPA-REG OUTCOME. ClinicalTrials.gov number, NCT01131676
Study type	Randomised controlled trial (RCT)
Study location	42 countries - not specified
Study setting	590 sites - North America [plus Australia and New Zealand], Latin America, Europe, Africa, or Asia
Study dates	Randomization from September 2010 through April 2013; date for last data collection point and follow-up not outlined

Sources of funding	Supported by Boehringer Ingelheim and Eli Lilly
Inclusion criteria	People with type 2 diabetes; adults (age 18 years of age or over); body mass index of 45 or less; eGFR of at least 30mL/min/1.73m2; established cardiovascular disease; no glucose-lowering agents for at least 12 weeks before randomisation and had a glycated hemoglobin level of at least 7.0% and no more than 9.0% or had received stable glucose-lowering therapy for at least 12 weeks before randomisation and had a glycated haemoglobin level of at least 7.0% and no more than 10.0%.
Exclusion criteria	Uncontrolled hyperglycaemia with glucose >240 mg/dL after an overnight fast during placebo run-in and confirmed by a second measurement (not on the same day); indication of liver disease, defined by serum levels of alanine aminotransferase, aspartate aminotransferase or alkaline phosphatase above 3x upper limit of normal during screening or run-in phase; planned cardiac surgery or angioplasty within 3 months; estimated glomerular filtration rate <30 mL/min/1.73 m2 (according to the Modification of Diet in Renal Disease equation) at screening or during the run-in phase; bariatric surgery within the past two years and other gastrointestinal surgeries that induce chronic malabsorption; blood dyscrasias or any disorders causes haemolysis or unstable red blood cells; medical history of cancer (except for basal cell carcinoma) and/or treatment for cancer within the last 5 years; contraindication to background therapy according to the local label; treatment with anti-obesity drugs 3 months prior to informed consent or any other treatment at time of screening leading to unstable body weight; treatment with systemic steroids at time of informed consent or change in dosage or thyroid hormones within 6 weeks prior to informed consent; any uncontrolled endocrine disorder except type 2 diabetes; pre-menopausal women (last menstruation no more than 1 year prior to informed consent) who were nursing, pregnant, or of child-bearing potential and were not practicing an acceptable method of birth control, or did not plan to continue using this method throughout the study, or did not agree to submit the periodic pregnancy testing during the trial (acceptable methods of birth control include tubal ligation, transdermal patch, intrauterine devices/systems, oral, implantable or injectable contraceptives, sexual abstinence, double barrier method, vasectomy of partner); alcohol or drug abuse within 3 months of informed consent that would interfere with trial participation or any ongoing condition leading to decreased compliance with study procedures or study drug intake; intake of an investigational drug in another trial within 30 days prior to intake of study medication in this trial or participating in another trial involving an investigational drug and/or follow-up; any clinical condition that would jeopardize patient safety while participating in this clinical trial (in Canada, this included current genito-urinal infection or genito-urinal infection within 2 weeks prior to informed consent); acute coronary syndrome, stroke or transient ischaemic attack within 2 months prior to informed consent; in South Africa: blood pressure >160/100 mmHg at screening.
Recruitment / selection of participants	No additional information.

Intervention(s)	Empagliflozin N=4687 10mg or 20mg of empagliflozin orally once a day. Concomitant therapy: Background glucose-lowering therapy was to remain unchanged for the first 12 weeks after randomisation, although intensification was permitted if the person had a confirmed fasting glucose level of more than 240mg/dL (>13.3 mmol/L). In cases of medical necessity, dose reduction or discontinuation of background medication could occur. After week 12, investigators were encouraged to adjust glucose-lowering therapy at their discretion to achieve glycemic control according to local guidelines.
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Around 10% of people had heart failure
Strata 2: People with atherosclerotic cardiovascular disease	People with atherosclerotic cardiovascular diseases Inclusion states "All the patients had established cardiovascular disease (defined by at least 1 of the following: history of myocardial infarction >2 months prior to informed consent; evidence of multi-vessel coronary artery disease; evidence of single-vessel coronary artery disease, ≥50% luminal narrowing during angiography; unstable angina >2 months prior to consent with evidence of single- or multi-vessel coronary artery disease; history of stroke (ischemic or hemorrhagic) >2 months prior to consent; occlusive peripheral artery)". Baseline characteristics: "more than 99% of patients had established cardiovascular disease".
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Mixed population Wanner 2018 defines 1498 people in the empagliflozin arm and 752 people in the placebo arm as having prevalent kidney disease in a paper discussing people with chronic kidney disease, therefore accepting the definition of chronic kidney disease provided by the study.
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 Assumed by mean age and time since diagnosis of type 2 diabetes
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	People with obesity Based on mean BMI
Subgroup 5: eGFR category at baseline	eGFR ≥30mL/min/1.73m2
Subgroup 6: Albuminuria category at baseline	Mixed population
Population subgroups	Subgroups reported for cardiovascular mortality and 3-point MACE including: race, ethnicity, body mass index, eGFR, cardiovascular risk, antidiabetic treatment,
Comparator	Placebo N=2333 Matching placebo orally once a day. Concomitant therapy: Background glucose-lowering therapy was to remain unchanged for the first 12 weeks after randomisation, although intensification was permitted if the person had a confirmed fasting glucose level of more than 240mg/dL (>13.3 mmol/L). In cases of medical necessity, dose reduction or discontinuation of background medication could occur. After week 12, investigators were encouraged to adjust glucose-lowering therapy at their discretion to achieve glycemic control according to local guidelines.
Number of participants	7020
Duration of follow-up	3.1 years (mean)
Indirectness	Not downgraded for indirectness - 77% of people were receiving previous glucose-lowering therapy

