National Institute for Health and Care Excellence

Final

Type 2 diabetes in adults: management (medicines update)

[F2.4] Evidence reviews for subsequent pharmacological management of type 2 diabetes – Appendix D3

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

FINAL

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Appendices

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

1. Galindo, 2023

Bibliographic Reference	Galindo, Rodolfo J; Moazzami, Bobak; Scioscia, Maria F; Zambrano, Cesar; Albury, Bonnie S; Saling, Jarrod; Vellanki, Priyathama; Pasquel, Francisco J; Davis, Georgia M; Fayfman, Maya; Peng, Limin; Umpierrez, Guillermo E; A Randomized Controlled Trial Comparing the Efficacy and Safety of IDegLira Versus Basal-Bolus in Patients With Poorly Controlled Type 2 Diabetes and Very High HbA1c >=9-15%: DUAL HIGH Trial.; Diabetes care; 2023; vol. 46 (no. 9); 1640-1645

1.1. Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	NCT03737240
Study type	Randomised controlled trial (RCT)
Study location	US
Study setting	Academic clinics
Study dates	01/2019 - 07/2022
Sources of funding	Grant funding: National Institutes of Health (NIH) and National Institute of Diabetes and Digestive and Kidney Disease Novo Nordisk
Inclusion criteria	• Males or females between the ages of 18 and 80 years • Type 2 diabetes, diagnosed for ≥ 6 months • HbA1c ≥ 9% - 15% • Previously treated with antidiabetic agents, including metformin, sulfonylurea, repaglinide/nateglinide, pioglitazone, DPP4 inhibitors,

	SGLT2 inhibitors, (monotherapy + basal insulin) or in combination therapy (2-3 agents), and/or on basal insulin (neutral protamine Hagedorn (NPH), mixed insulin, detemir or glargine U100) at a total daily dose (TDD) ≤50 units (stable doses of basal insulin for at least 90 days, defined as up to ±10% variability) • BMI ≤ 45 Kg/m2
Exclusion criteria	• Age < 18 or > 80 years • Subjects with type 1 diabetes or LADA: positive GAD-65 antibody and/or ketones • Subjects with a blood glucose > 400 mg/dL during the screening visit and laboratory evidence of diabetic ketoacidosis • Previous treatment with GLP-1 agonists (during prior 3 months) • Patients receiving treatment for active diabetic retinopathy or with proliferative retinopathy • Previous treatment with basal-bolus insulin (within prior 3 months, except transient treatment with during hospital admission) • Recurrent severe hypoglycemia or known hypoglycemia unawareness. • Personal or family history of medullary thyroid cancer or multiple endocrine neoplasia 2 • Patients with acute or chronic pancreatitis, pancreatic cancer Patients with clinically significant hepatic disease (cirrhosis, jaundice, end-stage liver disease) or significantly impaired renal function (GFR < 30 ml/min). • Treatment with oral or injectable corticosteroid (equivalent or higher than prednisone 5 mg/day), parenteral nutrition and immunosuppressive treatment. • Mental condition rendering the subject unable to understand the nature, scope, and possible consequences of the study • Hypersensitivity to study drug • Participating in another investigational drug trial The receipt of any investigational drug (within 3 months) prior to this trial. • Previously randomised in this trial • Heart Failure NYHA class 4 or uncontrolled hypertension (blood pressure > 180/110 mmHg) • Female subjects who are pregnant or breastfeeding at time of enrollment into the study • Females of childbearing potential who are not using adequate contraceptive methods (as required by local law or practice) • Known or suspected allergy to trial medications (degludec, liraglutide, aspart), excipients, or related products. • Subjects could be excluded based on PI's discretion • Unable to comply with trial protocol, and/or at investigator discretion
Recruitment / selection of participants	Patients with type 2 diabetes who had been treated with two or more oral antidiabetic agents and/or basal insulin (≤50 units/day) were recruited from academic clinic centres and randomised 1:1 to insluin degludec/liraglutide or basal bolus.
Intervention(s)	Insulin degludec/liraglutide administered subcutaneously

Cointervention	Oral antidiabetic agents and/or insulin
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	People without non-alcoholic fatty liver disease
Subgroup 4: People with obesity	Not stated/unclear

Subgroup 5: eGFR category at baseline	eGFR ≥30mL/min/1.73m2
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Comparator	Basal bolus daily
Number of participants	N=145
Duration of follow-up	6-month
Method of analysis	ITT
Additional comments	All patients randomised were included in the analysis.

1.2. Study arms

1.2.1. Insulin degludec/liraglutide (N = 72)

Administered subcutaneously. Maximum dose is 50 units/1.8 mg daily.

1.2.2. Basal-bolus Insulin (N = 73)

Maximum dose is 50 units daily.

1.3. Characteristics

1.3.1. Arm-level characteristics

Characteristic	Insulin degludec/liraglutide (N = 72)	Basal-bolus Insulin (N = 73)
% Male No of events	n = 28 ; % = 39	n = 35 ; % = 48
Mean age (SD)	54.5 (10.1)	53.8 (9.7)

Characteristic	Insulin degludec/liraglutide (N = 72)	Basal-bolus Insulin (N = 73)
Mean (SD)		
Black No of events	n = 63 ; % = 88	n = 61 ; % = 84
White No of events	n = 3 ; % = 4.2	n = 7 ; % = 9.6
Hispanic No of events	n = 6 ; % = 8.3	n = 5 ; % = 6.8
Presence of frailty Nominal	NR	NR
< 20 years No of events	n = 62 ; % = 86.2	n = 64 ; % = 87.7
> 20 years No of events	n = 10 ; % = 13.8	n = 9 ; % = 12.3
Cardiovascular risk factors Nominal	NR	NR
Smoking status Nominal	NR	NR
Alcohol consumption Nominal	NR	NR
Presence of severe mental illness Nominal	NR	NR
People with significant cognitive impairment Nominal	NR	NR
People with a learning disability Nominal	NR	NR
Number of people with obesity Nominal	NR	NR
Oral antidiabetic therapy No of events	n = 22 ; % = 30.6	n = 25 ; % = 34.3

Characteristic	Insulin degludec/liraglutide (N = 72)	Basal-bolus Insulin (N = 73)
Insulin only No of events	n = 10 ; % = 13.8	n = 12 ; % = 16.4
Oral and insulin therapy No of events	n = 40 ; % = 55.6	n = 36 ; % = 49.3
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

2. Galle, 2012

Bibliographic Reference	Galle, Jan; Kleophas, Werner; Dellanna, Frank; Schmid, Volkmar H R; Forkel, Claudia; Dikta, Gerhard; Krajewski, Vera; Fuchs, Winfried; Forst, Thomas; Pfutzner, Andreas; Comparison of the Effects of Pioglitazone versus Placebo when Given in Addition to Standard Insulin Treatment in Patients with Type 2 Diabetes Mellitus Requiring Hemodialysis: Results from the PIOren Study.; Nephron extra; 2012; vol. 2 (no. 1); 104-14

2.1. 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) Double-blind parallel group placebo-controlled RCT
Study location	Germany (12 sites)
Study setting	Outpatient
Study dates	2008 to 2010
Sources of funding	Sponsored by TAKEDA Pharma GmbH, Aachen, Germany
Inclusion criteria	• Aged 30-80 years inclusive • Diagnosis of type 2 diabetes • HbA1c level ≥6% and <10% • On haemodialysis with or without residual excretion • On insulin treatment ≥3 months • Insulin dose >20 IU/day

Exclusion criteria	• History of type 1 diabetes
	• Acute infections
	• History of
	  ○ hypersensitivity to the study drugs or to drugs with similar chemical structures
	  ○ severe or multiple allergies
	  ○ significant cardiovascular (e.g., CHF NYHA stage III–IV), respiratory, gastrointestinal, hepatic (e.g., ALAT >2.5 times normal reference range) or hematological disease
	• Progressive fatal disease other than kidney failure,
	• Treatment with thiazolidinediones within past 3 months.

Recruitment / selection of participants	Participants recruited from 12 centers in Germany and after screening visit were randomised to pioglitazone or placebo arm with subsequent 3 visits before final visit after 6 months treatment.
Intervention(s)	• Pioglitazone 30 mg once daily Oral pioglitazone 30 mg tablets once daily at breakfast for 26 weeks in addition to insulin therapy. Advice about changing insulin dosage and choice of insulin, left to investigator's discretion. Initial insulin dose could be reduced by 10% at randomisation visit at investigator's discretion. Insulin titrated to target FPG level 80-120 mg/dL. Use of concomitant medications permitted (except those inconsistent with exclusion criteria) and were to be held constant unless medical reason to change.
Cointervention	Insulin therapy (basal and prandial [bolus]) at discretion of site investigator.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Excluded "CHF NYHA stage III–IV", otherwise unclear. 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 with chronic kidney disease Included people on hemodialysis
Strata 4: People with type 2 diabetes	Not stated/unclear

mellitus and high cardiovascular risk	
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Comparator	• Placebo Oral placebo tablets one daily at breakfast for 26 weeks in addition to insulin therapy. Advice about changing insulin dosage and choice of insulin, left to investigator's discretion. Initial insulin dose could be reduced by 10% at randomisation visit at investigator's discretion. Insulin titrated to target FPG level 80-120 mg/dL. Use of concomitant medications permitted (except those inconsistent with exclusion criteria) and were to be held constant unless medical reason to change.
Number of participants	N=39
Duration of follow-up	26 weeks
Indirectness	None

Method of analysis	ITT ITT analysis used for adverse events. Modified ITT mITT analysis (all randomised participants who received study drug and had at least one post-baseline value for daily insulin dose) for HbA1c level and lipids.

2.2. Study arms

2.2.1. Pioglitazone 30 mg once daily (N = 20)

Oral pioglitazone tablets 30 mg once daily at breakfast for 26 weeks added to daily basal and prandial (bolus) insulin therapy.

2.2.2. Placebo (N = 19)

Oral placebo once daily at breakfast for 26 weeks added to daily basal and prandial (bolus) insulin therapy.

2.3. Characteristics

2.3.1. Arm-level characteristics

Characteristic	Pioglitazone 30 mg once daily (N = 20)	Placebo (N = 19)
% Male Sample size	n = 14 ; % = 70	n = 13 ; % = 68
Mean age (SD) (years) Mean (SD)	68.9 (6.8)	69.6 (9.4)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR

Characteristic	Pioglitazone 30 mg once daily (N = 20)	Placebo (N = 19)
Time since type 2 diabetes diagnosed (years) Mean (SD)	13.8 (9.8)	12.4 (8.2)
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
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

3. Gallwitz, 2011

Bibliographic Reference	Gallwitz, B.; Böhmer, M.; Segiet, T.; Mölle, A.; Milek, K.; Becker, B.; Helsberg, K.; Petto, H.; Peters, N.; Bachmann, O.; Exenatide twice daily versus premixed insulin aspart 70/30 in metformin-treated patients with type 2 diabetes: a randomized 26-week study on glycemic control and hypoglycemia; Diabetes Care; 2011; vol. 34 (no. 3); 604-6

3.1. Study details

Secondary publication of another included study- see primary study for details	No
Other publications associated with this study included in review	No
Trial name / registration number	NCT00434954
Study type	Randomised controlled trial (RCT)
Study location	68 sites in Germany
Study setting	No additional information
Study dates	No additional information
Sources of funding	Two authors are employed by Lilly Deutschland, Germany, a further author is employed by Eli Lilly Austria.
Inclusion criteria	Metformin treated adults with type 2 diabetes
Exclusion criteria	No additional information
Recruitment / selection of participants	No additional information

Intervention(s)	Exenatide (n=182) Patients received twice daily doese of exenatide; 5 ug for 4 weeks followied by 10 ug for the remainder of the 26 week trial
Cointervention	Metformin: Metformin therapy continued throughout the study 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	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear

Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	No additional information
Comparator	Inslin aspart (70/30) (n=181) Insulin aspart (70/30) was titrated to glucose targets of 5.0 - 7.2 mmol/L (fasting)and <10 mmol/L (2 h post prandial) after each main meal
Number of participants	363
Duration of follow-up	26 weeks
Indirectness	No additional information
Method of analysis	Other Not stated/unclear
Additional comments	Data were derived for all patients treated using a MMRM analysis, adjusting for baseline A1C

3.2. Study arms

3.2.1. Exenatide (N = 182)

Metformin treated adults with T2D received exenatide twice daily (4 weeks, 5 ug then 10 ug) for the remainder of the 26 weeks. Metformin was continued unchanged.

3.2.2. Insulin aspart 70/30 (N = 181)

Metformin treated adults with T2D received insulin aspart 70/30 twice daily, titrated to glucose targets of 5.0 - 7.2 mmol/L (fasting) and <10mmol/L (2h post prandial) after each main meal. Metformin was continued unchanged

3.3. Characteristics

3.3.1. Arm-level characteristics

Characteristic	Exenatide (N = 182)	Insulin aspart 70/30 (N = 181)
% Male Sample size	n = NR ; % = NR	n = NR ; % = NR
Mean age (SD) Mean (SD)	57 (10)	57 (9.9)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed (Years (mean, SD)) Mean (SD)	5 (4)	5 (5)
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Metformin use Sample size	n = 182 ; % = 100	n = 181 ; % = 100
Blood pressure-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Exenatide (N = 182)	Insulin aspart 70/30 (N = 181)
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

4. Gallwitz, 2012

Bibliographic Reference	Gallwitz, B.; Guzman, J.; Dotta, F.; Guerci, B.; Simó, R.; Basson, B. R.; Festa, A.; Kilja?ski, J.; Sapin, H.; Trautmann, M.; Schernthaner, G.; Exenatide twice daily versus glimepiride for prevention of glycaemic deterioration in patients with type 2 diabetes with metformin failure (EUREXA): an open-label, randomised controlled trial; Lancet; 2012; vol. 379 (no. 9833); 2270-8

4.1. 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	EUREXA / NCT00359762
Study type	Randomised controlled trial (RCT)
Study location	128 centres in 14 countries
Study setting	No additional information
Study dates	5 September 2006 to 29 March 2011
Sources of funding	Eli Lilly and Company; Amlyn Pharmaceuticals. Multiple authors declare funding and honoraria with numerous pharmaceutical companies
Inclusion criteria	Eligible participants had type 2 diabetes; were overweight to obese (BMI ≥25 kg/m² to <40 kg/m²; aged 18–85 years; had been on stable, maximum tolerated doses of metformin; and had developed suboptimum glycaemic control, defined by a glycated haemoglobin (HbA1c) concentration of ≥6·5% to ≤9·0%.
Exclusion criteria	Exclusion criteria were contraindications for metformin or glimepiride, according to the product-specific label; active or untreated malignancy or remission for less than 5 years; evidence of renal or liver disease or dysfunction; haemoglobinopathy or clinically significant chronic anaemia;

	active proliferative retinopathy or macular oedema; or severe gastrointestinal disease.
Recruitment / selection of participants	No additional information
Intervention(s)	Exenatide (n=515): Injected subcutaneously within 60 min before breakfast and evening meals, starting at 5 µg twice daily for 4 weeks, followed by 10 µg twice daily for the remaining study period of up to 4.5 years. If patients had daily episodes of nausea for more than 1 week, the 10 µg dose was reduced to 5 µg twice daily and could be increased again after nausea subsided. Exenatide received as add on to metformin.
Cointervention	Metformin; Patients were taking metformin at close to the recommended maximum dose, with a median dose of 2000 mg per day (IQR 1700 - 2550).
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	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	Glimepiride (n=514) The recommended starting dose for patients in the glimepiride group was 1 mg per day, given once daily immediately before breakfast. Attending physicians established the glimepiride dose as per their 9% after the first 3 months of treatment, or more than 7% at two consecutive visits 3 months apart after the first 6 months. Treatment continued for up to 4.5 years. Glimepiride received as add on to metformin.
Number of participants	1029
Duration of follow-up	3 years
Indirectness	No additional information
Method of analysis	Modified ITT
Additional comments	Analyses were by intention to treat with the caveat that only randomly assigned patients receiving at least one dose of study treatment, and with baseline and at least one post-baseline HbA1c measurement were included. The as-treated population were analysed according to treatment

	actually received and included only patients with at least 6 months' follow-up for HbA1c. A mixed model repeated measures analysis was utilised for continuous variables, with terms for visit, treatment, and interaction, and included the baseline value as a covariate. safety analyses was based on all patients who received study drug.

4.2. Study arms

4.2.1. Exenatide (N = 515)

Exenatide was injected subcutaneously starting at 5 µg twice daily for 4 weeks, followed by 10 µg twice daily for the remaining study period of up to 4.5 years. If patients had daily episodes of nausea for more than 1 week, the 10 µg dose was reduced to 5 µg twice daily and could be increased again after nausea subsided. Exenatide received as add on to metformin.

4.2.2. Glimepiride (N = 514)

Patients initially received 1 mg per day, given once daily immediately before breakfast. Attending physicians established the glimepiride dose as per their 9% after the first 3 months of treatment, or more than 7% at two consecutive visits 3 months apart after the first 6 months. Treatment continued for up to 4 years. Glimepiride received as add on to metformin.

4.3. Characteristics

4.3.1. Arm-level characteristics

Characteristic	Exenatide (N = 515)	Glimegiride (N = 514)
% Male Exenatide n = 490, Glimepiride n = 487 Sample size	n = 272 ; % = 56	n = 252 ; % = 52
Mean age (SD) (Years (mean, SD)) Exenatide n = 490, Glimepiride n = 487 Mean (SD)	56 (10)	56 (9.1)
Ethnicity Exenatide n = 490, Glimepiride n = 487 Sample size	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Exenatide (N = 515)	Glimegiride (N = 514)
White Sample size	n = 450 ; % = 92	n = 444 ; % = 91
Hispanic Sample size	n = 36 ; % = 7	n = 35 ; % = 7
African or Asian Sample size	n = 4 ; % = 0.8	n = 8 ; % = 2
Comorbidities Exenatide n = 490, Glimepiride n = 487 Sample size	n = NA ; % = NA	n = NA ; % = NA
Presence of frailty Exenatide n = 490, Glimepiride n = 487 Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed (Years (mean, SD)) Exenatide n = 490, Glimepiride n = 487 Mean (SD)	5.8 (4.8)	5.5 (4.3)
Smoking status Exenatide n = 490, Glimepiride n = 487 Sample size	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Exenatide n = 490, Glimepiride n = 487 Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Exenatide n = 490, Glimepiride n = 487 Sample size	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Exenatide n = 490, Glimepiride n = 487 Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Exenatide n = 490, Glimepiride n = 487 Sample size	n = NR ; % = NR	n = NR ; % = NR
Number of people with obesity Exenatide n = 490, Glimepiride n = 487	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Exenatide (N = 515)	Glimegiride (N = 514)
Sample size		
Other antidiabetic medication used Exenatide n = 490, Glimepiride n = 487 Sample size	n = NA ; % = NA	n = NA ; % = NA
Metformin use Sample size	n = 490 ; % = 100	n = 487 ; % = 100
Blood pressure-lowering medication used Exenatide n = 490, Glimepiride n = 487 Sample size	n = 340 ; % = 69	n = 367 ; % = 75
Statins/lipid-lowering medication used Exenatide n = 490, Glimepiride n = 487 Sample size	n = NR ; % = NR	n = NR ; % = NR
Other treatment being received Exenatide n = 490, Glimepiride n = 487 Sample size	n = NR ; % = NR	n = NR ; % = NR

5. Gallwitz, 2012

Bibliographic Reference	Gallwitz, B.; Rosenstock, J.; Rauch, T.; Bhattacharya, S.; Patel, S.; Eynatten, M.; Dugi, K. A.; Woerle, H. J.; 2-year efficacy and safety of linagliptin compared with glimepiride in patients with type 2 diabetes inadequately controlled on metformin: a randomised, double-blind, non-inferiority trial; Lancet; 2012; vol. 380 (no. 9840); 475-83

5.1. Study details

Secondary publication of another included study- see primary study for details	
Trial name / registration number	NCT00622284
Study type	Randomised controlled trial (RCT)
Study location	209 sites in 16 countries
Study setting	No additional information
Study dates	12 February 2008 to 21 December 2010.
Sources of funding	Boehringer Ingelheim. Multiple authors declare funding and honoraria with numerous pharmaceutical companies
Inclusion criteria	Aged 18–80 years with type 2 diabetes, receiving metformin at a stable dose of 1500 mg/day or more (or a maximum tolerated dose less than 1500 mg/day) alone or with one other oral antidiabetic drug, and a HbA1c measurement of 6·5–10·0% (on metformin alone) or 6·0–9·0% (on metformin and one additional oral antidiabetic drug) plus BMI of 40 kg/m² or less irrespective of ethnicity.
Exclusion criteria	Diagnoses of myocardial infarction, stroke, or transient ischaemic attack in the 6 months before screening, impaired hepatic function at screening, and treatment with rosiglitazone, pioglitazone, a glucagon-like peptide 1 (GLP-1) analogue or agonist, insulin, or an anti-obesity drug in the 3 months before screening.
Recruitment / selection of participants	No additional information
Intervention(s)	Linagliptin (n=776):

	All participants outside the USA received one 5 mg tablet of linagliptin plus one placebo capsule daily, participants in the USA received one 5 mg linagliptin tablet plus two placebo capsules daily for 104 weeks. Participants were instructed to take their study drug at the same time every day with water (150 mL). Rescue treatment (pioglitazone) could be started during the trial if a participant had a confirmed FPG higher than 13·3 mmol/L at any visit or HbA1c higher than 8·5% from week 28 to week 104.
Cointervention	Metformin: Participants were receiving a stable dose of 1500 mg/day or more (or a maximum tolerated dose less than 1500 mg/day as per eligibility criteria. Metformin therapy remained unchanged throughout the course of the trial
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Excluded "myocardial infarction, stroke, or transient ischaemic attack in the 6 months before screening,", otherwise unclear. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Not an inclusion/exclusion criteria. Baseline characteristics give eGFR categories but CKD diagnosis unclear.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type	Not stated/unclear

2 diabetes mellitus	
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	No additional information
Comparator	Glimepiride (n=775): All participants outside the USA received one glimepiride capsule (1-4 mg) plus one placebo tablet. Participants in the USA received one 1 mg, 2 mg, or 4 mg glimepiride capsule plus one placebo capsule plus one placebo tablet, or one 1 mg glimepiride capsule plus one 2 mg glimepiride capsule plus one placebo tablet. Participants were instructed to take their study drug at the same time every day with water (150 mL). Rescue treatment (pioglitazone) could be started during the trial if a participant had a confirmed FPG higher than 13·3 mmol/L at any visit or HbA1c higher than 8·5% from week 28 to week 104.
Number of participants	1552
Duration of follow-up	104 weeks
Indirectness	No additional information
Method of analysis	Per protocol Other
Additional comments	The primary efficacy analysis of change in HbA1c was assessed with ANCOVA with treatment and previous use of oral antidiabetic drugs as fixed factors and baseline HbA1c as a linear covariate. This analysis was done on the full analysis set using last observation carried forward to impute missing data; the full analysis set included all patients randomly assigned to study groups who received at least one dose of treatment, had

	a baseline HbA1c measurement, and had at least one on treatment HbA1c measurement. T

5.2. Study arms

5.2.1. Linagliptin (N = 776)

Participants outside the USA received one 5mg linagliptin tablet plus one placebo capsule; participants in the USA received one 5 mg linagliptin table plus 2 placebo capsules for 104 weeks. All participants continued with unchanged metformin dose throughout

5.2.2. Glimepiride (N = 775)

All participants outside the USA received one placebo tablet and one glimepiride (1-4mg) capsule daily; participants in the USA received one tablet and two glimepiride capsules daily (1-4mg) for 104 weeks. All participants continued with unchanged metformin dose throughout

5.3. Characteristics

5.3.1. Arm-level characteristics

Characteristic	Linagliptin (N = 776)	Glimepiride (N = 775)
% Male Sample size	n = 462 ; % = 60	n = 471 ; % = 61
Mean age (SD) (Years (mean, SD)) Mean (SD)	59.8 (9.4)	59.8 (9.4)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 660 ; % = 85	n = 659 ; % = 85
Asian Sample size	n = 94 ; % = 12	n = 96 ; % = 12
Black or African American Sample size	n = 20 ; % = 3	n = 18 ; % = 2

Characteristic	Linagliptin (N = 776)	Glimepiride (N = 775)
Other Sample size	n = 2 ; % = 0.26	n = 2 ; % = 0.26
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed Mean (SD)	NR (NR)	NR (NR)
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 Mean (SD)	NR (NR)	NR (NR)
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Use of OAD at screening: Monotherapy (linagliptin n=764, glimepiride n = 755) Sample size	n = 535 ; % = 70	n = 534 ; % = 71
Use of OAD at screening Dual therapy (linagliptin n=764, glimepiride n = 755) Sample size	n = 228 ; % = 30	n = 220 ; % = 29

Characteristic	Linagliptin (N = 776)	Glimepiride (N = 775)
Use of OAD at screening: Triple therapy (linagliptin n=764, glimepiride n = 755) Sample size	n = 1 ; % = 0.13	n = 1 ; % = 0.13
Metformin use (linagliptin n=764, glimepiride n = 755) Sample size	n = 764 ; % = 100	n = 755 ; % = 100
Blood pressure-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Statins/lipid-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR

6. Gao, 2023

Bibliographic Reference	Gao, Leili; Lee, Byung Wan; Chawla, Manoj; Kim, Joshua; Huo, Li; Du, Liying; Huang, Yan; Ji, Linong; Tirzepatide versus insulin glargine as second-line or third-line therapy in type 2 diabetes in the Asia-Pacific region: the SURPASS-AP-Combo trial.; Nature medicine; 2023; vol. 29 (no. 6); 1500-1510

6.1. Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.
Trial name / registration number	SURPASS-AP-Combo. NCT04093752.
Study type	Randomised controlled trial (RCT)
Study location	Multicentre trial (Asia-Pacific region).
Study setting	Outpatient follow-up.
Study dates	31 December 2019 to 27 January 2021 with final follow-up in 24 November 2021.
Sources of funding	Funded by Eli Lilly and Company.
Inclusion criteria	Insulin-naive adults (at least 18 years of age) with type 2 diabetes inadequately controlled (HbA1c 7.5-11%) despite stable treatment with metformin, with or without sulphonylurea, for at least 2 months; BMI at least 23 kg/m2 and stable body weight during the previous 3 months before enrolment.
Exclusion criteria	Type 1 diabetes; eGFR no less than 45mL/min/1.73m2; history of pancreatitis, proliferative diabetic retinopathy, diabetic maculopathy and non-proliferative diabetic retinopathy requiring acute treatment; history of severe hypoglycaemia and/or hypoglycaemia unawareness within the last 6 months; history of ketoacidosis or hyperosmolar state/coma; know

	clinically significant gastric emptying abnormality; having undergone or planning to undergo a gastric bypass surgery; restrictive bariatric surgery; chronic use of drugs that directly affect gastrointestinal motility; any of the following in the last 2 months: acute myocardial infarction; cerebrovascular accident; hospitalisation for congestive heart failure, NYHA III-IV heart failure; acute or chronic hepatitis or any other liver disease other than non-alcoholic fatty liver disease; ALT level more than 3.0 times the upper limit of the reference range; evidence of a significant, uncontrolled endocrine abnormality or family/personal history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2; a serum calcitonin level of at least 35 ng/L; known or suspected hypersensitivity to the study drug or related drugs; evidence of a significant active autoimmune abnormality that is likely to require concurrent treatment with systemic glucocorticoids in the next 12 months; a transplanted organ or awaiting an organ transplant; a history of active or untreated malignancy; remission from a clinically significant malignancy (other than basal or squamous cell skin cancer, in situ carcinomas of the cervix or in situ prostate cancer) for less than 5 years; a history of any other condition that may preclude the patient from following and completing the protocol; any haematological condition that may interfere with HbA1c measurement; any of the following therapies in the past three months: any glucose lowering agent other than metformin or sulphonylureas; prescription drugs that promote weight loss; chronic systemic glucocorticoid therapy (for at least 2 weeks - excluding topical, intraocular, intranasal or inhaled preparations).
Recruitment / selection of participants	No additional information.
Intervention(s)	Tirzepatide 5mg N=230 Tirzepatide 5mg subcutaneously once per week for 40 weeks. Tirzepatide 10mg N=228 Tirzepatide 10mg subcutaneously once per week for 40 weeks. Tirzepatide 15mg N=229 Tirzepatide 15mg subcutaneously once per week for 40 weeks. The starting dose for all people on tirzepatide was 2.5mg which was increased by 2.5mg every 4 weeks until the target dose was reached. If intolerable side effects were reached then the dose could be de-escalated to a lower, tolerated maintenance dose which could be continued for the remainder of the study, but dose de-escalation was not permitted after week 24.

Cointervention	People received metformin or metformin plus a sulphonylurea at randomisation. This was continued throughout the trial.
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Based on exclusion criteria
Strata 2: People with atherosclerotic cardiovascular disease	People without atherosclerotic cardiovascular diseases Based on exclusion criteria
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	eGFR ≥30mL/min/1.73m2 Based on exclusion criteria and baseline characteristics
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	No additional information.
Comparator	Insulin glargine N=230 Insulin glargine administered once daily at bedtime by subcutaneous injection starting at 6 IU/day titrated to maintain a fasting blood glucose target of 4.0-5.6 mmol/L based on SMBG levels.
Number of participants	917
Duration of follow-up	40 weeks.
Indirectness	No additional information.
Method of analysis	Modified ITT People who received at least 1 dose of study treatment.
Additional comments	No additional information.

6.2. Study arms

6.2.1. Tirzepatide 5mg (N = 230)

Tirzepatide 5mg subcutaneously once per week for 40 weeks. The starting dose for all people on tirzepatide was 2.5mg which was increased by 2.5mg every 4 weeks until the target dose was reached. If intolerable side effects were reached then the dose could be de-escalated to a lower, tolerated maintenance dose which could be continued for the remainder of the study, but dose de-escalation was not permitted after week 24. Concomitant therapy: People received metformin or metformin plus a sulphonylurea at randomisation. This was continued throughout the trial.

6.2.2. Tirzepatide 10mg (N = 228)

Tirzepatide 10mg subcutaneously once per week for 40 weeks. The starting dose for all people on tirzepatide was 2.5mg which was increased by 2.5mg every 4 weeks

until the target dose was reached. If intolerable side effects were reached then the dose could be de-escalated to a lower, tolerated maintenance dose which could be continued for the remainder of the study, but dose de-escalation was not permitted after week 24. Concomitant therapy: People received metformin or metformin plus a sulphonylurea at randomisation. This was continued throughout the trial.

6.2.3. Tirzepatide 15mg (N = 229)

Tirzepatide 15mg subcutaneously once per week for 40 weeks. The starting dose for all people on tirzepatide was 2.5mg which was increased by 2.5mg every 4 weeks until the target dose was reached. If intolerable side effects were reached then the dose could be de-escalated to a lower, tolerated maintenance dose which could be continued for the remainder of the study, but dose de-escalation was not permitted after week 24. Concomitant therapy: People received metformin or metformin plus a sulphonylurea at randomisation. This was continued throughout the trial.

6.2.4. Insulin glargine (N = 230)

Insulin glargine administered once daily at bedtime by subcutaneous injection starting at 6 IU/day titrated to maintain a fasting blood glucose target of 4.0-5.6 mmol/L based on SMBG levels. Concomitant therapy: People received metformin or metformin plus a sulphonylurea at randomisation. This was continued throughout the trial.

6.3. Characteristics

6.3.1. Arm-level characteristics

Characteristic	Tirzepatide 5mg (N = 230)	Tirzepatide 10mg (N = 228)	Tirzepatide 15mg (N = 229)	Insulin glargine (N = 230)
% Male Sample size	n = 134 ; % = 58.3	n = 126 ; % = 55.3	n = 129 ; % = 56.3	n = 118 ; % = 53.6
Mean age (SD) (years) Mean (SD)	53.1 (11.2)	53.5 (11.1)	54.3 (11.6)	55.6 (11.4)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Asian Sample size	n = 225 ; % = 97.8	n = 225 ; % = 98.7	n = 226 ; % = 98.7	n = 216 ; % = 98.2

Characteristic	Tirzepatide 5mg (N = 230)	Tirzepatide 10mg (N = 228)	Tirzepatide 15mg (N = 229)	Insulin glargine (N = 230)
White Sample size	n = 3 ; % = 1.3	n = 3 ; % = 1.3	n = 0 ; % = 0	n = 4 ; % = 1.8
Native Hawaaian or other Pacific Islander Sample size	n = 2 ; % = 0.9	n = 0 ; % = 0	n = 3 ; % = 1.3	n = 0 ; % = 0
Comorbidities Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Presence of frailty Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Time since type 2 diabetes diagnosed (years) Mean (SD)	7.43 (5.93)	7.9 (5.65)	7.64 (5.63)	7.65 (5.72)
Cardiovascular risk factors Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Smoking status Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Alcohol consumption Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Presence of severe mental illness Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
People with significant cognitive impairment Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
People with a learning disability Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Number of people with obesity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Tirzepatide 5mg (N = 230)	Tirzepatide 10mg (N = 228)	Tirzepatide 15mg (N = 229)	Insulin glargine (N = 230)
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Metformin Sample size	n = 121 ; % = 52.6	n = 121 ; % = 53.1	n = 118 ; % = 51.5	n = 116 ; % = 52.7
Metformin plus a sulphonylurea Sample size	n = 109 ; % = 47.4	n = 107 ; % = 46.9	n = 111 ; % = 48.5	n = 104 ; % = 47.3
Blood pressure-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Statins/lipid-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Other treatment being received Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA

7. Garber, 2009

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

7.1. Study details

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

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

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	Mixed population
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	Study included participants who were treatment naïve, and participants who had been treated previously with monotherapy which was discontinued at study entry, but without a washout period. Only outcomes that report the population who were switched from previous monotherapy are included in the analysis for review 1.2.
Comparator	Participants allocated to the comparator received once-daily 8 mg glimepiride administered orally. Glimepiride was initially administered as 2 mg once-daily, which doubled over the following 2 weeks until 8 mg was reached and maintained for the rest of the study. Participant also received once-daily subcutaneous placebo which was self-administered in the same manner as liraglutide.
Number of participants	746 randomised 251 received 1.2 mg liraglutide, 142 completed 246 received 1.8 mg liraglutide, 154 completed 248 received glimepiride, 130 completed
Duration of follow-up	52 weeks

Indirectness	None
Method of analysis	ITT
Additional comments	None

7.2. Study arms

7.2.1. 1.2 mg Liraglutide (N = 251)

Once daily 1.2 mg subcutaneous liraglutide

7.2.2. 1.8 mg Liraglutide (N = 247)

Once daily 1.8 mg subcutaneous liraglutide

7.2.3. Glimepiride (N = 248)

Once daily 8 mg oral glimepiride

7.3. Characteristics

7.3.1. Arm-level characteristics

Characteristic	1.2 mg Liraglutide (N = 251)	1.8 mg Liraglutide (N = 247)	Glimepiride (N = 248)
% Male Sample size	n = 117 ; % = 47	n = 121 ; % = 49	n = 133 ; % = 54
Mean age (SD) (years) Mean (SD)	53.7 (11)	52 (10.8)	53.4 (10.9)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 200 ; % = 80	n = 186 ; % = 75	n = 197 ; % = 77
Black Sample size	n = 34 ; % = 14	n = 30 ; % = 12	n = 30 ; % = 12

Characteristic	1.2 mg Liraglutide (N = 251)	1.8 mg Liraglutide (N = 247)	Glimepiride (N = 248)
Asian Sample size	n = 5 ; % = 2	n = 12 ; % = 6	n = 9 ; % = 4
Other Sample size	n = 12 ; % = 5	n = 19 ; % = 7	n = 7 ; % = 7
Comorbidities 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)	5.2 (5.5)	5.3 (5.1)	5.6 (5.1)
HbA1c (%) Mean (SD)	8.3 (1)	8.3 (1.1)	8.4 (1.2)
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)	127.6 (14.3)	128.1 (13.9)	130 (16.1)
Diastolic blood pressure Mean (SD)	78.5 (8.3)	78.8 (8.4)	79.5 (8.6)
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

Characteristic	1.2 mg Liraglutide (N = 251)	1.8 mg Liraglutide (N = 247)	Glimepiride (N = 248)
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Weight (kg) Mean (SD)	92.5 (19.2)	92.8 (20.7)	93.4 (19.2)
BMI (kg/m²) Mean (SD)	33.2 (5.6)	32.8 (6.3)	33.2 (5.6)
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Cholesterol and lipid levels Mean (SD)	NR (NR)	NR (NR)	NR (NR)
Albumin creatinine ratio Mean (SD)	NR (NR)	NR (NR)	NR (NR)
eGFR mL/min/1.73m2 Mean (SD)	NR (NR)	NR (NR)	NR (NR)
Other antidiabetic medication used Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Blood pressure-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
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

8. Garber, 2008

Bibliographic Reference	Garber, A. J.; Foley, J. E.; Banerji, M. A.; Ebeling, P.; Gudbjörnsdottir, S.; Camisasca, R. P.; Couturier, A.; Baron, M. A.; Effects of vildagliptin on glucose control in patients with type 2 diabetes inadequately controlled with a sulphonylurea; Diabetes Obes Metab; 2008; vol. 10 (no. 11); 1047-56

8.1. 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	NCT00099944
Study type	Randomised controlled trial (RCT)
Study location	114 centres in the USA, Sweden, Finland, Argentina and Lithuania
Study setting	NR
Study dates	NR
Sources of funding	Novartis Pharmaceuticals
Inclusion criteria	• People with T2DM who were inadequately controlled on SU monotherapy, with a baseline HbA1c of 7.5–11%. • Treated with an SU for ≥3 months and with a stable dose for ≥4 weeks before the screening visit. • Male or female (females of childbearing potential were required to use a medically approved contraceptive method) • 18–80 years of age • BMI of 22–45 kg/m2 • Fasting plasma glucose (FPG) < 15 mmol/l
Exclusion criteria	• History of type 1 or secondary forms of diabetes, myocardial infarction, unstable angina or coronary artery bypass surgery within the previous 6 months. • Congestive heart failure (New York Heart Association class III or IV), liver disease such as cirrhosis or chronic active hepatitis or use

	of any oral antidiabetic drug other than an SU within the past 2 months. • Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) greater than three times the upper limit of normal (ULN) • Direct bilirubin >1.3 times the ULN • Serum creatinine levels >220 mmol/l • Thyroid stimulating hormone outside the normal range or fasting triglycerides (TGs) >7.9 mmol/l
Recruitment / selection of participants	NR
Intervention(s)	Vildagliptin (50 mg given once or twice daily)
Cointervention	During screening any patient not previously receiving glimepiride 4 mg once daily was switched to this SU regimen. After randomization, the glimepiride dose could be reduced to 2 mg once daily, according to predefined criteria if hypoglycaemia occurred.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Excluded New York Heart Association class III or IV
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type	Not stated/unclear

2 diabetes mellitus	
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	NA
Comparator	Placebo
Number of participants	151 participants were randomised
Duration of follow-up	24 weeks
Indirectness	Directly applicable
Method of analysis	ITT Last observation carried forward for participants who discontinued early
Additional comments	NA

8.2. Study arms

8.2.1. Vildagliptin 50 mg (N = 170)

8.2.2. Vildagliptin 100 mg (N = 169)

8.2.3. Placebo (N = 176)

8.3. Characteristics

8.3.1. Arm-level characteristics

Characteristic	Vildagliptin 50 mg (N = 170)	Vildagliptin 100 mg (N = 169)	Placebo (N = 176)
% Male Characteristics for ITT population: Vildagliptin 50 mg: n=170; vildagliptin 100 mg: n=169; placebo: n=176 No of events	n = 78 ; % = 59.1	n = 79 ; % = 59.8	n = 84 ; % = 58.3
Mean age (SD) (years) Mean (SD)	58.6 (10.6)	58.2 (11.1)	57.9 (10.5)
Ethnicity - Caucasian Sample size	n = 91 ; % = 68.9	n = 93 ; % = 70.5	n = 97 ; % = 67.4
Ethnicity - Hispanic/Latino Sample size	n = 24 ; % = 18.2	n = 24 ; % = 18.2	n = 27 ; % = 18.8
Ethnicity - Black Sample size	n = 14 ; % = 10.6	n = 11 ; % = 8.3	n = 15 ; % = 10.4
Ethnicity - All other Sample size	n = 3 ; % = 2.3	n = 4 ; % = 3	n = 5 ; % = 3.4
Time since type 2 diabetes diagnosed (years) Mean (SD)	6.9 (5.2)	6.7 (5.3)	7.8 (5.8)
Cardiovascular risk factors Nominal	NR	NR	NR
Blood pressure Nominal	NR	NR	NR
Heart rate Nominal	NR	NR	NR
Smoking status Nominal	NR	NR	NR
Alcohol consumption Nominal	NR	NR	NR

Characteristic	Vildagliptin 50 mg (N = 170)	Vildagliptin 100 mg (N = 169)	Placebo (N = 176)
Presence of severe mental illness Nominal	NR	NR	NR
People with significant cognitive impairment Nominal	NR	NR	NR
People with a learning disability Nominal	NR	NR	NR
Number of people with obesity Nominal	NR	NR	NR
Other antidiabetic medication used Nominal	NR	NR	NR
Blood pressure-lowering medication used Nominal	NR	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR	NR
Other treatment being received Nominal	NR	NR	NR

9. Garber, 2007

Bibliographic Reference	Garber, A. J.; Schweizer, A.; Baron, M. A.; Rochotte, E.; Dejager, S.; Vildagliptin in combination with pioglitazone improves glycaemic control in patients with type 2 diabetes failing thiazolidinedione monotherapy: a randomized, placebo-controlled study; Diabetes Obes Metab; 2007; vol. 9 (no. 2); 166-74

9.1. 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	NCT00099853
Study type	Randomised controlled trial (RCT)
Study location	123 centres in the USA and Romania
Study setting	NR
Study dates	NR
Sources of funding	Novartis Pharmaceuticals
Inclusion criteria	Patients with T2DM who had been treated with TZD monotherapy for at least 3 months with a stable dose of at least 4 mg of rosiglitazone or 30 mg of pioglitazone for the past 4 weeks.
Exclusion criteria	Patients were excluded if they had a history of type 1 or secondary forms of diabetes, myocardial infarction, unstable angina or coronary artery bypass surgery within the previous 6 months. Congestive heart failure, liver diseases, such as cirrhosis or chronic active hepatitis, or use of any oral antidiabetic drug other than a TZD within the past 3 months also precluded participation. Patients with any of the following laboratory abnormalities were also excluded: alanine amino-transferase (ALT) or aspartate amino-transferase (AST)>2.5 times the upper limit of normal (ULN); direct bilirubin >1.3 times the ULN; serum creatinine levels >220 mmol/l, clinically significant abnormal thyroid stimulating hormone (TSH) or fasting triglycerides (TG) >7.9 mmol/l.

Recruitment / selection of participants	NR
Intervention(s)	Vildagliptin 50mg daily (n=147) Patients received 50 mg daily vildagliptin as a qd dose in addition to 45mg daily pioglitazone as a qd dose Vildagliptin 100mg daily (n=158) Patients received 100 mg daily vildagliptin as eqaully divided doses in addition to 45mg daily pioglitazone as a qd dose
Cointervention	Pioglitazone 45mg daily
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
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear

Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	NA
Comparator	Placebo (n=158) Patients received a placebo in addition to 45 mg daily pioglitazone
Number of participants	463
Duration of follow-up	24 weeks
Indirectness	NA
Method of analysis	ITT

9.2. Study arms

9.2.1. Vildagliptin 50 mg (N = 147)

Patients received 50 mg daily plus pioglitazone

9.2.2. Vildagliptin 100 mg (N = 158)

Patients received 100 mg daily plus pioglitazone

9.2.3. Placebo (N = 158)

Patients received placebo plus pioglitazone

9.3. Characteristics

9.3.1. Arm-level characteristics

Characteristic	Vildagliptin 50 mg (N = 147)	Vildagliptin 100 mg (N = 158)	Placebo (N = 158)
% Male Sample size	n = 68 ; % = 54.8	n = 61 ; % = 44.9	n = 70 ; % = 50.7
Mean age (SD) (Years (mean, SD)) Mean (SD)	54 (8.2)	54 (9.2)	54.8 (10.6)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Ethnicity - Causasian Sample size	n = 104 ; % = 83.9	n = 108 ; % = 79.4	n = 108 ; % = 78.3
Ethnicity - Hispanic or Latino Sample size	n = 12 ; % = 9.7	n = 12 ; % = 8.8	n = 10 ; % = 7.2
Ethnicity - Black Sample size	n = 6 ; % = 4.8	n = 11 ; % = 8.1	n = 13 ; % = 9.4
Ethnicity - All other Sample size	n = 2 ; % = 1.6	n = 5 ; % = 3.7	n = 7 ; % = 5.1
Comorbidities No of events	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)) Mean (SD)	4.7 (4.3)	4.6 (4.8)	4.8 (4.6)
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Vildagliptin 50 mg (N = 147)	Vildagliptin 100 mg (N = 158)	Placebo (N = 158)
Sample size			
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Cholesterol and lipid levels Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Albumin creatinine ratio Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
eGFR mL/min/1.73m2 Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Other antidiabetic medication used - Pioglitazone Sample size	n = 147 ; % = 100	n = 158 ; % = 100	n = 158 ; % = 100
Blood pressure-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Statins/lipid-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR

10. Garvey, 2023

Bibliographic Reference	Garvey, W Timothy; Frias, Juan P; Jastreboff, Ania M; le Roux, Carel W; Sattar, Naveed; Aizenberg, Diego; Mao, Huzhang; Zhang, Shuyu; Ahmad, Nadia N; Bunck, Mathijs C; Benabbad, Imane; Zhang, Xiaotian M; Tirzepatide once weekly for the treatment of obesity in people with type 2 diabetes (SURMOUNT-2): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial.; Lancet (London, England); 2023; vol. 402 (no. 10402); 613-626

10.1. Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.
Trial name / registration number	SURMOUNT-2. NCT04657003.
Study type	Randomised controlled trial (RCT)
Study location	Multicentre trial.
Study setting	Outpatient follow-up.
Study dates	March 29th 2021 to April 10th 2023.
Sources of funding	Funded by Eli Lilly and Company.
Inclusion criteria	At least 18 years of age; BMI at least 27 kg/m2; people diagnosed with type 2 diabetes; HbA1c 7-10% on stable therapy, either diet and exercise alone or oral antihyperglycaemia therapy for at least 3 months prior to screening (majority were receiving at least metformin).
Exclusion criteria	Change in body weight >5kg within 3 months prior to screening; prior or planned surgical treatment for obesity; treatment with AOMs, DPP-4 inhibitors, oral GLP-1 receptor agonist or any injectable therapy for type 2 diabetes within 3 months prior to screening.

Recruitment / selection of participants	No additional information.
Intervention(s)	Tirzepatide 10mg N=312 Tirzepatide 10mg once a week for 72 weeks. Tirzepatide 15mg N=311 Tirzepatide 15mg once a week for 72 weeks. Tirzepatide was initiated at 2.5mg once weekly and increased by 2.5mg every 4 weeks until the target dose was reached.
Cointervention	The lifestyle intervention included regular lifestyle counselling sessions delivered by a dietitian or qualified healthcare professional. To minimize the risk of hypoglycaemia, people taking sulfonylureas at randomisation had their dose halved. Antihypoglycaemia treatment was to be kept stable unless participants reached rescue criteria, at which point either their dose of existing therapy was increased or a new therapy was started.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear
Strata 2: People with atherosclerotic cardiovascular disease	People without atherosclerotic cardiovascular diseases
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear
Strata 4: People with type 2 diabetes mellitus and high	Not stated/unclear

cardiovascular risk	
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	People without non-alcoholic fatty liver disease
Subgroup 4: People with obesity	People with obesity Majority have a BMI category of at least 30.
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=315 Matching placebo.
Number of participants	938
Duration of follow-up	72 weeks.
Indirectness	No additional information.
Method of analysis	ACA Full analysis set ITT

10.2. Study arms

10.2.1. Tirzepatide 10mg (N = 312)

Tirzepatide 10mg once a week for 72 weeks. Tirzepatide was initiated at 2.5mg once weekly and increased by 2.5mg every 4 weeks until the target dose was reached. Concomitant therapy: The lifestyle intervention included regular lifestyle counselling sessions delivered by a dietitian or qualified healthcare professional. To minimize the risk of hypoglycaemia, people taking sulfonylureas at randomisation had their dose halved. Antihypoglycaemia treatment was to be kept stable unless participants reached rescue criteria, at which point either their dose of existing therapy was increased or a new therapy was started.

10.2.2. Tirzepatide 15mg (N = 311)

Tirzepatide 15mg once a week for 72 weeks. Tirzepatide was initiated at 2.5mg once weekly and increased by 2.5mg every 4 weeks until the target dose was reached. Concomitant therapy: The lifestyle intervention included regular lifestyle counselling sessions delivered by a dietitian or qualified healthcare professional. To minimize the risk of hypoglycaemia, people taking sulfonylureas at randomisation had their dose halved. Antihypoglycaemia treatment was to be kept stable unless participants reached rescue criteria, at which point either their dose of existing therapy was increased or a new therapy was started.

10.2.3. Placebo (N = 315)

Matching placebo. Concomitant therapy: The lifestyle intervention included regular lifestyle counselling sessions delivered by a dietitian or qualified healthcare professional. To minimize the risk of hypoglycaemia, people taking sulfonylureas at randomisation had their dose halved. Antihypoglycaemia treatment was to be kept stable unless participants reached rescue criteria, at which point either their dose of existing therapy was increased or a new therapy was started.

10.3. Characteristics

10.3.1. Arm-level characteristics

Characteristic	Tirzepatide 10mg (N = 312)	Tirzepatide 15mg (N = 311)	Placebo (N = 315)
% Male Sample size	n = 154 ; % = 49.4	n = 152 ; % = 48.9	n = 156 ; % = 49.5
Mean age (SD) (years) Mean (SD)	54.3 (10.7)	53.6 (10.6)	54.7 (10.5)

Characteristic	Tirzepatide 10mg (N = 312)	Tirzepatide 15mg (N = 311)	Placebo (N = 315)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Asian Sample size	n = 44 ; % = 14.1	n = 42 ; % = 13.5	n = 39 ; % = 12.4
Black or African American Sample size	n = 33 ; % = 10.6	n = 22 ; % = 7.1	n = 22 ; % = 7
Native Hawaiian or other Pacific Islander Sample size	n = 1 ; % = 0.3	n = 1 ; % = 0.3	n = 1 ; % = 0.3
White Sample size	n = 228 ; % = 73.1	n = 234 ; % = 75.2	n = 248 ; % = 78.7
Multiple Sample size	n = 6 ; % = 1.9	n = 12 ; % = 3.9	n = 5 ; % = 1.6
Comorbidities Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Hypertension Sample size	n = 201 ; % = 64.4	n = 202 ; % = 65	n = 217 ; % = 68.9
Dyslipidaemia Sample size	n = 181 ; % = 58	n = 182 ; % = 58.5	n = 210 ; % = 66.7
Atherosclerotic cardiovascular disease Sample size	n = 24 ; % = 7.7	n = 29 ; % = 9.3	n = 44 ; % = 14
Obstructive sleep apnoea Sample size	n = 23 ; % = 7.4	n = 26 ; % = 8.4	n = 29 ; % = 9.2
Osteoarthritis Sample size	n = 41 ; % = 13.1	n = 44 ; % = 14.1	n = 58 ; % = 18.4
Anxiety/depression Sample size	n = 43 ; % = 13.8	n = 34 ; % = 10.9	n = 34 ; % = 10.8
Non-alcoholic fatty liver disease Sample size	n = 49 ; % = 15.7	n = 59 ; % = 19	n = 54 ; % = 17.1

Characteristic	Tirzepatide 10mg (N = 312)	Tirzepatide 15mg (N = 311)	Placebo (N = 315)
Asthma or COPD Sample size	n = 21 ; % = 6.7	n = 27 ; % = 8.7	n = 30 ; % = 9.5
Polycystic ovary syndrome Sample size	n = 3 ; % = 1.9	n = 1 ; % = 0.6	n = 2 ; % = 1.3
Gout Sample size	n = 18 ; % = 5.8	n = 17 ; % = 5.5	n = 19 ; % = 6
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	8.8 (6.9)	8 (6.4)	8.8 (6.2)
Cardiovascular risk factors Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Number of people with obesity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
BMI >30 Sample size	n = 60 ; % = 19.2	n = 51 ; % = 16.4	n = 52 ; % = 16.5
BMI 30-35	n = 92 ; % = 29.5	n = 114 ; % = 36.7	n = 105 ; % = 33.3

Characteristic	Tirzepatide 10mg (N = 312)	Tirzepatide 15mg (N = 311)	Placebo (N = 315)
Sample size			
BMI 35-40 Sample size	n = 94 ; % = 30.1	n = 85 ; % = 27.3	n = 71 ; % = 22.5
BMI at least 40 Sample size	n = 66 ; % = 21.2	n = 61 ; % = 19.6	n = 87 ; % = 27.6
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Biguanides Sample size	n = 282 ; % = 90.4	n = 276 ; % = 88.7	n = 274 ; % = 87
Sulfonylureas Sample size	n = 78 ; % = 25	n = 78 ; % = 25.1	n = 94 ; % = 29.8
SGLT2 inhibitors Sample size	n = 63 ; % = 20.2	n = 62 ; % = 19.9	n = 66 ; % = 21
Thiazolidinediones Sample size	n = 11 ; % = 3.5	n = 11 ; % = 3.5	n = 11 ; % = 3.5
Alpha-glucosidase inhibitors Sample size	n = 2 ; % = 0.6	n = 2 ; % = 0.6	n = 4 ; % = 1.3
Others Sample size	n = 0 ; % = 0	n = 1 ; % = 0.3	n = 1 ; % = 0.3
Blood pressure-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Statins/lipid-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR

11. Garvey, 2020

Bibliographic Reference	Garvey, W. T.; Birkenfeld, A. L.; Dicker, D.; Mingrone, G.; Pedersen, S. D.; Satylganova, A.; Skovgaard, D.; Sugimoto, D.; Jensen, C.; Mosenzon, O.; Efficacy and Safety of Liraglutide 3.0 mg in Individuals With Overweight or Obesity and Type 2 Diabetes Treated With Basal Insulin: The SCALE Insulin Randomized Controlled Trial; Diabetes Care; 2020; vol. 43 (no. 5); 1085-1093

11.1. Study details

Trial name / registration number	SCALE insulin / NCT02963922
Study type	Randomised controlled trial (RCT)
Study location	53 sites globally
Study setting	No additional information
Study dates	February 2017 to September 2018
Sources of funding	Study was sponsored by Novo Nordisk. The authors declare multiple research grants and honoraria funded by multiple pharmaceutical companies
Inclusion criteria	Eligible individuals were aged ≥18 years with a BMI of ≥27 kg/m2, stable body weight (maximum 5 kg self-reported weight change within 90 days before screening), diagnosed with type 2 diabetes with an HbA1c ≥6.0 to ≤10% (42–86 mmol/mol) at screening, and receiving stable treatment with any basal insulin (≥90 days; no requirement for minimum or maximum dose) and ≤2 OADs.
Exclusion criteria	Individuals were excluded if they had type 1 diabetes, recurrent severe hypoglycemic episodes within the last year, or use of dipeptidyl peptidase 4 inhibitors, GLP-1 receptor agonists, bolus insulin, or medications known to induce significant weight change in the previous 90 days. Other exclusion criteria included a recent history of cardiovascular event; history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2; pregnancy, breast-feeding, or intention to become pregnant; or a history of pancreatitis.
Recruitment / selection of participants	No additional information
Intervention(s)	Liraglutide 3.0 mg (n=198) Administered once daily by subcutaneous injection. During the first 4 weeks post-randomisation, the dose was escalated by 0.6 mg weekly to reach the maintenance dose of 3.0 mg. To promote individual retention and improve data quality, individuals were permitted to stop and restart the

	study drug without re-escalating the dose, or with re-escalation if three consecutive doses had been missed.
Cointervention	Insulin / sulfonylureas At the investigator's discretion, individuals were recommended to reduce their dose of insulin or sulfonylureas (SUs) by 50% to lower the likelihood of SU-induced hypoglycemia. In individuals with HbA1c ≥8% (64 mmol/mol) at randomization, it was recommended to reduce the dose of basal insulin by 15–20%. Insulin doses were adjusted based on self-measured BG (SMBG) values to ensure that similar levels of fasting glucose were maintained between the two arms, regardless of background medication. In individuals using once-daily basal insulins, weekly adjustments were based on the mean of three prebreakfast SMBG values with a target range of 4 to 5 mmol/L (71–90 mg/dL). In individuals using twice-daily basal insulins, adjustment was based on the mean of three prebreakfast and predinner SMBG measurements. Basal insulin dose was not to exceed the entry dose within the first 5 weeks. Furthermore, the initiation of bolus insulin was permitted after the 5-week period and only after optimization of basal insulin dose. The type and dose of other OADs were kept constant throughout the trial, unless unacceptable hypoglycemia occurred that could not be managed by a reduction of basal insulin. Intensive behavioural therapy (IBT) IBT consisted of a hypocaloric diet, increased physical activity, and behavioural therapy delivered in frequent counselling sessions. Individuals attended a total of 23 individual or group counselling sessions during the 56-week period, delivered by a registered dietitian or similarly qualified health care professional. Concomitant diabetes medication;
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 Excluded "a recent history of cardiovascular event", prior unclear. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.

chronic kidney disease	
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Mixed population
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	No additional information
Comparator	Placebo (n=198) Administered once daily by subcutaneous injection. Intensive behavioural therapy (IBT) IBT consisted of a hypocaloric diet, increased physical activity, and behavioural therapy delivered in frequent counselling sessions. Individuals attended a total of 23 individual or group counselling sessions during the

	56-week period, delivered by a registered dietitian or similarly qualified health care professional. Concomitant diabetes medication; After randomization and at the investigator's discretion, individuals were recommended to reduce their dose of insulin or sulfonylureas (SUs) by 50% to lower the likelihood of SU-induced hypoglycemia. In individuals with HbA1c ≥8% (64 mmol/mol) at randomization, it was recommended to reduce the dose of basal insulin by 15–20%. Insulin doses were adjusted based on self-measured BG (SMBG) values to ensure that similar levels of fasting glucose were maintained between the two arms, regardless of background medication. In individuals using once-daily basal insulins, weekly adjustments were based on the mean of three prebreakfast SMBG values with a target range of 4 to 5 mmol/L (71–90 mg/dL). In individuals using twice-daily basal insulins, adjustment was based on the mean of three prebreakfast and predinner SMBG measurements. Basal insulin dose was not to exceed the entry dose within the first 5 weeks. Furthermore, the initiation of bolus insulin was permitted after the 5-week period and only after optimization of basal insulin dose. The type and dose of other OADs were kept constant throughout the trial, unless unacceptable hypoglycemia occurred that could not be managed by a reduction of basal insulin.
Number of participants	396
Duration of follow-up	56 weeks
Indirectness	No additional information
Method of analysis	ITT
Additional comments	Continuous primary and secondary end points were analysed using ANCOVA with randomized treatment, BMI and sex as factors, and baseline end point as a co variate. The estimates and SDs were pooled using Rubin's formula. All categorical end points were assessed at week 56 and analysed using logistic regression with the same factors and covariate as the continuous end point analysis.

11.2. Study arms

11.2.1. Liraglutide (N = 198)

Patients received daily 3 mg liraglutide via subcutaneous injection for 56 weeks as an adjunct to intensive behavioural therapy.

11.2.2. Placebo (N = 198)

Patients received daily placebo via subcutaneous injection for 56 weeks as an adjunct to intensive behavioural therapy.

11.3. Characteristics

11.3.1. Arm-level characteristics

Characteristic	Liraglutide (N = 198)	Placebo (N = 198)
% Male Sample size	n = 90 ; % = 45.5	n = 99 ; % = 50
Mean age (SD) (Years (mean, SD)) Mean (SD)	55.9 (11.3)	57.6 (10.4)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 174 ; % = 87.9	n = 180 ; % = 90.9
Black Sample size	n = 17 ; % = 8.6	n = 11 ; % = 5.6
Asian Sample size	n = 3 ; % = 1.5	n = 5 ; % = 2.5
Ethnicity: not Hispanic or Latino Sample size	n = 155 ; % = 78.3	n = 169 ; % = 85.4
Time since type 2 diabetes diagnosed (Years (mean, SD)) Mean (SD)	11.4 (6.8)	12.8 (6.9)
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Liraglutide (N = 198)	Placebo (N = 198)
Sample size		
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Biguanides Sample size	n = 175 ; % = 88.4	n = 176 ; % = 88.9
SUs Sample size	n = 68 ; % = 34.3	n = 71 ; % = 35.9
SGLT2i Sample size	n = 44 ; % = 22.2	n = 44 ; % = 22.2
Thiazolidinediones Sample size	n = 4 ; % = 2	n = 6 ; % = 3
Combination BG-lowering drugs (oral) Sample size	n = 4 ; % = 2	n = 6 ; % = 3
Alpha glucosidase inhibitors Sample size	n = 2 ; % = 1	n = 0 ; % = 0
Other BG-lowering drugs excluding insulins Sample size	n = 1 ; % = 0.5	n = 5 ; % = 2.5
Insulins/analogs (injection) Long-acting Sample size	n = 180 ; % = 90.9	n = 184 ; % = 92.9
Insulins/analogs (injection) intermediate acting Sample size	n = 18 ; % = 9.1	n = 14 ; % = 7.1
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

12. Genovese, 2013

Bibliographic Reference	Genovese, S.; Passaro, A.; Brunetti, P.; Comaschi, M.; Cucinotta, D.; Egan, C. G.; Chinea, B.; Bravi, F.; Di Pietro, C.; Pioglitazone randomised Italian study on metabolic syndrome (PRISMA): Effect of pioglitazone withmetformin on HDL-C levels in type 2 diabetic patients; J Endocrinol Invest; 2013; vol. 36 (no. 8); 606-616

12.1. Study details

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	NA
Trial name / registration number	NCT00772174
Study type	Randomised controlled trial (RCT)
Study location	Italy
Study setting	NR
Study dates	NR
Sources of funding	Takeda Italia SpA, Rome, Italy
Inclusion criteria	• Aged between 35-75 year • Diagnosed with T2DM and taking metformin (2000-3000 mg/day) for at least 3 months • Reduced HDL-C levels: <40 mg/dl in males and <50 mg/dl in females, irrespective of statin treatment • Central obesity (waist circumference ≥94 cm for men and ≥80 cm for women) • Women with childbearing potential were required to use effective contraception methods

Exclusion criteria	• Diagnosis of T1DM • Treatment with oral anti-diabetic drugs other than metformin or insulin in the 3 months preceding study entry • Treatment with fibrates or rifampicin • Any disease with malabsorption • Pregnant or lactating females • Acute or chronic pancreatitis • Familial polyposis coli • Medical history of MI, transient ischemic attacks or stroke in the past 6 months • Designation of class I-IV heart failure according to New York Heart Association (NYHA) criteria • Significant liver impairment (alanine amino transferase >2.5 upper limit of normal range) • Significant renal impairment (serum creatinine >1.5 mg/dl for men and >1.2 mg/dl for women) • Anemia of any etiology (defined as Hb levels <10.5 g/dl) or any other hematological disease • Diagnosis or suspicion of neoplastic disease • History of chronic alcohol or drug/substance abuse, or presence of other conditions that could affect study compliance • Known allergy or intolerance to study drugs • Participation in another trial in the 3 months preceding study entry
Recruitment / selection of participants	After an initial screening visit, eligible patients were randomly allocated to treatment arm.
Intervention(s)	Pioglitazone 15 mg t.i.d; titrated from 15 mg b.i.d, in the first 4 weeks
Cointervention	Metformin 850 mg t.i.d.
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Excluded "class I-IV heart failure according to New York Heart Association (NYHA) criteria"
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Excluded "medical history of MI, transient ischemic attacks or stroke in the past 6 months", prior unclear. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Excluded "significant renal impairment (serum creatinine >1.5 mg/dl for men and >1.2 mg/dl for women)", otherwise unclear. No information in baseline characteristics.

Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear Inclusion criteria: "Central obesity (waist circumference ≥94 cm for men and ≥80 cm for women)". However, baseline characteristics state that average BMI is 32.4 (SD 5.4) in the pioglitazone arm and 32.6 (5.3) in the placebo arm.
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	NA
Comparator	Placebo t.i.d. (b.i.d. first 4 weeks)
Number of participants	418 participants were screened and 213 participants were randomised. 110 participants were randomised to pioglitazone and 97 participants completed the treatment period. 103 participants were randomised to placebo and 97 participants completed the treatment period.
Duration of follow-up	24 weeks

Indirectness	Directly applicable
Method of analysis	Per protocol Methods state that "patients included in the ITT analysis that did not have major protocol violations and completed the overall study period were included in the per-protocol population" and "A level of compliance ranging between 80 to 120% was considered as satisfactory; deviations from this range were considered as major protocol violations and exclusion from the study" ITT Continuous secondary efficacy variables were analysed by analysis of variance (ANOVA) for repeated measure (visit) and one grouping factor (treatment).
Additional comments	Randomisation was stratified according to the presence of concomitant treatment with statins, and analysis considered the effect of statins.

12.2. Study arms

12.2.1. Pioglitazone (N = 110)

12.2.2. Placebo (N = 103)

12.3. Characteristics

12.3.1. Arm-level characteristics

Characteristic	Pioglitazone (N = 110)	Placebo (N = 103)
% Male Sample size	n = 65 ; % = 59.1	n = 62 ; % = 60.2
Mean age (SD) Mean (SD)	57 (8.6)	57.8 (8.2)
Ethnicity Caucasian Sample size	n = 110 ; % = 100	n = 103 ; % = 100
Comorbidities	n = 97 ; % = 89	n = 84 ; % = 81.6

Characteristic	Pioglitazone (N = 110)	Placebo (N = 103)
Sample size		
Hypertension n calculated by analyst Sample size	n = 73 ; % = 66	n = 66 ; % = 64.3
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed Mean (SD)	5.8 (4.8)	5.7 (5.4)
Cardiovascular risk factors Nominal	NR	NR
Smoking status Active cigarette smoking Sample size	n = 26 ; % = 23.6	n = 23 ; % = 22.3
Alcohol consumption Sample size	n = 27 ; % = 24.5	n = 30 ; % = 29.1
Presence of severe mental illness Nominal	NR	NR
People with significant cognitive impairment Nominal	NR	NR
People with a learning disability Nominal	NR	NR
Other antidiabetic medication used Nominal	NR	NR
Blood pressure-lowering medication used Nominal	NR	NR
Statins/lipid-lowering medication used Sample size	n = 42 ; % = 38.2	n = 44 ; % = 42.7
Other treatment being received Nominal	NR	NR

13. Gerstein Hertzel, 2019

Bibliographic Reference	Gerstein Hertzel, C; Colhoun Helen, M; Dagenais Gilles, R; Diaz, Rafael; Lakshmanan, Mark; Pais, Prem; Probstfield, Jeffrey; Botros Fady, T; Riddle Matthew, C; Ryden, Lars; Xavier, Denis; Atisso Charles, Messan; Dyal, Leanne; Hall, Stephanie; Rao-Melacini, Purnima; Wong, Gloria; Avezum, Alvaro; Basile, Jan; Chung, Namsik; Conget, Ignacio; Cushman William, C; Franek, Edward; Hancu, Nicolae; Hanefeld, Markolf; Holt, Shaun; Jansky, Petr; Keltai, Matyas; Lanas, Fernando; Leiter Lawrence, A; Lopez-Jaramillo, Patricio; Cardona, Munoz; Ernesto, German; Pirags, Valdis; Pogosova, Nana; Raubenheimer Peter, J; Shaw Jonathan, E; Sheu Wayne, H-H; Temelkova-Kurktschiev, Theodora; REWIND, Investigators; Dulaglutide and renal outcomes in type 2 diabetes: an exploratory analysis of the REWIND randomised, placebo-controlled trial.; Lancet (London, England); 2019; vol. 394 (no. 10193); 131-138

13.1. Study details

Secondary publication of another included study- see primary study for details	Primary publication for REWIND trial is Gerstein HC, Colhoun HM, Dagenais GR, et al. (2019) Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. Lancet. 2019 Jul 13;394(10193):121-130.
Other publications associated with this study included in review	NA
Trial name / registration number	REWIND / NCT01394952
Study type	Randomised controlled trial (RCT)
Study location	Multicentre trial, 370 sites in 24 countries.
Study setting	No additional information
Study dates	Assignment of participants to study arms took place between 18 August 2011 and 14 August 2013.
Sources of funding	Eli Lilley & Co.
Inclusion criteria	Eligible patients were men and women aged 50 years or older with established or newly detected type 2 diabetes and either a previous

	cardiovascular event or cardiovascular risk factors, whose glycated haemoglobin A1c (HbA1c) was 9·5% or less (with no lower limit), who were taking up to two oral glucose-lowering drugs with or without basal insulin therapy, and whose body-mass index (BMI) was at least 23 kg/m² and eGFR (calculated by the Modification of Diet in Renal Disease equation16) was at least 15 mL/min per 1·73 m².
Exclusion criteria	Key exclusion criteria were cardiovascular events or stroke within the previous 2 months, renal dialysis, severe hypoglycaemia within the past year, previous pancreatitis, bariatric surgery, or known abnormal gastric emptying.
Recruitment / selection of participants	No additional information
Intervention(s)	Weekly subcutaneous injections of masked dulaglutide 1·5 mg using a preloaded syringe. Participants were seen at 2 weeks, 3 months, and 6 months and then every 6 months for detailed assessments. HbA1c measurements were taken at least every 12 months and were used by investigators to manage glucose concentrations according to local country guidelines (including more frequent HbA1c testing or adding any medication apart from a GLP-1 receptor agonist or pramlintide). Serum creatinine and the urinary albumin-to-creatinine ratio (UACR) were measured in local laboratories every 12 months, and management of renal protective medications, blood pressure, and cardiovascular risk was at the discretion of the investigator throughout the trial, as informed by local guidelines
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure <10% with heart failure reported in primary publication
Strata 2: People with atherosclerotic cardiovascular disease	Mixed population Primary publication reports CV disease in dulaglutide arm = 31.5% and placebo arm = 31.4% CV disease includes: myocardial infarction, ischaemic stroke, unstable angina with ECG changes, myocardial ischaemia on imaging or stress test, or coronary/carotid/peripheral revascularisation.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Mixed population % with eGFR <60ml/min/1.73m2 = 28% in dulaglutide arm; 22.6% in placebo arm % with albuminuria = 34.5% in dulaglutide arm; 35.5% in placebo arm % with microalbuminuria =26.8% in dulaglutide arm; 27.3% in placebo arm

	% with macroalbuminuria = 7.7% in dulaglutide arm; 8.3% in placebo arm % with eGFR <60ml/min/1.73m2 and albuminuria = 10% dulaglutide arm; 11.0% placebo arm
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	People at higher risk of developing cardiovascular disease Mean age of 66.2 years in both arms Reported in parent publication: Dulaglutide arm = 4605 people (93.0%) with hypertension Placebo arm = 4619 people (93.3%) with hypertension
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Mixed population eGFR (mL/min per 1·73 m²) ≥90: dulaglutide arm = 26·2%, placebo arm = 25·0% eGFR (mL/min per 1·73 m²) 60–89: dulaglutide arm = 49·2%, placebo arm =49·9%

	eGFR (mL/min per 1·73 m²) 30–59: dulaglutide arm = 20·8%, placebo arm = 21·5% eGFR (mL/min per 1·73 m²)<30: dulaglutide arm = 1.0%, placebo arm = 1·0% Missing: dulaglutide arm = 2·7%, placebo = 2·6%
Subgroup 6: Albuminuria category at baseline	Mixed population Categories reported are: Microalbuminuria = UACR 3·39–33·9 mg/mmol (almost aligned with category A2) Macroalbuminuria = UACR >33·9 mg/mmol (almost aligned with category A3) Microalbuminuria = 26.8% in dulaglutide arm and 27.3% in placebo arm Macroalbuminuria = 7.7% in dulaglutide arm and 8.3% in placebo arm
Population subgroups	Exploratory subgroup analysis performed for three outcomes: renal composite outcome, sustained decline in eGFR and new macroalbuminuria. Subgroups: eGFR: < 60 mL/min per1.73 m2 and ≥ 60 mL/min per 1.73 m2 Baseline albuminuria status: normal/microalbuminuria/macroalbuminuria ACE inhibitor or ARB use: yes/no
Comparator	Weekly subcutaneous injections of 1·5 mg masked placebo using a preloaded syringe. Participants were seen at 2 weeks, 3 months, and 6 months and then every 6 months for detailed assessments. HbA1c measurements were taken at least every 12 months and were used by investigators to manage glucose concentrations according to local country guidelines (including more frequent HbA1c testing or adding any medication apart from a GLP-1 receptor agonist or pramlintide). Serum creatinine and the urinary albumin-to-creatinine ratio (UACR) were

	measured in local laboratories every 12 months, and management of renal protective medications, blood pressure, and cardiovascular risk was at the discretion of the investigator throughout the trial, as informed by local guidelines
Number of participants	9901
Duration of follow-up	Median follow up = 5.4 years Participants were seen at 2 weeks, 3 months, and 6 months and then every 6 months for detailed assessments. HbA1c, serum creatinine and urinary albumin-to-creatinine ratio (UACR) were measured every 12 months.
Indirectness	No additional information
Method of analysis	ITT
Additional comments	No additional information

13.2. Study arms

13.2.1. Dulaglutide (N = 4949)

Drug dose, frequency and route of admin: Weekly subcutaneous injection of masked dulaglutide 1.5mg using preloaded syringe. Duration: 5.4 years (median follow up). Participants were seen at 2 weeks, 3 months, 6 months, then every 6 months for detailed assessments. HbA1c and serum creatinine were measured at least once every 12 months. Concomitant therapy: management of renal protective medications, blood pressure and cardiovascular risk was at the discretion of the investigator, informed by local guidelines.

13.2.2. Placebo (N = 4952)

Drug dose, frequency and route of admin: Weekly subcutaneous injection of masked placebo 1.5 mg using preloaded syringe. Duration: 5.4 years (median follow up). Participants were seen at 2 weeks, 3 months, 6 months, then every 6 months for detailed assessments. HbA1c and serum creatine were measured at least once every 12 months. Concomitant therapy: management of renal protective medications, blood pressure and cardiovascular risk was at the discretion of the investigator, informed by local guidelines.

13.3. Characteristics

13.3.1. Arm-level characteristics

Characteristic	Dulaglutide (N = 4949)	Placebo (N = 4952)
% Male Sample size	n = 2643 ; % = 53.4	n = 2669 ; % = 53.9
Mean age (SD) (years) Mean (SD)	66.2 (6.5)	66.2 (6.5)
Ethnicity White Sample size	n = 3754 ; % = 75.9	n = 3744 ; % = 75.6
Comorbidities Sample size	n = 448 ; % = 9.1	n = 443 ; % = 8.9
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	10.5 (7.3)	10.6 (7.2)
HbA1c (%) Mean (SD)	7.3 (1.1)	7.4 (1.1)
Cardiovascular risk factors Sample size	n = NR ; % = NR	n = NR ; % = NR
Systolic blood pressure mmHg Mean (SD)	137.1 (16.6)	137.3 (17)
Diastolic blood pressure mmHg Mean (SD)	78.4 (9.8)	78.5 (9.9)
Heart rate Mean (SD)	NR (NR)	NR (NR)
Smoking status Mean (SD)	NR (NR)	NR (NR)

Characteristic	Dulaglutide (N = 4949)	Placebo (N = 4952)
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 No of events	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR
Weight Mean (SD)	NR (NR)	NR (NR)
BMI (kg/m²) Mean (SD)	32.3 (5.7)	32.3 (5.8)
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 (mg/mmol) Median (IQR)	1.8 (0.7 to 6.6)	1.88 (0.7 to 7.38)
eGFR mL/min/1.73m2 (ml/min/1.73 m2) Mean (SD)	77.2 (22.7)	76.6 (22.8)
Metformin Sample size	n = 4022 ; % = 81.3	n = 4015 ; % = 81.1
Sulfonylurea Sample size	n = 2270 ; % = 45.9	n = 2282 ; % = 46.1
Thiazolidinedione Sample size	n = 100 ; % = 2	n = 68 ; % = 1.4
SGLT2 inhibitor Sample size	n = 2 ; % = 0.1	n = 1 ; % = 0.1

Characteristic	Dulaglutide (N = 4949)	Placebo (N = 4952)
Insulin Sample size	n = 1189 ; % = 24	n = 1174 ; % = 23.7
ACE inhibitor Sample size	n = 2452 ; % = 49.5	n = 2463 ; % = 49.7
ARB Sample size	n = 1679 ; % = 33.9	n = 1693 ; % = 34.2
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

14. Gerstein Hertzel, 2019

Bibliographic Reference	Gerstein Hertzel, C; Colhoun Helen, M; Dagenais Gilles, R; Diaz, Rafael; Lakshmanan, Mark; Pais, Prem; Probstfield, Jeffrey; Riesmeyer Jeffrey, S; Riddle Matthew, C; Ryden, Lars; Xavier, Denis; Atisso Charles, Messan; Dyal, Leanne; Hall, Stephanie; Rao-Melacini, Purnima; Wong, Gloria; Avezum, Alvaro; Basile, Jan; Chung, Namsik; Conget, Ignacio; Cushman William, C; Franek, Edward; Hancu, Nicolae; Hanefeld, Markolf; Holt, Shaun; Jansky, Petr; Keltai, Matyas; Lanas, Fernando; Leiter Lawrence, A; Lopez-Jaramillo, Patricio; Cardona, Munoz; Ernesto, German; Pirags, Valdis; Pogosova, Nana; Raubenheimer Peter, J; Shaw Jonathan, E; Sheu Wayne, H-H; Temelkova-Kurktschiev, Theodora; REWIND, Investigators; Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial.; Lancet (London, England); 2019; vol. 394 (no. 10193); 121-130

14.1. Study details

Secondary publication of another included study- see primary study for details	This is the primary publication of the REWIND trial.
Other publications associated with this study included in review	Gerstein Hertzel, C, Colhoun Helen, M, Dagenais Gilles, R et al. (2019) Dulaglutide and renal outcomes in type 2 diabetes: an exploratory analysis of the REWIND randomised, placebo-controlled trial. Lancet (London, England) 394(10193): 131-138
Trial name / registration number	REWIND / NCT01394952
Study type	Randomised controlled trial (RCT)
Study location	Multi-centre trial. 371 sites in 24 countries. Europe, Latin America, USA & Canada, Asia Pacific
Study setting	No additional information.
Study dates	Between 18 August 2011 and 14 August 2013, patients were screened for eligibility. Follow up ended on 21 August 2018.
Sources of funding	Eli Lilley and Co.

Inclusion criteria	Men and women ≥50 years with established or newly diagnosed type 2 diabetes, HbA1c ≤ 9.5% (no lower limit) on up to two oral glucose lowering medicines, with or without basal insulin, and BMI ≥ 23 kg/m2. Participants ≥50 years had to have vascular disease, defined as: previous myocardial infarction, ischaemic stroke, revascularisation, hospital admission for unstable angina, or imaging showing evidence of myocardial ischaemia. Participants ≥ 55 years had to have myocardial ischaemia, stenosis exceeding 50% (coronary, carotid or lower extremity), left ventricular hypertrophy, eGFR < 60mL/min per 1.73m2, or albuminuria. Participants ≥60 years had to have at least two of the following: tobacco use, dyslipidaemia, hypertension, abdominal obesity.
Exclusion criteria	eGFR < 15mL/min per 1.73m2, cancer within the previous 5 years, severe hypoglycemia within the previous year, life expectancy of <1 year, coronary or cerebrovascular event within the previous 2 months, plans for revascularisation.
Recruitment / selection of participants	No additional information
Intervention(s)	Drug dose: Dulaglutide 1.5mg. Route of admin: subcutaneous injection. Frequency: once per week, on the same day and at around the same time each week. Duration: 3 week run-in period. All participants received placebo and were taught how to inject. Participants remained on pre-existing antihyperglycemic therapy, expect those taking DPP-4 inhibitors or GLP-1 receptor agonists - these were discontinued at the start of the run-in period. Concomitant therapy: Investigators were allowed to add any glucose lowering drugs during the trial, except for other GLP-1 agonists or pramlintide. Blood pressure, cardiovascular risk factors and other medical conditions were managed according to the discretion of the investigator or participant's usual physician.
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure <10% with heart failure
Strata 2: People with atherosclerotic	Mixed population Cardiovascular disease defined as: myocardial infarction, ischaemic stroke, unstable angina with electrocardiogram changes, myocardial

cardiovascular disease	ischaemia on imaging or stress test, or coronary, carotid, or peripheral revascularisation 1560 people (31.5%) in dulaglutide arm 1554 (31.4%) in placebo arm
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Exclusion criteria and baseline characteristics given by eGFR categories not CKD diagnosis.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	People at higher risk of developing cardiovascular disease Mean age of 66.2 years in both arms Dulaglutide arm = 4605 people (93.0%) with hypertension Placebo arm = 4619 people (93.3%) with hypertension
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 Mean age in both arms is 66.2 years Duration of diabetes 10.5 years (dulaglutide) / 10.6 years (placebo)
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	People with obesity Mean BMI in dulaglutide arm = 32.3 kg/m2 (5.7) Mean BMI in placebo arm = 32.3 kg/m2 (5.8)
Subgroup 5: eGFR category at baseline	eGFR ≥30mL/min/1.73m2

	Baseline eGFR category data taken from related renal study. Over 90% participants in both arms had baseline eGFR ≥30mL/min/1.73m2
Subgroup 6: Albuminuria category at baseline	Mixed population Abuminuria defined as UACR 3·39 mg/mmol or more. Dulaglutide arm = 1707 people (34.5%) with albuminuria Placebo arm = 1760 people (35.5%) with albuminuria
Population subgroups	Mean BMI is 32.3 (5.7) in dulaglutide arm Age: ≥ 66 years /< 66 years Sex: male / female Duration of diabetes: <5 years/5-10 years/≥10 years History of cardiovascular disease: yes / no Baseline HbA1c: ≥7.2%/<7.2% BMI (kg/m2): ≥32/32 Region: Europe/Latin America/USA & Canada/Asia Pacific For 3 point MACE outcome only
Comparator	Drug dose: Placebo containing the same excipients as the dulaglutide, 1.5mg. Route of admin: subcutaneous injection. Frequency: once per week, on the same day and at around the same time each week. Duration: ? All participants received placebo and were taught how to inject. 3 week run-in period. Participants remained on pre-existing antihyperglycemic therapy, expect those taking DPP-4 inhibitors or GLP-1 receptor agonists - these were discontinued at the start of the run-in period. Concomitant therapy: Investigators were allowed to add any glucose lowering drugs during the trial, except for other GLP-1 agonists or pramlintide. Blood pressure, cardiovascular risk factors and other medical conditions were managed according to the discretion of the investigator or participant's usual physician.
Number of participants	9901
Duration of follow-up	2 weeks, 3 months, 6 months and then every 3 months for drug dispensing and every 6 months for assessments, until 1200 primary outcomes had been collected.

	Median follow up = 5.4 years (IQR 5.1-5.9)
Indirectness	No additional information
Method of analysis	ITT
Additional comments	No additional information

14.2. Study arms

14.2.1. Dulaglutide (N = 4949)

Drug dose: Dulaglutide 1.5mg. Route of admin: subcutaneous injection. Frequency: once per week, on the same day and at around the same time each week. Duration: 5.4 years (median follow up). 3 week run-in period. All participants received placebo and were taught how to inject. Participants remained on pre-existing antihyperglycemic therapy, expect those taking DPP-4 inhibitors or GLP-1 receptor agonists - these were discontinued at the start of the run-in period. Concomitant therapy: Investigators were allowed to add any glucose lowering drugs during the trial, except for other GLP-1 agonists or pramlintide. Blood pressure, cardiovascular risk factors and other medical conditions were managed according to the discretion of the investigator or participant's usual physician.

14.2.2. Placebo (N = 4952)

Drug dose: Placebo containing the same excipients as the dulaglutide, 1.5mg. Route of admin: subcutaneous injection. Frequency: once per week, on the same day and at around the same time each week. Duration: 5.4 years (median follow up). 3 week run-in period. All participants received placebo and were taught how to inject. Participants remained on pre-existing antihyperglycemic therapy, expect those taking DPP-4 inhibitors or GLP-1 receptor agonists - these were discontinued at the start of the run-in period. Concomitant therapy: Investigators were allowed to add any glucose lowering drugs during the trial, except for other GLP-1 agonists or pramlintide. Blood pressure, cardiovascular risk factors and other medical conditions were managed according to the discretion of the investigator or participant's usual physician

14.3. Characteristics

14.3.1. Arm-level characteristics

Characteristic	Dulaglutide (N = 4949)	Placebo (N = 4952)
% Male Sample size	n = 2643 ; % = 53.4	n = 2669 ; % = 53.9
Mean age (SD) (years) Mean (SD)	66.2 (6.5)	66.2 (6.5)
Ethnicity White Sample size	n = 3754 ; % = 75.9	n = 3744 ; % = 75.6
Comorbidities Sample size	n = NA ; % = NA	n = NA ; % = NA
Cardiovascular disease % Myocardial infarction, ischaemic stroke, unstable angina with electrocardiogram changes, myocardial ischaemia on imaging or stress test, or coronary, carotid, or peripheral revascularisation. Sample size	n = 1560 ; % = 31.5	n = 1554 ; % = 31.4
Cardiovascular event Myocardial infarction or ischaemic stroke Sample size	n = 1028 ; % = 20.8	n = 1007 ; % = 20.3
Previous heart failure Sample size	n = 421 ; % = 8.5	n = 432 ; % = 8.7
Diabetic retinopathy Sample size	n = 448 ; % = 9.1	n = 443 ; % = 8.9
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed (years) Duration of diabetes Mean (SD)	10.5 (7.3)	10.6 (7.2)
HbA1c (%) Mean (SD)	7.3 (1.1)	7.4 (1.1)

Characteristic	Dulaglutide (N = 4949)	Placebo (N = 4952)
Cardiovascular risk factors Sample size	n = NA ; % = NA	n = NA ; % = NA
Hypertension Sample size	n = 4605 ; % = 93	n = 4619 ; % = 93.3
Blood pressure (mmHg) Mean (SD)	NA (NA)	NA (NA)
Systolic blood pressure Mean (SD)	137.1 (16.6)	137.3 (17)
Diastolic blood pressure Mean (SD)	78.4 (9.8)	78.5 (9.9)
Heart rate (/min) Mean (SD)	71.4 (10.7)	71.6 (11)
Smoking status Current tobacco use Sample size	n = 694 ; % = 14	n = 713 ; % = 14.4
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR
Weight Mean (SD)	NR (NR)	NR (NR)
BMI (kg/m²) Mean (SD)	32.3 (5.7)	32.3 (5.8)
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Dulaglutide (N = 4949)	Placebo (N = 4952)
Cholesterol and lipid levels (mmol/L) Mean (SD)	NA (NA)	NA (NA)
Cholesterol and lipid levels (mmol/L) Median (IQR)	NA (NA to NA)	NA (NA to NA)
Total cholesterol Mean (SD)	4.52 (1.16)	4.52 (1.16)
Total cholesterol Median (IQR)	NA (NA to NA)	NA (NA to NA)
LDL cholesterol Mean (SD)	2.56 (0.98)	2.56 (0.98)
LDL cholesterol Median (IQR)	NA (NA to NA)	NA (NA to NA)
HDL cholesterol Mean (SD)	1.18 (0.33)	1.18 (0.36)
HDL cholesterol Median (IQR)	NA (NA to NA)	NA (NA to NA)
Triglycerides Mean (SD)	NR (NR)	NR (NR)
Triglycerides Median (IQR)	1.6 (1.15 to 2.2)	1.6 (1.2 to 2.25)
Albumin creatinine ratio (mg/mmol) Median (IQR)	1.8 (0.7 to 6.6)	1.88 (0.7 to 7.38)
eGFR mL/min/1.73m2 (mL/min per 1·73 m²) Median (IQR)	75.3 (61.6 to 91.8)	74.7 (61.2 to 90.6)
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Metfomin Sample size	n = 4022 ; % = 81.3	n = 4015 ; % = 81.1

Characteristic	Dulaglutide (N = 4949)	Placebo (N = 4952)
Sulfonylurea Sample size	n = 2270 ; % = 45.9	n = 2282 ; % = 46.1
Insulin Sample size	n = 1189 ; % = 24	n = 1174 ; % = 23.7
DPP-4 inhibitor Sample size	n = 266 ; % = 5.4	n = 298 ; % = 6
Thiazolidinedione Sample size	n = 100 ; % = 2	n = 68 ; % = 1.4
Other glucose lowering medicines Sample size	n = 14 ; % = 0.3	n = 18 ; % = 0.4
Blood pressure-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
ACE inhibitor or ARB Sample size	n = 4009 ; % = 81	n = 4059 ; % = 82
Beta blocker Sample size	n = 2237 ; % = 45.2	n = 2274 ; % = 45.9
Other blood pressure lowering medicine Sample size	n = 2767 ; % = 55.9	n = 2833 ; % = 57.2
Statins/lipid-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Statins Sample size	n = 3279 ; % = 66.3	n = 3268 ; % = 66
Fibrates Sample size	n = 452 ; % = 9.1	n = 446 ; % = 9
Other treatment being received Sample size	n = NA ; % = NA	n = NA ; % = NA
eGFR range (mL/min per 1.73 m2) Sample size	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Dulaglutide (N = 4949)	Placebo (N = 4952)
≥ 90 mL/min per 1.73 m2 Sample size	n = 1299 ; % = 26.2	n = 1238 ; % = 25
60-89 mL/min per 1.73 m2 Sample size	n = 2435 ; % = 49.2	n = 2469 ; % = 49.9
30-59 mL/min per 1.73 m2 Sample size	n = 1031 ; % = 20.8	n = 1063 ; % = 21.5
<30 mL/min per 1.73 m2 Sample size	n = 50 ; % = 1	n = 55 ; % = 1.1
Missing Sample size	n = 134 ; % = 2.7	n = 127 ; % = 2.6

15. Giorgino, 2015

Bibliographic Reference	Giorgino, F.; Benroubi, M.; Sun, J. H.; Zimmermann, A. G.; Pechtner, V.; Efficacy and safety of once-weekly dulaglutide versus insulin glargine in patients with type 2 diabetes on metformin and glimepiride (AWARD-2); Diabetes Care; 2015; vol. 38 (no. 12); 2241-9

15.1. 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	AWARD-2 [NCT01075282]
Study type	Randomised controlled trial (RCT)
Study location	NR
Study setting	NR
Study dates	NR
Sources of funding	Eli Lilly and Company
Inclusion criteria	• Adults with an HbA1c of ≥ 7.0% (≥53mmol/mol) and ≤11.0% (≤97 mmol/mol) • BMI ≥ 23 and ≤ 45 kg/m2 • Stable weight for ≥ 3 months • Not optimally controlled with one, two, or three oral antihyperglycaemic medications (of which one had to be metformin or a sulfonylurea) for at least 3 months
Exclusion criteria	Participants were discontinued if they had received chronic insulin therapy at any time in the past or had taken GLP-1 receptor agonists within 3 months of screening.

Recruitment / selection of participants	There was a screening and lead-in period of ~10 to 12 weeks. During the first 2 to 3 weeks of the lead-in period, any other oral anti-hyperglycaemic medications were discontinued, and metformin and glimepiride therapy were initiated and/or adjusted to maximally tolerated doses within maximum locally approved doses (minimum dose required: 1,500 mg/day for metformin and 4 mg/day for glimepiride). Oral anti-hyperglycaemic medications were then stabilised for ~6 to 8 weeks before randomisation, where participants were required to have an HbA1c > 6.5% (> 48 mmol/mol) to be eligible.
Intervention(s)	• Dulaglutide 1.5 mg subcutaneously injected once weekly • Dulaglutide 0.75 mg subcutaneously injected once weekly
Cointervention	Metformin and glimepiride therapy - doses of glimepiride, followed by metformin, could be decreased or discontinued if the patient experienced recurrent hypoglycaemia. Add-on glycaemic rescue therapy was allowed for patients who met prespecified criteria for severe, persistent hyperglycaemia.
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 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	NA
Comparator	Once-daily oral glargine - Dosing was started at 10 units once daily. Participants were instructed to adjust insulin doses according to a standard titration algorithm with a target fasting plasma glucose (FPG) of <100 mg/dL (<5.6 mmol/L) and a recommended dose adjustment of 0 to 2 units for FPG of 100 to 119 mg/dL (5.6–6.7 mmol/L). Glargine dose adjustments occurred every 3 to 4 days for the first 4 weeks of treatment, followed by once weekly through week 8. After week 8, patients were to continue to adjust glargine per the titration algorithm; the glargine dose was also reviewed and revised, as needed, at subsequent office visits
Number of participants	810 participants were randomised and 3 participants discontinued prior to treatment. Out of 273 participants allocated to Dulaglutide 1.5 mg, 248 participants completed 52 weeks (11 participants received rescue therapy), and 242 participants completed 78 weeks (24 participants received rescue therapy). Out of 272 participants randomised to Dulaglutide 0.75 mg, 252 participants completed 52 weeks (20 participants received rescue therapy), and 243 participants completed 78 weeks (34 participants received rescue therapy). Out of 262 participants randomised to insulin glargine, 240 participants completed at 52 weeks (8 received rescue therapy), and 238 completed 78 weeks (16 participants received rescue therapy).
Duration of follow-up	52 weeks and 78 weeks
Indirectness	Directly applicable
Method of analysis	ITT Report states "Efficacy and safety analyses were based on the intent-to-treat (ITT) population consisting of all randomized patients who received at

	least one dose of study treatment. For the assessment of efficacy, weight, and hypoglycaemia events, only data obtained before initiation of rescue therapy were used. The changes from baseline in HbA1c and body weight at 52 and 78 weeks were analysed using ANCOVA with factors for treatment, country, and the baseline value as a covariate. The last observation was carried forward (LOCF) in the case of missing data."

15.2. Study arms

15.2.1. Dulaglutide 1.5 mg (N = 273)

15.2.2. Dulaglutide 0.75 mg (N = 272)

15.2.3. Insulin glargine (N = 262)

15.3. Characteristics

15.3.1. Arm-level characteristics

Characteristic	Dulaglutide 1.5 mg (N = 273)	Dulaglutide 0.75 mg (N = 272)	Insulin glargine (N = 262)
% Male Sample size	n = 144 ; % = 53	n = 136 ; % = 50	n = 134 ; % = 51
Mean age (SD) Mean (SD)	56 (10)	57 (9)	57 (9)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
American indian / Alaska native Sample size	n = 29 ; % = 11	n = 31 ; % = 11	n = 29 ; % = 11
Asian Sample size	n = 48 ; % = 18	n = 46 ; % = 17	n = 43 ; % = 16

Characteristic	Dulaglutide 1.5 mg (N = 273)	Dulaglutide 0.75 mg (N = 272)	Insulin glargine (N = 262)
Black or African American Sample size	n = 1 ; % = 0.4	n = 1 ; % = 0.4	n = 2 ; % = 1
Multiple Sample size	n = 2 ; % = 1	n = 1 ; % = 0.4	n = 4 ; % = 2
White Sample size	n = 193 ; % = 71	n = 193 ; % = 71	n = 184 ; % = 70
Hispanic Sample size	n = 98 ; % = 36	n = 96 ; % = 35	n = 97 ; % = 37
Non-Hispanic Sample size	n = 175 ; % = 64	n = 176 ; % = 65	n = 165 ; % = 63
Comorbidities Nominal	NR	NR	NR
Presence of frailty Nominal	NR	NR	NR
Time since type 2 diabetes diagnosed Mean (SD)	9 (6)	9 (6)	9 (6)
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

Characteristic	Dulaglutide 1.5 mg (N = 273)	Dulaglutide 0.75 mg (N = 272)	Insulin glargine (N = 262)
People with a learning disability Nominal	NR	NR	NR
Number of people with obesity Nominal	NR	NR	NR
Other antidiabetic medication used (mg/day) Mean (SD)	NA (NA)	NA (NA)	NA (NA)
Glimepiride dose Mean (SD)	6.3 (1.7)	6.3 (1.6)	6.2 (1.6)
Metformin dose Mean (SD)	2379 (480)	2412 (495)	2419 (475)
Prestudy treatment (%) Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
1 OAM Sample size	% = 16.5	% = 15.4	% = 16.2
2 OAMs Sample size	% = 67.8	% = 65.4	% = 66.4
2 OAMs Sample size	% = 15.8	% = 19.1	% = 17.4

16. Giugliano, 1993

Bibliographic Reference	Giugliano, D.; Quatraro, A.; Consoli, G.; Minei, A.; Ceriello, A.; Rosa, N.; D'Onofrio, F.; Metformin for obese, insulin-treated diabetic patients: improvement in glycaemic control and reduction of metabolic risk factors; Eur J Clin Pharmacol; 1993; vol. 44 (no. 2); 107-12

16.1. Study details

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	NA
Trial name / registration number	NR
Study type	Randomised controlled trial (RCT)
Study location	Unclear - authors were based in Italy
Study setting	Report states that participants were seen monthly on an outpatient basis.
Study dates	NR
Sources of funding	NR
Inclusion criteria	• Age at diagnosis of diabetes > 40 years • Duration of disease > 3 years • Duration of previous positive response to oral drugs > 1 years • Inadequate ambulatory metabolic control even when on maximal doses of sulfonylureas (glibenclamide or glipizide 15 mg per day).
Exclusion criteria	• Age > 70 years • Creatinine > 1.2 mg/dl-1 • Ischaemic or wasting disease

	• Acute severe diseases [Report also state that a complete medical examination was done to exclude intercurrent illness and cardiac, hepatic, renal or other endocrine disease.]
Recruitment / selection of participants	After an initial physical and biochemical assessment, the participants entered the 4-week run-in period, where they were given placebo in addition to the current insulin regimen. One week before the run-in period ended, participants were hospitalised and basal parameters were measured.
Intervention(s)	Metformin 850 mg b.d. given orally after lunch and dinner
Cointervention	The initial insulin dose was not increased, even if the metformin failure to improve diabetic control, and the daily insulin dose could be reduced if necessary. Participants who were taking medications other than antidiabetic therapy before the study continued their previous treatment during the period of observation.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Excluded "cardiac, hepatic, renal or other endocrine disease", details unclear. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Excluded "cardiac, hepatic, renal or other endocrine disease", details unclear. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Excluded "cardiac, hepatic, renal or other endocrine disease", details unclear. No information in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear

Subgroup 2: Onset of type 2 diabetes mellitus	People with type 2 diabetes first diagnosed above 40 years of age
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	People with obesity
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	NA
Comparator	Placebo
Number of participants	50 participants were randomised. It was not clear whether all participants completed the 6-month study period.
Duration of follow-up	6 months (outcomes were measured every month).
Indirectness	Directly applicable
Method of analysis	Not stated/unclear
Additional comments	NA

16.2. Study arms

16.2.1. Metformin (N = 27)

16.2.2. Placebo (N = 23)

16.3. Characteristics

16.3.1. Arm-level characteristics

Characteristic	Metformin (N = 27)	Placebo (N = 23)
% Male Sample size	n = 10 ; % = 37	n = 9 ; % = 39.1
Mean age (SD) Mean (SD)	11.5 (1.2)	11.7 (1.3)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed Mean (SD)	11.9 (1.2)	11.5 (1.2)
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

Characteristic	Metformin (N = 27)	Placebo (N = 23)
Number of people with obesity Sample size	n = 27 ; % = 100	n = 23 ; % = 100
Other antidiabetic medication used (U/day) Daily insulin dose Mean (SD)	90 (9)	88 (9.4)
Blood pressure-lowering medication used ACE inhibitor (lisinopril, 20 mg/day) or a calcium antagonist (nitrendipine, 20 mg/day) Sample size	n = 5 ; % = 18.5	n = 4 ; % = 17.4
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

17. Gohari, 2022

Bibliographic Reference	Gohari, Sepehr; Reshadmanesh, Tara; Khodabandehloo, Hadi; Karbalaee-Hasani, Amir; Ahangar, Hassan; Arsang-Jang, Shahram; Ismail-Beigi, Faramarz; Dadashi, Mohsen; Ghanbari, Samin; Taheri, Homa; Fathi, Mojtaba; Muhammadi, Muhammad Javad; Mahmoodian, Reyhaneh; Asgari, Atieh; Tayaranian, Mohammadreza; Moharrami, Mehdi; Mahjani, Mahsa; Ghobadian, Bijan; Chiti, Hossein; Gohari, Sheida; The effect of EMPAgliflozin on markers of inflammation in patients with concomitant type 2 diabetes mellitus and Coronary ARtery Disease: the EMPA-CARD randomized controlled trial.; Diabetology & metabolic syndrome; 2022; vol. 14 (no. 1); 170

17.1. Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.
Trial name / registration number	IRCT20190412043247N2
Study type	Randomised controlled trial (RCT)
Study location	Iran
Study setting	Hospital
Study dates	06/2020 - 03/2021
Sources of funding	Dr. Abidi Pharmaceutical company and Zanja University Medical Sciences (Grant Number: 1602001000)
Inclusion criteria	• Patients with type 2 diabetes with coronary artery disease. • All of patients are treated with Aspirin 80mg/Daily and anti diabetic drugs for at least 3 month prior to the beginning of study and had acceptable hemodynamic function.

Exclusion criteria	• Pregnancy, heart failure or arrhythmia, moderate to severe liver, kidney, hematologic or malabsorption disease, psychological and electrolyte imbalance, use of alcohol, anti-inflammatory or antioxidant drugs. • History of infection during last 1 month and major cardiac or cerebral accidents during 1 year or cardio-pulmonary surgeries. • History of usage or allergy to SGLT2 inhibitors drugs.
Recruitment / selection of participants	
Intervention(s)	Empagliflozin 10 mg
Cointervention	metformin, sulfonylurea, DPP4-i, insulin.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear
Strata 2: People with atherosclerotic cardiovascular disease	People with atherosclerotic cardiovascular diseases
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
Comparator	Placebo once daily, administered orally.
Number of participants	N=95
Duration of follow-up	26 weeks
Indirectness	
Method of analysis	ITT
Additional comments	All randomised participants were included in the analysis according to the treatment they were randomised to.

17.2. Study arms

17.2.1. Empagliflozin 10 mg (N = 47)

Taken once daily, orally administered.

17.2.2. Placebo (N = 48)

Taken once daily, orally administered.

17.3. Characteristics

17.3.1. Arm-level characteristics

Characteristic	Empagliflozin 10 mg (N = 47)	Placebo (N = 48)
% Male No of events	n = 23 ; % = 48.9	n = 16 ; % = 33.3
Mean age (SD) Mean (SD)	62.08 (8.02)	63.6 (7.82)
Ethnicity Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Cardiovascular risk factors Nominal	NR	NR
Smoking status Nominal	NR	NR
Alcohol consumption Nominal	NR	NR
People with significant cognitive impairment Nominal	NR	NR
People with a learning disability Nominal	NR	NR
Number of people with obesity Nominal	NR	NR
Metformin No of events	n = 46 ; % = 97.9	n = 46 ; % = 95.8
Sulfonylurea No of events	n = 17 ; % = 36.2	n = 13 ; % = 27.1

Characteristic	Empagliflozin 10 mg (N = 47)	Placebo (N = 48)
DPP4-inhibitors No of events	n = 8 ; % = 17	n = 4 ; % = 8.3
Insulin No of events	n = 4 ; % = 8.5	n = 3 ; % = 6.3

18. Göke, 2010

Bibliographic Reference	Göke, B.; Gallwitz, B.; Eriksson, J.; Hellqvist, A.; Gause-Nilsson, I.; Saxagliptin is non-inferior to glipizide in patients with type 2 diabetes mellitus inadequately controlled on metformin alone: a 52-week randomised controlled trial; Int J Clin Pract; 2010; vol. 64 (no. 12); 1619-31

18.1. Study details

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	Goke, Burkhard, Gallwitz, Baptist, Eriksson, Johan G et al. (2013) Saxagliptin vs. glipizide as add-on therapy in patients with type 2 diabetes mellitus inadequately controlled on metformin alone: long-term (52-week) extension of a 52-week randomised controlled trial. International journal of clinical practice 67(4): 307-16
Trial name / registration number	NCT00575588
Study type	Randomised controlled trial (RCT)
Study location	International, multicentre trial taking place at 130 study sites in Germany, Finland, United Kingdom, Hungary, India, South Korea, Netherlands, Norway, Russia, Slovakia and Vietnam.
Study setting	NR
Study dates	Between December 2007 and August 2010
Sources of funding	Bristol-Myers Squibb and AstraZeneca
Inclusion criteria	• Men and women aged >=18 years with T2D • HbA1c > 6.5% to 1% • Participant on a stable does of metformin monotherapy >= 1500 mg/day for at least 8 weeks prior to enrolment
Exclusion criteria	• Type 1 diabetes • History of diabetic ketoacidosis or hyperosmolar non-ketotic coma • Insulin therapy within 1 year of enrolment

	• Treatment with thiazolidinedione within the 12 weeks prior enrolment • Treatment with systemic glucocorticoids other than replacement therapy • Pervious DPP-4 inhibitor treatment • Donation of blood, plasma or platelets within 3 months prior to enrolment • Congestive heart failure defined as New York Heart Association class III or IV and/or known left ventricular ejection fraction <= 40% • Significant cardiovascular history within the past 6 months defined as myocardial infarction, coronary angioplasty or bypass graft(s), valvular disease or repair, unstable angina pectoris, transient ischaemic attack or cerebrovascular accident • History of haemoglobinopathies • Significant alcohol or drug abuse within the year prior to enrolment • Treatment with human immunodeficiency virus/antiviral drugs or cytochrome P450 3A4 inducers • Serum creatinine >= 1.5 mg/dL [>= 133 umol/L (men); >= 124 umol/L (women)] • Active liver disease and/or significant abnormal liver function [aspartate aminotransferase (AST) > 2 x upper limit of normal (ULN) and/or alanine aminotransferase (ALT) > 2 x ULN and/or total bilirubin > 2.0 md/dL (>34 umol/L)] • Any clinically significant abnormality upon screening
Recruitment / selection of participants	Patients were informed of the study purpose and potential risks, and gave written informed consent.
Intervention(s)	• Saxagliptin - saxagliptin 5 mg/day throughout the study • Glipizide - glipizide was titrated to an optimal effect (FPG ≤ 110 mg/dl [≤ 6.1 mmol/l]) or the highest tolerated dose during an 18-week titration period. Glipizide was initiated at 5 mg/day (morning dose) and titrated in 3-week intervals to a maximum of 20 mg/day. Titration steps were 10 mg/day (morning dose), followed by 15 mg/day (10 mg morning dose, 5 mg evening dose) and 20 mg/day (10 mg morning dose, 10 mg evening dose). Initial titration assessment was at week 3; subsequent re-assessment for titration occurred at weeks 6, 9, 12, 15 and 18. During the titration period, glipizide could be down-titrated once if hypoglycaemic events occurred and could thereafter be up-titrated once. Following the titration period, medication doses remained stable except for instances of glipizide down-titration to mitigate recurrent hypoglycaemia at the discretion of the study investigator; no up-titration was allowed. [Study medication was taken orally, immediately before or with a meal.]
Cointervention	• All patients received open-label metformin at 1500, 2000, 2500 or 3000 mg daily based on individual metformin dose at enrolment. The dose remained stable throughout the study. • Patients were assigned a glucometer and patient diary for the course of the initial 52-week treatment period and instructed to monitor their fingerstick glucose level regularly. Information about

	hypoglycaemic events (list of symptoms, fingerstick value if obtained) was to be entered into the patient diary. • Patients were given advice on diet and exercise.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Excluded "congestive heart failure defined as New York Heart Association class III or IV and/or known left ventricular ejection fraction ≤ 40%", otherwise unclear. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Excluded "CV history within the past 6 months", prior unclear. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear Unclear. Patients with significant cardiovascular history within the past 6 months (as myocardial infarction, coronary angioplasty or bypass graft(s), valvular disease or repair, unstable angina pectoris, transient ischaemic attack or cerebrovascular accident) were excluded.
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear

Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	NA
Comparator	NA
Number of participants	1279 participants enrolled, and 891 participants entered lead-in. 858 participants were then randomised and treated (428 to saxagliptin and 430 to glipizide). At 52 weeks, in the saxagliptin group, 312 participants completed (73%) and in the glipizide group, 321 participants completed (75%). At 104 week, in the saxagliptin group 165 participants completed (38.5%), and in the glipizide group 147 participants completed (34.2%).
Duration of follow-up	52 and 104 weeks
Indirectness	Directly applicable
Method of analysis	Per protocol At 52 weeks, a per-protocol analysis was reported, which included patients who completed the 52-week randomised treatment period, had both a baseline and week 52 HbA1c measurement and no significant protocol deviations. ITT • Efficacy variables were analysed in the full analysis set, defined as all randomised patients who received at least 1 dose of randomised study drug and had at least 1 non-missing baseline and at least 1 postbaseline efficacy data assessment. A mixed model for repeated measures was used to analyse changes in HbA1c and weight from baseline of the initial study to week 104, with terms for treatment group, baseline value, time and time by treatment group. • Safety and tolerability were analysed using descriptive statistics in all patients who took at least 1 dose of study drug.
Additional comments	• Throughout the study, patients were discontinued if they failed to meet prespecified, progressively more stringent glycaemic control

	criteria. Assessments took place at each visit to determine if study discontinuation criteria were met. • With 419 patients per treatment group, there was a 95% power to establish the non-inferiority comparison on change from baseline to week 52 in HbA1c at the 5% level, assuming that the standard deviation (SD) of change from baseline in HbA1c was 1.1%, with a non-inferiority limit set at 0.35% and a zero true difference between the 2 randomised treatments. The sample size assumed that 35% of randomised patients would be excluded from the PP analysis set.

18.2. Study arms

18.2.1. Saxagliptin (N = 428)

18.2.2. Glipizide (N = 430)

18.3. Characteristics

18.3.1. Arm-level characteristics

Characteristic	Saxagliptin (N = 428)	Glipizide (N = 430)
% Male Sample size	n = 212 ; % = 49.5	n = 232 ; % = 54
Mean age (SD) Mean (SD)	57.5 (10.26)	57.6 (10.37)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Asian Sample size	n = 73 ; % = 17.1	n = 65 ; % = 15.1
Black/African American Sample size	n = 1 ; % = 0.2	n = 0 ; % = 0
White Sample size	n = 352 ; % = 82.2	n = 362 ; % = 84.2

Characteristic	Saxagliptin (N = 428)	Glipizide (N = 430)
Other Sample size	n = 2 ; % = 0.5	n = 3 ; % = 0.7
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed Mean (SD)	5.5 (4.5)	5.4 (4.7)
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 Nominal	NR	NR
Other antidiabetic medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Metformin >= 1500 to < 2000 mg/day Sample size	n = 193 ; % = 45.1	n = 209 ; % = 48.6
Metformin >= 2000 to < 2500 mg/day Sample size	n = 131 ; % = 30.6	n = 143 ; % = 33.3
Metformin >= 2500 to < 3000 mg/day Sample size	n = 66 ; % = 15.4	n = 48 ; % = 11.2

Characteristic	Saxagliptin (N = 428)	Glipizide (N = 430)
Metformin >= 3000 mg/day Sample size	n = 37 ; % = 8.6	n = 30 ; % = 7
Metformin dose not reported Sample size	n = 1 ; % = 0.2	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

19. Goke, 2013

Bibliographic Reference	Goke, Burkhard; Gallwitz, Baptist; Eriksson, Johan G; Hellqvist, Asa; Gause-Nilsson, Ingrid; Saxagliptin vs. glipizide as add-on therapy in patients with type 2 diabetes mellitus inadequately controlled on metformin alone: long-term (52-week) extension of a 52-week randomised controlled trial.; International journal of clinical practice; 2013; vol. 67 (no. 4); 307-16

19.1. Study details

Secondary publication of another included study- see primary study for details	Parent study Goke 2010

20. Goodman, 2009

Bibliographic Reference	Goodman, M.; Thurston, H.; Penman, J.; Efficacy and tolerability of vildagliptin in patients with type 2 diabetes inadequately controlled with metformin monotherapy; Horm Metab Res; 2009; vol. 41 (no. 5); 368-73

20.1. Study details

Secondary publication of another included study- see primary study for details	NR
Other publications associated with this study included in review	NR
Trial name / registration number	NR
Study type	Randomised controlled trial (RCT)
Study location	Multicentre trial conducted at 67 centres in the USA and Europe
Study setting	NR
Study dates	NR
Sources of funding	Novartis Pharmaceutical Corporation
Inclusion criteria	• Patients with T2DM and a baseline HbA1c of 7.5 – 11 % who were receiving a stable dose of metformin 1,500 mg / day for at least 3 months • Male and female patients (non-fertile or of child bearing potential using a medically approved birth control method) • Aged 18 – 78 years • Body mass index (BMI) of 22– 40 kg/m2 • Fasting plasma glucose (FPG) < 270 mg / dl (< 15 mmol/ l) • Agreed to maintain the same dose of metformin throughout the study were eligible

Exclusion criteria	• Pregnant or lactating • Had a history of type 1 diabetes mellitus, diabetes resulting from pancreatic injury, or secondary forms of diabetes • Had acute metabolic diabetic complications within the past 6 months • Evidence of significant diabetic complications, liver disease • Significant renal dysfunction • Treatment with any oral antidiabetic other than metformin within 3 months of study entry • Chronic insulin treatment within the past 6 months • Any of the following significant laboratory abnormalities: alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2 times the upper limit of the normal (ULN) range, total bilirubin > 2 times ULN, direct bilirubin > ULN, serum creatinine levels ≥ 1.5 mg / dl (males) or ≥ 1.4 mg / dl (females) or a history of abnormal creatinine clearance.
Recruitment / selection of participants	Baseline evaluations were carried out at the screening visit and during the run-in period, and investigators ensured that participants maintained metformin treatment at a stable dose (≥ 1500 mg/day).
Intervention(s)	• Vildagliptin 100 mg given in the morning (AM) • Vildagliptin 100 mg given in the evening (PM)
Cointervention	• Intervention in addition to the ongoing stable dose of metformin. • Patients were educated about hypoglycaemic symptoms and treatment of hypoglycaemic events and were instructed to take a blood glucose measurement if a hypoglycaemic event was suspected
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 Excluded "significant renal dysfunction", otherwise unclear. No information in baseline characteristics.

Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	There was a subgroup analysis for BMI at baseline (< 30 kg/m2 and ≥30 kg/m2). It was not clear whether the analysis was pre-specified or post-hoc, however, the report did not state the number of participants in each subgroup, and did not report changes in the placebo group, and so an analysis could not be conducted. Similar subgroup analyses were reported for HbA1c category, age, sex, and region.
Comparator	Placebo
Number of participants	370 participants were enrolled in the study, and 287 participants completed the 24-week treatment period (77.6%): 101 participants in the vildagliptin AM group, 96 participants in the vildagliptin PM group, and 90 participants in the placebo group.
Duration of follow-up	24 weeks (assessments were carried out at weeks -4, 0 4, 8, 12, 16, 20, and 24)

Indirectness	Directly applicable
Method of analysis	ITT The intent-to-treat (ITT) population consisted of all randomized patients who received at least one dose of study drug and had at least one post-baseline primary efficacy variable assessment. The primary efficacy variable was change in HbA1c level from baseline to week 24 (or last observation carried forward. For all efficacy variables, unless stated otherwise, an analysis of covariance (ANCOVA) model was used, with treatment and region as classification terms, and corresponding baseline value as covariate. The safety population included all patients who received at least one dose of study drug and had at least one post-baseline safety assessment.
Additional comments	NA

20.2. Study arms

20.2.1. Vildagliptin AM (N = 125)

20.2.2. Vildagliptin PM (N = 123)

20.2.3. Placebo (N = 122)

20.3. Characteristics

20.3.1. Arm-level characteristics

Characteristic	Vildagliptin AM (N = 125)	Vildagliptin PM (N = 123)	Placebo (N = 122)
% Male Sample size	n = 66 ; % = 52.8	n = 65 ; % = 52.8	n = 82 ; % = 67.2
Mean age (SD) Mean (SD)	54.7 (10.3)	55.2 (11.4)	54.5 (9.7)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Vildagliptin AM (N = 125)	Vildagliptin PM (N = 123)	Placebo (N = 122)
Caucasian Sample size	n = 79 ; % = 63.2	n = 84 ; % = 68.3	n = 83 ; % = 68
Black Sample size	n = 11 ; % = 8.8	n = 9 ; % = 7.3	n = 7 ; % = 5.7
Asian Sample size	n = 1 ; % = 0.8	n = 2 ; % = 1.6	n = 0 ; % = 0
Hispanic or Latino Sample size	n = 31 ; % = 24.8	n = 28 ; % = 22.8	n = 32 ; % = 26.2
Pacific Islander Sample size	n = 1 ; % = 0.8	n = 0 ; % = 0	n = 0 ; % = 0
Other Sample size	n = 2 ; % = 1.6	n = 0 ; % = 0	n = 0 ; % = 0
Comorbidities Nominal	NR	NR	NR
Presence of frailty Nominal	NR	NR	NR
Time since type 2 diabetes diagnosed Nominal	NR	NR	NR
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	NR	NR	NR

Characteristic	Vildagliptin AM (N = 125)	Vildagliptin PM (N = 123)	Placebo (N = 122)
Nominal			
People with a learning disability Nominal	NR	NR	NR
Number of people with obesity Nominal	NR	NR	NR
Other antidiabetic medication used (mg) Metformin total daily dose Mean (SD)	1889 (373.4)	1869.9 (389.1)	1932.2 (410.7)
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

21. Gough, 2015

Bibliographic Reference	Gough, S C L; Bode, B W; Woo, V C; Rodbard, H W; Linjawi, S; Zacho, M; Reiter, P D; Buse, J B; One-year efficacy and safety of a fixed combination of insulin degludec and liraglutide in patients with type 2 diabetes: results of a 26-week extension to a 26-week main trial.; Diabetes, obesity & metabolism; 2015; vol. 17 (no. 10); 965-73

21.1. Study details

Secondary publication of another included study- see primary study for details	Parent study Gough 2014
Other publications associated with this study included in review	This is a 26-week extension study of the following parent study: Efficacy and safety of a fixed-ratio combination of insulin degludec and liraglutide (IDegLira) compared with its components given alone: results of a phase 3, open-label, randomised, 26-week, treat-to-target trial in insulin-naive patients with type 2 diabetes. Lancet Diabetes Endocrinol; 2014; vol. 2 (no. 11); 885-93.
Trial name / registration number	NCT01336023
Study type	Randomised controlled trial (RCT)
Study setting	

21.2. Study arms

21.2.1. Insulin degludec + liraglutide once daily (N = 833)

Administered subcutaneously at the same time each day.

21.2.2. Insulin degludec titrated once daily (N = 413)

Administered subcutaneously at the same time each day.

21.2.3. Liraglutide 1.8 mg once daily (N = 414)

Administered subcutaneously at the same time each day.

22. Gough, 2014

Bibliographic Reference	Gough, S. C.; Bode, B.; Woo, V.; Rodbard, H. W.; Linjawi, S.; Poulsen, P.; Damgaard, L. H.; Buse, J. B.; Nn- trial, investigators; Efficacy and safety of a fixed-ratio combination of insulin degludec and liraglutide (IDegLira) compared with its components given alone: results of a phase 3, open-label, randomised, 26-week, treat-to-target trial in insulin-naive patients with type 2 diabetes; Lancet Diabetes Endocrinol; 2014; vol. 2 (no. 11); 885-93

22.1. 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	Efficacy and safety of a fixed-ratio combination of insulin degludec and liraglutide (IDegLira) compared with its components given alone: results of a phase 3, open-label, randomised, 26-week, treat-to-target trial in insulin-naive patients with type 2 diabetes. Diabetes, obesity & metabolism; 2015; vol. 17 (no. 10); 965-73
Trial name / registration number	NCT01336023
Study type	Randomised controlled trial (RCT)
Study location	Conducted at 271 sites in 19 countries: • Australia • Canada • Finland • Germany • Hungary • India • Ireland • Italy • Malaysia • Mexico • Russian Federation • Singapore • Slovakia • South Africa • Spain • Taiwan

	• Thailand • United Kingdom • United states
Study setting	No additional information.
Study dates	05/2011 - 11/2012
Sources of funding	Novo Nordisk
Inclusion criteria	• Subjects with type 2 diabetes • HbA1c 7.0-10.0 % (both inclusive) with the aim of a median HbA1c of 8.3%. Accordingly, when approximately 50% of the randomised subjects have a HbA1c above 8.3%, the remaining subjects randomised must have a HbA1c of below or equal to 8.3%, or when approximately 50% of the randomised subjects have a HbA1c of below or equal to 8.3%, the remaining subjects randomised must have a HbA1c above 8.3% • Male or female, age 18 years or above (Taiwan: 20 years or above for a site 653 in Taiwan: Taichung Veterans General Hospital) • Subjects on stable dose of 1-2 oral antidiabetics (metformin [at least 1500 mg or max tolerated dose] or metformin [at least 1500 mg or max tolerated dose] + pioglitazone [at least 30 mg]) for at least 90 days prior to screening • BMI maximum 40 kg/m2
Exclusion criteria	• Adults (aged 18 years and older) with type 2 diabetes, • HbA1c of 7–10% (inclusive), a BMI of 40 kg/m² or less, • Previously treated with metformin with or without pioglitazone for at least 90 days before screening
Recruitment / selection of participants	Participants were randomly assigned (2:1:1) to once-daily injections of IDegLira, insulin degludec, or liraglutide. All injections were given with a 3 mL FlexPen injection device (Novo Nordisk, Bagsværd, Denmark)
Intervention(s)	Combined insulin degludec-liraglutide (IDegLira) Doses were given once daily at any time of day but at the same time each day.
Cointervention	Metformin +/- pioglitazone
Strata 1: People with type 2 diabetes	Not stated/unclear Excluded "congestive heart failure (NYHA class III–IV),", otherwise unclear. No information in baseline characteristics.

mellitus and heart failure	
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Excluded "diagnosis of unstable angina pectoris, cerebral stroke and/or myocardial infarction within the last 12 months", prior unclear. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria	Not stated/unclear

category at baseline	
Population subgroups	
Comparator	• Insulin degludec or; • Liraglutide Doses were given once daily at any time of day but at the same time each day.
Number of participants	N=1663
Duration of follow-up	26-week
Indirectness	No additional information.
Method of analysis	Per protocol ITT Modified ITT
Additional comments	Full analysis set (defined as all randomly assigned participants) used ITT Safety analysis set used modified ITT The primary outcome was also analysed in the per-protocol analysis set (i.e., all patients without any major protocol violations that might have affected the primary endpoint) and the completers analysis set (i.e., all patients who completed assigned treatment). These analyses were used as sensitivity analyses for the investigation of non-inferiority.

22.2. Study arms

22.2.1. Insulin degludec + liraglutide once daily (N = 833)

Administered subcutaneously at the same time each day.

22.2.2. Insulin degludec titrated once daily (N = 413)

Administered subcutaneously at the same time each day.

22.2.3. Liraglutide 1.8 mg once daily (N = 414)

Administered subcutaneously at the same time each day.

22.3. Characteristics

22.3.1. Arm-level characteristics

Characteristic	Insulin degludec + liraglutide once daily (N = 833)	Insulin degludec titrated once daily (N = 413)	Liraglutide 1.8 mg once daily (N = 414)
% Male No of events	n = 435 ; % = 52	n = 200 ; % = 48	n = 208 ; % = 50
Mean age (SD) Mean (SD)	55.1 (9.9)	54.9 (9.7)	55 (10.2)
White No of events	n = 513 ; % = 62	n = 257 ; % = 62	n = 258 ; % = 62
Black No of events	n = 72 ; % = 9	n = 23 ; % = 6	n = 28 ; % = 7
Asian No of events	n = 228 ; % = 27	n = 120 ; % = 29	n = 116 ; % = 28
Other No of events	n = 18 ; % = 2	n = 11 ; % = 3	n = 11 ; % = 3
Presence of frailty Nominal	NR	NR	NR
Time since type 2 diabetes diagnosed Mean (SD)	6.6 (5.1)	7 (5.3)	7.2 (6.1)
Smoking status Nominal	NR	NR	NR
Alcohol consumption Nominal	NR	NR	NR
Presence of severe mental illness Nominal	NR	NR	NR

Characteristic	Insulin degludec + liraglutide once daily (N = 833)	Insulin degludec titrated once daily (N = 413)	Liraglutide 1.8 mg once daily (N = 414)
People with significant cognitive impairment Nominal	NR	NR	NR
People with a learning disability Nominal	NR	NR	NR
Metformin No of events	n = 691 ; % = 83	n = 343 ; % = 83	n = 338 ; % = 82
Metformin + pioglitazone No of events	n = 142 ; % = 17	n = 70 ; % = 17	n = 75 ; % = 18
Other treatment being received Nominal	NR	NR	NR

23. Gram, 2011

Bibliographic Reference	Gram, J.; Henriksen, J. E.; Grodum, E.; Juhl, H.; Hansen, T. B.; Christiansen, C.; Yderstræde, K.; Gjessing, H.; Hansen, H. M.; Vestergaard, V.; Hangaard, J.; Beck-Nielsen, H.; Pharmacological treatment of the pathogenetic defects in type 2 diabetes: the randomized multicenter South Danish Diabetes Study; Diabetes Care; 2011; vol. 34 (no. 1); 27-33

23.1. Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	Christensen 2011 Skov 2014
Trial name / registration number	NCT00121966
Study type	Randomised controlled trial (RCT)
Study location	Denmark
Study setting	Hospital centres
Study dates	01/2003 - 07/2007
Sources of funding	No additional information.
Inclusion criteria	BMI >25 kg/m2 and fasting plasma C-peptide >300 pmol/l, treatment for at least 3 months with stable doses of oral antidiabetic medications and/or insulin, and A1C >7.0%.
Exclusion criteria	Congestive heart failure, impaired renal function, and known intolerance to metformin or rosiglitazone and/or treatment with glitazones <30 days before randomisation

Recruitment / selection of participants	
Intervention(s)	Insulin aspart + metformin (n=45) Insulin NPH + metformin (n=45)
Cointervention	• Insulin
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Excluded "congestive heart failure"
Strata 2: People with atherosclerotic cardiovascular disease	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 Excluded "impaired renal function", otherwise unclear. No information in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Mixed population
Subgroup 3: People with non-alcoholic	Not stated/unclear

fatty liver disease	
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	
Comparator	Insulin NPH + placebo (n=45) Insulin aspart + placebo (n=45)
Number of participants	N=371 randomised
Duration of follow-up	2 years
Method of analysis	ITT
Additional comments	This was an 8-arm 2x4 factorial trial (NPH Insulin, Insulin aspart; Placebo, Metformin, Rosiglitazone, Metformin + Rosiglitazone). Outcome data for NPH Insulin + Placebo and Insulin aspart + Placebo arms was combined; outcome data for Metformin + NPH insulin and Metformin + Insulin aspart arms was combined. Baseline and outcome data for other 4 arms including rosiglitazone was not extracted.

23.2. Study arms

23.2.1. NPH Insulin titrated + placebo twice daily (N = 46)

Administered subcutaneously

23.2.2. NPH insulin titrated + metformin 1000-2000 mg daily (N = 45)

Subcutaneous NPH insulin and oral metformin.

23.2.3. Insulin aspart titrated + placebo twice daily (N = 48)

Administered subcutaneously

23.2.4. Insulin aspart titrated + metformin 1000-2000 mg daily daily (N = 45)

Subcutaneous insulin aspart and oral metformin.

23.3. Characteristics

23.3.1. Arm-level characteristics

Characteristic	NPH Insulin titrated + placebo twice daily (N = 46)	NPH insulin titrated + metformin 1000-2000 mg daily (N = 45)	Insulin aspart titrated + placebo twice daily (N = 48)	Insulin aspart titrated + metformin 1000-2000 mg daily daily (N = 45)
% Male No of events	n = 33 ; % = 72	n = 26 ; % = 58	n = 23 ; % = 48	n = 28 ; % = 62
Mean age (SD) Mean (SD)	55.8 (7.7)	55.4 (8.5)	57.1 (8.5)	56.1 (8.2)
Ethnicity Nominal	NR	NR	NR	NR
Presence of frailty Nominal	NR	NR	NR	NR
Time since type 2 diabetes diagnosed Mean (SD)	7.3 (4.3)	8.2 (4)	9.1 (5.5)	8.7 (4.5)
HbA1c Mean (SD)	8.7 (1.3)	8.9 (1.2)	8.5 (1.2)	8.5 (1.2)
Smoking status Nominal	NR	NR	NR	NR
Alcohol consumption Nominal	NR	NR	NR	NR

Characteristic	NPH Insulin titrated + placebo twice daily (N = 46)	NPH insulin titrated + metformin 1000-2000 mg daily (N = 45)	Insulin aspart titrated + placebo twice daily (N = 48)	Insulin aspart titrated + metformin 1000-2000 mg daily daily (N = 45)
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 treatment being received No of events	n = 36 ; % = 78	n = 38 ; % = 84	n = 34 ; % = 71	n = 31 ; % = 69

24. Grandy, 2014

Bibliographic Reference	Grandy, S; Langkilde, A M; Sugg, J E; Parikh, S; Sjostrom, C D; Health-related quality of life (EQ-5D) among type 2 diabetes mellitus patients treated with dapagliflozin over 2 years.; International journal of clinical practice; 2014; vol. 68 (no. 4); 486-94

24.1. Study details

Secondary publication of another included study- see primary study for details	Parent study Bolinder 2012 Bolinder et al. (2012). Effects of dapagliflozin on body weight, total fat mass, and regional adipose tissue distribution in patients with type 2 diabetes mellitus with inadequate glycemic control on metformin. J Clin Endocrinol Metab; 2012; vol. 97 (no. 3); 1020-31
Other publications associated with this study included in review	Ljunggren 2012, Bolinder 2014
Trial name / registration number	NCT00855166

25. Grandy, 2016

Bibliographic Reference	Grandy, S; Sternhufvud, C; Ryden, A; Sugg, J; Rohwedder, K; Patient-reported outcomes among patients with type 2 diabetes mellitus treated with dapagliflozin in a triple-therapy regimen for 52 weeks.; Diabetes, obesity & metabolism; 2016; vol. 18 (no. 3); 306-9

25.1. Study details

Secondary publication of another included study- see primary study for details	Parent study Matthaei 2015B Matthaei, S.; Bowering, K.; Rohwedder, K.; Grohl, A.; Parikh, S. Dapagliflozin improves glycemic control and reduces body weight as add-on therapy to metformin plus sulfonylurea: a 24-week randomized, double-blind clinical trial. Diabetes Care; 2015; vol. 38 (no. 3); 365-72.

25.2. Study arms

25.2.1. Dapagliflozin 10 mg daily (N = 108)

Administered orally

25.2.2. Placebo daily (N = 108)

Administered orally

26. Green Jennifer, 2015

Bibliographic Reference	Green Jennifer, B; Bethel M, Angelyn; Armstrong Paul, W; Buse John, B; Engel Samuel, S; Garg, Jyotsna; Josse, Robert; Kaufman Keith, D; Koglin, Joerg; Korn, Scott; Lachin John, M; McGuire Darren, K; Pencina Michael, J; Standl, Eberhard; Stein Peter, P; Suryawanshi, Shailaja; Van de Werf, Frans; Peterson Eric, D; Holman Rury, R; TECOS, Study; Group; Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes.; The New England journal of medicine; 2015; vol. 373 (no. 3); 232-42

26.1. Study details

Secondary publication of another included study- see primary study for details	Parent study for TECOS trial
Other publications associated with this study included in review	Bethel et al (2019) Progression of glucose-lowering diabetes therapy in TECOS. Endocrinology, Diabetes and Metabolism; 2019; vol. 2 (no. 1); e00053 Green et al (2013) Rationale, design, and organization of a randomized, controlled Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) in patients with type 2 diabetes and established cardiovascular disease. American heart journal; 2013; vol. 166 (no. 6); 983-989e7 Nauck et al (2019) Sitagliptin does not reduce the risk of cardiovascular death or hospitalization for heart failure following myocardial infarction in patients with diabetes: observations from TECOS. Cardiovascular diabetology; 2019; vol. 18 (no. 1); 116
Trial name / registration number	TECOS ClinicalTrials.gov number NCT00790205
Study type	Randomised controlled trial (RCT)
Study location	Multicentre study. 673 sites from 38 countries. Sites were distributed with the aim of enrolling one third of participants from each of Europe, Australasia, and the Americas.
Study setting	Usual care providers
Study dates	Randomisation from December 2008 through July 2012. The study was closed in March 2015, after the requisite minimum of 1300 patients were

	confirmed to have had a primary composite outcome. Median follow-up was 3.0 years (interquartile range, 2.3 to 3.8; maximum, 5.7).
Sources of funding	Merck Sharp & Dohme;
Inclusion criteria	1. Patient has T2DM with HbA1c of ≥6.5% (48 mmol/mol) and ≤8.0% (64 mmol/mol). HbA1c must be documented within 3 months prior to study enrolment, while receiving: • Metformin, pioglitazone, or a sulfonylurea as monotherapy or any dual combination of metformin, pioglitazone, or a sulfonylurea continuously without alteration in dose for at least 3 months. Note: patients who have received insulin for only a short period (i.e. less than 14 days) during a hospitalisation or for the management of acute illness will not be excluded for that reason. OR • A stable dose of insulin (±20% of the scheduled total daily insulin dose) either alone or in combination with a stable dose of metformin for at least 3 months. The use of supplemental/sliding scale insulin during the prior 3 months is permissible, as long as the total daily insulin dose is within ±20% of the scheduled total daily insulin dose. Note: Patients who have required modification of their usual daily insulin dose for a short period (<14 days) during a hospitalisation or for the management of acute illness will not be excluded for that reason. 2. Patient is able to see a usual care provider at least twice per year. 3. Patient is ≥50 years of age with pre-existing vascular disease, defined as having any one of the following: • History of a major clinical manifestation of coronary artery disease (i.e., MI, surgical or percutaneous [balloon and/or stent] coronary revascularization procedure, or coronary angiography showing at least one stenosis ≥50% in a major epicardial artery or branch vessel) • Ischemic cerebrovascular disease, including: ◦ History of ischemic stroke. Strokes not known to be hemorrhagic will be allowed as part of this criterion; ◦ History of carotid arterial disease as documented by ≥50% stenosis documented by carotid ultrasound, magnetic resonance imaging (MRI), or angiography, with or without symptoms of neurologic deficit. • Atherosclerotic peripheral arterial disease, as documented by objective evidence such as amputation due to vascular disease, current symptoms of intermittent claudication confirmed by an ankle-brachial pressure index or toe brachial pressure index less than 0.9, or history of surgical or percutaneous revascularization procedure. 4. Female patients agree to use an effective method of contraception or must not otherwise be at risk of becoming pregnant.

	5. Patient understands the study procedures, alternative treatments available, and the risks involved with the study, and voluntarily agrees to participate by providing written informed consent. 6. Patient agrees to provide permission to obtain all medical records necessary for complete data ascertainment during the follow-up period.
Exclusion criteria	1. Patient has a history of type 1 diabetes mellitus or a history of ketoacidosis. 2. Patient has a history of ≥2 episodes of severe hypoglycemia during the 12 months prior to enrollment. Severe hypoglycemia (hypoglycemia requiring assistance) refers to instances in which the patient was sufficiently disoriented or incapacitated as to require help from another individual or from medical personnel (whether or not this assistance was actually provided). 3. Patient has taken an approved or investigational DPP-4 inhibitor agent (e.g., sitagliptin, alogliptin, saxagliptin, or vildagliptin), GLP-1 analogues (eg, exenatide, exenatide LAR, or liraglutide), or a thiazolidinedione other than pioglitazone within the past 3 months. 4. Patient has cirrhosis of the liver, as assessed by medical history. 5. Patient is enrolled in another experimental protocol which involves the use of an investigational drug or device, or an intervention that would interfere with the conduct of the trial. 6. Patient has a planned or anticipated revascularization procedure. 7. Pregnancy or planned pregnancy during the trial period. 8. Patient has medical history that indicates a life expectancy of less than 2 years or might limit the individual's ability to take trial treatments for the duration of the study. 9. Patient has a history or current evidence of any condition, therapy, lab abnormality, or other circumstance which, in the opinion of the investigator or coordinator, might pose a risk to the patient, make participation not in the patient's best interest, confound the results of the study (e.g., if patient cannot comply with requirements of the study), or interfere with the patient's participation for the full duration of the study. 10. Patient has an estimated GFR (calculated based on serum creatinine via the MDRD formula) <30 mL/ min per 1.73 m2. 11. Patient has a known allergy or intolerance to sitagliptin. 12. Patient has previously been enrolled in the trial.
Recruitment / selection of participants	Not stated

Intervention(s)	Sitagliptin 100 mg daily (or 50 mg daily if the baseline eGFR was ≥30 and <50 ml per minute per 1.73 m2) Concomitant therapy: open label antihyperglycemic agents encouraged as required with the aim of achieving individually appropriate HbA1c targets in all patients.
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure 18% of study participants had prior congestive heart failure (80% rule in protocol - over 80% did not have prior congestive heart failure)
Strata 2: People with atherosclerotic cardiovascular disease	People with atherosclerotic cardiovascular diseases Patients had established CVD (defined as a history of major coronary artery disease, ischemic cerebrovascular disease or atherosclerotic peripheral arterial disease)
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Excluded "eGFR less than 30 ml per minute per 1.73 m2 of body-surface area at baseline", otherwise unclear. Baseline characteristics categorise by eGFR but not CKD diagnosis.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	People at higher risk of developing cardiovascular disease Patients had established CVD (defined as a history of major coronary artery disease, ischemic cerebrovascular disease or atherosclerotic peripheral arterial 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	Not stated/unclear

fatty liver disease	
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	eGFR ≥30mL/min/1.73m2
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	Subgroup analyses (HZ, 95%CI) in supplementary appendix for Primary Composite Cardiovascular Outcome by: Age subgroups Sex Race Region Diabetes duration Diabetes therapy at baseline Prior congestive heart failure HbA1c subgroups Renal function subgroups History of hypertension Systolic and diastolic BP subgroups BMI subgroups Smoking status Medicines taken at time of randomisation
Comparator	Matching placebo
Number of participants	14,671 included in ITT population

	14,735 randomised (64 excluded as did not provide consent or had Good Clinical Practice deviations)
Duration of follow-up	Median follow-up was 3.0 years (interquartile range, 2.3 to 3.8; maximum, 5.7).
Indirectness	Patients had T2DM and established cardiovascular disease.
Method of analysis	Per protocol ITT
Additional comments	Non-inferiority trial (RR of 1.3 used as the marginal upper boundary). Test for non-inferiority using per-protocol method (primary composite cardiovascular outcome) Test for non-inferiority using per-protocol method (secondary composite cardiovascular outcome) Subsequent superiority trial analyses using ITT for primary and secondary composite cardiovascular outcome.

26.2. Study arms

26.2.1. Sitagliptin (N = 7332)

100 mg daily (or 50 mg daily if the baseline eGFR was ≥30 and <50 ml per minute per 1.73 m2). Concomitant therapy: open label antihyperglycemic agents encouraged as required with the aim of achieving individually appropriate HbA1c targets in all patients.

26.2.2. Placebo (N = 7339)

Matching placebo. Concomitant therapy: open label antihyperglycemic agents encouraged as required with the aim of achieving individually appropriate HbA1c targets in all patients.

26.3. Characteristics

26.3.1. Arm-level characteristics

Characteristic	Sitagliptin (N = 7332)	Placebo (N = 7339)
% Male Sample size	n = 5198 ; % = 70.9	n = 5176 ; % = 70.5
Mean age (SD) Mean (SD)	65.4 (7.9)	65.5 (8)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 4955 ; % = 67.6	n = 5002 ; % = 68.2
Black Sample size	n = 206 ; % = 2.8	n = 241 ; % = 3.3
Asian Sample size	n = 1654 ; % = 22.6	n = 1611 ; % = 22
Other Sample size	n = 517 ; % = 7.1	n = 485 ; % = 6.6
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) Duration of diabetes: (year of randomization – year of diagnosis) + 1. Mean (SD)	11.6 (8.1)	11.6 (8.1)
HbA1c (%) Mean (SD)	7.2 (0.5)	7.2 (0.5)
Cardiovascular risk factors Sample size	n = NA ; % = NA	n = NA ; % = NA
Prior cardiovascular disease Sample size	n = 5397 ; % = 73.6	n = 5466 ; % = 74.5

Characteristic	Sitagliptin (N = 7332)	Placebo (N = 7339)
Prior myocardial infarction Sample size	n = 3133 ; % = 42.7	n = 3122 ; % = 42.5
(Prior) >=50% coronary stenosis Sample size	n = 3804 ; % = 51.9	n = 3883 ; % = 52.9
Prior PCI (percutaneous coronary intervention) Sample size	n = 2814 ; % = 38.9	n = 2900 ; % = 40.1
(Prior) CABG (coronary artery bypass graft) Sample size	n = 1845 ; % = 25.2	n = 1819 ; % = 24.8
Prior cerebrovascular disease Sample size	n = 1806 ; % = 24.6	n = 1782 ; % = 24.3
Prior Peripheral arterial disease Sample size	n = 1217 ; % = 16.6	n = 1216 ; % = 16.6
Prior Congestive heart failure Sample size	n = 1303 ; % = 17.8	n = 1340 ; % = 18.3
NYHA class 3 or higher Sample size	n = 171 ; % = 2.3	n = 202 ; % = 2.8
Blood pressure (mmHg) Mean (SD)	NA (NA)	NA (NA)
Systolic blood pressure Mean (SD)	135 (16.9)	135 (17.1)
Diastolic blood pressure Mean (SD)	77.1 (10.3)	77.2 (10.6)
Heart rate Mean (SD)	NR (NR)	NR (NR)
Smoking status Sample size	n = NA ; % = NA	n = NA ; % = NA
Never smoked Sample size	n = 3583 ; % = 48.9	n = 3566 ; % = 48.6

Characteristic	Sitagliptin (N = 7332)	Placebo (N = 7339)
Prior smoker Sample size	n = 2884 ; % = 39.3	n = 2960 ; % = 40.3
Current smoker Sample size	n = 865 ; % = 11.8	n = 813 ; % = 11.1
Alcohol consumption Sample size	n = NA ; % = NA	n = NA ; % = NA
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR
Weight Mean (SD)	NR (NR)	NR (NR)
BMI (kg/m2) Mean (SD)	30.2 (5.6)	30.2 (5.7)
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)	166.1 (44.8)	165.4 (45.9)
LDL cholesterol Mean (SD)	91.2 (63.8)	90.7 (51.2)
HDL cholesterol Mean (SD)	43.5 (12)	43.4 (13)
Triglycerides Mean (SD)	166 (101)	164.8 (98.8)

Characteristic	Sitagliptin (N = 7332)	Placebo (N = 7339)
Albumin creatinine ratio (mg/g) Urinary albumin: creatinine ratio. Data available for only 5148 patients (n= 2606 for sitagliptin, n=2542 for placebo). Median (IQR)	10.3 (3.5 to 34.6)	11.4 (3.6 to 36.2)
eGFR mL/min/1.73m2 MDRD formula used to calculate eGFR. Site-reported values are presented. Sample size	n = NR ; % = NR	n = NR ; % = NR
eGFR mL/min/1.73m2 MDRD formula used to calculate eGFR. Site-reported values are presented. Mean (SD)	74.9 (21.3)	74.9 (20.9)
<50 mL/min/1.73 m Sample size	n = 686 ; % = 9.5	n = 683 ; % = 9.4
<50 mL/min/1.73 m Mean (SD)	NR (NR)	NR (NR)
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Metformin Sample size	n = 5936 ; % = 81	n = 6030 ; % = 82.2
Sulfonylurea Sample size	n = 3346 ; % = 45.6	n = 3299 ; % = 45
Thiazolidinedione Sample size	n = 196 ; % = 2.7	n = 200 ; % = 2.7
Insulin Sample size	n = 1724 ; % = 23.5	n = 1684 ; % = 22.9
Blood pressure-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Beta-blocker Sample size	n = 4647 ; % = 63.4	n = 4675 ; % = 63.7
ACE inhibitor or ARB (angiotensin-receptor blocker) Sample size	n = 5743 ; % = 78.3	n = 5812 ; % = 79.2

Characteristic	Sitagliptin (N = 7332)	Placebo (N = 7339)
Calcium channel blocker Sample size	n = 2444 ; % = 33.3	n = 2517 ; % = 34.3
Diuretic Sample size	n = 2976 ; % = 40.6	n = 3044 ; % = 41.5
Statins/lipid-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Statin Sample size	n = 5851 ; % = 79.8	n = 5868 ; % = 80
Ezetimibe Sample size	n = 386 ; % = 5.3	n = 375 ; % = 5.1
Other treatment being received Sample size	n = NA ; % = NA	n = NA ; % = NA
Aspirin Sample size	n = 5764 ; % = 78.6	n = 5754 ; % = 78.4
Other antiplatelet Sample size	n = 1593 ; % = 21.7	n = 1594 ; % = 21.7
Hispanic or Latino Not a subcategory of Race/ethnicity Sample size	n = 886 ; % = 12.1	n = 912 ; % = 12.4

27. Green, 2013

Bibliographic Reference	Green, Jennifer B; Bethel, M Angelyn; Paul, Sanjoy K; Ring, Arne; Kaufman, Keith D; Shapiro, Deborah R; Califf, Robert M; Holman, Rury R; Rationale, design, and organization of a randomized, controlled Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) in patients with type 2 diabetes and established cardiovascular disease.; American heart journal; 2013; vol. 166 (no. 6); 983-989e7

27.1. Study details

Secondary publication of another included study- see primary study for details	TECOS trial. Green et al (2015) Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes. The New England journal of medicine; 2015; vol. 373 (no. 3); 232-42
Other publications associated with this study included in review	Bethel M, A, Engel S, S, Stevens S, R et al. (2019) Progression of glucose-lowering diabetes therapy in TECOS. Endocrinology, Diabetes and Metabolism 2(1): e00053 Nauck Michael, A, McGuire Darren, K, Pieper Karen, S et al. (2019) Sitagliptin does not reduce the risk of cardiovascular death or hospitalization for heart failure following myocardial infarction in patients with diabetes: observations from TECOS. Cardiovascular diabetology 18(1): 116 McGuire, Darren K, Van de Werf, Frans, Armstrong, Paul W et al. (2016) Association Between Sitagliptin Use and Heart Failure Hospitalization and Related Outcomes in Type 2 Diabetes Mellitus: Secondary Analysis of a Randomized Clinical Trial. JAMA cardiology 1(2): 126-35
Trial name / registration number	TECOS ClinicalTrials.gov number NCT00790205

28. Green, 2024

Bibliographic Reference	Green, Jennifer B; Everett, Brendan M; Ghosh, Alokananda; Younes, Naji; Krause-Steinrauf, Heidi; Barzilay, Joshua; Desouza, Cyrus; Inzucchi, Silvio E; Pokharel, Yashashwi; Schade, David; Scrymgeour, Alexandra; Tan, Meng H; Utzschneider, Kristina M; Mudaliar, Sunder; Cardiovascular Outcomes in GRADE (Glycemia Reduction Approaches in Type 2 Diabetes: A Comparative Effectiveness Study).; Circulation; 2024

28.1. Study details

Secondary publication of another included study- see primary study for details	Group 2022 (Grade Study Research Group). Glycemia Reduction in Type 2 Diabetes - Microvascular and Cardiovascular Outcomes. New England Journal of Medicine; 2022; vol. 387 (no. 12); 1075-1088.
Trial name / registration number	The Grade Research Study Group [NCT01794143]

29. Grey, 2014

Bibliographic Reference	Grey, A.; Bolland, M.; Fenwick, S.; Horne, A.; Gamble, G.; Drury, P. L.; Reid, I. R.; The skeletal effects of pioglitazone in type 2 diabetes or impaired glucose tolerance: A randomized controlled trial; Eur J Endocrinol; 2014; vol. 170 (no. 2); 255-262

29.1. Study details

Trial name / registration number	ACTRN12607000610437
Study type	Randomised controlled trial (RCT)
Study location	NR
Study setting	All visits took place at a clinical research facility
Study dates	Recruitment occurred between October 2008 and April 2011. The final 1-year study visit occurred in April 2012
Sources of funding	Grant support from the Health Research Council of New Zealand. Two authors declare funding from multiple pharmaceutical companies
Inclusion criteria	Eligible participants were >30 years with T2DM, defined by a fasting blood glucose >7 mmol/l and/or serum glucose >11 mmol/l 2 h after ingesting 75 g oral glucose, or IGT, defined by fasting blood glucose 6–7 mmol/l and/or serum glucose 7.8–11 mmol/l 2 h after ingesting 75 g oral glucose. Participants receiving insulin needed to have had a stable daily dose for the 3 months preceding enrolment.
Exclusion criteria	Current TZD use; congestive heart failure New York Heart Association grade 2 or higher; advanced renal dysfunction (estimated glomerular filtration rate (eGFR) <30 ml/min); clinical liver disease; current malignancy; body weight >120 kg; previous vertebral, hip, forearm, or humerus fracture; BMD T-score at dual total hip or L1–L4 < -2; serum 25OHD <30 nmol/l; other metabolic bone disease; current use of medications known to influence bone metabolism; and previous use of an amino bisphosphonate.
Recruitment / selection of participants	Participants were recruited by newspaper advertisement, by sending written invitation from primary care clinics or by direct invitation from a secondary care clinic.
Intervention(s)	Pioglitazone (n=43) Patients received 15 mg pioglitazone daily for the first month, and thereafter 30 mg daily for the remaining 11 months.
Cointervention	No other study medication was administered.

Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Excluded “congestive heart failure New York Heart Association grade 2 or higher”.
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 Excluded “advanced renal dysfunction (estimated glomerular filtration rate (eGFR) <30 ml/min)”, otherwise unclear. No information in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear

Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	NA
Comparator	Placebo (n=43) Patients received a daily capsule of placebo for 12 months
Number of participants	86
Duration of follow-up	12 months
Indirectness	Although publication states patients have eitherT2DM or impaired glucose intolerance, only 1 patient does not have T2DM therefore no need to mark down for indirectness
Method of analysis	ITT
Additional comments	

29.2. Study arms

29.2.1. Pioglitazone (N = 43)

Patients received 15 mg pioglitazone daily for the first month and then 30 mg there after for the remaining 11 months

29.2.2. Placebo (N = 43)

Patients received oral placebo for 12 months

29.3. Characteristics

29.3.1. Arm-level characteristics

Characteristic	Pioglitazone (N = 43)	Placebo (N = 43)
% Male Sample size	n = 21 ; % = 49	n = 23 ; % = 53
Mean age (SD) (Years (mean, SD)) Mean (SD)	NR (NR)	NR (NR)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed Mean (SD)	NR (NR)	NR (NR)
Smoking status Sample size	n = 1 ; % = 2	n = 5 ; % = 12
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Insulin Sample size	n = 5 ; % = 12	n = 12 ; % = 28
Other oral hypoglycemic Sample size	n = 33 ; % = 77	n = 37 ; % = 86
Statins/lipid-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Other treatment being received	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Pioglitazone (N = 43)	Placebo (N = 43)
Sample size		

30. Groop, 2017

Bibliographic Reference	Groop, P. H.; Cooper, M. E.; Perkovic, V.; Hocher, B.; Kanasaki, K.; Haneda, M.; Schernthaner, G.; Sharma, K.; Stanton, R. C.; Toto, R.; Cescutti, J.; Gordat, M.; Meinicke, T.; Koitka-Weber, A.; Thiemann, S.; von Eynatten, M.; Linagliptin and its effects on hyperglycaemia and albuminuria in patients with type 2 diabetes and renal dysfunction: the randomized MARLINA-T2D trial; Diabetes, Obesity and Metabolism; 2017; vol. 19 (no. 11); 1610-1619

30.1. Study details

Secondary publication of another included study- see primary study for details	No
Other publications associated with this study included in review	For blood pressure and heart rate data, as well as additional adverse event data see: • Cooper, M. E., Perkovic, V., Groop, P. H., Hocher, B., Hehnke, U., Meinicke, T., ... & von Eynatten, M. (2019). Hemodynamic effects of the dipeptidyl peptidase-4 inhibitor linagliptin with renin–angiotensin system inhibitors in type 2 diabetic patients with albuminuria. *Journal of hypertension*, *37*(6), 1294.
Trial name / registration number	MARLINA-T2D/NCT01792518
Study type	Randomised controlled trial (RCT) Double-blind placebo-controlled RCT.
Study location	International (Canada, Denmark, Finland, France, Germany, Japan, the Philippines, South Korea, Spain, Taiwan, USA and Vietnam)
Study setting	Outpatient
Study dates	02/2013 to 12/2015
Sources of funding	Supported by the Boehringer Ingelheim and Eli Lilly and Company, Diabetes Alliance.
Inclusion criteria	• Aged 18–80 years with type 2 diabetes • HbA1c 6.5% to 10.0% (48-86 mmol/mol) • BMI≤40 kg/m2 at screening • eGFR≥30 mL/min/1.73 m2, based on the Modification of Diet in Renal Disease (MDRD) study equation

	• Treatment-naive or receiving ≤2 oral glucose-lowering drugs (metformin, sulphonylureas, meglitinides or alpha-glucosidase inhibitors) and/or basal insulin • Renal dysfunction : urinary albumin-to-creatinine ratio (UACR) between 30 and 3000 mg/g, or albuminuria >30 mg/L of urine or >30 µg/min clearly documented in the previous 12 months or detected at screening; albuminuria had then to be confirmed with a geometric mean (gMean) UACR value between 30 and 3000 mg/g from 3 consecutive first-void morning urine samples collected 14 to 16 days before randomization. In addition, each individual was required to be receiving a stable dose of an ACE inhibitor or an ARB but not both (dual or triple blockade of the RAAS was not permitted); additional antihypertensive agents other than RAAS inhibitors were permitted. All antihypertensive agents had to have been administered at the same dose for at least the 10 preceding weeks.
Exclusion criteria	• >240 mg/dL (13.3 mmol/L) after overnight fast during screening/placebo run-in, confirmed by second measurement • Mean arterial blood pressure (SBP+2 DBP)/3 > 110 mmHg at screening or on Day -1 • Dual or triple blockade of the renin–angiotensin–aldosterone system (RAAS) • History of non-diabetic renal disease, renal transplant recipients or signs of acute or chronic UTI • Acute coronary syndrome, stroke or transient ischaemic attack within 3 months prior to informed consent • Use of any DPP-4 inhibitor, GLP-1 agonist, SGLT2 inhibitor, dopamine agonist, bile-acid sequestrant or insulin (except basal insulin), anti-obesity drug within 10 weeks prior to informed consent • Bariatric surgery within 2 years and other gastrointestinal surgeries that induce chronic malabsorption • Indication of liver disease (ALT, AST or alkaline phosphatase >3× ULN) during screening and/or placebo run-in periods • History of pancreatitis
Recruitment / selection of participants	Participants recruited from 80 clinical centres in 12 countries. Individuals randomised 1:1 after 2-wk placebo run-in period to linagliptin or placebo group for 24 weeks. Randomisation stratified by HbA1c at screening (<8.5%, ≥8.5%) and gMean of UACR (<300 mg/g, ≥300 mg/g) measured on 3 consecutive days leading into start of placebo run-in, and used block size of 4. Sequence generated by study sponsor and concealed using central interactive voice and web response system. UACR measured throughout study at each visit from 3 morning samples collected on day of visit and preceding 2 days. Participants were required to be naive to oral glucose-lowering drugs or receiving <3 such drugs (metformin, sulphonylureas, meglitinides, alpha-glucosidase inhibitors) and/or insulin.
Intervention(s)	• Linagliptin 5mg once daily Double-blind oral linagliptin 5 mg once daily for 24 weeks.

Cointervention	All participants were on anti-hypertensive drug treatment. Participants could receive up to 2 oral antidiabetic drugs (metformin, sulphonylureas, meglitinides, alpha-glucosidase inhibitors) and/or insulin.
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 Excluded "a cardiovascular event within the previous 3 months", unclear prior to this. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	People with chronic kidney disease Included people with "renal dysfunction, (a urinary albumin-to-creatinine ratio (UACR) between 30 and 3000 mg/g, or albuminuria >30 mg/L of urine or >30 µg/min clearly documented in the previous 12 months or detected at screening; albuminuria had then to be confirmed with a geometric mean (gMean) UACR value between 30 and 3000 mg/g from 3 consecutive first-void morning urine samples collected 14 to 16 days before randomization)." Around 95% had a UACR of ≥30mg/g
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: Indication of liver disease (ALT, AST or alkaline phosphatase >3× ULN) during screening and/or placebo run-in periods

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 Inclusion criteria: UACR 30-3000 mg/g
Comparator	• Placebo Matched (double-blind) placebo for 24 weeks.
Number of participants	N=360
Duration of follow-up	24 weeks
Indirectness	None
Method of analysis	Modified ITT mITT (full analysis set, all randomised participants who received at least 1 dose of study drug, underwent baseline HbA1c and UACR measurements and at least 1 on-treatment HbA1c or UACR measurement) for HbA1c change from baseline, UACR change, eGFR change. mITT (safety set, all randomised participants who received at least 1 dose of study drug) for adverse events.

30.2. Study arms

30.2.1. Linagliptin 5mg once daily (N = 182)

Oral linagliptin 5 mg once daily for 24 weeks.

30.2.2. Placebo (N = 178)

Placebo for 24 weeks.

30.3. Characteristics

30.3.1. Arm-level characteristics

Characteristic	Linagliptin 5mg once daily (N = 182)	Placebo (N = 178)
% Male Sample size	n = 116 ; % = 63.7	n = 113 ; % = 63.5
Mean age (SD) (years) Mean (SD)	61 (10)	60.1 (9.3)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Asian Sample size	n = 117 ; % = 64.3	n = 122 ; % = 68.5
Black/African-American Sample size	n = 8 ; % = 4.4	n = 3 ; % = 1.7
Hawaiian/Pacific Islander Sample size	n = 1 ; % = 0.5	n = 0 ; % = 0
White Sample size	n = 56 ; % = 30.8	n = 53 ; % = 29.8
Comorbidities Nominal	NA	NA
Presence of frailty Nominal	NA	NA
Time since type 2 diabetes diagnosed Sample size	n = NA ; % = NA	n = NA ; % = NA
Less than 1 year Sample size	n = 11 ; % = 6.1	n = 7 ; % = 4
>1 to 5 years Sample size	n = 25 ; % = 13.9	n = 40 ; % = 23
>5 to 10 years Sample size	n = 47 ; % = 26.1	n = 56 ; % = 32.2

Characteristic	Linagliptin 5mg once daily (N = 182)	Placebo (N = 178)
More than 10 years Sample size	n = 97 ; % = 53.9	n = 71 ; % = 40.8
Cardiovascular risk factors Nominal	NR	NR
Smoking status Nominal	NR	NR
Alcohol consumption Nominal	NR	NR
Presence of severe mental illness Nominal	NA	NA
People with significant cognitive impairment Nominal	NA	NA
People with a learning disability Nominal	NA	NA
Number of people with obesity Nominal	NA	NA
Other antidiabetic medication used Linagliptin, n=180; placebo, n=174 Sample size	n = NA ; % = NA	n = NA ; % = NA
Oral antidiabetic monotherapy Includes metformin Sample size	n = 64 ; % = 35.6	n = 65 ; % = 37.4
Metformin monotherapy Sample size	n = 59 ; % = 32.8	n = 62 ; % = 35.6
Oral antidiabetic combination therapy without insulin Sample size	n = 42 ; % = 23.3	n = 47 ; % = 27
Insulin Sample size	n = 64 ; % = 35.6	n = 48 ; % = 27.6

Characteristic	Linagliptin 5mg once daily (N = 182)	Placebo (N = 178)
Blood pressure-lowering medication used Sample size	n = 182 ; % = 100	n = 178 ; % = 100
Angiotensin II receptor blockers (ARBs) Sample size	n = 120 ; % = 65.9	n = 120 ; % = 67.4
Calcium antagonists Sample size	n = 79 ; % = 43.4	n = 88 ; % = 49.4
Angiotensin-converting enzyme (ACE) inhibitors Sample size	n = 62 ; % = 34.1	n = 58 ; % = 32.6
Diuretics Sample size	n = 52 ; % = 28.6	n = 54 ; % = 30.3
Beta-blockers Sample size	n = 40 ; % = 22	n = 47 ; % = 26.4
Other Sample size	n = 11 ; % = 6	n = 15 ; % = 8.4
Statins/lipid-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Statins Sample size	n = 109 ; % = 59.9	n = 107 ; % = 60.1
Other treatment being received Nominal	NA	NA

31. Group, 2022

Bibliographic Reference	Group, Grade Study Research; Nathan, D. M.; Lachin, J. M.; Bebu, I.; Burch, H. B.; Buse, J. B.; Cherrington, A. L.; Fortmann, S. P.; Green, J. B.; Kahn, S. E.; Kirkman, M. S.; Krause-Steinrauf, H.; Larkin, M. E.; Phillips, L. S.; Pop-Busui, R.; Steffes, M.; Tiktin, M.; Tripputi, M.; Wexler, D. J.; Younes, N.; Glycemia Reduction in Type 2 Diabetes - Microvascular and Cardiovascular Outcomes; New England Journal of Medicine; 2022; vol. 387 (no. 12); 1075-1088

31.1. Study details

Secondary publication of another included study- see primary study for details	Parent study for Grade Study Research Group
Other publications associated with this study included in review	Nathan, David M, Lachin, John M, Balasubramanyam, Ashok et al. (2022) Glycemia Reduction in Type 2 Diabetes - Glycemic Outcomes. The New England journal of medicine 387(12): 1063-1074 Green, Jennifer B, Everett, Brendan M, Ghosh, Alokananda et al. (2024) Cardiovascular Outcomes in GRADE (Glycemia Reduction Approaches in Type 2 Diabetes: A Comparative Effectiveness Study). Circulation Kirkman, M Sue, Tripputi, Mark, Krause-Steinrauf, Heidi et al. (2024) Comparative Effects of Randomized Second-line Therapy for Type 2 Diabetes on a Composite Outcome Incorporating Glycemic Control, Body Weight, and Hypoglycemia: An Analysis of Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE). Diabetes care Cherrington, Andrea L, Tripputi, Mark T, Younes, Naji et al. (2024) Impact of Glucose-Lowering Medications on Health-Related Quality of Life in Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE). Diabetes care Rasouli, N, Younes, N, Ghosh, A et al. (2024) Longitudinal Effects of Glucose-Lowering Medications on β-Cell Responses and Insulin Sensitivity in Type 2 Diabetes: the GRADE Randomized Clinical Trial. Diabetes care
Trial name / registration number	The Grade Research Study Group [NCT01794143]
Study type	Randomised controlled trial (RCT)
Study location	36 clinical centres - it appeared that these were based in the US

Study setting	Unclear
Study dates	Randomisation took place in July 2013 and enrolment concluded in August 2017. The trial cohort was followed until April 2021
Sources of funding	National Institute of Diabetes and Digestive and Kidney Diseases and others. The manufacturers contributed trial medications under clinical-trial agreements with the NIDDK but had no role in the design, conduct, or analysis of the trial: donated medications and supplies were from Becton Dickinson, Bristol Myers Squibb, Merck, Novo Nordisk, Roche Diagnostics, and Sanofi.
Inclusion criteria	• Patients who had received a diagnosis of type 2 diabetes mellitus at 30 years of age or older, with the exception of American Indians and Alaska Natives, in whom the age at diagnosis was 20 years or older • Diabetes had been diagnosed within the previous 10 years and treated with at least 500 mg of metformin per day, but no other glucose-lowering medications • Glycated haemoglobin level of 6.8 to 8.5% (50.8 to 69.4 mmol per mole) at the time of randomization
Exclusion criteria	• History of a major cardiovascular event in the year before randomization • New York Heart Association functional classification of III or higher • Estimated glomerular filtration rate (eGFR) of less than 30 ml per minute per 1.73 m2 of body-surface area
Recruitment / selection of participants	Participants were recruited from participating clinical centres after protocol approval by local IRBs. Clinical centres used electronic databases, community-based advertising, social media, mailings, and other means of local recruitment. Screening included reviewing medical histories from the volunteers (most will have had a diagnosis of diabetes based on clinical criteria), focusing on age, timing of the diagnosis of diabetes, and on medication use. Once eligibility was confirmed, people proceeded to the run-in period to determine suitability for randomization.
Intervention(s)	• Glimepiride - dose was increased from 1 to 2 mg to a maximum of 8 mg per day, administered in divided doses, on the basis of glucose levels monitored by the participants and to avoid hypoglycaemia • Liraglutide - multi-dose pen initiated at 0.6 mg once daily escalated to a maximum dose of 1.8 mg daily, depending on gastrointestinal side effects • Sitagliptin - dose of 100 mg was administered and adjusted depending on the participant’s kidney function.
Cointervention	During the run-in period, the metformin dose was increased to at least 1000 mg per day, with a target maximal does (one that could be taken without unacceptable side effects) of 2000 mg per dat. Immediate-release or extended-release formulations of metformin were supplied to all participants.

Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Excluded "History of congestive heart failure (NYHA 3 or greater)", otherwise unclear. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Excluded "a history of a major cardiovascular event in the year before randomization", prior unclear. Baseline characteristics provide "Self-reported history of heart attack or stroke was 6.5%", other CVD unclear.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Excluded "and an estimated glomerular filtration rate (eGFR) of less than 30 ml per minute per 1.73 m2", otherwise unclear. No information in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Mixed population

Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	BMI - stratify by tertiles: 18.2-30.7, 30.7-36.3, and 36.3-74.3
Comparator	Insulin glargine was administered daily at an initial dose of up to 20 U and was adjusted on the basis of glucose levels monitored by the participants and to avoid hypoglycaemia.
Number of participants	11,259 participants were screened and 5,047 were randomised. Of 1,263 participants randomised to insulin, 5 (0.4%) did not initiate treatment, 42 (3.3%) died prior to the end of the study, 83 (6.8%) did not complete the study, 223 (17.7%) discontinued treatment, and 176 (13.9%) used non-study glucose lowering medications. Of 1,254 participants randomised to glimepiride, 2 (0.2%) did not initiate treatment, 43 (3.4%) died prior to the end of the study, 69 (5.7%) did not complete the study, 329 (26.2%) discontinued treatment, and 208 (16.6%) used non-study glucose lowering medications. Of 1,262 participants randomised to liraglutide, 3 (0.2%) did not initiate treatment, 27 (2.1%) died prior to the end of the study, 79 (6.4%) did not complete the study, 314 (24.9%) discontinued treatment, and 136 (10.8%) used non-study glucose lowering medications. Of 1,268 participants randomised to sitagliptin, 1 (0.1%) did not initiate treatment, 41 (3.2%) died prior to the end of the study, 83 (6.8%) did not complete the study, 264 (20.8%) discontinued treatment, and 193 (15.2%) used non-study glucose lowering medications.
Duration of follow-up	Mean (and median) follow-up of 5.0 years (interquartile range, 4.1 to 6.0; range, 0 to 7.6)
Indirectness	Directly applicable
Method of analysis	Per protocol Included results only for participants who continued to take their assigned glucose-lowering medications and who did not take glucose-lowering medications other than those that were part of the trial regimen. ITT Report states that all analyses were conducted in accordance with the intention-to-treat principle. Analyses included hazard ratios and confidence limits from the Cox proportional-hazards model.
Additional comments	NA

31.2. Study arms

31.2.1. Glimepiride (N = 1254)

Secondary publication of another included study- see primary study for details	NA	NA	NA
Other publications associated with this study included in review	Nathan, David M, Lachin, John M, Balasubramanyam, Ashok et al. (2022) Glycemia Reduction in Type 2 Diabetes - Glycemic Outcomes. The New England journal of medicine 387(12): 1063-1074	Nathan, David M, Lachin, John M, Balasubramanyam, Ashok et al. (2022) Glycemia Reduction in Type 2 Diabetes - Glycemic Outcomes. The New England journal of medicine 387(12): 1063-1074	Nathan, David M, Lachin, John M, Balasubramanyam, Ashok et al. (2022) Glycemia Reduction in Type 2 Diabetes - Glycemic Outcomes. The New England journal of medicine 387(12): 1063-1074
Trial name / registration number	The GRADE Study [NCT01794143]	The GRADE Study [NCT01794143]	The GRADE Study [NCT01794143]

31.2.2. Liraglutide (N = 1262)

Secondary publication of another included study- see primary study for details	NA	NA	NA
Other publications associated with this study included in review	Nathan, David M, Lachin, John M, Balasubramanyam, Ashok et al. (2022) Glycemia Reduction in Type 2 Diabetes - Glycemic Outcomes. The New England journal of medicine 387(12): 1063-1074	Nathan, David M, Lachin, John M, Balasubramanyam, Ashok et al. (2022) Glycemia Reduction in Type 2 Diabetes - Glycemic Outcomes. The New England journal of medicine 387(12): 1063-1074	Nathan, David M, Lachin, John M, Balasubramanyam, Ashok et al. (2022) Glycemia Reduction in Type 2 Diabetes - Glycemic Outcomes. The New England journal of medicine 387(12): 1063-1074

Trial name / registration number	The GRADE Study [NCT01794143]	The GRADE Study [NCT01794143]	The GRADE Study [NCT01794143]

31.2.3. Sitagliptin (N = 1268)

Secondary publication of another included study- see primary study for details	NA	NA	NA
Other publications associated with this study included in review	Nathan, David M, Lachin, John M, Balasubramanyam, Ashok et al. (2022) Glycemia Reduction in Type 2 Diabetes - Glycemic Outcomes. The New England journal of medicine 387(12): 1063-1074	Nathan, David M, Lachin, John M, Balasubramanyam, Ashok et al. (2022) Glycemia Reduction in Type 2 Diabetes - Glycemic Outcomes. The New England journal of medicine 387(12): 1063-1074	Nathan, David M, Lachin, John M, Balasubramanyam, Ashok et al. (2022) Glycemia Reduction in Type 2 Diabetes - Glycemic Outcomes. The New England journal of medicine 387(12): 1063-1074
Trial name / registration number	The GRADE Study [NCT01794143]	The GRADE Study [NCT01794143]	The GRADE Study [NCT01794143]

31.2.4. Insulin glargine (N = 1263)

Secondary publication of another included study- see primary study for details	NA	NA	NA
Other publications associated with this study included in review	Nathan, David M, Lachin, John M, Balasubramanyam, Ashok et al. (2022) Glycemia Reduction in Type 2 Diabetes - Glycemic Outcomes. The New England	Nathan, David M, Lachin, John M, Balasubramanyam, Ashok et al. (2022) Glycemia Reduction in Type 2 Diabetes - Glycemic Outcomes. The New England	Nathan, David M, Lachin, John M, Balasubramanyam, Ashok et al. (2022) Glycemia Reduction in Type 2 Diabetes - Glycemic Outcomes. The New England

	journal of medicine 387(12): 1063-1074	journal of medicine 387(12): 1063-1074	journal of medicine 387(12): 1063-1074
Trial name / registration number	The GRADE Study [NCT01794143]	The GRADE Study [NCT01794143]	The GRADE Study [NCT01794143]

31.3. Characteristics

31.3.1. Study-level characteristics

Characteristic	**Study (N = 5047)**
% Male n calculated by analyst Sample size	n = 3210 ; % = 63.3
Ethnicity Sample size	n = NR ; % = NR
Caucasian Sample size	n = 3321 ; % = 65.8
African Ancestry Sample size	n = 999 ; % = 19.8
Hispanic Sample size	n = 939 ; % = 18.6
Asian Sample size	n = 182 ; % = 3.6
American Indian Sample size	n = 141 ; % = 2.8
Pacific Islander Sample size	n = 30 ; % = 0.6
Presence of frailty Nominal	NR
Time since type 2 diabetes diagnosed Mean (SD)	4.2 (2.7)
HbA1c	7.5 (0.5)

Characteristic	Study (N = 5047)
Mean (SD)	
Cardiovascular risk factors Nominal	NR
Smoking status Sample size	n = 696 ; % = 13.8
Alcohol consumption Nominal	NR
Presence of severe mental illness Nominal	NR
People with significant cognitive impairment Nominal	NR
People with a learning disability Nominal	NR
Weight (kg) Mean (SD)	99.9 (22.3)
BMI Mean (SD)	34.3 (6.8)
Number of people with obesity Nominal	NR
Other antidiabetic medication used (mg) Daily metformin dose Mean (SD)	1994 (205)
Other treatment being received Nominal	NR

31.3.2. Arm-level characteristics

Characteristic	Glimepiride (N = 1254)	Liraglutide (N = 1262)	Sitagliptin (N = 1268)	Insulin glargine (N = 1263)
Comorbidities Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Glimepiride (N = 1254)	Liraglutide (N = 1262)	Sitagliptin (N = 1268)	Insulin glargine (N = 1263)
Hypertension Sample size	n = 963 ; % = 76.8	n = 980 ; % = 77.7	n = 963 ; % = 75.9	n = 973 ; % = 77
Dyslipidaemia Sample size	n = 1213 ; % = 96.7	n = 1208 ; % = 95.7	n = 1220 ; % = 96.2	n = 1211 ; % = 95.9
Diabetic peripheral neuropathy Sample size	n = 517 ; % = 41.2	n = 549 ; % = 43.5	n = 542 ; % = 42.7	n = 507 ; % = 40.1
Reported having had a heart attack or stroke Sample size	n = 76 ; % = 6.1	n = 77 ; % = 6.1	n = 91 ; % = 7.2	n = 80 ; % = 6.3
Blood pressure-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
ACEI/ARB Sample size	n = 742 ; % = 59.2	n = 738 ; % = 58.5	n = 729 ; % = 57.5	n = 724 ; % = 57.3
BP meds (other than ACEi/ARB) Sample size	n = 24 ; % = 1.9	n = 29 ; % = 2.3	n = 35 ; % = 2.8	n = 30 ; % = 2.4
BP meds (any) Sample size	n = 865 ; % = 69	n = 890 ; % = 70.5	n = 859 ; % = 67.7	n = 882 ; % = 69.8
Statins/lipid-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Lipid lowering use (any) Sample size	n = 857 ; % = 68.3	n = 795 ; % = 63	n = 844 ; % = 66.6	n = 825 ; % = 65.3
Statin use Sample size	n = 824 ; % = 65.7	n = 765 ; % = 60.6	n = 818 ; % = 64.5	n = 803 ; % = 63.6

32. Grunberger, 2018

Bibliographic Reference	Grunberger, G.; Camp, S.; Johnson, J.; Huyck, S.; Terra, S. G.; Mancuso, J. P.; Jiang, Z. W.; Golm, G.; Engel, S. S.; Lauring, B.; Ertugliflozin in patients with Stage 3 chronic kidney disease and type 2 diabetes mellitus: the VERTIS RENAL randomized study; Diabetes Ther; 2018; vol. 9 (no. 1); 49-66

32.1. 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	VERTIS RENAL/NCT01986855
Study type	Randomised controlled trial (RCT) Double-blind parallel group placebo-controlled RCT for 52 weeks. At 26 weeks, blinding was broken for study sponsor only.
Study location	International (121 centres in 13 countries, Argentina, Bulgaria, Colombia, Hungary, Israel, Mexico, Philippines, Poland, Romania, Russia, South Africa, UK and USA)
Study setting	Outpatient
Study dates	12/2013 to 09/2016
Sources of funding	Merck Sharp & Dohme Corp. subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA and Pfizer Inc.
Inclusion criteria	• Aged ≥25 years-old • Type 2 diabetes diagnosis (American Diabetes Association) • Stage 3 CKD (eGFR≥30 and <60 mL/min/1.73 m2 using MDRD equation) with stable renal function (change in eGFR<10 mL/min/1.73 m2 between screening and • HbA1c level 7-10.5% inclusive if not on metformin, otherwise HbA1c level 6.5-10% inclusive.

	• Engaging in diet and exercise with or without use of anti-hyperglycaemic mono- or combination therapy (except metformin, rosiglitazone, and other SGLT2 inhibitors)

Exclusion criteria	• History of
	  ○ type 1 diabetes mellitus
	  ○ ketoacidosis
	  ○ renal-related issues (including nephrotic range proteinuria (>3000 mg/day) with hypoalbuminemia and edema, rapidly progressive glomerulonephritis, lupus nephritis, renal or systemic vasculitis, renal artery stenosis with renovascular hypertension, or ischemic nephropathy, familial renal glucosuria, renal dialysis, renal transplant, or renal disease requiring treatment with immunosuppressive agents)
	• Active obstructive uropathy
	• Indwelling urinary catheter

Recruitment / selection of participants	Participants recruited from 121 sites in 13 countries. After screening, all eligible participants entered 2-wk single-blind placebo run-in period although those on metformin at screening underwent at least 10-wk wash-off period before this. Participants with ≥80% compliance (based on pill count) were randomised 1:1:1 to one of three arms using interactive voice response system/web response system according to computer-generated schedule with block size of 6, and stratified on pre-treatment (week -2) eGFR measurement (eGFR ≥45 to <60 mL/min/1.73 m2 [Stage 3A CKD]; eGFR>30 to ≤45 mL/min/1.73 m2 [Stage 3B CKD]), presence/absence of history of cardiovascular disease or heart failure, and presence of insulin at randomisation. Trial was initially conducted for 26 weeks and extended for additional 26 weeks and 2-wk post-treatment follow up, with participants staying in originally allocated groups.
Intervention(s)	• Ertugliflozin 15 mg once daily • Ertugliflozin 15 mg once daily Oral ertugliflozin pill 15 and 5 mg once daily in morning for 52 weeks. Participants and trial personnel were blinded for duration of 52-week trial but blinding for study sponsor was broken at 26 weeks. Packaging of drugs and placebo were identical to maintain blinding.
Cointervention	Diet, exercise with or without anti-hyperglycaemic drug treatment (97% of participants were on such treatment at screening)
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear 50% had a medical history of CV disease or heart failure, but breakdown unclear. Only able to determine that the population would not fall into the 'with HF' stratum.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear 50% had a medical history of CV disease or heart failure, but breakdown unclear. Only able to determine that the population would not fall into the 'with CVD' stratum.

Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	People with chronic kidney disease Included people with "stage 3 CKD [estimated glomerular filtration rate (eGFR) ≥ 30 to < 60 mL/min/1.73 m2] ". CKD classification based on eGFR but this was 'study-classified'. Stable renal function was defined as a change in eGFR < 10 mL/min/1.73 m2 between screening and visit 3 (week – 2), with eGFR measurement ≥ 30 to < 60 mL/min/1.73 m2 at both visits.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	eGFR ≥30mL/min/1.73m2 Inclusion criteria eGFR ≥30 and <60
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Comparator	• Placebo Oral placebo pill once daily for 52 weeks.
Number of participants	N=467

Duration of follow-up	52 weeks + 2-wk post-treatment follow up.
Indirectness	None
Method of analysis	ITT ITT analysis (all randomised participants) for safety assessment Modified ITT mITT analysis for efficacy endpoints (all randomised participants with at least 1 measurement of endpoint) of HbA1c level in overall Stage 3 CKD cohort, and of body weight and systolic blood pressure in Stage 3A CKD subgroup.
Additional comments	After completion of initial 26 week phase, investigators discovered via analysis of retained plasma samples that ~17% of participants in trial had used metformin (and had not reported its use) during trial, which was prohibited according to protocol. This contrasts with use of hyperglycaemic rescue medication, which was permitted by protocol and reported to investigators. This prompted post-hoc analysis for 26 week data in participants who tested positive for metformin use and those who did not.

32.2. Study arms

32.2.1. Ertugliflozin 15 mg once daily (N = 155)

Oral ertugliflozin pill 15 mg once daily for 52 weeks in addition to diet, exercise and, if any, background anti-hyperglycaemic drug treatment.

32.2.2. Ertugliflozin 5 mg once daily (N = 158)

Oral ertugliflozin pill 15 mg once daily for 52 weeks in addition to diet, exercise and, if any, background anti-hyperglycaemic drug treatment.

32.2.3. Placebo (N = 154)

Placebo pill once daily for 52 weeks in addition to diet, exercise and, if any, background anti-hyperglycaemic drug treatment.

32.3. Characteristics

32.3.1. Arm-level characteristics

Characteristic	Ertugliflozin 15 mg once daily (N = 155)	Ertugliflozin 5 mg once daily (N = 158)	Placebo (N = 154)
% Male Sample size	n = 75 ; % = 48.4	n = 84 ; % = 53.2	n = 72 ; % = 46.8
Mean age (SD) (years) Mean (SD)	67.5 (8.5)	66.7 (8.3)	67.5 (8.9)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Asian Sample size	n = 20 ; % = 12.9	n = 16 ; % = 10.1	n = 9 ; % = 5.8
American Indian/Alaska Native Sample size	n = 0 ; % = 0	n = 0 ; % = 0	n = 1 ; % = 0.6
Black/African American Sample size	n = 9 ; % = 5.8	n = 6 ; % = 3.8	n = 4 ; % = 2.6
Hispanic or Latino Sample size	n = 31 ; % = 20	n = 29 ; % = 18.4	n = 27 ; % = 17.5
Multiple Sample size	n = 7 ; % = 4.5	n = 9 ; % = 5.7	n = 6 ; % = 3.9
White Sample size	n = 119 ; % = 76.8	n = 127 ; % = 80.4	n = 134 ; % = 87
Presence of frailty Nominal	NR	NR	NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	14.5 (8.5)	14.9 (9)	13.1 (8.1)
Cardiovascular risk factors Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Ertugliflozin 15 mg once daily (N = 155)	Ertugliflozin 5 mg once daily (N = 158)	Placebo (N = 154)
Medical history of CV disease or heart failure Sample size	n = 77 ; % = 49.7	n = 79 ; % = 50	n = 76 ; % = 49.4
Smoking status Nominal	NR	NR	NR
Alcohol consumption Nominal	NR	NR	NR
Presence of severe mental illness Nominal	NR	NR	NR
People with significant cognitive impairment Nominal	NR	NR	NR
People with a learning disability Nominal	NR	NR	NR
Number of people with obesity Nominal	NR	NR	NR
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Currently on antidiabetic medication Sample size	n = 148 ; % = 95.5	n = 153 ; % = 96.8	n = 151 ; % = 98.1
Biguanides Sample size	n = 38 ; % = 24.5	n = 41 ; % = 25.9	n = 36 ; % = 23.4
DPP4 inhibitors Sample size	n = 20 ; % = 12.9	n = 22 ; % = 13.9	n = 21 ; % = 13.6
GLP-1 receptor agonists Sample size	n = 3 ; % = 1.9	n = 3 ; % = 1.9	n = 7 ; % = 4.5

Characteristic	Ertugliflozin 15 mg once daily (N = 155)	Ertugliflozin 5 mg once daily (N = 158)	Placebo (N = 154)
Insulins and analogs Sample size	n = 87 ; % = 56.1	n = 89 ; % = 56.3	n = 85 ; % = 55.2
Sulphonylureas Sample size	n = 60 ; % = 38.7	n = 65 ; % = 41.1	n = 63 ; % = 40.9
Other Sample size	n = 9 ; % = 5.8	n = 8 ; % = 5.1	n = 8 ; % = 5.2
Blood pressure-lowering medication used Nominal	NR	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR	NR
Other treatment being received Nominal	NR	NR	NR

33. Gu, 2019

Bibliographic Reference	Gu, T.; Ma, J.; Zhang, Q.; Zhu, L.; Zhang, H.; Xu, L.; Cheng, J.; Shi, B.; Li, D.; Shao, J.; et, al.; Comparative effect of saxagliptin and glimepiride with a composite endpoint of adequate glycaemic control without hypoglycaemia and without weight gain in patients uncontrolled with metformin therapy: results from the SPECIFY study, a 48-week, multi-centre, randomized, controlled trial; Diab Obes Metab; 2019; vol. 21 (no. 4); 939-948

33.1. 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	SPECIFY [NCT02280486]
Study type	Randomised controlled trial (RCT)
Study location	11 sites in China
Study setting	NR
Study dates	December 2014 to October 2011
Sources of funding	AstraZeneca
Inclusion criteria	• between 25 and 75 years of age • body mass index (BMI) between 20 and 30 kg/m2 • using a stable dose of metformin (=1500 mg/d) for at least 8 weeks without adequate glycaemic control (HbA1c between 7.0% and 9.5%

Exclusion criteria	• being treated with any investigational drug within 1 month prior to this trial or had undergone treatment with corticosteroids within the past 2 months • had impaired renal function, defined as serum-creatinine ≥132.6 μmoL/L • had clinically significant, active history or incidence of cardiovascular disease over the past 12 months • acute or chronic diseases that may cause tissue hypoxia, positive glutamic acid decarboxylase antibody, proliferative retinopathy or muscular oedema requiring acute treatment.
Recruitment / selection of participants	Participants completed a 1-week run-in period of a stable dose of metformin (1500 mg) and a 48-week treatment period before they were randomised
Intervention(s)	• Saxagliptin initiated and maintained at 5 mg every morning • Glimepiride initially administered at 1 mg every morning and titrated at 4-week intervals from 1 to 6 mg, if fasting blood glucose (FBG) was greater than 6.1 mmol/L.
Cointervention	Metformin
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Excluded "a clinically significant, active history or incidence of cardiovascular disease over the past 12 months", prior unclear. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Excluded "impaired renal function, defined as serum-creatinine ≥132.6 μmoL/L,", otherwise unclear. No information in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear

Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	People who do not have obesity Inclusion criteria "body mass index (BMI) between 20 and 30 kg/m2"
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	NA
Comparator	NA
Number of participants	2388 participants were randomised. 194 participants were allocated to saxagliptin, of which 3 withdrew before treatment, 28 discontinued, and 163 completed the 48-week treatment. 194 participants were allocated to glimepiride, of which, 6 withdrew before treatment, 26 discontinued, and 162 completed the 48-week treatment.
Duration of follow-up	48 weeks
Indirectness	Directly applicable
Method of analysis	Per protocol Outcomes of glycaemic control and bodyweight were also analysed per-protocol. ITT

	The full analysis set used an intention-to-treat principle, and a last observation carried forward approach was used.
Additional comments	NA

33.2. Study arms

33.2.1. Saxagliptin (N = 194)

33.2.2. Glimepiride (N = 194)

33.3. Characteristics

33.3.1. Arm-level characteristics

Characteristic	Saxagliptin (N = 194)	Glimepiride (N = 194)
% Male Sample size	n = 119 ; % = 63.6	n = 109 ; % = 58.6
Mean age (SD) Mean (SD)	54.2 (9.4)	52.8 (9.5)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed Mean (SD)	5.2 (4.1)	4.9 (4.5)
Cardiovascular risk factors Nominal	NR	NR
Smoking status	NR	NR

Characteristic	Saxagliptin (N = 194)	Glimepiride (N = 194)
Nominal		
Alcohol consumption Nominal	NR	NR
Presence of severe mental illness Nominal	NR	NR
People with significant cognitive impairment Nominal	NR	NR
People with a learning disability Nominal	NR	NR
Number of people with obesity Nominal	NR	NR
Albumin creatinine ratio Median (IQR)	9.85 (2.98 to 27.58)	9.8 (4.1 to 22)
eGFR mL/min/1.73m2 Nominal	NR	NR
Other antidiabetic medication used Nominal	NR	NR
Blood pressure-lowering medication used Nominal	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

34. Guja, 2018

Bibliographic Reference	Guja, C.; Frías, J. P.; Somogyi, A.; Jabbour, S.; Wang, H.; Hardy, E.; Rosenstock, J.; Effect of exenatide QW or placebo, both added to titrated insulin glargine, in uncontrolled type 2 diabetes: the DURATION-7 randomized study; Diabetes, obesity & metabolism; 2018; vol. 20 (no. 7); 1602-1614

34.1. Study details

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	NA
Trial name / registration number	DURATION-7 [NCT02229383]
Study type	Randomised controlled trial (RCT)
Study location	126 centres in 6 countries (Hungary, Poland, Romania, Slovakia, South Africa and the USA)
Study setting	NA
Study dates	September 2014 and August 2016
Sources of funding	AstraZeneca
Inclusion criteria	• People with T2DM aged ≥ 18 years • On a stable regimen comprising IG ≥20 units/d for ≥6 weeks, in combination with diet and exercise alone or with stable doses of metformin ≥1500 mg/d for >8 weeks ± a sulphonylurea. • HbA1c of 7.5% to 12.0% (59-108 mmol/mol and fasting plasma glucose (FPG) <15.6 mmol/L (<280 mg/dL) at screening • HbA1c of 7.0% to 10.5% (53-91 mmol/mol) at randomization

Exclusion criteria	• Serum calcitonin concentration ≥40 pg/mL [≥40 ng/L] at screening • Clinically significant abnormal free T4 values or patients needing initiation or adjustment of thyroid treatment according to the investigator. Abnormal thyroid-stimulating hormone value at screening was further evaluated by free T4. Patients with clinically significant abnormal free T4 values were excluded • Known active proliferative retinopathy • History of, or currently have, acute or chronic pancreatitis, or have triglyceride concentrations ≥500 mg/dL [≥5.65 mmol/L] at screening • History or presence of inflammatory bowel disease or other severe gastrointestinal diseases, particularly those that may impact gastric emptying, such as gastroparesis or pyloric stenosis • History of gastric bypass surgery or gastric banding surgery, or either procedure is planned during the time period of the study. Current use of gastric balloons is also excluded. • Significant hepatic disease, including, but not limited to, acute hepatitis, chronic active hepatitis, or severe hepatic insufficiency, including patients with ALT and/or AST >3 × upper limit of normal and/or TB >2 mg/dL [>34.2 µmol/L] ○ Patients with TB >2 mg/dL [>34.2 µmol/L] and documented Gilbert's syndrome were allowed to participate • Positive serological test for hepatitis B or hepatitis C • Known history of hepatotoxicity with any medication • Known history of severe hepatobiliary disease • Clinically significant cardiovascular disease or procedure within 3 months of screening, including but not limited to myocardial infarction, clinically significant arrhythmia, unstable angina, coronary artery bypass surgery, or angioplasty; or are expected to require coronary artery bypass surgery or angioplasty during the course of the study • Presence or history of severe congestive heart failure (New York Heart Association class IV) • History of renal transplantation, or currently receiving renal dialysis, or has a creatinine clearance <30 mL/min [0.50 mL/s] as calculated by the Cockcroft-Gault formula • If on metformin, has a serum creatinine level ≥1.5 mg/dL in males, ≥1.4 mg/dL in females, or creatinine clearance <60 mL/min [<1.0 mL/s] as calculated by the Cockcroft-Gault formula • Known or suspected human immunodeficiency virus infection • History of organ transplantation • Presence or history of medullary thyroid carcinoma or MEN 2 OR a family history of medullary thyroid carcinoma or MEN 2 • Malignancy (with the exception of basal and squamous cell carcinoma of the skin) within 5 years of screening • Hemoglobinopathy, haemolytic anaemia, or chronic anaemia (haemoglobin concentration <11.5 g/dL [<115 g/L] for males, <10.5 g/dL [<105 g/L] for females) or any other condition known to interfere with the HbA1c methodology • Has donated blood or had a significant blood loss within 2 months of first dose of study medication or is planning to donate blood during the study • Has donated plasma within 7 days before first dose of study medication

	• Any exposure to exenatide or any glucagon-like peptide-1 analogue
	• Administration of any antihyperglycemic therapy, other than sulphonylurea, insulin, or metformin, for more than 14 days (consecutive or not) during the 12 weeks before screening. In addition, administration of any antihyperglycaemic therapy, other than sulphonylurea, insulin, or metformin, at any dose, at any time during the 4 weeks before screening
	• Has been treated, is currently being treated, or is expected to require or undergo treatment with any of the following treatment-excluded medications:
	  ○ Any dipeptidyl peptidase-4 inhibitor within 3 months before screening
	  ○ Systemic corticosteroids within 3 months before screening by oral, intravenous, intra-articular, or intramuscular route; or potent, inhaled, or intrapulmonary steroids known to have a high rate of systemic absorption
	  ○ Prescription or over-the-counter weight loss medications within 3 months before screening
	• Has a clinically significant medical condition that could potentially affect study participation and/or personal well-being, as judged by the investigator
	• Has clinically significant abnormal laboratory test values (clinical chemistry, haematology, urinalysis) as judged by the investigator at screening
	• Has known contraindication, allergies, or hypersensitivity to any component of exenatide once weekly
	• Has known contraindication, allergies, or hypersensitivity to insulin glargine or excipients
	• If taking metformin, has a contraindication to metformin use, including known metabolic or lactic acidosis, or any condition associated with hypoperfusion, hypoxemia, dehydration, or sepsis
	• Has evidence of current abuse of drugs or alcohol or a history of abuse that, in the investigator's opinion, would cause the individual to be noncompliant

Recruitment / selection of participants	The study included a screening visit, and an 8-week insulin titration phase. 808 participants were screened, 511 entered the insulin titration phase, and 464 participants were randomised.
Intervention(s)	Exenatide 2 mg once weekly with microspheres self-administered by subcutaneous injection in the abdomen, thigh or upper abdomen.
Cointervention	Patients continued prior metformin use throughout the study, while sulfonylureas were discontinued at the start of insulin titration, if applicable. Insulin was titrated according to the Initiate Insulin by Aggressive Titration and Education (INITIATE) algorithm, and was administered at the same time each day, preferably at bedtime.
Strata 1: People with type 2 diabetes	Not stated/unclear Excluded "Presence or history of severe congestive heart failure (New York Heart Association class IV) ", otherwise unclear. No information in baseline characteristics.

mellitus and heart failure	
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Excluded "Clinically significant cardiovascular disease or procedure within 3 months of screening, including but not limited to myocardial infarction, clinically significant arrhythmia, unstable angina, coronary artery bypass surgery, or angioplasty", prior unclear. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Excluded "History of renal transplantation, or is currently receiving renal dialysis, or has a creatinine clearance <30 mL/min [0.50 mL/s] as calculated by the Cockcroft-Gault formula", otherwise unclear. No information in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Mixed population
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria	Not stated/unclear

category at baseline	
Population subgroups	NA
Comparator	Placebo with microspheres self-administered once weekly by subcutaneous injection in the abdomen, thigh or upper abdomen.
Number of participants	464 participants were randomised. Of the 233 participants allocated to exenatide, 1 patient was not treated, 211 completed treatment, and 213 completed the study. Of the 123 participants allocated to placebo, 207 participants completed treatment and 208 participants completed the study
Duration of follow-up	28 weeks
Indirectness	Directly applicable
Method of analysis	ITT ITT population was defined as all randomized patients who received ≥1 dose of study drug with ≥1 post-baseline HbA1c assessment. The primary endpoint was assessed using a mixed effects model for repeated measures (MMRM).
Additional comments	Insulin titration was not strictly adhered to after randomization in all patients, despite FPG values being above those specified in the INITIATE titration algorithm (4.0-5.5 mmol/L [72-99 mg/dL]). The report stated that this probably reflects real-world clinical practice, due to clinical inertia and concern about body weight gain and increased hypoglycaemia.

34.2. Study arms

34.2.1. Exenatide (N = 233)

34.2.2. Placebo (N = 231)

34.3. Characteristics

34.3.1. Arm-level characteristics

Characteristic	Exenatide (N = 233)	Placebo (N = 231)
% Male Sample size	n = 114 ; % = 49.4	n = 107 ; % = 46.5

Characteristic	Exenatide (N = 233)	Placebo (N = 231)
Mean age (SD) Mean (SD)	57.8 (9)	57.6 (10.3)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 205 ; % = 88.7	n = 196 ; % = 85.2
Black Sample size	n = 19 ; % = 8.2	n = 28 ; % = 12.2
Asian Sample size	n = 4 ; % = 1.7	n = 2 ; % = 0.9
Other Sample size	n = 3 ; % = 1.3	n = 4 ; % = 1.7
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed Mean (SD)	11.5 (6.6)	11.1 (6.1)
Smoking status Nominal	NR	NR
Alcohol consumption Nominal	NR	NR
Presence of severe mental illness Nominal	NR	NR
People with significant cognitive impairment Nominal	NR	NR
People with a learning disability Nominal	NR	NR
Number of people with obesity >= 30 kg/m2 Sample size	n = 157 ; % = 68	n = 166 ; % = 72.2
Other antidiabetic medication used	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Exenatide (N = 233)	Placebo (N = 231)
Sample size		
Metformin alone Sample size	n = 121 ; % = 52.4	n = 117 ; % = 50.9
Prior SU alone Sample size	n = 8 ; % = 3.5	n = 10 ; % = 4.3
Metformin + prior SU Sample size	n = 73 ; % = 31.6	n = 70 ; % = 30.4
None Sample size	n = 29 ; % = 12.6	n = 33 ; % = 14.3
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR
Insuline glargine dose (units/day) Mean (SD)	50.1 (21.4)	52 (25)

35. Gullaksen, 2023

Bibliographic Reference	Gullaksen, Soren; Vernstrom, Liv; Sorensen, Steffen S; Ringgaard, Steffen; Laustsen, Christoffer; Funck, Kristian L; Poulsen, Per L; Laugesen, Esben; Separate and combined effects of semaglutide and empagliflozin on kidney oxygenation and perfusion in people with type 2 diabetes: a randomised trial.; Diabetologia; 2023; vol. 66 (no. 5); 813-825

35.1. 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	SEMPA [EudraCT 2019-000781-38]
Study type	Randomised controlled trial (RCT)
Study location	Denmark
Study setting	Aarhaus University Hospital
Study dates	Participants were screened from June 2019 to May 2021. Data were collected between August 2019 and February 2022.
Sources of funding	Novo Nordisk Foundation, Central Denmark Region Research Fund and Danish Medical Associations Research Foundation
Inclusion criteria	• Diagnosis of type 2 diabetes (HbA1c 48 mmol/mol [6.5%]) • (1) Aged ≥ 50 years with established CVD (e.g. previous cardiovascular, cerebrovascular or peripheral vascular disease), heart failure or CKD (eGFR <60 ml/min per1.73 m2) OR aged (2) aged 60 years and at high risk of CVD (e.g. smoker, micro-or macroalbuminuria or persistent hypertension despite antihypertensive treatment).

Exclusion criteria	• eGFR <60 ml/min per 1.73 m2 but, as a result of new data from the CREDENCE trial, this was adjusted to eGFR <45 ml/min per 1.73m2 • Treatment with an SGLT2i, GLP-1ra or DPP4-i within 30 days before randomization or insulin other than basal or premixed within 30 days before randomization. Participants were eligible after a 30 days wash-out period of SGLT2i, GLP-1ra or DPP4-i • A history of an acute coronary or cerebrovascular event within 90 days before randomization
Recruitment / selection of participants	The Danish Health Data Authority provided data extractions with information on persons with a diagnosis of type 2 diabetes living in the Central Region of Denmark. These persons were contacted by letter. If they responded, we sent written information about the project. Potentially eligible persons were invited for a screening visit, where the potential for inclusion or exclusion was evaluated through interviews, physical examinations, and medical records before the final enrolment in the study
Intervention(s)	Empagliflozin 10 mg once daily
Cointervention	NR
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Inclusion criteria was history of CVD, CHF or eGFR <60; or CV risk factors, but breakdown unclear. Baseline characteristics give history of CVD around 60%, but that includes CHF and breakdown unclear.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Inclusion criteria was history of CVD, CHF or eGFR <60; or CV risk factors, but breakdown unclear. Baseline characteristics give history of CVD around 60%, but that includes CHF and breakdown unclear.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Inclusion criteria was history of CVD, CHF or eGFR <60; or CV risk factors, but breakdown unclear.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear Inclusion criteria stated that participants either had established cardiovascular disease or were deemed to be at increased risk of CVD (e.g. smoker, micro-or macroalbuminuria or persistent hypertension despite antihypertensive treatment)

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 Exclusion criteria included participants with eGFR <45 ml/min per 1.73 m2
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	NA
Comparator	Placebo
Number of participants	20 participants were randomised to empagliflozin and 20 participants were randomised to placebo. In the empagliflozin arm, 1 participant was lost to follow-up and 1 participant did not take the treatment; at baseline data were available for 18 participants and at 32 weeks data were available for 17 participants. In the placebo arm, 2 participants were lost to follow-up; at baseline, data were available for 19 participants and at 32 weeks data were available for 18 participants.
Duration of follow-up	16 and 32 weeks
Indirectness	Directly applicable
Method of analysis	ITT Weight outcomes were reported as estimated marginal means (95% CI) and estimated marginal mean difference (95% CI)

Additional comments	There were an additional 2 arms in this trial, however, these were not included as treatment was not maintained for 24 weeks, meaning they were not eligible for inclusion. These were semaglutide followed by semaglutide + placebo and semaglutide followed by semaglutide + empagliflozin.

35.2. Study arms

35.2.1. Empagliflozin (N = 20)

35.2.2. Placebo (N = 20)

35.3. Characteristics

35.3.1. Arm-level characteristics

Characteristic	Empagliflozin (N = 20)	Placebo (N = 20)
% Male Sample size	n = 13 ; % = 65	n = 14 ; % = 70
Mean age (SD) (years) Mean (SD)	13 (65)	14 (70)
Ethnicity Nominal	NR	NR
Comorbidities History of CVD Sample size	n = 11 ; % = 55	n = 9 ; % = 45
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed Median (IQR)	10 (5 to 18.5)	8 (4 to 10)
Cardiovascular risk factors Nominal	NR	NR
Yes	n = 6 ; % = 30	n = 4 ; % = 20

Characteristic	Empagliflozin (N = 20)	Placebo (N = 20)
Sample size		
No Sample size	n = 8 ; % = 40	n = 9 ; % = 45
Former Sample size	n = 6 ; % = 30	n = 7 ; % = 35
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 Mean (SD)	28.3 (4.7)	28.9 (4.6)
Number of people with obesity Nominal	NA	NA
Other antidiabetic medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Metformin Sample size	n = 18 ; % = 90	n = 18 ; % = 90
Insulin therapy Sample size	n = 6 ; % = 30	n = 4 ; % = 20
Blood pressure-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Renin-angiotensin-aldosterone system blocker Sample size	n = 14 ; % = 70	n = 16 ; % = 80
Calcium antagonist Sample size	n = 9 ; % = 45	n = 11 ; % = 55

Characteristic	Empagliflozin (N = 20)	Placebo (N = 20)
Beta-blocker Sample size	n = 6 ; % = 30	n = 4 ; % = 20
Thiazide/loop diuretics Sample size	n = 10 ; % = 50	n = 8 ; % = 40
Statins/lipid-lowering medication used Statin Sample size	n = 15 ; % = 75	n = 18 ; % = 90
Other treatment being received Nominal	NR	NR

36. Guo, 2020

Bibliographic Reference	Guo, W.; Tian, W.; Lin, L.; Xu, X.; Liraglutide or insulin glargine treatments improves hepatic fat in obese patients with type 2 diabetes and nonalcoholic fatty liver disease in twenty-six weeks: A randomized placebo-controlled trial; Diabetes Research & Clinical Practice; 2020; vol. 170; 108487

36.1. Study details

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	NA
Trial name / registration number	ChiCTR2000035091
Study type	Randomised controlled trial (RCT)
Study location	Chin
Study setting	Single-centre study at 900 Hospital of the Joint Logistics Team in China
Study dates	Enrolment took place between September 2016 to July 2018
Sources of funding	Natural Science Foundation of Fujian Province and 900 Hospital of the Joint Logistics Team Internal Hospital Project
Inclusion criteria	• Age 30–60 years at screening • Diagnosis of type 2 diabetes inadequately controlled (HbA1c > 6.5%) under metformin monotherapy (at a stable dose of 20000 mg/day for at least 3 months) • Clinically diagnosed with NAFLD: the diagnosis of NAFLD requires that (a) there is hepatic steatosis by imaging or histology, (b) there is no significant alcohol consumption, (c) there are no competing etiologies for hepatic steatosis, and (d) there are no co-existing causes for chronic liver disease • BMI of > 25 kg/m2 at screening

Exclusion criteria	• Contraindications for H-MRS (e.g., metallic implants, pacemakers, or claustrophobia) • Type 1 diabetes or episodes of ketoacidosis • Severe hepatic impairment [aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels • 3 times the upper limit of normal or renal functions (creatinine clearance, 30 mL/min) • Women planning prospective pregnancy • Established diagnosis of chronic liver disease other than NAFLD • History or current episode of pancreatitis or other pancreatic diseases
Recruitment / selection of participants	NR
Intervention(s)	Liraglutide subcutaneous injection at a starting dose of 0.6 mg 1/day and increased by weekly forced titration to 1.8 mg.
Cointervention	Metformin was administered at a constant dose. All patients accepted the recommendations of national health service standards on lifestyle change, including exercise, weight loss and diet adjustment.
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	People with non-alcoholic fatty liver disease
Subgroup 4: People with obesity	Not stated/unclear Report states that population was obese, however, inclusion criteria states that "BMI of > 25 kg/m2 at screening" and mean baseline BMI was below 30 kg/m2
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	NA
Comparator	• Insulin glargine - 10 IU subcutaneously at bedtime and titrated by 1 unit each day to achieve a fasting plasma glucose (FPG) < 7 mmol/L • Placebo - taken once daily in the evening
Number of participants	128 participants were assessed for eligibility and 96 were randomised. Of the 32 participants allocated to insulin, 30 completed the trial. Of the 32 participants assigned to liraglutide, 31 completed the trial. Of 32 participants allocated to placebo, 30 completed the trial.
Duration of follow-up	4, 8, 12, 16, 20, and 26 weeks
Indirectness	Directly applicable
Method of analysis	Not stated/unclear Treatment effects were analysed by analysis of covariance (ANCOVA)

Additional comments	NA

36.2. Study arms

36.2.1. Insulin glargine (N = 32)

36.2.2. Liraglutide (N = 32)

36.2.3. Placebo (N = 32)

36.3. Characteristics

36.3.1. Arm-level characteristics

Characteristic	Insulin glargine (N = 32)	Liraglutide (N = 32)	Placebo (N = 32)
% Male Sample size	n = 18 ; % = 60	n = 16 ; % = 52	n = 20 ; % = 67
Mean age (SD) Mean (SD)	52 (8.7)	53.1 (6.3)	52.6 (3.9)
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
Cardiovascular risk factors Nominal	NR	NR	NR

Characteristic	Insulin glargine (N = 32)	Liraglutide (N = 32)	Placebo (N = 32)
Smoking status Nominal	NR	NR	NR
Alcohol consumption Nominal	NR	NR	NR
Presence of severe mental illness Nominal	NR	NR	NR
People with significant cognitive impairment Nominal	NR	NR	NR
People with a learning disability Nominal	NR	NR	NR
Number of people with obesity Nominal	NR	NR	NR
Other antidiabetic medication used Nominal	NR	NR	NR
Blood pressure-lowering medication used Nominal	NR	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR	NR
Other treatment being received Nominal	NR	NR	NR

37. Gurkan, 2014

Bibliographic Reference	Gurkan, E.; Tarkun, I.; Sahin, T.; Cetinarslan, B.; Canturk, Z.; Evaluation of exenatide versus insulin glargine for the impact on endothelial functions and cardiovascular risk markers; Diabetes Res Clin Pract; 2014; vol. 106 (no. 3); 567-75

37.1. Study details

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	NA
Trial name / registration number	NR
Study type	Randomised controlled trial (RCT)
Study location	Turkey
Study setting	NR
Study dates	NR
Sources of funding	None
Inclusion criteria	• T2DM patients between 40 and 70 years old with HbA1c of 7–9.5% (53–80 mmol/mol) • BMI 25–45 kg/m2 • Have regularly used metformin 2 x 1 g/day for at least 2 months
Exclusion criteria	• History of insulin- or incretin-based treatment • Previous coronary angioplasty, acute coronary syndrome and cerebrovascular event within 6 months, impaired hepatic and renal function, systolic blood pressure >= 180 mmHg, diastolic blood pressure >= 100 mmHg or uncontrolled HT

	• Active smokers
Recruitment / selection of participants	Patient enrolment lasted 18 months on average
Intervention(s)	Exenatide 5 mcg 2 x 1 s.c. at least 30 min before the meal for 4 weeks. Dose was subsequently increased to 2 x 10 mcg s.c.
Cointervention	Participants continued receiving metformin 2 g/day
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 Excluded "a previous coronary angioplasty, acute coronary syndrome and cerebrovascular event within 6 months", prior unclear. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Excluded "impaired hepatic and renal function", otherwise unclear. No information in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with	Not stated/unclear

non-alcoholic fatty liver disease	
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	NA
Comparator	Participants were started on insulin 0.2 U/kg and dose administered at bedtime. Dose was increased by two units in patients with a mean 3-day fasting plasma glucose (FPG) >= 100 mg/dL, which was obtained through phone visits. Dose increase was continued until FPG was between 80–99 mg/dL.
Number of participants	34 participants were randomised and the baseline characteristics state that there were 17 participants in the exenatide arm and 17 participants in the insulin arm. The report states that two patients were excluded later, however, it was unclear which arm these participants had been assigned to.
Duration of follow-up	26 weeks
Indirectness	Directly applicable
Method of analysis	Not stated/unclear
Additional comments	NA

37.2. Study arms

37.2.1. Exenatide (N = 17)

37.2.2. Insulin glargine (N = 17)

37.3. Characteristics

37.3.1. Arm-level characteristics

Characteristic	Exenatide (N = 17)	Insulin glargine (N = 17)
% Male Sample size	n = 5 ; % = 29.4	n = 7 ; % = 42
Mean age (SD) Mean (SD)	52.18 (7.26)	53.12 (6.99)
Ethnicity Nominal	NA	NA
Comorbidities Sample size	n = NA ; % = NA	n = NA ; % = NA
Hypertension Sample size	n = 17 ; % = 100	n = 14 ; % = 82
Coronary artery disease Sample size	n = 2 ; % = 12	n = 1 ; % = 6
Sedentary lifestlye Sample size	n = 1 ; % = 6	n = 4 ; % = 2
Dyslipidemia Sample size	n = 15 ; % = 88	n = 14 ; % = 82
Presence of frailty Nominal	NA	NA
Time since type 2 diabetes diagnosed (years) Defined as DM age Mean (SD)	6.88 (3.26)	7.59 (4.26)
Cardiovascular risk factors Nominal	NR	NR
Smoking status Sample size	n = 1 ; % = 6	n = 1 ; % = 6

Characteristic	Exenatide (N = 17)	Insulin glargine (N = 17)
Alcohol consumption Nominal	NR	NR
Presence of severe mental illness Nominal	NR	NR
People with significant cognitive impairment Nominal	NR	NR
People with a learning disability Nominal	NR	NR
Number of people with obesity Nominal	NR	NR
Other antidiabetic medication used Nominal	NR	NR
Blood pressure-lowering medication used n calculated by analyst from % Sample size	n = NA ; % = NA	n = NA ; % = NA
Beta-blockers Sample size	n = 4 ; % = 24	n = 4 ; % = 22
ACE/ARB Sample size	n = 15 ; % = 88	n = 15 ; % = 88
Statins/lipid-lowering medication used n calculated by analyst from % Sample size	n = NA ; % = NA	n = NA ; % = NA
Statin Sample size	n = 13 ; % = 76	n = 13 ; % = 76
Fibrate Sample size	n = 2 ; % = 12	n = 1 ; % = 6
Other treatment being received Nominal	NR	NR

38. Guzman, 2017

Bibliographic Reference	Guzman, C. B.; Zhang, X. M.; Liu, R.; Regev, A.; Shankar, S.; Garhyan, P.; Pillai, S. G.; Kazda, C.; Chalasani, N.; Hardy, T. A.; Treatment with LY2409021, a glucagon receptor antagonist, increases liver fat in patients with type 2 diabetes; Diabetes Obes Metab; 2017; vol. 19 (no. 11); 1521-1528

38.1. 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	NCT02111096
Study type	Randomised controlled trial (RCT)
Study location	35 study centres in 3 countries (Greece, Taiwan, United States/Puerto Rico)
Study setting	NR
Study dates	NR
Sources of funding	Eli Lilly and Company
Inclusion criteria	• 18 to <80 years • Diagnosis of T2D • On an optimally effective and stable dose of metformin and a sulfonylurea • HbA1c ≥7% and ≤10% • BMI ≥20 and <40 kg/m2

Exclusion criteria	• Hepatitis B, hepatitis C or clinical signs/symptoms of liver diseases • Hepatic aminotransferases (alanine aminotransferase [ALT] or aspartate aminotransferase [AST]) >2x upper limit if normal (ULN) • elevated alkaline phosphatase (>ULN) unrelated to bone metabolic disease • elevated bilirubin level (>ULN) • history of multiple endocrine neoplasia • SBP> 160 mm Hg or DSP >90 mm Hg • use of systemic glucocorticoid therapy, amiodarone, methotrexate, isoniazid, or tamoxifen • average weekly alcohol intake that exceeds 2 units per day for males and 1 unit per day for females
Recruitment / selection of participants	There was a 1-week screening period, a 2-week lead-in period, a 12-month treatment period, 4-month posttreatment safety follow-up period and an additional 6-month posttreatment safety follow-up visit if needed.
Intervention(s)	Sitagliptin 100 mg administered orally once daily
Cointervention	Insulin was allowed as a rescue therapy based on pre-specified fasting glucose or HbA1c criteria
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear

Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	NA
Comparator	Placebo administered orally once daily
Number of participants	299 participants entered the study and 174 participants were randomised. The study was a 2-arm trial that also investigated the effect of LY2409021, although the results from this arm were not included as this intervention was not specified in the protocol. 41 participants were allocated to sitagliptin and 68 participants were allocated to placebo. Of those allocated to sitagliptin, 8 participants discontinued before 6 months and 33 discontinued between 6 and 12 months. Of those randomised to placebo, 18 participants discontinued before 6 months, and 48 participants discontinued between 6 and 12 months.
Duration of follow-up	6 and 12 months
Indirectness	Directly applicable
Method of analysis	ITT

	Efficacy and safety analyses were conducted on the intent-to-treat population defined as all randomised patients who received at least 1 dose of randomised study drug.
Additional comments	The trial was terminated early as the sponsor decided that the overall risk-benefit profile of LY2409021 was unlikely to support its use as a chronic treatment for T2D, and investigators were instructed to take patients off study medication and complete the 4-month safety follow-up visit. Due to this, data were limited for the 12-month treatment period.

38.2. Study arms

38.2.1. Sitagliptin (N = 41)

38.2.2. Placebo (N = 68)

38.3. Characteristics

38.3.1. Arm-level characteristics

Characteristic	Sitagliptin (N = 41)	Placebo (N = 68)
% Male Sample size	n = 31 ; % = 75.6	n = 37 ; % = 54.4
Mean age (SD) Mean (SD)	57.1 (9)	57.8 (8.2)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Not hispanic or latino Sample size	n = 21 ; % = 51.2	n = 25 ; % = 36.8
Hispanic or Latino Sample size	n = 19 ; % = 46.3	n = 42 ; % = 61.8
Not reported Sample size	n = 1 ; % = 2.4	n = 1 ; % = 1.5
Causcasian Sample size	n = 31 ; % = 75.6	n = 51 ; % = 75

Characteristic	Sitagliptin (N = 41)	Placebo (N = 68)
Asian Sample size	n = 2 ; % = 4.9	n = 5 ; % = 7.4
African-American Sample size	n = 6 ; % = 14.6	n = 11 ; % = 16.2
Multiple Sample size	n = 2 ; % = 4.9	n = 1 ; % = 1.5
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	10.9 (6.5)	10.2 (6.3)
Cardiovascular risk factors Nominal	NR	NR
Smoking status Nominal	NR	NR
Alcohol consumption Nominal	NR	NR
Presence of severe mental illness Nominal	NR	NR
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

Characteristic	Sitagliptin (N = 41)	Placebo (N = 68)
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

39. Haering, 2015

Bibliographic Reference	Haering, Hans-Ulrich; Merker, Ludwig; Christiansen, Anita Vedel; Roux, Flavien; Salsali, Afshin; Kim, Gabriel; Meinicke, Thomas; Woerle, Hans J; Broedl, Uli C; Empagliflozin as add-on to metformin plus sulphonylurea in patients with type 2 diabetes.; Diabetes research and clinical practice; 2015; vol. 110 (no. 1); 82-90

39.1. Study details

Secondary publication of another included study- see primary study for details	Parent study Haering 2013
Other publications associated with this study included in review	

40. Handelsman, 2019

Bibliographic Reference	Handelsman, Y.; Mathieu, C.; Del Prato, S.; Johnsson, E.; Kurlyandskaya, R.; Iqbal, N.; Garcia-Sanchez, R.; Rosenstock, J.; Sustained 52-week efficacy and safety of triple therapy with dapagliflozin plus saxagliptin versus dual therapy with sitagliptin added to metformin in patients with uncontrolled type 2 diabetes; Diabetes, Obesity and Metabolism; 2019; vol. 21 (no. 4); 883-892

40.1. 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	NCT02284893
Study type	Randomised controlled trial (RCT)
Study location	Hungary, Mexico, Poland, Romania, South Africa and the USA
Study setting	NR
Study dates	The first patient visit for the study took place on 22 December 2014 and the last patient visit took place on 26 October 2016
Sources of funding	Bristol-Myers Squibb and AstraZeneca
Inclusion criteria	• Men and women aged at least 18 years • Inadequately controlled T2D defined as HbA1c of 8% to 10.5% (64-91 mmol/mol) at screening • Participants had undergone stable metformin therapy for at least 8 weeks prior to enrolment (≥1500 mg/d) and had received no other anti-diabetes agent for more than 14 days during the 12 weeks prior to screening

	• BMI greater than 20 kg/m2 at the enrolment visit and a fasting plasma glucose (FPG) level of at least 270 mg/dL (≤15 mmol/L) at randomisation
Exclusion criteria	• Diagnosis of type 1 diabetes • History of cardiovascular disease within 3 months of screening, • Hepatic insufficiency • Medical history of diabetic ketoacidosis • Renal impairment (defined as creatinine clearance <60 mL/min or serum creatinine ≥1.5 mg/dL in men or ≥1.4 mg/dL in women) • History of acute pancreatitis • Haemoglobinopathy
Recruitment / selection of participants	There was a 2-week screening period, a 2-week lead-in period, an initial 26-week randomized, double-blind treatment period, and an extension 26-week site-blind and patient-blind treatment period.
Intervention(s)	• Dapagliflozin 10 mg/d and saxagliptin 5 mg/d • Sitagliptin 100 mg/d
Cointervention	• During the lead-in period, patients continued to receive background MET medication (≥1500 mg/d), and during the treatment period participants continued to receive metformin therapy. • Participants meeting the criterion for rescue medication at any time (FPG > 270 mg/dL [>15.0 mmol/L] before Week 6; FPG > 240 mg/dL [13.3 mmol/L] during Weeks 7-11; FPG > 200 mg/dL [>11.1 mmol/L] during Weeks 12 to 26; and HbA1c > 8% [>=64 mmol/mol] during Weeks 27 to 51) received basal insulin or other anti-diabetes agents, with the exception of glucagon-like peptide-1 receptor agonists, other DDP-4 or SGLT2 inhibitors and metformin.
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure 1.1% had a recent history of congestive heart failure.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Excluded "history of cardiovascular disease within 3 months of screening", prior unclear. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Excluded "renal impairment (defined as creatinine clearance <60 mL/min or serum creatinine ≥1.5 mg/dL in men or ≥ 1.4 mg/dL in women)", otherwise unclear. No information in baseline characteristics.

Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	NA
Comparator	Sitagliptin 5 mg daily
Number of participants	The number of patients enrolled was 861; of these, 487 entered the lead-in period and 461 were randomized to receive at least one dose of medication during the double-blind treatment period (DAPA plus SAXA, n = 232; SITA, n = 229). Of the 461 patients randomized, 411 (89.2%) completed the short-term 26-week treatment period, 402 (87.2%) entered the long-term 26-week extension period and 378 (82.0%) (DAPA plus SAXA, n = 198; SITA, n = 180) completed the study.
Duration of follow-up	26 and 52 weeks

Indirectness	Directly applicable
Method of analysis	ITT Efficacy and safety analyses included all randomized patients who received at least one dose of study medication.

40.2. Study arms

40.2.1. Dapagliflozin + saxagliptin (N = 232)

40.2.2. Sitagliptin (N = 229)

40.3. Characteristics

40.3.1. Arm-level characteristics

Characteristic	Dapagliflozin + saxagliptin (N = 232)	Sitagliptin (N = 229)
% Male Sample size	n = 100 ; % = 43.1	n = 110 ; % = 48
Mean age (SD) Mean (SD)	55.9 (8.9)	55.8 (9.6)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 153 ; % = 65.9	n = 149 ; % = 65.1
Black or African-American Sample size	n = 34 ; % = 14.7	n = 32 ; % = 14
Asian Sample size	n = 8 ; % = 3.4	n = 12 ; % = 5.2
Other Sample size	n = 37 ; % = 15.9	n = 36 ; % = 15.7

Characteristic	Dapagliflozin + saxagliptin (N = 232)	Sitagliptin (N = 229)
Comorbidities Recent history of congestive cardiac failure Sample size	n = 2 ; % = 0.9	n = 3 ; % = 1.3
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	7.9 (5.7)	8.2 (5.2)
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
Number of people with obesity (kg/m2) >=30 kg/m2 Sample size	n = 151 ; % = 65.1	n = 147 ; % = 64.2
Other antidiabetic medication used Metformin dose Sample size	n = NA ; % = NA	n = NA ; % = NA
<1500 mg/d Sample size	n = 1 ; % = 0.4	n = 1 ; % = 0.4
1500 to 1700 mg/d	n = 66 ; % = 28.4	n = 73 ; % = 31.9

Characteristic	Dapagliflozin + saxagliptin (N = 232)	Sitagliptin (N = 229)
Sample size		
1701 to 2499 mg/d Sample size	n = 112 ; % = 48.3	n = 108 ; % = 47.2
>=2500 mg/d Sample size	n = 53 ; % = 22.8	n = 47 ; % = 20.5
Blood pressure-lowering medication used Nominal	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

41. Hanefeld, 2004

Bibliographic Reference	Hanefeld, M.; Brunetti, P.; Schernthaner, G. H.; Matthews, D. R.; Charbonnel, B. H.; One-year glycemic control with a sulfonyurea plus pioglitazone versus a sulfonylurea plus metformin in patients with type 2 diabetes; Diabetes Care; 2004; vol. 27 (no. 1); 141-7

41.1. Study details

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	2-year efficacy results reported in: • Charbonnel, B., Schernthaner, G., Brunetti, P., Matthews, D. R., Urquhart, R., Tan, M. H., & Hanefeld, M. (2005). Long-term efficacy and tolerability of add-on pioglitazone therapy to failing monotherapy compared with addition of gliclazide or metformin in patients with type 2 diabetes. *Diabetologia*, *48*, 1093-1104. 2 year lipid/cholesterol results reported in: • Betteridge, D. J., & Verges, B. (2005). Long-term effects on lipids and lipoproteins of pioglitazone versus gliclazide addition to metformin and pioglitazone versus metformin addition to sulphonylurea in the treatment of type 2 diabetes. *Diabetologia*, *48*, 2477-2481. Charbonnel 2005
Trial name / registration number	Not reported
Study type	Randomised controlled trial (RCT) Double-blind, double-dummy, parallel-group RCT
Study location	International (Canada, Belgium, Denmark, Estonia, Finland, Hungary, Italy, Lithuania, Netherlands, Slovak Republic, Sweden, UK)
Study setting	Outpatient (Diabetes centres)
Study dates	10/2000 to 06/2003
Sources of funding	Takeda Europe R&D Centre and Eli Lilly and Company, USA

Inclusion criteria	• Aged 35-75 years • Diagnosis of type 2 diabetes • Diabetes inadequately managed with sulphonylurea monotherapy (≥50% maximal recommended dose or at maximal tolerated dose ≥3-mo) • Stable or worsening glycaemic control≥3-mo • HbA1c level 7.5-11% inclusive at screening • Fasting C-peptide≥1.5 ng/ml at screening • If female, postmenopausal or sterilized or using adequate contraception
Exclusion criteria	• Type 1 diabetes or ketoacidosis • History of myocardial infarction, transient ischemic attacks, or stroke in previous 6-mo • Symptomatic heart failure • Malabsorption or pancreatitis • Familial polyposis coli • Malignant disease in previous 10 years • History of, or states associated with, lactic acidosis or hypoxemia • Substance abuse • Pregnant or breast-feeding women • Previous treatment with metformin, pioglitazone or other thiazolidinediones
Recruitment / selection of participants	Patients were randomised using block randomisation via a central telephone system.
Intervention(s)	• Pioglitazone 15-45 mg daily Oral pioglitazone 15-45 mg daily for 104 months, in addition to concurrent sulphonylurea therapy. Initial 12-week forced dose-titration period (increased at weeks 4, 8, and 12) followed by 92-week maintenance period. Maximal pioglitazone dose established at week 12 remained unchanged in 92-week maintenance period. Cessation of titration or down titration permitted only if tolerability issues (e.g. actual hypoglycaemia or increased risk of it). Participants continued to next dose unless: (i) risk of hypoglycaemia (increase postponed for 1 visit from week 4 to week 8, or week 8 dose maintained for rest of study); (ii) reported symptomatic hypoglycaemia (one-step reduction followed by increase at next visit if possible); or (iii) adverse events requiring dose reduction (one-step reduction at weeks 8 or 12 (or week 16 for Pioglitazone v Gliclazide trial) with no further down titration).
Cointervention	• Sulphonylurea + Placebo (Metformin placebo for pioglitazone arm; Pioglitazone placebo for metformin arm) Prestudy sulphonylurea dose maintained for duration of trial and no increases permitted. Sulphonylurea dose could be down titrated only if symptomatic hypoglycaemia (increase to original dose at next visit if possible).

Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Excluded symptomatic heart failure.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Excluded "MI, stroke or transient ischaemic attack in the previous 6 months", prior to this unclear. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear

Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Comparator	• Metformin 850 mg/1700 mg/2550 mg daily Initial 12-week forced dose-titration period (increased at weeks 4, 8, and 12) followed by 92-week maintenance period. Maximal metformin dose established at week 12 remained unchanged in 92-week maintenance period.
Number of participants	N=639
Duration of follow-up	92 weeks
Indirectness	None
Method of analysis	Per protocol PP analysis (all randomised participants who received at least one dose of study drug after randomisation and who has at least one HbA1c assessment at week 72 or later) also conducted for all outcomes Modified ITT mITT LOCF analysis (all randomised participants who received at least one dose of study drug after randomisation and who has at least one post-baseline HbA1c assessment) for all outcomes

41.2. Study arms

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

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

41.2.2. Metformin 850-2550 mg daily (N = 320)

Oral metformin 580-2550 mg daily + pioglitazone placebo for 104 weeks, in addition to concurrent sulphonylurea therapy

41.3. Characteristics

41.3.1. Study-level characteristics

Characteristic	Study (N =)
Other antidiabetic medication used Type of concurrent sulphonylurea therapy Sample size	n = NA ; % = NA
Glibenclamide Sample size	n = 268 ; % = 42
Gliclazide Sample size	n = 198 ; % = 31
Glimepiride Sample size	n = 121 ; % = 19

41.3.2. Arm-level characteristics

Characteristic	Pioglitazone 15-45 mg daily (N = 319)	Metformin 850-2550 mg daily (N = 320)
% Male Sample size	n = 171 ; % = 53.6	n = 175 ; % = 54.7
Mean age (SD) (years) Mean (SD)	60 (8.8)	60 (8)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Black Sample size	n = 2 ; % = 0.6	n = 3 ; % = 0.9
Caucasian Sample size	n = 317 ; % = 99.4	n = 315 ; % = 98.4
Other Sample size	n = 0 ; % = 0	n = 2 ; % = 0.6
Comorbidities Nominal	NR	NR

Characteristic	Pioglitazone 15-45 mg daily (N = 319)	Metformin 850-2550 mg daily (N = 320)
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	7 (5.6)	7.1 (5.6)
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
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

42. Hanefeld, 2011

Bibliographic Reference	Hanefeld, M.; Pfützner, A.; Forst, T.; Kleine, I.; Fuchs, W.; Double-blind, randomized, multicentre, and active comparator controlled investigation of the effect of pioglitazone, metformin, and the combination of both on cardiovascular risk in patients with type 2 diabetes receiving stable basal insulin therapy: the PIOCOMB study; Cardiovasc Diabetol; 2011; vol. 10; 65

42.1. 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	PIOCOMB
Study type	Randomised controlled trial (RCT)
Study location	Germany
Study setting	NR
Study dates	NR
Sources of funding	NR
Inclusion criteria	• T2DM patients treated with insulin (i.e., long acting basal insulin analogs, NPH insulin or combination insulin) in 1-2 daily doses for at least 3 months with or without oral antidiabetic drugs (OAD) except thiazolidinediones (TZD) prior to study entry • Aged between 30 and 75 years • BMI of ≥25 kg/m2 • Baseline HbA1c between 6.5 and 8.5%

Exclusion criteria	• Uncontrolled hypertension • Cardiovascular events within the previous year • Well established contraindications for metformin or pioglitazone regimens
Intervention(s)	• metformin 850 mg bid • pioglitazone 15 mg bid • metformin 850 mg bid + pioglitazone 15 mg bid
Cointervention	During an initial run-in phase of at least 2 weeks pre-existing insulin glargine therapy was titrated to an FBG of ≤ 7.8 mmol/L and other oral antidiabetics were stopped. If another insulin was used as previous therapy further treatment used insulin glargine.
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 Excluded "cardiovascular events within the previous year", prior unclear. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	People at higher risk of developing cardiovascular disease The report states "Average baseline results revealed FBG of 8.35 (± 2.17) mmol/L, hs-CRP of 3.21 (± 2.54) mg/L, and MMP-9 of 566.0 (± 266.2) ng/mL, representing a high-risk population for CVD despite suboptimal therapy with insulin."
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type	Not stated/unclear

2 diabetes mellitus	
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	NA
Comparator	NA
Number of participants	121 participants were randomised and 6.6% were excluded as they failed to provide either evaluable baseline or at least one post-baseline value for MMP-9. Of 39 participants allocated to metformin 3 were excluded. Of 37 participants allocated to pioglitazone, 3 were excluded, and of 37 participants allocated to combination treatment 2 were excluded.
Duration of follow-up	6 months
Indirectness	Directly applicable
Method of analysis	ITT ITT analysis was performed for the efficacy outcomes. Participants who terminated treatment before end of 6 months were included with their individual last value under LOCF.
Additional comments	Interventions were described as add-on therapy. However, participants receiving other treatments for diabetes were included, and stopped treatment during the run-in period. Therefore, the strategy has been assigned as switching.

42.2. Study arms

42.2.1. Metformin (N = 42)

42.2.2. Pioglitazone (N = 40)

42.2.3. Pioglitazone + metformin (N = 39)

42.3. Characteristics

42.3.1. Arm-level characteristics

Characteristic	Metformin (N = 42)	Pioglitazone (N = 40)	Pioglitazone + metformin (N = 39)
% Male Sample size	n = 23 ; % = 54.8	n = 25 ; % = 62.5	n = 26 ; % = 66.7
Mean age (SD) Mean (SD)	64.2 (7.3)	61.5 (7.1)	63.3 (7.9)
Ethnicity Caucasian Sample size	n = 42 ; % = 100	n = 40 ; % = 100	n = 39 ; % = 100
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Hypertension Sample size	n = 37 ; % = 88.1	n = 36 ; % = 90	n = 31 ; % = 79.5
Coronary heart disease Sample size	n = 13 ; % = 31	n = 7 ; % = 17.5	n = 3 ; % = 7.7
Presence of frailty Nominal	NR	NR	NR
Time since type 2 diabetes diagnosed Mean (SD)	12.3 (6.8)	9.8 (5.8)	11 (5.7)
Cardiovascular risk factors Nominal	NR	NR	NR
Blood pressure	NR	NR	NR

Characteristic	Metformin (N = 42)	Pioglitazone (N = 40)	Pioglitazone + metformin (N = 39)
Nominal			
Smoking status Nominal	NR	NR	NR
Alcohol consumption Nominal	NR	NR	NR
Presence of severe mental illness Nominal	NR	NR	NR
People with significant cognitive impairment Nominal	NR	NR	NR
People with a learning disability Nominal	NR	NR	NR
Number of people with obesity Nominal	NR	NR	NR
Other antidiabetic medication used Nominal	NR	NR	NR
Blood pressure-lowering medication used Sample size	n = 39 ; % = 92.9	n = 37 ; % = 92.5	n = 30 ; % = 76.9
Statins/lipid-lowering medication used Sample size	n = 22 ; % = 52.4	n = 19 ; % = 47.5	n = 18 ; % = 46.2
Other treatment being received Nominal	NR	NR	NR

43. Hao, 2022

Bibliographic Reference	Hao, Zhaohu; Huang, Xiao; Shao, Hailin; He, Feng; Efficacy and Safety of Dapagliflozin versus Liraglutide in Patients with Overweight or Obesity and Type 2 Diabetes Mellitus: a Randomised Controlled Clinical Trial in Tianjin, China; Journal of diabetes research; 2022; vol. 2022; 4126995

43.1. Study details

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	NA
Trial name / registration number	trial registration code: ChiCTR1800019864
Study type	Randomised controlled trial (RCT)
Study location	China
Study setting	Metabolic Disease Management Center (MMC) at Tianjin Fourth Central Hospital
Study dates	October 2019 to January 2020 (specifically during COVID-19 pandemic in China)
Sources of funding	Supported by the Exceptional Young Talents Fostering Foundation 2021 of the Tianjin Fourth Central Hospital
Inclusion criteria	(a) age 18+ years, (b) body mass index ≥24kg/m2 (overweight or obese), (c) stable dose of metformin (≥1500 mg/d) alone or in combination with premixed insulin for ≥8 weeks, and (d) HbA1c ≥7%.
Exclusion criteria	(a) type 1 and other special types of diabetes such as gestational diabetes, (b) severe mental illness and unclear consciousness, (c) active tuberculosis and other infectious diseases, and (d) high risk for volume depletion, hypotension, and/or electrolyte imbalances (in the opinion of the investigator). Laboratory exclusion criteria included haemoglobin <120g/L (male), <110 g/L (female), or thyroid-stimulating hormone levels outside the central laboratory normal range.

Recruitment / selection of participants	Patients with T2DM who visited the Metabolic Disease Management Center (MMC) at Tianjin Fourth Central Hospital from October 2019 to January 2020 were recruited for the study.
Intervention(s)	Dapagliflozin Liraglutide
Cointervention	Metformin
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	People without atherosclerotic cardiovascular diseases 17.8% of participants with coronary atherosclerotic heart disease reported in baseline characteristics table.
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	Not stated/unclear

fatty liver disease	
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	NA
Comparator	NA
Number of participants	360
Duration of follow-up	24 weeks
Indirectness	None
Method of analysis	ACA Not stated/unclear
Additional comments	180 randomised to each group. There were 166 and 143 patients in the dapagliflozin and liraglutide groups, respectively, at week 24 (baseline data and %s based on these numbers and not the numbers randomised)

43.2. Study arms

43.2.1. Liraglutide 1.2mg/d (N = 180)

subcutaneously injected 0.6 mg/d at the beginning, and this dose increased to 1.2 mg/d by the second week. If intolerance occurred during the process, the dose was adjusted to 0.6 mg/d.

43.2.2. Dapagliflozin 10mg (N = 180)

initiated at 5 mg and titrated up to 10 mg by the second week unless (in the opinion of the investigator) the patient was unable to tolerate titration to 10 mg, in which case the dose was maintained at 5 mg.

43.3. Characteristics

43.3.1. Arm-level characteristics

Characteristic	Liraglutide 1.2mg/d (N = 180)	Dapagliflozin 10mg (N = 180)
% Male Sample size	n = 83 ; % = 58	n = 107 ; % = 64.5
Mean age (SD) Mean (SD)	51.9 (11.1)	51.8 (11.4)
Ethnicity Nominal	NR	NR
Comorbidities Sample size	n = NA ; % = NA	n = NA ; % = NA
coronary atherosclerotic heart disease Sample size	n = 29 ; % = 20.3	n = 26 ; % = 15.7
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed Mean (SD)	6.5 (5.8)	6.1 (5.5)
Cardiovascular risk factors Sample size	n = NA ; % = NA	n = NA ; % = NA
Hypertension Sample size	n = 108 ; % = 75.5	n = 126 ; % = 75.9
Smoking status Sample size	n = NA ; % = NA	n = NA ; % = NA
Smoking history Sample size	n = 60 ; % = 42	n = 73 ; % = 44
Alcohol consumption Sample size	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Liraglutide 1.2mg/d (N = 180)	Dapagliflozin 10mg (N = 180)
Drinking history Sample size	n = 22 ; % = 15.4	n = 28 ; % = 16.9
Presence of severe mental illness Nominal	NR	NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Nominal	NR	NR
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR
Overweight or obese Sample size	n = 143 ; % = 100	n = 166 ; % = 100
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Metformin Sample size	n = 143 ; % = 100	n = 166 ; % = 100
metformin + SU Sample size	n = 40 ; % = 28	n = 51 ; % = 30.7
Blood pressure-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
ACEI/ARB Sample size	n = 80 ; % = 55.9	n = 95 ; % = 56.5
Statins/lipid-lowering medication used Sample size	n = 51 ; % = 35.7	n = 50 ; % = 29.8
Other treatment being received Sample size	n = NA ; % = NA	n = NA ; % = NA
Aspirin	n = 26 ; % = 18.2	n = 29 ; % = 17.3

Characteristic	Liraglutide 1.2mg/d (N = 180)	Dapagliflozin 10mg (N = 180)
Sample size		

44. Haring, 2014

Bibliographic Reference	Haring, H. U.; Merker, L.; Seewaldt-Becker, E.; Weimer, M.; Meinicke, T.; Broedl, U. C.; Woerle, H. J.; Empaglif lozin as add-on to metformin in patients with type 2 diabetes: A 24-week, randomized, double-blind, placebo-controlled trial; Diabetes Care; 2014; vol. 37 (no. 6); 1650-1659

44.1. Study details

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	Merker, L, Haring, H-U, Christiansen, A V et al. (2015) Empagliflozin as add-on to metformin in people with Type 2 diabetes. Diabetic medicine : a journal of the British Diabetic Association 32(12): 1555-67
Trial name / registration number	EMPA-REG MET [NCT01159600]
Study type	Randomised controlled trial (RCT)
Study location	148 centres in 12 countries (Canada, China, France, Germany, India, Korea, Mexico, Slovakia, Slovenia, Taiwan, Turkey, and the U.S.).
Study setting	NR
Study dates	July 2010 to February 2012
Sources of funding	Boehringer Ingelheim and Eli Lilly
Inclusion criteria	• Aged ≥18 years • BMI ≤45 kg/m2 • Inadequately controlled type 2 diabetes (HbA1c ≥7% to ≤10% [≥53 to ≤86 mmol/mol]) despite undergoing a diet and exercise program and a stable (unchanged for ≥12 weeks prior to randomization) immediate release metformin regimen
Exclusion criteria	• Uncontrolled hyperglycaemia (glucose level >13.3 mmol/L) after an overnight fast confirmed by a second measurement • Acute coronary syndrome, stroke, or transient ischemic attack within 3 months prior to informed consent

	• Indication of liver disease (alanine aminotransferase, alkaline aminotransferase, or alkaline phosphatase levels more than three times the upper limit of normal) • Impaired kidney function (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m2) during screening or run-in • Contraindications to metformin according to the local label • Bariatric surgery or other gastrointestinal surgeries that induce chronic malabsorption; medical history of cancer (except for basal cell carcinoma) or treatment for cancer within the last 5 years • Blood dyscrasias or any disorders causing haemolysis or unstable erythrocytes • Treatment with anti-obesity drugs 3 months prior to consent • Use of any treatment at screening leading to unstable body weight • Treatment with systemic steroids at the time of consent • Change in the dosage of thyroid hormones within 6 weeks prior to consent • Alcohol or drug abuse within 3 months of consent • Investigational drug in take in another trial within 30 days prior to the current trial
Recruitment / selection of participants	Participants were randomised following an open-label placebo run-in
Intervention(s)	• Once-daily therapy (in the morning with water) with empagliflozin10 mg • Once-daily therapy (in the morning with water) with empagliflozin 25 mg
Cointervention	• Metformin therapy (≥1,500 mg/day, the maximum tolerated dose, or the maximum dose according to the local label) • Rescue medication treatment was initiated during the treatment period if, between weeks 1 and 12, a patient had a glucose level >13.3 mmol/L after an overnight fast; between weeks 12 and 24 a patient had a glucose level >11.1 mmol/L after an overnight fast; or an HbA1c level >8.5% (>69 mmol/mol). In cases of hypoglycaemia, rescue medication was to be reduced or discontinued. • Where hyperglycaemia or hypoglycaemia could not be controlled, the patient was discontinued from the trial.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Excluded "acute coronary syndrome, stroke, or transient ischemic attack within 3 months prior to informed consent", prior unclear. No information in baseline characteristics.

Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Excluded "impaired kidney function (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m2)", otherwise unclear. No information in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	NA
Comparator	Placebo

Number of participants	638 participants were randomised. Of 207 participants allocated to placebo, 184 participants completed the 24-week treatment period, 138 entered the extension study, 17 prematurely discontinued, and 121 completed the extension study. Of 217 participants allocated to empagliflozin 10 mg, 209 participants completed the 24-week treatment period in the initial study, 173 participants entered the extension study, 11 prematurely discontinued, and 162 completed the extension study. Of 214 participants assigned to empagliflozin 25 mg, 1 participant was not treated, 196 completed the 24-week treatment period in the initial study, 152 entered the extension study, 13 discontinued prematurely, and 139 completed the extension study.
Duration of follow-up	24 weeks and 76 weeks
Indirectness	Directly applicable
Method of analysis	Other • The methods describe that treatment effects were assessed in the full analysis set (defined as participants who received ≥1 dose of study drug and had a baseline HbA1c measurement in the initial study) using an ANCOVA model. All values observed after a participant started antidiabetes rescue therapy were set to missing, and a last observation carried forward approach was used to impute missing data. • A restricted maximum likelihood-based mixed model repeated measures approach was using in the full analysis set [extracted data] and in full-analysis set-completers using observed cases.

44.2. Study arms

44.2.1. Empagliflozin 10 mg (N = 217)

44.2.2. Empagliflozin 25 mg (N = 214)

44.2.3. Placebo (N = 207)

44.3. Characteristics

44.3.1. Arm-level characteristics

Characteristic	Empagliflozin 10 mg (N = 217)	Empagliflozin 25 mg (N = 214)	Placebo (N = 207)
% Male Sample size	n = 92 ; % = 42	n = 93 ; % = 44	n = 91 ; % = 44
Mean age (SD) Mean (SD)	55.5 (9.9)	55.6 (10.2)	56 (9.7)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 112 ; % = 52	n = 113 ; % = 53	n = 113 ; % = 55
Asian Sample size	n = 99 ; % = 46	n = 98 ; % = 46	n = 92 ; % = 44
Black/African-American Sample size	n = 4 ; % = 2	n = 0 ; % = 0	n = 2 ; % = 1
American-Indian/Alaska Native Sample size	n = 2 ; % = 1	n = 2 ; % = 1	n = 0 ; % = 0
Comorbidities Nominal	NR	NR	NR
Presence of frailty Nominal	NR	NR	NR
Time since type 2 diabetes diagnosed Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
<1 year Sample size	n = 20 ; % = 9	n = 19 ; % = 9	n = 19 ; % = 9
>1 to 5 years Sample size	n = 78 ; % = 36	n = 69 ; % = 32	n = 83 ; % = 40
>5 to 10 years Sample size	n = 68 ; % = 31	n = 74 ; % = 35	n = 65 ; % = 31

Characteristic	Empagliflozin 10 mg (N = 217)	Empagliflozin 25 mg (N = 214)	Placebo (N = 207)
Greater than 10 years Sample size	n = 51 ; % = 24	n = 51 ; % = 24	n = 40 ; % = 19
Cardiovascular risk factors Nominal	NR	NR	NR
Smoking status Nominal	NR	NR	NR
Alcohol consumption Nominal	NR	NR	NR
Presence of severe mental illness Nominal	NR	NR	NR
People with significant cognitive impairment Nominal	NR	NR	NR
People with a learning disability Nominal	NR	NR	NR
Number of people with obesity Nominal	NR	NR	NR
Other antidiabetic medication used Nominal	NR	NR	NR
Blood pressure-lowering medication used Nominal	NR	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR	NR
Other treatment being received Nominal	NR	NR	NR

45. Haring, 2013

Bibliographic Reference	Haring, H. U.; Merker, L.; Seewaldt-Becker, E.; Weimer, M.; Meinicke, T.; Woerle, H. J.; Broedl, U. C.; Empagliflozin as add-on to metformin plus sulfonylurea in patients with type 2 diabetes: A 24-week, randomized, double-blind, placebo-controlled trial; Diabetes Care; 2013; vol. 36 (no. 11); 3396-3404

45.1. Study details

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	Haering, Hans-Ulrich, Merker, Ludwig, Christiansen, Anita Vedel et al. (2015) Empagliflozin as add-on to metformin plus sulphonylurea in patients with type 2 diabetes. Diabetes research and clinical practice 110(1): 82-90
Trial name / registration number	EMPA-REG METSU [NCT01159600]
Study type	Randomised controlled trial (RCT)
Study location	148 centres in 12 countries (Canada, China, France, Germany, India, Korea, Mexico, Slovakia, Slovenia, Taiwan, Turkey, and the U.S.)
Study setting	NR
Study dates	July 2010 to February 2012
Sources of funding	Boehringer Ingelheim and Eli Lilly and Company
Inclusion criteria	• Aged ≥18 years • BMI ≤ 45 kg/m2 • With adequately controlled type 2 diabetes (HbA1c ≥7 to ≤10%) despite a diet and exercise program and a stable regimen (unchanged for ≥12 weeks prior to randomization) of metformin immediate release plus a sulfonylurea.
Exclusion criteria	• Uncontrolled hyperglycaemia (glucose level >13.3 mmol/L) after an overnight fast, confirmed by a second measurement)

	• Acute coronary syndrome, stroke or transient ischemic attack within 3 months prior to consent • Indication of liver disease, impaired kidney function (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m2) during screening or run-in • Contraindications to metformin or sulfonylurea according to the local label • Gastrointestinal surgeries that induce chronic malabsorption, history of cancer (except basal cell carcinoma) or treatment for cancer within 5 years • Blood dyscrasias or any disorders causing haemolysis or unstable erythrocytes, treatment with anti-obesity drugs 3 months prior to consent • Use of any treatment at screening that leads to unstable body weight, treatment with systemic steroids at time of consent, change in dosage of thyroid hormones within 6 weeks of consent • Alcohol or drug abuse within 3 months of consent • Investigational drug intake within 30 days of the trial.
Recruitment / selection of participants	NR
Intervention(s)	• Empagliflozin 10 mg once-daily in the morning with water • Empagliflozin 25 mg once-daily in the morning with water
Cointervention	• Treatment was given as add-on therapy to metformin (≥1500 mg/day or maximum tolerated dose according to local label) plus a sulfonylurea (greater than or equal to half the maximum recommended dose or the maximum tolerated dose, or the maximum dose according to local label). • Rescue medication was initiated during the treatment period if, between weeks 1 and 12, a patient had a glucose level >13.3 mmol/L after an overnight fast or, between weeks 12 and 24, a patient had a glucose level >11.1 mmol/L after an overnight fast or HbA1c >8.5%. In cases of hypoglycaemia, rescue medication was reduced or discontinued. Where hyper- or hypoglycemia could not be controlled, the patient was discontinued from the trial.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Excluded "acute coronary syndrome, stroke or transient ischemic attack within 3 months prior to consent", prior unclear. No information in baseline characteristics.

Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Excluded "impaired kidney function (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m2) ", otherwise unclear. No information in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	eGFR ≥30mL/min/1.73m2 Participants with eGFR<30 mL/min/1.73m2 were excluded
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	NA
Comparator	Placebo

Number of participants	1010 participants on metformin and a sulfonylurea were screened, and 722 entered the study. 669 participants were randomised. 225 participants were allocated to placebo, 201 of these participants completed the 24-week treatment and 145 entered the extension study, with 127 completing the extension study. 225 participants were allocated to empagliflozin 10 mg, 208 of these participants completed the 24-week treatment and 163 entered the extension study, with 150 completing the extension study. 218 participants were allocated to empagliflozin 25 mg, 199 of these participants completed the 24-week treatment and 165 entered the extension study, with 150 completing the extension study.
Duration of follow-up	24, 52 and 76 weeks
Indirectness	Directly applicable
Method of analysis	Other Defined as full analysis set - participants who had received ≥1 dose of the randomised study drug and had a baseline HbA1c measurement in the initial study. A last observation carried forward approach was used to impute missing data. Treatment differences wee assessed using ANCOVA with baseline HBA1c and baseline value of the endpoint as linear covariates and baseline eGFR, region and treatment as fixed effects. MMRM sensitivity analyses were also conducted in the FAS and FAS-completers using observed cases.
Additional comments	The study also included an arm with participants who had HbA1c >10%. However, these participants had not been randomised and so were not relevant to the review.

45.2. Study arms

45.2.1. Empagliflozin 25 mg (N = 218)

45.2.2. Empagliflozin 10 mg (N = 226)

45.2.3. Placebo (N = 225)

45.3. Characteristics

45.3.1. Arm-level characteristics

Characteristic	Empagliflozin 25 mg (N = 218)	Empagliflozin 10 mg (N = 226)	Placebo (N = 225)
% Male Sample size	n = 114 ; % = 53	n = 113 ; % = 50	n = 112 ; % = 50
Mean age (SD) Mean (SD)	57.4 (9.3)	57 (9.2)	56.9 (9.2)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Asian Sample size	n = 125 ; % = 58	n = 129 ; % = 57	n = 127 ; % = 56
White Sample size	n = 85 ; % = 39	n = 89 ; % = 40	n = 88 ; % = 39
Black/African American Sample size	n = 3 ; % = 1	n = 3 ; % = 1	n = 7 ; % = 3
American-Indian/Alaska Native Sample size	n = 3 ; % = 1	n = 4 ; % = 2	n = 3 ; % = 1
Presence of frailty Nominal	NR	NR	NR
Time since type 2 diabetes diagnosed Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
<1 year Sample size	n = 7 ; % = 3	n = 3 ; % = 1	n = 2 ; % = 1
>15 years Sample size	n = 43 ; % = 20	n = 59 ; % = 26	n = 36 ; % = 16
5-10 years Sample size	n = 79 ; % = 37	n = 74 ; % = 33	n = 94 ; % = 42
>10 years Sample size	n = 87 ; % = 40	n = 89 ; % = 40	n = 93 ; % = 41

Characteristic	Empagliflozin 25 mg (N = 218)	Empagliflozin 10 mg (N = 226)	Placebo (N = 225)
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
BMI (kg/m2) Mean (SD)	28.3 (5.5)	28.3 (5.4)	27.9 (4.9)
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

46. Harreiter, 2021

Bibliographic Reference	Harreiter, J.; Just, I.; Leutner, M.; Bastian, M.; Brath, H.; Schelkshorn, C.; Klepochova, R.; Krssak, M.; Kautzky-Willer, A.; Combined exenatide and dapagliflozin has no additive effects on reduction of hepatocellular lipids despite better glycaemic control in patients with type 2 diabetes mellitus treated with metformin: EXENDA, a 24-week, prospective, randomized, placebo-controlled pilot trial; Diabetes, Obesity & Metabolism; 2021; vol. 23 (no. 5); 1129-1139

46.1. Study details

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	NA
Trial name / registration number	EXENDA [EudraCT 2016-000574-38]
Study type	Randomised controlled trial (RCT)
Study location	Austria
Study setting	Medical University of Vienna
Study dates	Recruitment was conducted between June 2017 and May 2019
Sources of funding	AstraZeneca
Inclusion criteria	• Men and women with T2DM • Glycated haemoglobin (HbA1c) level >=48 and <=97 mmol/mol (6.5%-11%) • Age 18 to 75 years • Body mass index (BMI) >=25 kg/m2 • metformin treatment >=1000 mg daily with a stable dose for at least 8 weeks

Exclusion criteria	• Other diabetes diagnosis than T2DM • Patients on other antidiabetic medication (Sulfonylurea, Glitazone, insulin for more than 2 weeks (see below), SGLT2 inhibitors, GLP1 agonist, nateglinid, repaglinid, acarbose, DPP4 inhibitors) • Subjects currently or previously treated with insulin (with the exception of emergency situations in which insulin was given for less than 14 consecutive days, but not within the last 3 months before screening) • Known intolerance against study medication • Contraindications including hypersensitivity known to metformin according to the local label • Recurrent urinary tract infections • GFR < 60 mL/min/1.73 m² • Liver enzymes above 3-fold normal range • Bilirubin higher 3-fold normal range • Any other clinical condition that would jeopardize patient's safety while participating in this clinical trial • Disease at screening (other than NAFLD) such as relevant cardiovascular, gastrointestinal, hepatic, neurologic, psychiatric, endocrine (i.e. pancreatic) except T2DM, hematologic, malignant, infection or other major systemic diseases making implementation of the protocol or interpretation of the study results difficult • History of pancreatitis • Known autoimmune disease or chronic inflammatory condition • Myocardial infarction or stroke within 6 months prior to screening • Blood dyscrasias or any disorders causing haemolysis or unstable Red Blood Cell (e.g. malaria, babesiosis, haemolytic anaemia) • Other liver disease including chronic viral hepatitis (B or C), alcohol abuse, hemochromatosis, alpha-1antitrypsin deficiency, autoimmune hepatitis, Wilson's disease, primary sclerosing cholangitis or primary biliary cirrhosis, or liver cirrhosis of any aetiology • Malignancy within the last 5 years before randomisation • Medullary thyroid cancer • Family history of multiple endocrine neoplasia syndrome

	• Alcohol or drug abuse within the 3 months prior to informed consent that would interfere with trial participation or any ongoing condition leading to a decreased compliance to study procedures or study drug intake • Presence of any absolute or relative contraindication for the conduct of an MRI investigation, such as cardiac pacemakers, ferromagnetic haemostatic clips in the central nervous system, metallic splinters in the eye, ferromagnetic or electronically operated active devices like automatic cardioverter defibrillators, cochlear implants, insulin pumps and nerve stimulators, prosthetic heart valves etc. • History of bariatric surgery • Treatment with anti-obesity drugs (e.g. sibutramine, orlistat) 3 months prior to informed consent or any other treatment at the time of screening (i.e. surgery, aggressive diet regimen, etc.) leading to unstable body weight • Subjects receiving antihypertensive medication and/or thyroid hormones, the dose(s) of which have not been stable for at least 6 weeks prior to baseline • Current treatment with systemic steroids at time of informed consent (Treatment with local and inhaled steroids is allowed) • Use of drugs potentially associated with NAFLD for more than 2 consecutive weeks in the 6 months prior to screening. • Use of anti-NASH drugs (thiazolidinediones, vitamin E, UDCA, SAM-e, betaine, milk thistle, anti-TNF therapies,) in the 3 months prior to randomization. • Donation of blood (> 400 mL) during the previous 3 months prior to the screening visit or during the duration of the study • Participation in another trial with an investigational drug within 30 days prior to informed consent. • Any subject who is the investigator or any sub-investigator, research assistant, pharmacist, study coordinator, other staff thereof, directly involved in the conduct of the protocol. • Pre-menopausal women (last menstruation ≤1 year prior to informed consent) who: • are nursing or pregnant or • are of child-bearing potential and are not practising an acceptable method of birth control, or do not plan to continue using this method throughout the study and do not agree to submit to periodic pregnancy testing during participation in the trial.

Recruitment / selection of participants	Patients were recruited from a diabetes outpatient clinic and affiliated hospitals.
Intervention(s)	Exenatide + Dapagliflozin: • Initial and maintenance doses of exenatide were 2 mg. • Exenatide was administered subcutaneously once weekly. • The initial and maintenance doses of Dapagliflozin were 10 mg and dapagliflozin was administered orally once daily.
Cointervention	• Metformin >= 1000 mg daily • Dapagliflozin 100 mg daily The study participants received guided application training of exenatide/placebo using material provided by AstraZeneca. All participants received dapagliflozin.
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 Excluded "*Myocardial infarction or stroke within 6 months prior to screening", prior unclear. No information in baseline characteristics.*
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Excluded "*GFR < 60 mL/min/1.73 m²",* otherwise unclear. No information in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear

Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear Information on number of participants with steatosis hepatitis, however, no information specifically on NAFLD
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	Dapagliflozin + placebo • Initial and maintenance doses of placebo were 2 mg. • Placebo was administered subcutaneously once weekly.
Number of participants	563 participants were assessed for eligibility and 30 patients were randomised. 16 participants were allocated to the exenatide + dapagliflozin arm, and 14 participants were randomised to the placebo and dapagliflozin arm
Duration of follow-up	24 weeks
Indirectness	Directly applicable
Method of analysis	Per protocol Per-protocol analysis was performed, however, reference to per-protocol analysis was only provided in the HCLs, visceral and subcutaneous adipose lipids section of the results section, where is was stated that results were comparable (no data were provided). ITT Last observation carried forward was used to substitute missing results. Continuous variables were summarized using means and standard

	deviations, and categorical variables by counts and percentages. Differences between treatment groups after 24 weeks were tested using analysis of covariance (ANCOVA) with treatment as a fixed factor and adjustment for the baseline outcome as a covariate. Adjustment for sex, age and BMI was conducted in a further statistical model.
Additional comments	NA

46.2. Study arms

46.2.1. Exenatide (N = 16)

46.2.2. Placebo (N = 14)

46.3. Characteristics

46.3.1. Arm-level characteristics

Characteristic	Exenatide (N = 16)	Placebo (N = 14)
Mean age (SD) Mean (SD)	59.4 (8.5)	60.9 (7.4)
Ethnicity White ethnicity Sample size	n = 6 ; % = 37.5	n = 4 ; % = 28.6
Comorbidities Steatosis hepatitis Sample size	n = 11 ; % = 68.8	n = 11 ; % = 78.6
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed Mean (SD)	7.3 (5.2)	5.8 (4.7)
Cardiovascular risk factors Nominal	NR	NR
Smoking status	n = 4 ; % = 25	n = 1 ; % = 7.1

Characteristic	Exenatide (N = 16)	Placebo (N = 14)
Sample size		
Alcohol consumption Sample size	n = 10 ; % = 62.5	n = 9 ; % = 64.3
Presence of severe mental illness Nominal	NR	NR
People with significant cognitive impairment Nominal	NR	NR
People with a learning disability Nominal	NR	NR
Number of people with obesity Nominal	NR	NR
Other antidiabetic medication used Sample size	n = 16 ; % = 100	n = 14 ; % = 100
Blood pressure-lowering medication used Nominal	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR
Female Sample size	n = 6 ; % = 37.5	n = 4 ; % = 28.6

47. Hartemann-Heurtier, 2009

Bibliographic Reference	Hartemann-Heurtier, A.; Halbron, M.; Golmard, J. L.; Jacqueminet, S.; Bastard, J. P.; Rouault, C.; Ayed, A.; Pieroni, L.; Clément, K.; Grimaldi, A.; Effects of bed-time insulin versus pioglitazone on abdominal fat accumulation, inflammation and gene expression in adipose tissue in patients with type 2 diabetes; Diabetes Res Clin Pract; 2009; vol. 86 (no. 1); 37-43

47.1. Study details

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	NA
Trial name / registration number	NCT00159211
Study type	Randomised controlled trial (RCT)
Study location	France
Study setting	Participants were recruited in the diabetes department of Pitie-Salpetriere Hospital in Paris
Study dates	Recruitment took place from May 2005 to October 2006
Sources of funding	Public funds from Assistance Publique des Hopitaux de Paris.
Inclusion criteria	• Type 2 diabetes • Men or women with BMI ≥26 kg/m2 • Aged 18–80 years • HbA1c between 7.5% and 9.5%, and treated with maximal tolerated and stable doses of sulfonylurea and metformin for ≥6 months

Exclusion criteria	• Prior use of insulin or glitazone • Use of other affecting glycaemic control agents • ASAT or ALAT >2.5-fold above the upper limit of normal level • Glomerular filtration rate <60 ml/min • Heart failure ≥ grade 2 • Haemoglobin <10 g/dl • Inability to provide informed consent
Recruitment / selection of participants	Volunteers were recruited in the diabetes department of Pitie-Salpetriere Hospital in Paris and the nature and potential risks of the study were explained to all subjects before obtaining theirwritten informed consent.
Intervention(s)	Pioglitazone (30 mg/day) (Actos; TAKEDA). At follow-up visits (2 and 4 months) pioglitazone dose was increased form 30 to 45 mg/day. At the end of the study, pioglitazone daily dose was 30 mg, 45mg and 15 mg in respectively 8 (57%), 5 (36%) and 1 (7%) patients.
Cointervention	Sulfonylurea and metformin were continued.
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Excluded "heart failure grade 2 and above"
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 Excluded "glomerular filtration rate <60 ml/min", otherwise unclear. No information in baseline characteristics
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear

Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	NA
Comparator	Human NPH insulin (0.2 IU/kg/day) (Umuline NPH; LILLY) at bedtime for 24 weeks. Patients were contacted weekly by phone to discuss dosage changes. At the end of the study, the mean insulin dose was 0.3 ± 0.1 IU/kg/day.
Number of participants	Twenty-eight participants were randomised. One patient in the insulin treatment group withdrew after 1 day because of hypoglycaemia and was not included in the analysis. One patient in the pioglitazone group withdrew after 4 months because of a 5 kg weight gain but was included in the analysis.
Duration of follow-up	24 weeks
Indirectness	Directly applicable
Method of analysis	Not stated/unclear Unclear, methods state that descriptive statistics used numbers of patients and percentages for qualitative variables and means and standard deviations for quantitative ones.
Additional comments	NA

47.2. Study arms

47.2.1. Pioglitazone (N = 14)

47.2.2. Insulin (N = 14)

47.3. Characteristics

47.3.1. Arm-level characteristics

Characteristic	Pioglitazone (N = 14)	Insulin (N = 14)
% Male Percentage calculated by analyst. Data were only reported for 13 participants in the insulin arm as data were not included for one patient that discontinued after 1 day due to hypoglycaemia. Sample size	n = 9 ; % = 64.3	n = 7 ; % = 53.8
Mean age (SD) Data were only reported for 13 participants in the insulin arm as data were not included for one patient that discontinued after 1 day due to hypoglycaemia. Mean (SD)	62 (10)	58 (10)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	12 (4.5)	12 (6)
Cardiovascular risk factors Nominal	NR	NR
Smoking status Nominal	NR	NR

Characteristic	Pioglitazone (N = 14)	Insulin (N = 14)
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

48. Hattori, 2018

Bibliographic Reference	Hattori, S.; Anti-inflammatory effects of empagliflozin in patients with type 2 diabetes and insulin resistance; Diabetol Metab Syndr; 2018; vol. 10 (no. 1); 93

48.1. Study details

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	NA
Trial name / registration number	UMIN Clinical Registry (UMIN000021552)
Study type	Randomised controlled trial (RCT)
Study location	Japan
Study setting	Clinic
Study dates	NR
Sources of funding	None
Inclusion criteria	Patients without a history of medication with SGLT2 inhibitors and with HbA1c > 6.2% regardless of diet, exercise, and medical treatment other than SGLT2 inhibitors for at least 12 weeks. Had insulin resistance (BMI > 28 or homeostatic model assessment of insulin resistance [HOMA-IR] > 1.73 or fasting immunoreactive insulin [IRI] > 10 and fasting blood glucose [FBG] < 180).
Exclusion criteria	NR

Recruitment / selection of participants	NR
Intervention(s)	Empagliflozin
Cointervention	All patients continued with their administered oral hypoglycemic drugs (sulfonylureas, metformin, or an α-glucosidase inhibitor). Only ~60% were on these agents so unclear if population relevant for 1.2, however, possible also on insulin and does state empagliflozin was an 'add-on' treatment.
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	NR
Comparator	Placebo
Number of participants	102
Duration of follow-up	1 year
Indirectness	Serious indirectness. Assumption made that all people were on antihyperglycaemia medication or insulin treatment at baseline, as empagliflozin described as an 'add-on' treatment and population described as "HbA1c > 6.2% regardless of diet, exercise, and medical treatment other than SGLT2 inhibitors for at least 12 weeks". However, not completely clear as baseline characteristics only report the type of AHA on for ~60% of people.
Additional comments	No missingness reported

48.2. Study arms

48.2.1. Empagliflozin (N = 51)

Empagliflozin 10mg

48.2.2. Placebo (N = 51)

48.3. Characteristics

48.3.1. Arm-level characteristics

Characteristic	Empagliflozin (N = 51)	Placebo (N = 51)
% Male Sample size	n = 38 ; % = 74.5	n = 41 ; % = 80.4
Mean age (SD) Mean (SD)	57.4 (12.3)	58.1 (9.71)
Ethnicity Nominal	NR	NR
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed Mean (SD)	NR (NR)	NR (NR)
Cardiovascular risk factors Sample size	n = NR ; % = NR	n = NR ; % = NR
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Mean (SD)	NR (NR)	NR (NR)
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Empagliflozin (N = 51)	Placebo (N = 51)
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Sulfonlyurea Sample size	n = 10 ; % = 19.6	n = 11 ; % = 21.6
Metformin Sample size	n = 12 ; % = 23.5	n = 12 ; % = 23.5
Alpha glucosidase inhibitors Sample size	n = 7 ; % = 13.7	n = 8 ; % = 15.7
Blood pressure-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
angiotensin II receptor blocker Sample size	n = 17 ; % = 33.3	n = 16 ; % = 31.4
Calcium channel blocker Sample size	n = 10 ; % = 19.6	n = 20 ; % = 19.6
Statins/lipid-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Statins Sample size	n = 16 ; % = 31.4	n = 17 ; % = 33.3
Fibrates Sample size	n = 10 ; % = 19.6	n = 9 ; % = 17.6

49. Heerspink, 2022

Bibliographic Reference	Heerspink, Hiddo J L; Sattar, Naveed; Pavo, Imre; Haupt, Axel; Duffin, Kevin L; Yang, Zhengyu; Wiese, Russell J; Tuttle, Katherine R; Cherney, David Z I; Effects of tirzepatide versus insulin glargine on kidney outcomes in type 2 diabetes in the SURPASS-4 trial: post-hoc analysis of an open-label, randomised, phase 3 trial.; The lancet. Diabetes & endocrinology; 2022; vol. 10 (no. 11); 774-785

49.1. Study details

Secondary publication of another included study- see primary study for details	Parent study Del Prato 2021

50. Heine, 2005

Bibliographic Reference	Heine, R. J.; Gaal, L. F.; Johns, D.; Mihm, M. J.; Widel, M. H.; Brodows, R. G.; Exenatide versus insulin glargine in patients with suboptimally controlled type 2 diabetes: a randomized trial; Ann Intern Med; 2005; vol. 143 (no. 8); 559-69

50.1. Study details

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	Secnik Boye, Kristina, Matza, Louis S, Oglesby, Alan et al. (2006) Patient-reported outcomes in a trial of exenatide and insulin glargine for the treatment of type 2 diabetes. Health and quality of life outcomes 4: 80 [reports HR-QoL outcomes]
Trial name / registration number	NCT00082381
Study type	Randomised controlled trial (RCT)
Study location	82 sites om 13 countries
Study setting	NR
Study dates	Between June 2003 and April 2004
Sources of funding	Eli Lilly and Company, Inc., and Amylin Pharmaceuticals, Inc.
Inclusion criteria	• Patients with T2D who could not achieve adequate glycaemic control with combination metformin and sulfonylurea therapy at maximally effective doses • Haemoglobin A1c level ranging from 7.0% to 10.0% at the time of screening • Body mass index ranging from 25 kg/m2 to 45 kg/m2 • A history of stable body weight (≤10% variation for 3 months before screening)

Exclusion criteria	Participants were excluded if they: • had participated in an interventional medical, surgical, or pharmaceutical study within 30 days before screening • had more than 3 episodes of severe hypoglycemia within 6 months before screening • were undergoing therapy for a malignant disease other than basal-cell or squamous-cell skin cancer • had cardiac disease that was class III or IV according to the New York Heart Association criteria • had a serum creatinine concentration of greater than 135 umol/L (>1.5 mg/dL) for men or greater than 110 umol/L (>1.2 mg/dL) for women or had obvious clinical signs or symptoms of liver disease • were receiving long-term (lasting longer than 2 weeks) systemic glucocorticoid therapy or had received such therapy within 2 weeks immediately before screening • had used any prescription drug to promote weight loss within 3 months before screening • had been treated (for more than 2 consecutive weeks) with insulin within 3 months before screening, with thiazolidinediones within 4 months before screening, with alpha-glucosidase inhibitors within 3 months before screening, or with meglitinides within 3 months before screening.
Recruitment / selection of participants	Patients were recruited according to local investigators' practices and advertising, and all participants gave informed written consent before participation. Within 2 weeks after screening, patients who met the inclusion criteria were randomly assigned.
Intervention(s)	Exenatide (before morning and evening meals) at a fixed dosage of 5 ug twice daily for 4 weeks; the dose was increased to 10 ug twice daily for the remainder of the study. Daily glucose monitoring was not required for patients randomly assigned to receive exenatide.
Cointervention	Metformin and sulfonylurea doses were fixed at pre-study levels unless patients experienced hypoglycaemia; in these instances, a 50% reduction in sulfonylurea dose was recommended
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Excluded "had cardiac disease that was class III or IV according to the New York Heart Association criteria", otherwise unclear. No information in baseline characteristics
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.

Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	NA
Comparator	Insulin glargine (at bedtime) initial dosage of 10 U/d; then, using a fixed dose algorithm to adjust the dose, they self-titrated the dose in 2-U increments every 3 days to achieve a fasting blood glucose target level of less than 5.6 mmol/L (<100 mg/dL) on daily glucose monitoring

Number of participants	844 participants were screened, 555 participants were enrolled, 549 participants received >= 1 dose of study drug. Out of 282 participants randomised to the exenatide group. 54 withdrew (19.4%), and 228 completed the study. Out of 267 people who were allocated to the insulin glargine group, 25 withdrew (9.7%) and 242 completed the study.
Duration of follow-up	12 and 26 weeks
Indirectness	Directly applicable
Method of analysis	Per protocol Defined as patients who had at least 12 weeks of exposure to study medication, had no violations of the inclusion or exclusion criteria obtained at screening, and met no discontinuation criteria. Only per-protocol analysis was reported for HR-QoL. ITT Defined as any patient who had at least 1 post-baseline measurement of the dependent variable. Likelihood- based mixed-effect model repeated measures (MMRM) analyses were performed. There was no imputation of missing data. [Extracted data]
Additional comments	Sample size was determined based on change in HbA1c. Based on an estimated 10% drop-pout, 446 patients were required to provide 90% power.

50.2. Study arms

50.2.1. Exenatide (N = 282)

50.2.2. Insulin glargine (N = 267)

50.3. Characteristics

50.3.1. Arm-level characteristics

Characteristic	Exenatide (N = 282)	Insulin glargine (N = 267)
% Male n calculated by analyst Sample size	n = 155 ; % = 55	n = 151 ; % = 56.6

Characteristic	Exenatide (N = 282)	Insulin glargine (N = 267)
Mean age (SD) Mean (SD)	59.8 (8.8)	58 (9.5)
Ethnicity n calculated by analyst Sample size	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 225 ; % = 79.8	n = 215 ; % = 80.5
Black Sample size	n = 2 ; % = 0.7	n = 3 ; % = 1.1
Asian Sample size	n = 5 ; % = 1.8	n = 2 ; % = 0.7
Hispanic Sample size	n = 44 ; % = 15.6	n = 40 ; % = 15
Other Sample size	n = 6 ; % = 2.1	n = 7 ; % = 2.6
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed Mean (SD)	9.9 (6)	9.2 (5.7)
Cardiovascular risk factors Nominal	NR	NR
Smoking status Nominal	NR	NR
Alcohol consumption Nominal	NR	NR
Presence of severe mental illness Nominal	NR	NR

Characteristic	Exenatide (N = 282)	Insulin glargine (N = 267)
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

51. Heise, 2022

Bibliographic Reference	Heise, T.; Mari, A.; DeVries, J. H.; Urva, S.; Li, J.; Pratt, E. J.; Coskun, T.; Thomas, M. K.; Mather, K. J.; Haupt, A.; et, al.; Effects of subcutaneous tirzepatide versus placebo or semaglutide on pancreatic islet function and insulin sensitivity in adults with type 2 diabetes: a multicentre, randomised, double-blind, parallel-arm, phase 1 clinical trial; The lancet. Diabetes & endocrinology; 2022; vol. 10 (no. 6); 418-429

51.1. 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	NCT03951753
Study type	Randomised controlled trial (RCT)
Study location	2 centres in Germany
Study setting	Study centres
Study dates	Participants were screened between June 28, 2019 and April 8, 2021
Sources of funding	Eli Lilly
Inclusion criteria	• Aged 20 to 74 years • Had T2D for at least 6 months • Were being treated with lifestyle advice and stable does of metformin, with, or without another oral antihyperglycemic 3 months before study entry • HbA1c of 53 to 83 mmol/mol (7.0 to 9.5%) if the participants was being treated with metformin only or 48 to 75 mmol/mol (6.5 to 9.0%) if the participants was being treated with metformin in combination with another oral antihyperglycaemic

Exclusion criteria	• Type 1 diabetes • Have had more than 1 episode of severe hypoglycaemia, as defined by the American Diabetes Association criteria, within 6 months before screening or has a history of hypoglycaemia unawareness or poor recognition of hypoglycaemic symptoms • Have had 1 or more episodes of ketoacidosis or hyperosmolar state/coma requiring hospitalization within the 6 months prior to screening • Have a history of proliferative retinopathy or maculopathy as determined by the investigator based on a recent (<1.5 years) ophthalmologic examination • Impaired renal estimated glomerular filtration rate <45 mL/min/1.73 m2 calculated by Chronic Kidney Disease-Epidemiology • Have taken any glucose-lowering medications other than allowed OAMs any time during the last 3 months before screening or during the screening period; short-term use of insulin (<14 days) for treatment of acute conditions is allowed in the 3 month period prior to entry and after randomisation • Have a history or current cardiovascular, respiratory, hepatic, renal, GI, endocrine, haematological or neurological disorders capable of significantly altering the absorption, metabolism or elimination of drugs; of constituting a risk when taking the IP; or of interfering with the interpretation of data • Have acute or chronic pancreatitis or a history of acute idiopathic pancreatitis; patients who had cholecystolithiasis and/or cholecystectomy in the past, with no long-term complications, are eligible for participation • Have a known clinically significant gastric emptying abnormality (e.g., severe diabetic gastroparesis or gastric outlet obstruction) or have undergone gastric bypass (bariatric) surgery or restrictive bariatric surgery • Have a personal or family history of medullary thyroid carcinoma (MTC), multiple endocrine neoplasia syndrome type 2 (MEN 2), or a screening calcitonin ≥20 pg/mL at screening • Have had acute myocardial infarction, congestive heart failure NYHA class III or IV, and/or cerebrovascular accident (stroke]) within 3 months prior to screening; for patients taking SGLT-2 inhibitors: any history of congestive heart failure, myocardial infarction, unstable angina, or stroke • Have findings in the 12-lead ECG at screening (Visit 1) that, in the opinion of the investigator, may increase the risks of potentially clinically relevant worsening associated with participation in the study • Have an active or untreated malignancy or have been in remission from a clinically significant malignancy (other than basal or squamous cell skin cancer, in situ carcinomas of the cervix, or in situ prostate cancer) for <5 years prior to screening • Have evidence of human immunodeficiency virus (HIV) and/or positive HIV antibodies • Have evidence of hepatitis B or positive hepatitis B surface antigen and/or evidence of hepatitis C virus (HCV) or hepatitis C antibody (at screening)

	• Have serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2·5X the upper limit of normal (ULN) or total bilirubin level (TBL) >1.5X ULN; • Have had a blood donation of 450 mL or more in the last 3 months or any blood donation within the last month prior to screening • Have had a blood transfusion or severe blood loss within the last 3 months or have known hemoglobinopathy, haemolytic anaemia, sickle cell anaemia, or have a haemoglobin value <11 g/dL (males) or <10 g/dL (females), or any other condition known to interfere with haemoglobin A1c measurement • Have a history of drug or alcohol abuse; and/or smoke >10 cigarettes per day or the equivalent; or are unable or unwilling to refrain from nicotine during CRU admission; • Have an average weekly alcohol intake that exceeds 21 units per week (males) and 14 units per week (females) • Have evidence of significant active neuropsychiatric disease as determined by the investigator; • Have been treated with prescription drugs that promote weight loss, including over-the-counter medications within 3 months prior to screening or between Visit 1 and randomisation • Have received chronic (lasting >14 consecutive days) systemic glucocorticoid therapy (excluding topical, intra-articular, and inhaled preparations) within 1 month before screening, or between Visit 1 and randomisation • Have received treatment with a drug that has not received regulatory approval for any indication within 1 month prior to screening; if the previous study drug has a long half-life, 3 months or 5 half-lives (whichever is longer) should have passed • Are persons who have previously completed or withdrawn after randomisation from this study • Have previous exposure or known allergies to tirzepatide or related compounds, or have an intolerance to GLP-1RAs • Are currently enrolled in a clinical study involving an IP or any other type of medical research judged not to be scientifically or medically compatible with this study
Recruitment / selection of participants	184 participants were assessed for eligibility and 117 participants were enrolled and randomised
Intervention(s)	Tirzepatide (subcutaneous once per week) - dose was escalated to a 15 mg mainteance dose (2.5 mg, 5.0 mg, 7.5 mg, 10.0 mg, and12.5 mg for 4 weeks each, followed by 15 mg for the remaining 8 weeks Semaglutide (subcutaneous once per week) - dose was escalate to 1 mg (0.25 mg and 0.5 mg for 4 weeks each, followed by 1 mg for 20 weeks)
Cointervention	Oral antihyperglycemics medicines other than metformin were discontinued 4 weeks before baseline measures were done
Strata 1: People with type 2	Not stated/unclear

diabetes mellitus and heart failure	Excluded "congestive heart failure NYHA class III or IV", otherwise unclear. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Excluded "Have had acute myocardial infarction, congestive heart failure NYHA class III or IV, and/or cerebrovascular accident (stroke]) within 3 months prior to screening", prior unclear. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Excluded "Impaired renal estimated glomerular filtration rate <45 mL/min/1·73 m2", otherwise unclear. No information in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria	Not stated/unclear

category at baseline	
Population subgroups	NA
Comparator	Placebo (subcutaneous once per week)
Number of participants	Tirzepatide - 45 participants were allocated, 41 participants completed the study, and 39 participants were included in the pharmacodynamic analysis set for primary outcome analysis Semaglutide - 44 participants were allocated, 43 participants completed the study, and 39 participants were included in the pharmacodynamic analysis set for primary outcome analysis Placebo - 28 participants were assigned, 24 completed the study, and 24 participants were included in the pharmacodynamic analysis set for primary outcome analysis
Duration of follow-up	28 weeks
Indirectness	Directly applicable
Method of analysis	Not stated/unclear Outcomes of HbA1c and weight - conducted on data from all randomised participants who received at least 1 dose of the study drug and have evaluable data. Imputation for missing data and multiplicity adjustment were not performed. Analyses were conducted using mixed models for repeated outcomes. Outcomes of mortality and hypoglycaemia and severe hypoglycaemic episodes were analysed in the safety populations which comprised all randomly assigned participants who received at least one dose of a study drug.
Additional comments	Sample size calculations were conducted based on the clamp disposition index outcomes

51.2. Study arms

51.2.1. Tirzepatide (N = 45)

51.2.2. Semaglutide (N = 44)

51.2.3. Placebo (N = 28)

51.3. Characteristics

51.3.1. Arm-level characteristics

Characteristic	Tirzepatide (N = 45)	Semaglutide (N = 44)	Placebo (N = 28)
% Male Sample size	n = 31 ; % = 69	n = 34 ; % = 77	n = 21 ; % = 75
Mean age (SD) Mean (SD)	61.1 (7.1)	63.7 (5.9)	60.4 (7.6)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Black or African American Sample size	n = 1 ; % = 2	n = 0 ; % = 0	n = 0 ; % = 0
White Sample size	n = 44 ; % = 98	n = 44 ; % = 100	n = 28 ; % = 100
Hispanic or Latinx Sample size	n = 0 ; % = 0	n = 0 ; % = 0	n = 0 ; % = 0
Not Hispanic or Latinx Sample size	n = 45 ; % = 100	n = 44 ; % = 100	n = 28 ; % = 100
Comorbidities Nominal	NR	NR	NR
Presence of frailty Nominal	NR	NR	NR
Time since type 2 diabetes diagnosed Mean (SD)	10.24 (5.8)	12.73 (6.1)	10.95 (6.78)
Cardiovascular risk factors Nominal	NR	NR	NR

Characteristic	Tirzepatide (N = 45)	Semaglutide (N = 44)	Placebo (N = 28)
Smoking status Nominal	NR	NR	NR
Alcohol consumption Nominal	NR	NR	NR
Presence of severe mental illness Nominal	NR	NR	NR
People with significant cognitive impairment Nominal	NR	NR	NR
People with a learning disability Nominal	NR	NR	NR
Number of people with obesity Nominal	NR	NR	NR
Other antidiabetic medication used Nominal	NR	NR	NR
Blood pressure-lowering medication used Nominal	NR	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR	NR

52. Henriksen, 2011

Bibliographic Reference	Henriksen, Kim; Byrjalsen, Inger; Qvist, Per; Beck-Nielsen, Henning; Hansen, Gitte; Riis, Bente J; Perrild, Hans; Svendsen, Ole Lander; Gram, Jeppe; Karsdal, Morten A; Christiansen, Claus; Efficacy and safety of the PPARgamma partial agonist balaglitazone compared with pioglitazone and placebo: a phase III, randomized, parallel-group study in patients with type 2 diabetes on stable insulin therapy.; Diabetes/metabolism research and reviews; 2011; vol. 27 (no. 4); 392-401

52.1. 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	NCT00515632
Study type	Randomised controlled trial (RCT)
Study location	Denmark, Sweden, Finland,
Study setting	NR
Study dates	Participants were recruited between 29 June 2007 and 28 November 2008
Sources of funding	Den Danske Forskningsfond [Authors were also employees of and owned stocks in Nordic Bioscience]
Inclusion criteria	• Type 2 diabetes mellitus being diagnosed at least 3 months earlier according to the 1999 World Health Organisation criteria; • Aged >= 18 years • BMI >= 25 kg/m2 • HbA1c >= 7% • Failure of anti-hyperglycaemic therapy, i.e. insulin at a dose of at least 30 U/day (for at least 75 days) plus metformin and/or other oral anti-diabetic drugs.

Exclusion criteria	• Prior or current use of a PPAR. agonist • Hospitalization for a major cardiovascular event • A scheduled major cardiovascular intervention • Heart failure (New York Heart Association I–IV) • Uncontrolled treated blood pressure >180 mmHg and/or diastolic blood pressure > 95 mmHg • Serum creatinine > 130 µmol/L • Alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, or alkaline phosphatase >2.5 times the upper limit of normal • Haemoglobin significantly (but not more than 1 mmol/L) below the lower limit of normal or haemoglobinopathy interfering with a valid HbA1c assay • Haematuria • Known diabetic macular oedema • Contraindication to or intolerance of study medication • A pre-existing medical condition precluding safe participation • Abuse of alcohol or drugs, or presence of any condition that in the investigator's opinion might have led to poor adherence to the study protocol • Recent use (<3 months) of an investigational drug • Use of any drug, such as systemic corticosteroids, which could interfere with glucose levels; diagnosis of clinically significant disease/disorder which could interfere with the results • Planned surgery • Pregnancy, breast feeding, planning a pregnancy, or not using adequate contraceptive methods.
Recruitment / selection of participants	After inclusion, subjects were instructed to discontinue all oral anti-diabetic drugs and continue with normal insulin dose.
Intervention(s)	Pioglitazone 45 mg as a single tablet once daily at breakfast
Cointervention	• Participants were instructed to discontinue all oral anti-diabetic drugs and continue with normal insulin dose. • During the study insulin adjustments were permitted to resolve short-term acute diseases and to avoid hypoglycaemia • Participants were instructed to continue their usual diet
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Excluded "heart failure (New York Heart Association I–IV)"
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.

Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	NA
Comparator	Matching placebo as a single tablet once daily at breakfast

Number of participants	587 participants were screened and 409 participants were randomised. The study also included two balaglitazone arms which were not eligible for inclusion. 109 participants were assigned to the placebo arm; 75 participants completed the study and 32 did not complete. 102 participants were assigned tot he the pioglitazone arm, 85 participants completed and 17 did not.
Duration of follow-up	26 weeks
Indirectness	Directly applicable
Method of analysis	ITT Not clearly stated, however, all subjects who received at least one dose of randomised study drug and who had an evaluable baseline and at least one evaluable post-baseline efficacy measurement were included in the efficacy analysis. Primary endpoint data were assessed with analysis of covariance to determine last squares means of change from baseline. All subjects who received at least one dose of randomized study drug were included in the safety analysis.
Additional comments	Sample size calculations were based on on power to detect treatment difference for HbA1c change and for body weight change

52.2. Study arms

52.2.1. Pioglitazone (N = 102)

52.2.2. Placebo (N = 109)

52.3. Characteristics

52.3.1. Arm-level characteristics

Characteristic	Pioglitazone (N = 102)	Placebo (N = 109)
Mean age (SD) Mean (SD)	60.1 (8.6)	60.9 (7.8)
Ethnicity % calculated by analyst Sample size	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Pioglitazone (N = 102)	Placebo (N = 109)
Caucasian Sample size	n = 101 ; % = 99	n = 105 ; % = 99
Asian Sample size	n = 1 ; % = 1	n = 0 ; % = 0
Other Sample size	n = 0 ; % = 0	n = 1 ; % = 1
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed Mean (SD)	13.8 (7.4)	12.6 (7.3)
Cardiovascular risk factors Nominal	NR	NR
Smoking status Nominal	NR	NR
Alcohol consumption Nominal	NR	NR
Presence of severe mental illness Nominal	NR	NR
People with significant cognitive impairment Nominal	NR	NR
People with a learning disability Nominal	NR	NR
Number of people with obesity Nominal	NR	NR
Other antidiabetic medication used Sample size	n = 45 ; % = 42	n = 51 ; % = 50
MET Sample size	n = 20 ; % = 19	n = 22 ; % = 22

Characteristic	Pioglitazone (N = 102)	Placebo (N = 109)
SU Sample size	n = 3 ; % = 3	n = 0 ; % = 0
Others Sample size	n = 8 ; % = 8	n = 4 ; % = 4
MET + SU Sample size	n = 3 ; % = 3	n = 1 ; % = 1
MET + other Sample size	n = 0 ; % = 0	n = 0 ; % = 0
SU + other Sample size	n = 0 ; % = 0	n = 1 ; % = 1
MET + SU + other Sample size	n = 39 ; % = 37	n = 31 ; % = 30
Blood pressure-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Renin-angiotensin drugs Sample size	n = 83 ; % = 78	n = 83 ; % = 78
Other anti-hypotensive drugs Sample size	n = 3 ; % = 3	n = 1 ; % = 1
Statins/lipid-lowering medication used Sample size	n = 75 ; % = 71	n = 84 ; % = 79
Other treatment being received Acetylsalicylic acid Sample size	n = 60 ; % = 59	n = 69 ; % = 65
Women (%) Sample size	n = 40 ; % = 31	n = 40 ; % = 38
Insulin dose (U/day) Mean (SD)	78.4 (40.3)	75.2 (39.1)

53. Hermansen, 2007

Bibliographic Reference	Hermansen, K.; Kipnes, M.; Luo, E.; Fanurik, D.; Khatami, H.; Stein, P.; Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, in patients with type 2 diabetes mellitus inadequately controlled on glimepiride alone or on glimepiride and metformin; Diabetes Obes Metab; 2007; vol. 9 (no. 5); 733-45

53.1. Study details

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	NA
Trial name / registration number	Sitagliptin 035
Study type	Randomised controlled trial (RCT)
Study location	Methods state that the study is multinational, but no further information provided
Study setting	NR
Study dates	NR
Sources of funding	Merck & Co. Inc
Inclusion criteria	• Aged >=18 and <=75 years • Type 2 diabetes • Either i) already taking glimepiride alone (at any dose) or in combination with metformin (at any dose), (ii) taking another oral hypoglycaemic agent in monotherapy or in dual- or triple-combination therapy or (iii) patients not taking any oral hypoglycaemic agent over the prior 8 weeks

Exclusion criteria	• History of type 1 diabetes • Were treated with insulin within 8 weeks of the screening visit • Had renal dysfunction (creatinine clearance <45 ml/min or <60 ml/min if on metformin) • Had a history of hypersensitivity, intolerance or a contraindication to the use of glimepiride, sulphonylurea agents, metformin or pioglitazone
Recruitment / selection of participants	No information around recruitment and selection. At screening patients were instructed to receive glimepiride alone {stratum 1} or glimepiride + metformin (stratum 2) based on their oral hypoglycaemia agent regimen at screening and their baseline HbA1c. Patients with HbA1c >=7.5% and <=10.5% who were already taking a stable dose of glimepiride (>=4 mg/day up to a maximum daily dose of 8 mg/day) alone or in combination with metformin (>=1500 mg/day up to a maximum daily dose of 3000 mg/day) for at least 10 weeks directly entered a 2-week, single-blind placebo run-in period. Patients who were not on oral hypoglycaemic agent with HbA1c >=9%, who were taking other oral hypoglycaemic agent in monotherapy with HbA1c >=7.5%, or who were taking other oral hypoglycaemic agents in dual or triple therapy with HbA1c >=6.5% and <=10.5%, discontinued their prior regimen and were switched to treatment with glimepiride alone or glimepiride in combination with metformin. Following the switch in treatments, these patients entered a dose titration period of up to 4 weeks and then a dose stabilization run-in period of up to 10 weeks. If HbA1c was >=7.5% and <=10.5% after this run-in period, patients entered a 2-week, single-blind placebo run-in period. Patients with adequate compliance (>=75%) during the placebo run-in period underwent baseline evaluations and were randomised to either sitagliptin or placebo.
Intervention(s)	Once-daily sitagliptin 100mg
Cointervention	Patients were assigned to either stratum 1 (glimepiride only >=4mg/day up to a maximum daily dose of 8 mg/day) or stratum 2 (glimepiride in combination with metformin >= 1500 mg/day up to a maximum daily dose of 3000 mg/day). Patients not meeting specific, progressively lower glycaemic goals [fasting plasma glucose (FPG) >270 mg/dl between randomisation and Week 6, FPG >240 mg/dl week 6 to week 12, or FPG >200 mg/dl Week 12 to Week

	24 were provided open-label rescue therapy (pioglitazone 30 mg/day) until the completion of the study period.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Excluded “renal dysfunction (creatinine clearance < 45 ml/min or < 60 ml/min if on metformin)”, otherwise unclear. No information in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear

Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	NA
Comparator	Placebo
Number of participants	1098 participants were screened and 411 were included in the study. Stratum 1: 106 participants were assigned to receive sitagliptin, and 83 completed the study. 106 participants were assigned to placebo and 87 completed the study. Stratum 2: 116 participants were assigned to receive sitagliptin and 102 completed the study. 113 participants were assigned to placebo and 92 completed the study.
Duration of follow-up	24 weeks
Indirectness	Directly applicable
Method of analysis	Not stated/unclear Efficacy - Described as all-patients-treated population that consisted of all randomized patients who received at least one dose of study drug and who had both baseline and at least one post-baseline efficacy measurement. Missing data were handled using the last-observation carried forward method. HbA1c was analysed using ANCOVA and were adjusted for baseline HbA1c and stratum. Safety analyses- performed in the all-patients-as-treated population which included randomized patients who received at least one dose of double-blind study medication. [for these outcomes it is assumed that this analysis is performed "as treated"]
Additional comments	The study was designed to detect a true difference of 0.5% in the mean change from baseline in HbA1c between a sitagliptin and placebo for a two-tailed test at alpha 0.05 (two sided) with greater than 99% power for the entire cohort and with greater than 90% power for each stratum.

53.2. Study arms

53.2.1. Stratum 1 - Sitagliptin (N = 106)

Stratum 1 includes cointervention with glimepiride only

53.2.2. Stratum 1 - Placebo (N = 106)

Stratum 1 includes cointervention with glimepiride only

53.2.3. Stratum 2 - Sitagliptin (N = 116)

Stratum 2 includes cointervention with glimepiride + metformin

53.2.4. Stratum 2 - Placebo (N = 113)

Stratum 2 includes cointervention with glimepiride + metformin

53.3. Characteristics

53.3.1. Arm-level characteristics

Characteristic	Stratum 1 - Sitagliptin (N = 106)	Stratum 1 - Placebo (N = 106)	Stratum 2 - Sitagliptin (N = 116)	Stratum 2 - Placebo (N = 113)
% Male Sample size	n = 56 ; % = 52.8	n = 58 ; % = 54.7	n = 61 ; % = 52.6	n = 59
Mean age (SD) Mean (SD)	54.4 (10.3)	55.2 (10.2)	56.6 (8.8)	57.7 (8.9)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Caucasian Sample size	n = 61 ; % = 57.5	n = 59 ; % = 55.7	n = 75 ; % = 64.7	n = 81 ; % = 71.7
Black Sample size	n = 7 ; % = 6.6	n = 3 ; % = 2.8	n = 3 ; % = 2.6	n = 9 ; % = 8
Hispanic Sample size	n = 26 ; % = 24.5	n = 25 ; % = 23.6	n = 13 ; % = 11.2	n = 7 ; % = 6.2

Characteristic	Stratum 1 - Sitagliptin (N = 106)	Stratum 1 - Placebo (N = 106)	Stratum 2 - Sitagliptin (N = 116)	Stratum 2 - Placebo (N = 113)
Asian Sample size	n = 6 ; % = 5.7	n = 12 ; % = 11.3	n = 16 ; % = 13.8	n = 13 ; % = 11.5
Other Sample size	n = 6 ; % = 5.7	n = 7 ; % = 6.6	n = 9 ; % = 7.8	n = 3 ; % = 2.7
Comorbidities Nominal	NR	NR	NR	NR
Presence of frailty Nominal	NR	NR	NR	NR
Time since type 2 diabetes diagnosed Mean (SD)	7.2 (5)	8 (6.5)	9.3 (5.7)	10.6 (6.8)
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
Combination therapy Sample size	n = 29 ; % = 27.4	n = 29 ; % = 27.4	n = 111 ; % = 95.7	n = 107 ; % = 94.7
Monotherapy Sample size	n = 66 ; % = 62.3	n = 69 ; % = 65.1	n = 5 ; % = 4.3	n = 3 ; % = 2.7

Characteristic	Stratum 1 - Sitagliptin (N = 106)	Stratum 1 - Placebo (N = 106)	Stratum 2 - Sitagliptin (N = 116)	Stratum 2 - Placebo (N = 113)
absence Sample size	n = 11 ; % = 10.4	n = 8 ; % = 7.5	n = 0 ; % = 0	n = 3 ; % = 2.7
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

54. Hiramatsu, 2018

Bibliographic Reference	Hiramatsu, T.; Asano, Y.; Mabuchi, M.; Imai, K.; Iguchi, D.; Furuta, S.; Liraglutide relieves cardiac dilated function than DPP-4 inhibitors; Eur J Clin Invest; 2018; vol. 48 (no. 10); e13007

54.1. 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	None
Study type	Randomised controlled trial (RCT) Parallel group RCT
Study location	Konan City, Japan
Study setting	Outpatient
Study dates	Not reported but participants recruited from patients referred to Konan Kosei Hospital from 10/2010 to 06/2013.
Sources of funding	None reported
Inclusion criteria	• Diagnosis of type 2 diabetes mellitus • Non-optimal glycaemia control • Renal impairment • eGFR 30-60 mL/min/1.73 m2 inclusive
Exclusion criteria	• History of type 2 diabetes • Diabetic ketoacidosis • Severely impaired insulin secretion (serum C-peptide<2.0 ng/mL) • Requires use of high-dose insulin (>20 U/d)

	• Hepatic or cardiac failure, and atrial fibrillation
Recruitment / selection of participants	Participants recruited from patients referred to Konan Kosei Hospital, Konan City, Japan from 10/2010 to 06/2013 and randomised to 1 of 3 arms. Allocation performed using sequentially numbered envelopes. Participants who died or began dialysis therapy for end stage renal disease were withdrawn from study protocol.
Intervention(s)	• Liraglutide 0.9 mg daily Subcutaneous injection of liraglutide 0.9 mg daily for 48 months switching from insulin and other antidiabetic agents or adding to insulin, alpha-glucosidase inhibitor or glinide.
Cointervention	None, insulin, alphaglucosidase inhibitor, or glinide.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Reports NYHA class but also excludes people with heart failure, so difficult to say
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	People with chronic kidney disease Intention is to study drugs in people with impaired renal function - therefore, even though it doesn't state chronic kidney disease, the lowered CKD means we will treat this as CKD. Study defined as 'renal impairment' and this matches criteria of other studies classifying as CKD.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type	Not stated/unclear

2 diabetes mellitus	
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	eGFR ≥30mL/min/1.73m2 Inclusion criteria eGFR 30-60 mL/min/1.73m2 inclusive
Subgroup 6: Albuminuria category at baseline	Mixed population Reports mean baseline ACR
Comparator	• Sitagliptin 50 mg daily • Linagliptin 5 mg daily Oral sitagliptin 50 mg daily or linagliptin 5 mg daily for 48 months, switching from insulin and other antidiabetic agents or adding to insulin, alpha-glucosidase inhibitor or glinide.
Number of participants	N=139
Duration of follow-up	48 months
Indirectness	None
Method of analysis	Not stated/unclear Type of analysis not explicitly reported but appears to be completers as includes all participants except those who died or began dialysis for end stage renal disease.

54.2. Study arms

54.2.1. Liraglutide 0.9 mg daily (N = 45)

Subcutaneous injection of liraglutide 0.9 mg daily for 48 months switching from insulin and other antidiabetic agents or adding to insulin, alpha-glucosidase inhibitor or glinide.

54.2.2. Sitagliptin 50 mg daily (N = 49)

Oral sitagliptin 50 mg daily for 48 months switching from insulin and other antidiabetic agents or adding to insulin, alpha-glucosidase inhibitor or glinide.

54.2.3. Linagliptin 5 mg daily (N = 45)

Oral linagliptin 5 mg daily switching from insulin and other antidiabetic agents or adding to insulin, alpha-glucosidase inhibitor or glinide.

54.3. Characteristics

54.3.1. Arm-level characteristics

Characteristic	Liraglutide 0.9 mg daily (N = 45)	Sitagliptin 50 mg daily (N = 49)	Linagliptin 5 mg daily (N = 45)
% Male Nominal	NR	NR	NR
Mean age (SD) (years) Mean (SD)	70.5 (5.7)	69.9 (8.5)	69 (7.7)
Ethnicity Nominal	NR	NR	NR
Comorbidities Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
NYHA Class I Article reports classes as 'I', 'H' and 'M' so not clear which NYHA categories these are Sample size	n = 15 ; % = 46.9	n = 16 ; % = 47.1	n = 16 ; % = 50
NYHA Class H Sample size	n = 12 ; % = 37.5	n = 13 ; % = 38.2	n = 11 ; % = 34.4
NYHA Class M Sample size	n = 5 ; % = 15.6	n = 5 ; % = 14.7	n = 5 ; % = 15.6
Presence of frailty Nominal	NR	NR	*empty data*

Characteristic	Liraglutide 0.9 mg daily (N = 45)	Sitagliptin 50 mg daily (N = 49)	Linagliptin 5 mg daily (N = 45)
Time since type 2 diabetes diagnosed (years) Mean (SD)	9.2 (7)	8.8 (8.3)	8.3 (0.4)
Cardiovascular risk factors Nominal	NR	NR	NR
Heart rate Nominal	NR	NR	NR
Smoking status Nominal	NR	NR	NR
Alcohol consumption Nominal	NR	NR	NR
Presence of severe mental illness Nominal	NR	NR	NR
People with significant cognitive impairment Nominal	NR	NR	NR
People with a learning disability Nominal	NR	NR	NR
Weight Nominal	NR	NR	NR
Number of people with obesity Nominal	NR	NR	NR
None Sample size	n = 23 ; % = 71.9	n = 24 ; % = 70.6	n = 21 ; % = 65.6
Alpha-glucosidase inhibitors Sample size	n = 3 ; % = 9.4	n = 4 ; % = 11.8	n = 4 ; % = 12.5
Glinides Sample size	n = 3 ; % = 9.4	n = 3 ; % = 8.8	n = 2 ; % = 6.3
Insulin	n = 3 ; % = 9.4	n = 3 ; % = 8.8	n = 3 ; % = 9.4

Characteristic	Liraglutide 0.9 mg daily (N = 45)	Sitagliptin 50 mg daily (N = 49)	Linagliptin 5 mg daily (N = 45)
Sample size			
Blood pressure-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Angiotensin II receptor blockers Sample size	n = 27 ; % = 84.4	n = 28 ; % = 82.3	n = 26 ; % = 81.3
Calcium-channel blockers Sample size	n = 20 ; % = 62.5	n = 21 ; % = 61.7	n = 21 ; % = 65.6
Statins/lipid-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Statin-lowering regimen Sample size	n = 24 ; % = 75	n = 25 ; % = 73.5	n = 24 ; % = 73.5
Other treatment being received Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Diuretics Sample size	n = 17 ; % = 53.1	n = 18 ; % = 52.9	n = 18 ; % = 56.3

55. Hollander, 2009

Bibliographic Reference	Hollander, P.; Li, J.; Allen, E.; Chen, R.; Saxagliptin added to a thiazolidinedione improves glycemic control in patients with type 2 diabetes and inadequate control on thiazolidinedione alone; J Clin Endocrinol Metab; 2009; vol. 94 (no. 12); 4810-9

55.1. Study details

Secondary publication of another included study- see primary study for details	Hollander 2011
Other publications associated with this study included in review	NA
Trial name / registration number	CV181-013 [NCT00295633]
Study type	Randomised controlled trial (RCT)
Study location	Multicentre study in the US
Study setting	Unclear, patients were recruited from 172 outpatient centres
Study dates	March 13, 2006 to October 28, 2007
Sources of funding	Bristol-Myers Squibb and AstraZeneca
Inclusion criteria	• Aged 18 to 77 years • T2D treated with a stable dose of TZD monotherapy [pioglitazone 30 or 45 mg once per day (qd) or rosiglitazone 4 or 8mg qd, or in two divided doses of 4 mg twice per day (bid)] for at least 12 wk before screening • HbA1c of at least 7.0% and no more than 10.0% at screening, fasting C-peptide concentration at least 0.3 nmol/litre, and a body mass index (BMI) of no more than 40 kg/m2

	The study eligibility protocol was amended to reflect the range of current baseline characteristics for patients with T2D on TZD therapy: • the HbA1c inclusion range was expanded to at least 7.0% and more than 10.5%, and the BMI inclusion range was expanded to no more than 45 kg/m2
Exclusion criteria	• History of any anti-hyperglycaemic therapy other than pioglitazone 30 or 45 mg qd, rosiglitazone 4 or 8 mg qd, or 4 mg bid during the 12 week before screening • History of diabetic ketoacidosis, hyperosmolar nonketotic coma, or symptoms of poorly controlled diabetes and those receiving insulin therapy within 1 year of screening (with the exception of insulin therapy during a hospitalization or use in gestational diabetes) • Immunocompromised • Treated with potent CYP3A4 inhibitors or inducers • Had a cardiovascular event within 6 months before study entry or New York Heart Association stage III/IV congestive heart failure and/or known left ventricular ejection fraction of 40% or less • Had significant renal, liver, or psychiatric history • Had significant alcohol or drug abuse within the previous year • Had active liver disease or clinically significant abnormalities on screening tests of hepatic, renal, endocrine, metabolic, or haematological function.
Recruitment / selection of participants	Participants were recruited from an outpatient setting. Eligible patients enrolled in a 2-week, single-blind, dietary and exercise placebo and TZD lead-in period. Good compliance (80 to 120%) with placebo during the kead-in period was required for eligibility for the short-term treatment period.
Intervention(s)	Saxagliptin 2.5 mg qd plus open-label TZD therapy Saxagliptin 5 mg qd plus open-label TZD therapy [Saxagliptin was to be taken daily before the morning meal]
Cointervention	• Open-label pioglitazone or rosiglitazone according to the participant's current regimen • If determined to be medically appropriate, a switch from rosiglitazone to pioglitazone was permitted based on recent safety concerns regarding rosiglitazone • Patients receiving 4 mg total daily dose (TDD) of rosiglitazone received 30 mg pioglitazone qd and patients receiving 8 mg TDD (including 4 mg twice daily) of rosiglitazone received 45 mg pioglitazone qd • A protocol-mandated, progressively more stringent algorithm was used to determine insufficient glycaemic control during the long-term extension period to ethically retain patients for safety analysis; the rescue criteria were HbA1C >8% at weeks 30, 37, and 50, and HbA1C >7.5% at week 63.

	• If criteria for administering open-label metformin rescue were satisfied and serum creatinine was within acceptable levels (serum creatinine <1.5 mg/dL [<132.6 µmol/L] males or <1.4 mg/dL [<123.8 µmol/L] females), patients who were rescued during the long-term period continued in the study and received 500 mg open-label metformin with titration to a maximum of 2500 mg in addition to their long-term blinded study medication and open-label TZD. Patients not controlled after 3 months on a maximum tolerated dose of metformin were to be discontinued from the study and referred for additional antihyperglycaemic therapy. Patients were not eligible for metformin rescue and were discontinued from the study if serum creatinine levels were outside the acceptable range.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Excluded “New York Heart Association stage III/IV congestive heart failure”, otherwise unclear. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Excluded “a cardiovascular event within 6 months before study entry”, prior unclear. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear

Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	NA
Comparator	Placebo plus open-label TZD therapy
Number of participants	1200 participants enrolled, 614 entered lead-in, and 565 were randomised and treated. Of 196 participants assigned to saxagliptin 2.5 mg, 36 withdrew from the trial, and 159 completed. Of 186 participants assigned to saxagliptin 5 mg, 46 withdrew from the trial, and 140 completed. Of 184 participants assigned to placebo, 46 withdrew from the trial and 138 completed.
Duration of follow-up	24 and 76 weeks (76 weeks included 24 week initial and 52-week extension period)
Indirectness	Directly applicable
Method of analysis	Not stated/unclear HbA1c was assessed using a repeated measures analysis and an analysis of covariance (ANCOVA). Bodyweight and BMI were summarised or analysed with an ANCOVA on a last observation carried forward basis.
Additional comments	NA

55.2. Study arms

55.2.1. Saxagliptin 2.5 mg (N = 195)

55.2.2. Saxagliptin 5 mg (N = 186)

55.2.3. Placebo (N = 184)

55.3. Characteristics

55.3.1. Arm-level characteristics

Characteristic	Saxagliptin 2.5 mg (N = 195)	Saxagliptin 5 mg (N = 186)	Placebo (N = 184)
% Male Sample size	n = 106 ; % = 54.4	n = 89 ; % = 47.8	n = 85 ; % = 46.2
Mean age (SD) Mean (SD)	54.9 (9.7)	53.2 (10.6)	54 (10.1)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 109 ; % = 55.9	n = 99 ; % = 53.2	n = 101 ; % = 54.9
Asian Sample size	n = 67 ; % = 34.4	n = 66 ; % = 35.5	n = 63 ; % = 34.2
Black/African-American Sample size	n = 5 ; % = 2.6	n = 10 ; % = 5.4	n = 7 ; % = 3.8
Other Sample size	n = 14 ; % = 7.2	n = 11 ; % = 5.9	n = 13 ; % = 7.1
Comorbidities Nominal	NR	NR	NR
Presence of frailty Nominal	NR	NR	NR
Time since type 2 diabetes diagnosed Mean (SD)	5.3 (4.6)	5.2 (5.6)	5.1 (5.4)
Cardiovascular risk factors	NR	NR	NR

Characteristic	Saxagliptin 2.5 mg (N = 195)	Saxagliptin 5 mg (N = 186)	Placebo (N = 184)
Nominal			
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
Other antidiabetic medication used % calculated by analyst as a percentage of total participants in each arm Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
45 mg pioglitazone Sample size	n = 25 ; % = 13	n = 37 ; % = 20	n = 32 ; % = 17
8 mg rosiglitazone Sample size	n = 40 ; % = 21	n = 36 ; % = 19	n = 35 ; % = 19
30 mg pioglitazone Sample size	n = 77 ; % = 39	n = 71 ; % = 38	n = 76 ; % = 41
4 mg rosiglitazone Sample size	n = 53 ; % = 27	n = 42 ; % = 23	n = 41 ; % = 22
Blood pressure-lowering medication used Nominal	NR	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR	NR

Characteristic	Saxagliptin 2.5 mg (N = 195)	Saxagliptin 5 mg (N = 186)	Placebo (N = 184)
Other treatment being received Nominal	NR	NR	NR

56. Hollander, 2018

Bibliographic Reference	Hollander, P.; Liu, J.; Hill, J.; Johnson, J.; Jiang, Z. W.; Golm, G.; Huyck, S.; Terra, S. G.; Mancuso, J. P.; Engel, S. S.; et, al.; Ertugliflozin Compared with Glimepiride in Patients with Type 2 Diabetes Mellitus Inadequately Controlled on Metformin: the VERTIS SU Randomized Study; Diabetes Ther; 2018; vol. 9 (no. 1); 193-207

56.1. 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	VERTIS SU [NCT01999218]
Study type	Randomised controlled trial (RCT)
Study location	The study was conducted at 232 centres across 16 countries (Argentina, Canada, Czech Republic, Hungary, South Korea, Lithuania, Mexico, the Philippines, Poland, Romania, Russia, Slovakia, South Africa, Taiwan, Ukraine, and the US)
Study setting	NR
Study dates	The study started on December 17, 2013, and the last patient completed phase A on April 28, 2016.
Sources of funding	Merck Sharp & Dohme Corp (subsidiary of Merck & Co.) and Pfizer Inc.
Inclusion criteria	• Aged at least 18 years with T2DM and inadequate glycaemic control (HbA1c >= 53 and <= 75 mmol/mol [>=7.0% and <=9.0%]) on >= 1500 mg/day of metformin monotherapy for at least 8 weeks at screening • Patients on this regimen for less than 8 weeks, on lower doses of metformin, or on any dose of metformin with another antihyperglycemic agent at screening were eligible if they met the

	above criteria after the appropriate dose/medication adjustment, stabilization, or washout period.
Exclusion criteria	• History of type 1 diabetes mellitus or of ketoacidosis • Weight not stable (>= 5% change in body weight in previous 6 months) • Treatment in previous 12 weeks with insulin or any other type of injectable AHA, pioglitazone or rosiglitazone, other SGLT2 inhibitors, bromocriptine, or colesevelam, or any other AHAs, with the exceptions of SUs administered at less than 50% of the maximum approved dose, dipeptidyl peptidase-4 (DPP-4) inhibitors, meglitinides, and alpha-glucosidase inhibitors • History of myocardial infarction (MI), unstable angina, arterial revascularization, stroke, transient ischemic attack, or New York Heart Association functional class III–IV heart failure within 3 months of screening • Any active, obstructive uropathy or indwelling urinary catheter • Mean value for triplicate sitting systolic BP > 160 mmHg and/or diastolic BP > 90 mmHg (patients on BP medication must have been on a stable regimen for at least 4 weeks prior to randomization) • Estimated glomerular filtration rate <55 mL/min/1.73 m2 • Serum creatinine ≥ 115 umol/L (1.3 mg/dL) in men or ≥ 106 umol/L (1.2 mg/dL) in women
Recruitment / selection of participants	Participants who met inclusion criteria could proceed directly into a 2-week, single-blind placebo run-in period prior to randomisation. Patients with adequate compliance during the placebo run-in period (≥ 80% based on pill count) and who met all other entry criteria were randomised.
Intervention(s)	• Ertugliflozin 15 mg once daily (QD) • Ertugliflozin 5 mg QD • Glimepiride titrated from 1 mg up to 6 or 8 mg QD (to either maximum dose according to the local country label or maximum tolerated dose). [To manage both hyperglycaemia and hypoglycaemia, the dose of glimepiride/matching placebo was to be up- and/or down-titrated throughout the study duration on the basis of finger-stick glucose determinations performed in the clinic or at home, and by the investigator's clinical assessment of the patient's glycaemic status] [Ertugliflozin and glimepiride tablets were packaged identically relative to their matching placebos.]
Cointervention	Interventions were given as an add-on to metformin therapy. Glycaemic rescue therapy with open-label sitagliptin was prescribed for patients meeting progressively more stringent glycaemic rescue criteria. Rescued patients continued on their study medication and background metformin.
Strata 1: People with type 2	Not stated/unclear Excluded "New York Heart Association stage III/IV congestive heart failure", otherwise unclear. No information in baseline characteristics.

diabetes mellitus and heart failure	
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Excluded “myocardial infarction (MI), unstable angina, arterial revascularization, stroke, transient ischemic attack within 3 months of screening”, prior unclear. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Excluded “estimated glomerular filtration rate (eGFR)\55 mL/min/ 1.73 m2”, otherwise unclear. No information in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria	Not stated/unclear

category at baseline	
Population subgroups	NA
Comparator	NA
Number of participants	2,985 participants were assessed for eligibility, and 1,326 participants were randomised. Out of 441 participants allocated to ertugliflozin 15 mg, 440 participants received treatment, 83 (18.8%) discontinued study medication, and 357 (81% completed week 52 on study medication. Out of 448 participants allocated to ertugliflozin 5 mg, 108 (24.1%) discontinued study medication, and 340 (75.9%) completed week 52 on study medication. Out of 437 participants allocated to glimepiride, 89 (20.4%) discontinued study medication and 348 (79.6%) completed week 52 on study medication.
Duration of follow-up	52 weeks
Indirectness	Directly applicable
Method of analysis	Per protocol Sensitivity analyses were conducted for the primary and key secondary efficacy endpoints in the per protocol (PP) population (all randomized patients who took at least one dose of study medication, with a measurement of the analysis endpoint at both baseline and week 52, and without significant protocol deviations) with an ANCOVA model. ITT Defined as: full -analysis set - all randomized patients who took at least one dose of study drug and had at least one measurement of the respective endpoint). The pre-specified composite endpoints were analyzed using the Miettinen and Nurminen method in the FAS population, with missing data imputed using the last observation carried forward method.
Additional comments	The primary hypothesis was that ertugliflozin 15 mg was non-inferior to glimepiride on HbA1c (non-inferiority criterion: upper bound of the 95% confidence interval [CI] about the treatment difference <0.3%).

56.2. Study arms

56.2.1. Ertugliflozin 15 mg (N = 441)

56.2.2. Ertugliflozin 5 mg (N = 448)

56.2.3. Glimepiride (N = 437)

56.3. Characteristics

56.3.1. Arm-level characteristics

Characteristic	Ertugliflozin 15 mg (N = 441)	Ertugliflozin 5 mg (N = 448)	Glimepiride (N = 437)
% Male Sample size	n = 191 ; % = 43.4	n = 227 ; % = 50.7	n = 224 ; % = 51.3
Mean age (SD) Mean (SD)	58 (9.9)	58.8 (9.7)	57.8 (9.2)
Ethnicity Mean (SD)	NA (NA)	NA (NA)	NA (NA)
White Mean (SD)	316 (71.8)	332 (74.1)	318 (72.8)
Asian Mean (SD)	85 (19.3)	81 (18.1)	73 (16.7)
Black or African American Mean (SD)	19 (4.3)	17 (3.8)	25 (5.7)
Other Mean (SD)	20 (4.5)	18 (4)	21 (4.8)
Comorbidities Nominal	NR	NR	NR
Presence of frailty Nominal	NR	NR	NR
Time since type 2 diabetes diagnosed Mean (SD)	7.5 (5.7)	7.4 (5.7)	7.5 (5.6)
Smoking status Nominal	NR	NR	NR

Characteristic	Ertugliflozin 15 mg (N = 441)	Ertugliflozin 5 mg (N = 448)	Glimepiride (N = 437)
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
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

57. Hollander, 2011

Bibliographic Reference	Hollander, Priscilla L; Li, Jia; Frederich, Robert; Allen, Elsie; Chen, Roland; Safety and efficacy of saxagliptin added to thiazolidinedione over 76 weeks in patients with type 2 diabetes mellitus.; Diabetes & vascular disease research; 2011; vol. 8 (no. 2); 125-35

57.1. Study details

Secondary publication of another included study- see primary study for details	Parent study Hollander 2009

58. Holman Rury, 2016

Bibliographic Reference	Holman Rury, R; Bethel Mary, Angelyn; George, Jyothis; Sourij, Harald; Doran, Zoe; Keenan, Joanne; Khurmi Nardev, S; Mentz Robert, J; Oulhaj, Abderrahim; Buse John, B; Chan Juliana, C; Iqbal, Nayyar; Kundu, Sudeep; Maggioni Aldo, P; Marso Steven, P; Ohman, Peter; Pencina Michael, J; Poulter, Neil; Porter Lisa, E; Ramachandran, Ambady; Zinman, Bernard; Hernandez Adrian, F; Rationale and design of the EXenatide Study of Cardiovascular Event Lowering (EXSCEL) trial.; American heart journal; 2016; vol. 174; 103-10

58.1. Study details

Secondary publication of another included study- see primary study for details	Holman Rury, R; Bethel M, Angelyn; Mentz Robert, J et al. (2017) Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes. The New England journal of medicine; 2017; vol. 377 (no. 13); 1228-1239
Other publications associated with this study included in review	Mentz, Robert J; Bethel, M Angelyn; Gustavson, Stephanie et al. (2017) Baseline characteristics of patients enrolled in the Exenatide Study of Cardiovascular Event Lowering (EXSCEL). American heart journal; 2017; vol. 187; 1-9
Trial name / registration number	EXSCEL trial. ClinicalTrials.gov number, NCT01144338

59. Holman, 2017

Bibliographic Reference	Holman, Rury R.; Bethel, Angelyn M.; Mentz, Robert J.; Thompson, Vivian P.; Lokhnygina, Yuliya; Buse, John B.; Chan, Juliana C; Choi, Jasmine; Gustavson, Stephanie M.; Iqbal, Nayyar; Maggioni, Aldo P.; Marso, Steven P.; Ohman, Peter; Pagidipati, Neha J.; Poulter, Neil; Ramachandran, Ambady; Zinman, Bernard; Hernandez, Adrian F.; EXSCEL Study group; Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes.; The New England journal of medicine; 2017; vol. 377 (no. 13); 1228-1239

59.1. Study details

Secondary publication of another included study- see primary study for details	This is the primary study of the EXSCEL trial. The information for the data extraction from this trial is included in this record.
Other publications associated with this study included in review	Holman, R. R., Bethel, M. A., George, J., et al. (2016). Rationale and design of the EXenatide Study of Cardiovascular Event Lowering (EXSCEL) trial. American heart journal, 174, 103–110. Mentz, Robert J; Bethel, M Angelyn; Gustavson, Stephanie et al. (2017) Baseline characteristics of patients enrolled in the Exenatide Study of Cardiovascular Event Lowering (EXSCEL). American heart journal; 2017; vol. 187; 1-9
Trial name / registration number	EXSCEL trial. ClinicalTrials.gov number, NCT01144338
Study type	Randomised controlled trial (RCT)
Study location	35 countries: Argentina, Australia, Austria, Belgium, Brazil, Bulgaria, Canada, Chile, China, Colombia, Czech Republic, Germany, Hong Kong, Hungary, Israel, Italy, Latvia, Lithuania, Malaysia, Mexico, The Netherlands, New Zealand, Philippines, Poland, Republic of Korea, Romania, Russia, Slovakia, Spain, South Africa, Taiwan, Thailand, United Kingdom, USA
Study setting	687 sites - North and South America, Europe, Africa, Asia, and Australasia.
Study dates	Randomization from June 2010 through September 2015; planned date for closeout of follow-up was from December 5, 2016 to May 11, 2017.
Sources of funding	Amylin Pharmaceuticals

Inclusion criteria	Adults (aged 18 years and older) with type 2 diabetes (defined as a glycated haemoglobin level of 6.5 to 10.0% [48 to 86 mmol per mole]) with or without additional cardiovascular risk factors or previous cardiovascular events (history of major clinical manifestation of coronary artery disease, ischemic cerebrovascular disease, or atherosclerotic peripheral arterial disease). Patients needed to be able to see a usual care provider at least twice a year. Female patients needed to agree to use an effective methods or contraception or must not otherwise be at risk of becoming pregnant Patients were allowed to take up to three oral glucose lowering agents or to receive insulin, either alone or in combination with up to two oral glucose-lowering agents.
Exclusion criteria	Diagnosis of T1DM or history of ketoacidosis, history of (two or more episodes) of severe hypoglycaemia (defined as hypoglycaemia for which a patient received third-party assistance) within 12 months of enrolment, previous treatment with a GLP-1 receptor agonist, enrolment in another experimental protocol for investigational drug or device that would interfere with trial, planned or anticipated revascularization procedure, pregnancy or planned pregnancy during trial period, females who are breastfeeding, medical history indicating life expectancy of <2 years or might limit ability to take trial treatment for the length of trial, history or current indication of any condition, therapy, laboratory abnormality, or other circumstance that may lead to unacceptable risk to patient, confound trial results or lead to interference with patient's complete participation, end-stage renal disease estimated glomerular filtration rate (eGFR) at entry of less than 30 ml per minute per 1.73 m2 of body-surface area, known allergy or intolerance to exenatide, history of gastroparesis, personal or family history of medullary thyroid cancer or Multiple Endocrine Neoplasia Type 2 or calcitonin level of >40ng/L at baseline, previous randomisation in EXCSEL trial, history of pancreatitis, employee of Amylin Pharmaceuticals, LLC, Bristol-Myers Squibb Company, or AstraZeneca.
Recruitment / selection of participants	The trial was designed to include at enrollment approximately 70% with prior cardiovascular events and 30% without prior cardiovascular events.
Intervention(s)	Exenatide (Bydureon, GLP-1 [glucagon-like peptide-1] receptor agonist) 2 mg extended release once weekly self-administered subcutaneous injection. N = 7356 Concomitant therapy: Participants were able to take open-label glucose-lowering agents (including DPP-4 inhibitors but excluding GLP-1 receptor agonists) as part of their usual care based on local guidelines. Concomitant medication changes were allowed at any time point but usual care providers were asked not to promote this directly after randomization unless there were safety concerns.
Strata 1: People with type 2	People without heart failure Around 16% of people had a history of heart failure

diabetes mellitus and heart failure	
Strata 2: People with atherosclerotic cardiovascular disease	Mixed population Reported that 73.1% had previous CVD. Previous cardiovascular events were defined as a history of major clinical manifestation of coronary artery disease, ischemic cerebrovascular disease, or atherosclerotic peripheral arterial disease.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Excluded end-stage kidney disease or an estimated glomerular filtration rate (eGFR) at entry of less than 30 ml per minute per 1.73 m2 of body-surface area, unclear about other CKD. No information on CKD specifically in baseline characteristics, only eGFR categories.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	People at higher risk of developing cardiovascular disease Previous cardiovascular disease, mean age is higher, median BMI is above 30, some people were current smokers, some people were former smokers.
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 Presumed based on median age and duration of diabetes
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Mixed population Based on categories for BMI provided (though majority had a BMI >30)
Subgroup 5: eGFR category at baseline	eGFR ≥30mL/min/1.73m2
Subgroup 6: Albuminuria	Not stated/unclear

category at baseline	
Population subgroups	Subgroups reported for primary composite outcome of 3-point MACE including: race, type of glucose lowering therapy, history or no history of cardiovascular event, history or no history of heart failure, BMI and kidney function.
Comparator	Placebo N = 7396 2 mg (unloaded microspheres) once weekly self-administered subcutaneous injection. Concomitant therapy: Participants were able to take open-label glucose-lowering agents (including DPP-4 inhibitors but excluding GLP-1 receptor agonists) as part of their usual care based on local guidelines. Concomitant medication changes were allowed at any time point but usual care providers were asked not to promote this directly after randomization unless there were safety concerns.
Number of participants	14752
Duration of follow-up	3.2 years (median)
Indirectness	Intervention indirectness - 15% of people were not receiving any form of glucose lowering therapy before the study.
Method of analysis	ITT
Additional comments	Time-to-event analyses were performed with Cox proportional-hazards model for primary, secondary, and exploratory outcomes in the intention-to-treat population, stratified according to history of cardiovascular disease, with trial regimen as an explanatory variable. The Kaplan–Meier method was used to calculate event rates. Baseline characteristics were summarized as means and standard deviations, medians and interquartile ranges, or percentages. The primary composite outcome was analyzed in prespecified subgroups that were defined according to baseline characteristics, including race, type of glucose lowering therapy, history or no history of a cardiovascular event or heart failure, body-mass index, and kidney function. Repeated measures, such as body weight, were analyzed with the use of longitudinal models with mixed effects, with differences between the trial groups estimated by least squares mean differences with 95% confidence intervals.

59.2. Study arms

59.2.1. Exenatide (N = 7356)

Exenatide (Bydureon, GLP-1 [glucagon-like peptide-1] receptor agonist) 2 mg extended release once weekly self-administered subcutaneous injection. Concomitant therapy: Participants were able to take open-label glucose-lowering agents (including DPP-4 inhibitors but excluding GLP-1 receptor agonists) as part of their usual care based on local guidelines. Concomitant medication changes were allowed at any time point but usual care providers were asked not to promote this directly after randomization unless there were safety concerns.

59.2.2. Placebo (N = 7396)

Placebo 2 mg (unloaded microspheres) once weekly self-administered subcutaneous injection. Concomitant therapy: Participants were able to take open-label glucose-lowering agents (including DPP-4 inhibitors but excluding GLP-1 receptor agonists) as part of their usual care based on local guidelines. Concomitant medication changes were allowed at any time point but usual care providers were asked not to promote this directly after randomization unless there were safety concerns.

59.3. Characteristics

59.3.1. Arm-level characteristics

Characteristic	Exenatide (N = 7356)	Placebo (N = 7396)
% Male Sample size	n = 4562 ; % = 62	n = 4587 ; % = 62
Mean age (SD) (years) Median (IQR)	62 (56 to 68)	62 (56 to 68)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 5554 ; % = 75.5	n = 5621 ; % = 76
Black Sample size	n = 442 ; % = 6	n = 436 ; % = 5.9
Asian Sample size	n = 725 ; % = 9.9	n = 727 ; % = 9.8

Characteristic	Exenatide (N = 7356)	Placebo (N = 7396)
Indian (American) or Alaskan Native Sample size	n = 38 ; % = 0.5	n = 35 ; % = 0.5
Native Hawaiian or other Pacific Islander Sample size	n = 18 ; % = 0.2	n = 17 ; % = 0.2
Hispanic Sample size	n = 577 ; % = 7.8	n = 557 ; % = 7.5
Hispanic or Latino Sample size	n = 1506 ; % = 20.5	n = 1520 ; % = 20.6
Not hispanic or latino Sample size	n = 5849 ; % = 79.5	n = 5875 ; % = 79.4
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR
Prior cardiovascular event at randomisation Defined as history of major clinical manifestation of coronary artery disease, ischemic cerebrovascular disease, or atherosclerotic peripheral arterial disease. Sample size	n = 5394 ; % = 73.3	n = 5388 ; % = 49.6
History of coronary artery disease Sample size	n = 3898 ; % = 53	n = 3896 ; % = 52.7
History of cerebrovascular disease Two patients missing from Exenatide total N Sample size	n = 1233 ; % = 16.8	n = 1276 ; % = 17.3
History of peripheral arterial disease One patient missing from Exenatide total N Sample size	n = 1400 ; % = 19	n = 1400 ; % = 18.9
History of congestive heart failure One patient missing from Exenatide total N Sample size	n = 1161 ; % = 15.8	n = 1228 ; % = 16.6
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

Characteristic	Exenatide (N = 7356)	Placebo (N = 7396)
<5 years 26 missing from Exenatide total N; 28 missing from Placebo total N Sample size	n = 1032 ; % = 14.1	n = 980 ; % = 13.3
≥5 to <15 years 26 missing from Exenatide total N; 28 missing from Placebo total N Sample size	n = 3612 ; % = 49.3	n = 3654 ; % = 49.6
15 years or greater 26 missing from Exenatide total N; 28 missing from Placebo total N Sample size	n = 2687 ; % = 36.7	n = 2734 ; % = 37.1
HbA1c (%) Median (IQR)	8 (7.3 to 8.9)	8 (7.3 to 8.9)
Cardiovascular risk factors Sample size	n = NR ; % = NR	n = NR ; % = NR
Blood pressure Mean (SD)	NR (NR)	NR (NR)
Heart rate Mean (SD)	NR (NR)	NR (NR)
Smoking status Sample size	n = NA ; % = NA	n = NA ; % = NA
Current smoker Sample size	n = 864 ; % = 11.8	n = 857 ; % = 11.6
Former smoker Sample size	n = 2902 ; % = 39.5	n = 2889 ; % = 39.1
Never smoker Sample size	n = 3587 ; % = 48.8	n = 3646 ; % = 49.3
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Exenatide (N = 7356)	Placebo (N = 7396)
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR
Weight Mean (SD)	NR (NR)	NR (NR)
BMI (kg/m²) Median (IQR)	31.8 (28.2 to 36.2)	31.7 (28.2 to 36.1)
Number of people with obesity (kg/m²) defined as ≥30 kg/m2; 69 exenatide and 81 placebo patients missing from total N Sample size	n = 4628 ; % = 63.5	n = 4611 ; % = 63
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 Median (IQR)	76.6 (61.3 to 92)	76 (61 to 92)
Other antidiabetic medication used Sample size	n = 7249 ; % = 98.5	n = 7275 ; % = 98.4
Insulin Sample size	n = 1036 ; % = 14.1	n = 997 ; % = 13.5
Insulin plus 1 oral agent Sample size	n = 1742 ; % = 23.7	n = 1795 ; % = 24.3
Insulin plus 1 oral agent Sample size	n = 619 ; % = 8.4	n = 647 ; % = 8.7
Sulfonylurea Sample size	n = 2697 ; % = 36.7	n = 2704 ; % = 36.6
DPP-4 inhibitor Total	n = 1118 ; % = 15.2	n = 1085 ; % = 14.7

Characteristic	Exenatide (N = 7356)	Placebo (N = 7396)
Sample size		
DPP-4 inhibitor - Sitagliptin Sample size	n = 758 ; % = 10.3	n = 725 ; % = 9.8
DPP-4 inhibitor - Vildagliptin Sample size	n = 201 ; % = 2.7	n = 193 ; % = 2.6
DPP-4 inhibitor - Alogliptin Sample size	n = 0 ; % = 0	n = 3 ; % = 0.04
DPP-4 inhibitor - Saxagliptin Sample size	n = 106 ; % = 1.4	n = 101 ; % = 1.4
DPP-4 inhibitor - Linagliptin Sample size	n = 51 ; % = 0.7	n = 63 ; % = 0.9
SGLT-2 inhibitor (total) Sample size	n = 49 ; % = 1.2	n = 28 ; % = 0.7
SGLT-2 inhibitor - Dapagliflozin Sample size	n = 39 ; % = 0.9	n = 19 ; % = 0.4
SGLT-2 inhibitor - other Sample size	n = 10 ; % = 0.2	n = 9 ; % = 0.2
Thiazolidinedione Sample size	n = 292 ; % = 4	n = 287 ; % = 3.9
Biguanides Sample size	n = 5618 ; % = 76.4	n = 5677 ; % = 76.8
GLP - 1 agonist (other than study drug) Sample size	n = 0 ; % = 0	n = 2 ; % = 0.0002
GLP-1 receptor agonist (other than study drug) - Liraglutide Sample size	n = 0 ; % = 0	n = 2 ; % = 0.0002
Receiving mono-glucose lowering therapy Oral agents Sample size	n = 3070 ; % = 41.7	n = 3165 ; % = 42.8
Receiving dual-glucose lowering therapy Oral agents	n = 2469 ; % = 33.6	n = 2452 ; % = 33.2

Characteristic	Exenatide (N = 7356)	Placebo (N = 7396)
Sample size		
Receiving ≥3 glucose lowering therapies Oral agents Sample size	n = 674 ; % = 9.2	n = 661 ; % = 8.9
Pramlintide Sample size	n = 1 ; % = 0.0001	n = 2 ; % = 0.0002
Non -sulfonylurea secretagogues Sample size	n = 97 ; % = 1.3	n = 105 ; % = 1.4
Other antihyperglycemic agents Sample size	n = 25 ; % = 0.6	n = 33 ; % = 0.8
Blood pressure-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
ACE inhibitor Sample size	n = 3535 ; % = 48.1	n = 3647 ; % = 49.3
Angiotensin-receptor blockers Sample size	n = 2334 ; % = 31.7	n = 2272 ; % = 30.7
Diuretics - total Sample size	n = 3216 ; % = 43.7	n = 3227 ; % = 43.6
Diuretic - Thiazide Sample size	n = 1968 ; % = 26.8	n = 1932 ; % = 26.1
Beta-blockers Sample size	n = 4082 ; % = 55.5	n = 4129 ; % = 55.8
Aldosterone antagonist (e.g. spironolactone) Sample size	n = 456 ; % = 6.2	n = 456 ; % = 6.2
Hydralazine Sample size	n = 64 ; % = 0.9	n = 59 ; % = 0.8
Calcium channel blockers Sample size	n = 2380 ; % = 32.4	n = 2330 ; % = 31.5
Alpha 1 blockers Sample size	n = 560 ; % = 7.6	n = 529 ; % = 7.2

Characteristic	Exenatide (N = 7356)	Placebo (N = 7396)
Nitrates Sample size	n = 1003 ; % = 13.6	n = 972 ; % = 13.1
Renin inhibitor (e.g. aliskerin) Sample size	n = 34 ; % = 0.5	n = 37 ; % = 0.5
Other antihypertensive Sample size	n = 432 ; % = 5.9	n = 473 ; % = 6.4
Statins/lipid-lowering medication used Sample size	n = 5374 ; % = 77.9	n = 5636 ; % = 76.2
Statin Sample size	n = 5465 ; % = 74.3	n = 5380 ; % = 72.7
Ezetimibe Sample size	n = 347 ; % = 4.7	n = 364 ; % = 4.9
Fibrate Sample size	n = 650 ; % = 8.8	n = 641 ; % = 8.7
Niacin Sample size	n = 113 ; % = 1.5	n = 151 ; % = 2
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR
Ranolazine Sample size	n = 35 ; % = 0.5	n = 38 ; % = 0.5
Digoxin/digitalis glycoside Sample size	n = 173 ; % = 2.4	n = 184 ; % = 2.5
Aspirin Sample size	n = 4713 ; % = 64.1	n = 4667 ; % = 63.1
Low molecular weight heparin Sample size	n = 16 ; % = 0.2	n = 10 ; % = 0.1
Vitamin K antagonist (e.g. warfarin/coumarol) Sample size	n = 414 ; % = 5.6	n = 377 ; % = 5.1

Characteristic	Exenatide (N = 7356)	Placebo (N = 7396)
Direct thrombin inhibitors Sample size	n = 45 ; % = 0.6	n = 39 ; % = 0.5
Other anti-platelet agents Sample size	n = 261 ; % = 3.5	n = 303 ; % = 4.1
Clopidogrel/ticlopidine Sample size	n = 1255 ; % = 17.1	n = 1269 ; % = 17.2
Hormone replacement therapy Sample size	n = 300 ; % = 4.1	n = 258 ; % = 3.5
Chronic non-steroidal antiinflammatory drugs Sample size	n = 320 ; % = 4.4	n = 324 ; % = 4.4
Chronic COX2 inhibitors Sample size	n = 45 ; % = 0.6	n = 45 ; % = 0.6
Fish oil Sample size	n = 498 ; % = 6.8	n = 492 ; % = 6.7
Proton pump inhibitors Sample size	n = 1428 ; % = 19.4	n = 1427 ; % = 19.3
Factor Xa inhibitor Sample size	n = 35 ; % = 0.5	n = 49 ; % = 0.7

60. Home, 2015

Bibliographic Reference	Home, P. D.; Shamanna, P.; Stewart, M.; Yang, F.; Miller, M.; Perry, C.; Carr, M. C.; Efficacy and tolerability of albiglutide versus placebo or pioglitazone over 1year in people with type 2 diabetes currently taking metformin and glimepiride: HARMONY 5; Diabetes Obes Metab; 2015; vol. 17 (no. 2); 179-187

60.1. Study details

Trial name / registration number	NCT00839527
Study type	Randomised controlled trial (RCT)
Study location	234 centres in 9 countries (USA, Germany, Hong Kong, India, Peru, Philippines, Russia, Spain and the UK)
Study setting	No additional information
Study dates	NR
Sources of funding	sponsored by GlaxoSmithKline.
Inclusion criteria	Participants were≥18 years old with a historical diagnosis of T2DM and inadequate glycaemic control on their current regimen of metformin and a sulfonylurea. The metformin dose (≥1500 mg/day or maximum tolerated) was stable and the sulfonylurea dose was equivalent to ≥4 mg/day of glimepiride for ≥3 months before screening. Other inclusion criteria included a body mass index (BMI) from ≥20.0 to ≤45.0 kg/m2, glycated haemoglobin (HbA1c) 7.0–10.0% [mmol/mol=10.93 (%-unit – 2.15)] [8], fasting C-peptide ≥0.26 nmol/l, and creatinine clearance >60 ml/min (calculated using the Cockcroft–Gault formula).
Exclusion criteria	Exclusion criteria included a history of cancer (except non-melanoma skin cancers) not in remission for 3 years, treated diabetic gastroparesis, current symptomatic biliary disease, a history of pancreatitis, previous significant gastrointestinal surgery, or recent clinically significant cardiovascular disease. Biochemical exclusion criteria included defined more extreme abnormalities of liver function tests, circulating lipase and amylase and plasma triglycerides
Recruitment / selection of participants	No additional information
Intervention(s)	Pioglitazone (n=288) Patients received 30 mg/day oral pioglitazone for 156 weeks

Cointervention	Metformin: Patients maintained their current dose of metformin (>1500 mg/day) throughout the trial and the sulfonylurea dose was equivalent to ≥4 mg/day of glimepiride for ≥3 months before screening
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Excluded “recent clinically significant cardiovascular disease”, otherwise unclear. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Excluded “recent clinically significant cardiovascular disease”, otherwise unclear. Baseline characteristics only provides previous MI.
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	NR
Comparator	Placebo (n=116): Patients received oral placebo daily for 156 weeks Patients maintained their current dose of metformin (>1500 mg/day) throughout the trial and the sulfonylurea dose was equivalent to ≥4 mg/day of glimepiride for ≥3 months before screening
Number of participants	685
Duration of follow-up	156 weeks
Indirectness	No additional information
Method of analysis	Modified ITT

60.2. Study arms

60.2.1. Pioglitazone (N = 288)

Patients received 30 mg pioglitazone orally each day for 156 weeks

60.2.2. Placebo (N = 116)

Patients received a placebo orally each day for 156 weeks

60.3. Characteristics

60.3.1. Arm-level characteristics

Characteristic	Pioglitazone (N = 288)	Placebo (N = 116)
% Male Sample size	n = 148 ; % = 53.4	n = 70 ; % = 60.9
Mean age (SD) (Years (mean, SD)) Mean (SD)	55.7 (9.4)	55.7 (9.6)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Black Sample size	n = 24 ; % = 8.7	n = 10 ; % = 8.7
Asian Sample size	n = 39 ; % = 14.1	n = 15 ; % = 13
White Sample size	n = 203 ; % = 73.3	n = 80 ; % = 69.6
Other Sample size	n = 11 ; % = 4	n = 10 ; % = 8.7
Time since type 2 diabetes diagnosed (Years (mean, SD)) Mean (SD)	9.2 (6.1)	9.3 (6.1)
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability	NR (NR)	NR (NR)

Characteristic	Pioglitazone (N = 288)	Placebo (N = 116)
Mean (SD)		
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Metformin + Glimepiride Sample size	n = 288 ; % = 100	n = 116 ; % = 100
Blood pressure-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Statins/lipid-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR

61. Hong, 2012

Bibliographic Reference	Hong, E S; Khang, A R; Yoon, J W; Kang, S M; Choi, S H; Park, K S; Jang, H C; Shin, H; Walford, G A; Lim, S; Comparison between sitagliptin as add-on therapy to insulin and insulin dose-increase therapy in uncontrolled Korean type 2 diabetes: CSI study.; Diabetes, obesity & metabolism; 2012; vol. 14 (no. 9); 795-802

61.1. Study details

Trial name / registration number	NCT01100125
Study type	Randomised controlled trial (RCT)
Study location	Korea
Study setting	No additional information
Study dates	NR
Sources of funding	National Research Foundation grant funded by the Korean government and from a grant from the Seoul National University Bindang Hospital
Inclusion criteria	diagnosis of T2D; age 30–70; HbA1c 7.5–11.0%; fasting plasma glucose (FPG) <15 mmol/l (270 mg/dl) and BMI 18–35 kg/m2. The eligible patients also had to have received insulin injections for at least 3 months; at a dose of at least 10 U/day and for a minimum of 4 weeks prior to enrolment. Female patients had to be non-fertile or of childbearing potential using a medically approved birth control method.
Exclusion criteria	Patients with type 1 diabetes, gestational diabetes or diabetes with identifiable secondary causes, significant renal impairment (estimated creatinine clearance <50 ml/min) or elevated (>100) alanine or aspartate aminotransferase (ALT or AST). Patients who were taking medications, aside from antidiabetic medications, known to affect glycaemic control, such as glucocorticoids were also excluded
Intervention(s)	Sitagliptin (n=70) Patients received 100 mg daily sitaglptin
Cointervention	Insulin Subjects were asked to use the same formulation throughout the study
Strata 1: People with type 2 diabetes	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.

mellitus and 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 diabetes mellitus and chronic kidney disease	Not stated/unclear Excluded “significant renal impairment (estimated creatinine clearance < 50 ml/min)”, otherwise unclear. No information in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria	Not stated/unclear

category at baseline	
Population subgroups	No additional information
Comparator	Insulin (n=70) Subjects were guided to increase their daily insulin dose by ≥10% at random and by a further ≥10% at the 12-week follow-up, if their HbA1c was not within the target level (≤7.0%), depending on the frequency of insulin injection. For example, if 20 U of glargine insulin was used once a day, the subject was guided to increase the dose to ≥22 U at random and to ≥24 U at 12 weeks. If 20–10 U mixed insulin was used twice a day, the subject was guided to increase the dose to ≥22–11 U twice at random and to ≥24–12 U at 12 weeks. In addition to this 20% increase, subjects were allowed to adjust their insulin dose by 2 U every week, based on the self-monitoring of their blood glucose
Number of participants	140
Duration of follow-up	24 weeks
Indirectness	No additional information
Method of analysis	ACA
Additional comments	Efficacy analyses were based on the full analysis set population, consisting of all randomized subjects who received at least one dose of study medication and who had both a baseline and at least one follow-up measurement. Changes in parameters from the baseline values were evaluated using paired t-tests. Analysis of covariance (ancova) models with treatment as a classification variable and baseline measure as the covariate were used for all efficacy variables to test the primary and secondary endpoints. Missing data were imputed using the last-observation-carried-forward method.

61.2. Study arms

61.2.1. Sitagliptin (100 mg) (N = 70)

Patients received 100 mg sitagliptin daily for 24 weeks

61.2.2. Insulin (N = 70)

Patients received increased dose of insulin for 24 weeks

61.3. Characteristics

61.3.1. Arm-level characteristics

Characteristic	Sitagliptin (100 mg) (N = 70)	Insulin (N = 70)
% Male Sitagliptin n = 61, Insulin n = 63 Sample size	n = 33 ; % = 53.7	n = 32 ; % = 50.9
Mean age (SD) (Years (mean, SD)) Sitagliptin n = 61, Insulin n = 63 Mean (SD)	58.8 (14.3)	59.6 (13)
Ethnicity Sitagliptin n = 61, Insulin n = 63 Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed Sitagliptin n = 61, Insulin n = 63 Mean (SD)	NR (NR)	NR (NR)
Smoking status Sitagliptin n = 61, Insulin n = 63 Sample size	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Sitagliptin n = 61, Insulin n = 63 Mean (SD)	NR (NR)	NR (NR)
Presence of severe mental illness Sitagliptin n = 61, Insulin n = 63 Sample size	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sitagliptin n = 61, Insulin n = 63 Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sitagliptin n = 61, Insulin n = 63 Sample size	n = NR ; % = NR	n = NR ; % = NR
Number of people with obesity Sitagliptin n = 61, Insulin n = 63 Sample size	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Sitagliptin (100 mg) (N = 70)	Insulin (N = 70)
Other antidiabetic medication used Sitagliptin n = 61, Insulin n = 63 Sample size	n = NA ; % = NA	n = NA ; % = NA
Sulfonylurea Sample size	n = 15 ; % = 24.6	n = 15 ; % = 23.8
Glinides Sample size	n = 8 ; % = 13.1	n = 10 ; % = 15.9
Metformin Sample size	n = 28 ; % = 45.9	n = 26 ; % = 41.3
Thiazolidinedione Sample size	n = 4 ; % = 6.6	n = 2 ; % = 3.2
Alpha-glucosidase inhibitor Sample size	n = 19 ; % = 31.1	n = 27 ; % = 42.9
Blood pressure-lowering medication used Sitagliptin n = 61, Insulin n = 63 Sample size	n = NR ; % = NR	n = NR ; % = NR
Statins/lipid-lowering medication used Sitagliptin n = 61, Insulin n = 63 Sample size	n = NR ; % = NR	n = NR ; % = NR
Other treatment being received Sitagliptin n = 61, Insulin n = 63 Sample size	n = NR ; % = NR	n = NR ; % = NR

62. Hong, 2023

Bibliographic Reference	Hong, Jun Hwa; Moon, Jun Sung; Seong, Kayeon; Lim, Soo; Comparison of therapeutic efficacy and safety of sitagliptin, dapagliflozin, or lobeglitazone adjunct therapy in patients with type 2 diabetes mellitus inadequately controlled on sulfonylurea and metformin: Third agent study.; Diabetes research and clinical practice; 2023; vol. 203; 110872

62.1. 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	NCT02338921
Study type	Randomised controlled trial (RCT) Triple-blind, active-controlled, parallel-group RCT
Study location	Seongnam, Gyeonggi, South Korea
Study setting	Outpatient
Study dates	01/2015 to 12/2021
Sources of funding	Supported by grants from the Korean Diabetes Association (S.L., 2015F-7) and Seoul National University Bundang Hospital (14-2015-0014)
Inclusion criteria	• Adults ≥20 and <80 years diagnosed with type 2 diabetes • HbA1c≥7% after treatment with metformin (500-2550 mg daily) and a sulphonylurea (glimepiride: 1-8 mg daily; gliclazide 40-320 mg daily or 30-120 mg daily for sustained release form)
Exclusion criteria	• Type 1 diabetes diagnosis, gestational diabetes, or secondary diabetes due to pancreatitis or pancreatectomy • Taking drugs that affect glucose levels (e.g. glucocorticoids) • Severe liver disease

	• Renal impairment (eGFR<60 ml/min/1.73 m2) • Advanced heart failure (NYHA class 3 and 4)
Recruitment / selection of participants	Eligible participants randomised using computer-generated random number table. Insulin used as rescue therapy if HbA1c>10% at any study visit.
Intervention(s)	• Dapagliflozin 10 mg daily Oral dapagliflozin for 2 years in addition to metformin and a sulphonylurea.
Cointervention	• Metformin • Sulphonylurea All participants continued with metformin (500-2550 mg daily) and a sulphonylurea (glimepiride: 1-8 mg daily; gliclazide 40-320 mg daily or 30-120 mg daily for sustained release form) for duration of trial. Dose adjustments to these were permitted at physician's discretion.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Exclusion criteria: NYHA class 3 and 4 only
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 5: eGFR category at baseline	eGFR ≥30mL/min/1.73m2 Exclusion criteria: eGFR<60 mL/min/1.73 m2
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	
Comparator	• Sitagliptin 100 mg dail Oral sitagliptin for 2 years in addition to metformin and a sulphonylurea.
Number of participants	N=72 randomised (N=64 completers [N=25 in both dapagliflozin and sitagliptin arms, N=24 in lobeglitazone arm])
Duration of follow-up	24 months
Indirectness	None
Method of analysis	Modified ITT mITT analysis (all randomised participants treated with at least one dose study medication),
Additional comments	Outcome data for lobeglitazone arm has not been extracted because this was not an intervention of interest.

62.2. Study arms

62.2.1. Dapagliflozin 10 mg daily (N = 26)

Oral dapagliflozin 10 mg daily for 2 years, in addition to metformin and a sulphonylurea.

62.2.2. Sitagliptin 100 mg daily (N = 26)

Oral sitagliptin 100 mg daily for 2 years, in addition to metformin and a sulphonylurea.

62.2.3. Lobeglitazone 0.5 mg daily (N = 26)

Oral lobeglitazone 0.5 mg daily for 2 years, in addition to metformin and a sulphonylurea.

62.3. Characteristics

62.3.1. Arm-level characteristics

Characteristic	Dapagliflozin 10 mg daily (N = 26)	Sitagliptin 100 mg daily (N = 26)	Lobeglitazone 0.5 mg daily (N = 26)
% Male Sample size	n = 14 ; % = 53.8	n = 16 ; % = 61.5	n = 17 ; % = 65.4
Mean age (SD) (years) Mean (SD)	56.1 (10.9)	60.3 (8.6)	59.1 (8.9)
Ethnicity Nominal	NR	NR	NR
Comorbidities Nominal	NR	NR	NR
Presence of frailty Nominal	NR	NR	NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	13.5 (6.9)	12.4 (7.8)	11.5 (6.3)
Cardiovascular risk factors Nominal	NR	NR	NR
Smoking status Nominal	NR	NR	NR
Alcohol consumption Nominal	NR	NR	NR

Characteristic	Dapagliflozin 10 mg daily (N = 26)	Sitagliptin 100 mg daily (N = 26)	Lobeglitazone 0.5 mg daily (N = 26)
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 Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Metformin Sample size	n = 26 ; % = 100	n = 26 ; % = 100	n = 26 ; % = 100
Sulphonylurea Sample size	n = 26 ; % = 100	n = 26 ; % = 100	n = 26 ; % = 100
Blood pressure-lowering medication used Anti-hypertensive agents used at baseline Sample size	n = 16 ; % = 61.5	n = 14 ; % = 53.8	n = 12 ; % = 46.2
Statins/lipid-lowering medication used Statins used at baseline Sample size	n = 18 ; % = 69.2	n = 15 ; % = 57.7	n = 16 ; % = 61.5
Other treatment being received Nominal	NR	NR	NR

63. Husain, 2019

Bibliographic Reference	Husain, Mansoor; Birkenfeld Andreas, L; Donsmark, Morten; Dungan, Kathleen; Eliaschewitz Freddy, G; Franco Denise, R; Jeppesen Ole, K; Lingvay, Ildiko; Mosenzon, Ofri; Pedersen Sue, D; Tack Cees, J; Thomsen, Mette; Vilsboll, Tina; Warren Mark, L; Bain Stephen, C; PIONEER, 6; Investigators; Oral Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes.; The New England journal of medicine; 2019; vol. 381 (no. 9); 841-851

63.1. Study details

Secondary publication of another included study- see primary study for details	PIONEER-6 parent paper
Other publications associated with this study included in review	Bain, Stephen C, Mosenzon, Ofri, Arechavaleta, Rosario et al. (2019) Cardiovascular safety of oral semaglutide in patients with type 2 diabetes: Rationale, design and patient baseline characteristics for the PIONEER 6 trial. Diabetes, obesity & metabolism 21(3): 499-508
Trial name / registration number	PIONEER6- ClinicalTrials.gov number, NCT02692716
Study type	Randomised controlled trial (RCT)
Study location	21 countries - Africa, Asia, Europe, Latin America, North America and the Middle East.
Study setting	214 sites
Study dates	Patients were randomised to the different arms between January and August 2017; Last point of data collection/follow-up not specified
Sources of funding	Novo Nordisk
Inclusion criteria	People with type 2 diabetes; 50 years of age or older who had established cardiovascular disease or chronic kidney disease, or who were 60 years of age or older and had cardiovascular risk factors only.
Exclusion criteria	Treatment with any GLP-1 receptor agonist, dipeptidyl peptidase 4 inhibitor, or pramlintide within 90 days before screening; New York Heart Association class 4 heart failure; planned coronary-artery, carotid-artery, or peripheral-artery revascularization; myocardial infarction, stroke, or hospitalization for unstable angina or transient ischemic attack within 60

	days before screening; long-term or intermittent hemodialysis or peritoneal dialysis, or severe renal impairment (estimated glomerular filtration rate [GFR], <30 ml per minute per 1.73 m2 of body surface area); and proliferative retinopathy or maculopathy resulting in active treatment.
Recruitment / selection of participants	not specified; assumed all meeting inclusion criteria were selected.
Intervention(s)	Once-daily oral Semaglutide (target dose, 14 mg)
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Excluded "New York Heart Association class 4 heart failure". 12% of people had chronic heart failure class 2-3 at baseline
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Recruited patients at high cardiovascular risk (age of ≥50 years with established cardiovascular or chronic kidney disease, or age of ≥60 years with cardiovascular risk factors only) 84.7% of people were over the age of 50 with established cardiovascular or chronic kidney disease. 898 (28.2%) of these had CKD but overlap unclear to know the proportion with CVD.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Mixed population Recruited patients at high cardiovascular risk (age of ≥50 years with established cardiovascular or chronic kidney disease, or age of ≥60 years with cardiovascular risk factors only) 84.7% of people were over the age of 50 with established cardiovascular or chronic kidney disease. 898 (28.2%) of these had CKD.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	People at higher risk of developing cardiovascular disease inclusion of people with established cardiovascular disease or cardiovascular risk factors; but also inclusion of people with kidney disease, for which cardiovardiovascular risk was unknown.
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
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	established cardiovascular disease or chronic kidney disease vs people with cardiovascular risk factors only.
Comparator	Placebo
Number of participants	3183 patients were randomly assigned to oral semaglutide (1591 patients) or placebo (1592 patients)
Duration of follow-up	15.9 months (median)
Indirectness	No additional information.
Method of analysis	ITT Other A stratified Cox proportional hazards model was used for the primary analysis, with treatment group as a fixed factor, and stratification based on evidence of cardiovascular disease/advanced chronic kidney disease at screening.
Additional comments	A stratified Cox proportional hazards model was used for the primary analysis, with treatment group as a fixed factor, and stratification based on evidence of cardiovascular disease/advanced chronic kidney disease at screening

63.2. Study arms

63.2.1. Semaglutide (N = 1591)

14 mg orally once daily (target dose) in addition to standard of care treatment

63.2.2. Placebo (N = 1592)

in addition to standard of care treatment

63.3. Characteristics

63.3.1. Arm-level characteristics

Characteristic	Semaglutide (N = 1591)	Placebo (N = 1592)
% Male Sample size	n = 1084 ; % = 68.1	n = 1092 ; % = 68.6
Mean age (SD) (years) Mean (SD)	66 (7)	66 (7)
Ethnicity Race Sample size	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 1148 ; % = 72.2	n = 1152 ; % = 72.4
Black or African American Sample size	n = 89 ; % = 5.6	n = 103 ; % = 6.5
Asian Sample size	n = 324 ; % = 20.4	n = 306 ; % = 19.2
Other Sample size	n = 30 ; % = 1.9	n = 31 ; % = 1.9
Comorbidities Sample size	n = NA ; % = NA	n = NA ; % = NA
Prior myocardial infarction Sample size	n = 561 ; % = 35.3	n = 589 ; % = 37

Characteristic	Semaglutide (N = 1591)	Placebo (N = 1592)
Prior stroke or transient ischaemic attack Sample size	n = 242 ; % = 15.2	n = 263 ; % = 16.5
Prior coronary, carotid, or peripheral arterial revascularisation Sample size	n = 733 ; % = 46.1	n = 768 ; % = 48.2
>50% stenosis on angiography/imaging of coronary, carotid/lower extremity arteries Sample size	n = 427 ; % = 26.8	n = 453 ; % = 28.5
History of symptomatic coronary heart disease Sample size	n = 356 ; % = 22.4	n = 375 ; % = 23.6
Asymptomatic cardiac ischemia Sample size	n = 97 ; % = 6.1	n = 92 ; % = 5.8
Chronic heart failure NYHA class 2–3 Sample size	n = 188 ; % = 11.8	n = 200 ; % = 12.6
Moderate renal impairment Sample size	n = 463 ; % = 29.1	n = 435 ; % = 27.3
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	14.7 (8.5)	15.1 (8.5)
HbA1c (%) Mean (SD)	8.2 (1.6)	8.2 (1.6)
Cardiovascular risk factors Age ≥50 yr and established CVD or chronic kidney disease Sample size	n = 1350 ; % = 84.9	n = 1345 ; % = 84.5
Blood pressure (mmHg) Mean (SD)	NA (NA)	NA (NA)
Systolic blood pressure Mean (SD)	135 (18)	136 (18)

Characteristic	Semaglutide (N = 1591)	Placebo (N = 1592)
Diastolic blood pressure Mean (SD)	76 (10)	76 (10)
Heart rate Mean (SD)	NR (NR)	NR (NR)
Smoking status Current smokers Sample size	n = 184 ; % = 11.6	n = 165 ; % = 10.4
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR
Weight (kg) Mean (SD)	91 (21.4)	90.8 (21)
BMI (kg/m2) Mean (SD)	32.3 (6.6)	32.3 (6.4)
Number of people with obesity BMI >30kg/m2 (does not provide ethnicity adjusted values) Sample size	n = 940 ; % = 59.1	n = 963 ; % = 60.5
Cholesterol and lipid levels (mg/dL) Coefficient of variation	NA	NA
Cholesterol and lipid levels (mg/dL) Mean (SD)	NA (NA)	NA (NA)
LDL cholesterol Geometric mean (CoV %) Coefficient of variation	45	41

Characteristic	Semaglutide (N = 1591)	Placebo (N = 1592)
LDL cholesterol Geometric mean (CoV %) Mean (SD)	77 (NA)	79 (NA)
Albumin creatinine ratio Mean (SD)	NR (NR)	NR (NR)
eGFR mL/min/1.73m2 Sample size	n = NA ; % = NA	n = NA ; % = NA
eGFR mL/min/1.73m2 Mean (SD)	74 (21)	74 (21)
>60 mL/min/1.73m2 Sample size	n = 1150 ; % = 72.3	n = 1158 ; % = 72.7
>60 mL/min/1.73m2 Mean (SD)	NA (NA)	NA (NA)
<60 mL/min/1.73m2 Sample size	n = 434 ; % = 27.3	n = 422 ; % = 26.5
<60 mL/min/1.73m2 Mean (SD)	NA (NA)	NA (NA)
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Biguanides Sample size	n = 1221 ; % = 76.7	n = 1242 ; % = 78
Insulins Sample size	n = 968 ; % = 60.8	n = 962 ; % = 60.4
Sulfonylureas Sample size	n = 517 ; % = 32.5	n = 510 ; % = 32
SGLT2 inhibitors Sample size	n = 165 ; % = 10.4	n = 140 ; % = 8.8
Thiazolidinediones Sample size	n = 65 ; % = 4.1	n = 53 ; % = 3.3

Characteristic	Semaglutide (N = 1591)	Placebo (N = 1592)
Alpha glucosidase inhibitors Sample size	n = 36 ; % = 2.3	n = 43 ; % = 2.7
DPP4 inhibitors Sample size	n = 2 ; % = 0.1	n = 0 ; % = 0
GLP-1 analogues Sample size	n = 1 ; % = 0.1	n = 0 ; % = 0
Other Sample size	n = 26 ; % = 1.6	n = 26 ; % = 1.6
Blood pressure-lowering medication used Sample size	n = 1495 ; % = 94	n = 1493 ; % = 93.8
Statins/lipid-lowering medication used Sample size	n = 1336 ; % = 84	n = 1376 ; % = 86.4
Other treatment being received Sample size	n = NA ; % = NA	n = NA ; % = NA
Antithrombotic/antiplatelet medication Sample size	n = 1248 ; % = 78.4	n = 1279 ; % = 80.3
Diuretics Sample size	n = 621 ; % = 39	n = 640 ; % = 40.2
Cardiovascular risk factors Age ≥60 yr and cardiovascular risk factors only Sample size	n = 241 ; % = 15.1	n = 247 ; % = 15.5

64. Iacobellis, 2020

Bibliographic Reference	Iacobellis, G.; Gra-Menendez, S.; Effects of dapagliflozin on epicardial fat thickness in patients with type 2 diabetes and obesity; Obesity; 2020; vol. 28 (no. 6); 1068-1074

64.1. 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	NCT02235298
Study type	Randomised controlled trial (RCT)
Study location	US - report states that participants were screened at the University of Miami
Study setting	NR
Study dates	Participants were screened between May 2017 and May 2019
Sources of funding	AstraZeneca
Inclusion criteria	• T2DM • HbA1c ≤ 8 % measured at least 1 month prior to the study • BMI ≥ 27 kg/m2 • Prior treatment with metformin only • Aged ≥ 18 and ≤ 65 years • Normal and stable hemodynamic status
Exclusion criteria	• Type 1 diabetes • Current use of insulin, other SGLT2is, GLP-1A dipeptidyl peptidase 4 inhibitors, pramlintide, sulfonylureas, or thiazolidinediones • History of diabetic ketoacidosis • History of diabetic macrovascular or microvascular complications

	• Known contraindications to dapagliflozin, such as glomerular filtration rate < 60 mL/min/1.73 m2 • Signs or symptoms of hypovolemia • Patients with active bladder cancer or with a prior history of bladder cancer • Acute or chronic infective diseases, including genital mycotic infections • Clinical signs or symptoms of New York Heart Association class III to IV HF • History, symptoms, or signs of coronary artery disease (CAD) • Clinical or laboratory evidence of chronic active liver diseases • Cancer or chemotherapy • Current use of systemic corticosteroids or use in the 3 months prior to this study • Known or suspected allergy to dapagliflozin, excipients, or related products • Patients who were pregnant, who were breastfeeding, or who had the intention of becoming pregnant • Female patients of childbearing potential who were not using adequate contraceptive methods • Patients with poor glycaemic control (HbA1c level > 8%) were excluded to maximize long term patient retention.
Recruitment / selection of participants	Patients were screened among those routinely referred to the Division of Endocrinology, Diabetes, and Metabolism outpatient clinic at the University of Miami.
Intervention(s)	Dapagliflozin was administered with a starting dose of 5 mg daily (for the first 4 weeks) and subsequent increments to 10 mg daily.
Cointervention	• The metformin regimen was continued. • Metformin was started from a dosage of 500 mg twice daily to a maximum of 1,000 mg twice daily • Patients received full training and titration instructions by a registered nurse • Both groups received lifestyle and diabetes education as part of the standard care. Patients in both groups were advised to continue with their usual dietary habits and physical activity.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Excluded “clinical signs or symptoms of New York Heart Association class III to IV HF”, otherwise unclear. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Excluded “history of diabetic macrovascular or microvascular complications; history, symptoms, or signs of coronary artery disease (CAD)”, otherwise unclear. No information in baseline characteristics.

Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Excluded “glomerular filtration rate < 60 mL/min/1.73 m2”, otherwise unclear. No information in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear Inclusion criteria: "BMI ≥ 27 kg/m2"
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	NR
Comparator	Placebo + metformin - Metformin was started from a dosage of 500 mg twice daily to a maximum of 1,000 mg twice daily

Number of participants	500 participants were assessed for eligibility and 100 participants were randomised. Out of 50 participants who were allocated to the dapagliflozin arm, 42 participants completed (84%). Out of 50 participants allocated to the placebo arm, 42 participants completed (84%).
Duration of follow-up	12 and 24 weeks
Indirectness	Directly applicable
Method of analysis	ITT Missing data of patients who were lost to follow-up were handled with multiple imputation (MI) by using the Markov chain Monte Carlo method. Other A "completer analysis" was reported, however, it wasn't clear whether this included all participants with data at week 24, or whether this only includes participants who adhered to the intervention.
Additional comments	Power calculations were based on the outcome of epicardial fat thickness.

64.2. Study arms

64.2.1. Dapagliflozin (N = 50)

64.2.2. Placebo (N = 50)

64.3. Characteristics

64.3.1. Arm-level characteristics

Characteristic	Dapagliflozin (N = 50)	Placebo (N = 50)
% Male Sample size	n = 21 ; % = 42	n = 20 ; % = 40
Mean age (SD) Mean (SD)	52 (9)	51 (11)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Dapagliflozin (N = 50)	Placebo (N = 50)
White Sample size	n = 20 ; % = 40	n = 21 ; % = 42
Hispanic Sample size	n = 25 ; % = 50	n = 22 ; % = 44
African Amercian Sample size	n = 5 ; % = 10	n = 7 ; % = 14
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed Nominal	NR	NR
Cardiovascular risk factors Nominal	NR	NR
Smoking status Nominal	NR	NR
Alcohol consumption Nominal	NR	NR
Presence of severe mental illness Nominal	NR	NR
People with significant cognitive impairment Nominal	NR	NR
People with a learning disability Nominal	NR	NR
Number of people with obesity Nominal	NR	NR
Other antidiabetic medication used