Method of analysis	ITT
Additional comments	Cox proportional-hazards model, with study group, age, sex, baseline body-mass index, baseline glycated haemoglobin level, baseline eGFR, and geographic region as factors; Kaplan–Meier estimates for death from any cause;

535.2. Study arms

535.2.1. Empagliflozin (N = 4687)

10mg or 20mg of empagliflozin orally once a day. Concomitant therapy: Background glucose-lowering therapy was to remain unchanged for the first 12 weeks after randomisation, although intensification was permitted if the person had a confirmed fasting glucose level of more than 240mg/dL (>13.3 mmol/L). In cases of medical necessity, dose reduction or discontinuation of background medication could occur. After week 12, investigators were encouraged to adjust glucose-lowering therapy at their discretion to achieve glycemic control according to local guidelines.

535.2.2. Placebo (N = 2333)

Matching placebo orally once a day. Concomitant therapy: Background glucose-lowering therapy was to remain unchanged for the first 12 weeks after randomisation, although intensification was permitted if the person had a confirmed fasting glucose level of more than 240mg/dL (>13.3 mmol/L). In cases of medical necessity, dose reduction or discontinuation of background medication could occur. After week 12, investigators were encouraged to adjust glucose-lowering therapy at their discretion to achieve glycemic control according to local guidelines.

535.3. Characteristics

535.3.1. Arm-level characteristics

Characteristic	Empagliflozin (N = 4687)	Placebo (N = 2333)
% Male Sample size	n = 3336 ; % = 71.2	n = 1680 ; % = 72
Mean age (SD) (years) Mean (SD)	63.1 (8.6)	63.2 (8.8)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Empagliflozin (N = 4687)	Placebo (N = 2333)
White Sample size	n = 3403 ; % = 72.6	n = 1678 ; % = 71.9
Asian Sample size	n = 1006 ; % = 21.5	n = 511 ; % = 21.9
Black/African-American Sample size	n = 237 ; % = 5.1	n = 120 ; % = 5.1
Other/missing Sample size	n = 41 ; % = 0.9	n = 24 ; % = 1
Not hispanic or latino Sample size	n = 3835 ; % = 81.8	n = 1912 ; % = 82
Hispanic or Latino Sample size	n = 847 ; % = 18.1	n = 418 ; % = 17.9
Comorbidities Sample size	n = 4657 ; % = 99.4	n = 2307 ; % = 98.9
Coronary artery disease Sample size	n = 3545 ; % = 75.6	n = 1763 ; % = 75.6
Multi-vessel coronary artery disease Sample size	n = 2179 ; % = 46.5	n = 1100 ; % = 47.1
History of myocardial infarction Sample size	n = 2190 ; % = 46.7	n = 1083 ; % = 46.4
Coronary artery bypass graft Sample size	n = 1175 ; % = 25.1	n = 563 ; % = 24.1
History of stroke Sample size	n = 1084 ; % = 23.1	n = 553 ; % = 23.7
Peripheral artery disease Sample size	n = 982 ; % = 21	n = 479 ; % = 20.5
Single vessel coronary artery disease Sample size	n = 498 ; % = 10.6	n = 238 ; % = 10.2
cardiac failure	n = 462 ; % = 9.9	n = 244 ; % = 10.5

Characteristic	Empagliflozin (N = 4687)	Placebo (N = 2333)
Sample size		
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed Sample size	n = NA ; % = NA	n = NA ; % = NA
≤1 years Sample size	n = 128 ; % = 2.7	n = 52 ; % = 2.2
>1 to 5 years Sample size	n = 712 ; % = 15.2	n = 371 ; % = 15.9
>5 to 10 years Sample size	n = 1175 ; % = 25.1	n = 571 ; % = 24.5
>10 years Sample size	n = 2672 ; % = 57	n = 1339 ; % = 57.4
HbA1c Mean (SD)	NR (NR)	NR (NR)
Cardiovascular risk factors Mean (SD)	NA (NA)	NA (NA)
Blood pressure (mmHg) Mean (SD)	NA (NA)	NA (NA)
Systolic blood pressure Mean (SD)	135.3 (16.9)	135.8 (17.2)
Diastolic blood pressure Mean (SD)	76.6 (9.7)	76.8 (10.1)
Heart rate Mean (SD)	NR (NR)	NR (NR)
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Empagliflozin (N = 4687)	Placebo (N = 2333)
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 (kg) Mean (SD)	86.2 (18.9)	86.6 (19.1)
BMI (kg/m2) Mean (SD)	30.6 (5.3)	30.7 (5.2)
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR
Cholesterol and lipid levels (mg/dL) Mean (SD)	NA (NA)	NA (NA)
Total cholesterol Mean (SD)	163.5 (44.2)	161.9 (43.1)
LDL cholesterol Mean (SD)	85.9 (*empty data*)	84.9 (35.3)
HDL cholesterol Mean (SD)	44.6 (11.9)	44 (11.3)
Triglycerides Mean (SD)	170.5 (129.7)	170.7 (121.2)
Albumin creatinine ratio Sample size	n = NA ; % = NA	n = NA ; % = NA
<30 mg/g Sample size	n = 2789 ; % = 59.5	n = 1382 ; % = 59.2
30 to 300 mg/g Sample size	n = 1338 ; % = 28.5	n = 675 ; % = 28.9

Characteristic	Empagliflozin (N = 4687)	Placebo (N = 2333)
>300 mg/g Sample size	n = 509 ; % = 25.9	n = 260 ; % = 26
eGFR mL/min/1.73m2 Sample size	n = NA ; % = NA	n = NA ; % = NA
eGFR mL/min/1.73m2 Mean (SD)	74.2 (21.6)	73.8 (21.1)
>90 mL/min/1.73m2 Sample size	n = 1050 ; % = 22.4	n = 488 ; % = 20.9
>90 mL/min/1.73m2 Mean (SD)	NA (NA)	NA (NA)
60 to <90mL/min/1.73m2 Sample size	n = 2423 ; % = 51.7	n = 1238 ; % = 53.1
60 to <90mL/min/1.73m2 Mean (SD)	NA (NA)	NA (NA)
<60mL/min/1.73m2 Sample size	n = 1212 ; % = 25.9	n = 607 ; % = 26
<60mL/min/1.73m2 Mean (SD)	NA (NA)	NA (NA)
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Metformin Sample size	n = 3459 ; % = 73.8	n = 1734 ; % = 74.3
Insulin Sample size	n = 2252 ; % = 48	n = 1135 ; % = 48.6
Sulfonylurea Sample size	n = 2014 ; % = 43	n = 992 ; % = 42.5
DPP-4 inhibitor Sample size	n = 529 ; % = 11.3	n = 267 ; % = 11.4
Thiazolidinedione	n = 198 ; % = 4.2	n = 101 ; % = 4.3

Characteristic	Empagliflozin (N = 4687)	Placebo (N = 2333)
Sample size		
GLP-1 agonist Sample size	n = 126 ; % = 2.7	n = 70 ; % = 3
Receiving mono-glucose lowering therapy Sample size	n = 1380 ; % = 29.4	n = 691 ; % = 29.6
Receiving dual-glucose lowering therapy Sample size	n = 2259 ; % = 48.2	n = 1148 ; % = 49.2
ACE inhibitors/ARBs Sample size	n = 3798 ; % = 81	n = 1868 ; % = 80.1
Beta blockers Sample size	n = 3056 ; % = 65.2	n = 1498 ; % = 64.2
Diuretics Sample size	n = 2047 ; % = 43.7	n = 988 ; % = 42.3
Calcium channel blockers Sample size	n = 1529 ; % = 32.6	n = 788 ; % = 33.8
Mineralocorticoid receptor antagonists Sample size	n = 305 ; % = 6.5	n = 136 ; % = 5.8
Renin inhibitors Sample size	n = 27 ; % = 0.6	n = 19 ; % = 0.8
Other anti-hypertensive therapy Sample size	n = 383 ; % = 8.2	n = 191 ; % = 8.2
Statins Sample size	n = 3630 ; % = 77.4	n = 1773 ; % = 76
Fibrates Sample size	n = 431 ; % = 9.2	n = 199 ; % = 8.5
Ezetimibe Sample size	n = 189 ; % = 4	n = 81 ; % = 3.5
Niacin Sample size	n = 91 ; % = 1.9	n = 35 ; % = 1.5

Characteristic	Empagliflozin (N = 4687)	Placebo (N = 2333)
Other lipid-lowering therapy Sample size	n = 365 ; % = 7.8	n = 175 ; % = 7.5
Acetylsalicylic acid Sample size	n = 3876 ; % = 82.7	n = 1927 ; % = 82.6
Clopidogrel Sample size	n = 494 ; % = 10.5	n = 249 ; % = 10.7
Vitamin K antagonists Sample size	n = 266 ; % = 5.7	n = 156 ; % = 6.7
Blood pressure-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
ACE inhibitors/ARBs Sample size	n = 3798 ; % = 81	n = 1868 ; % = 80.1
Statins/lipid-lowering medication used See Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Other treatment being received Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA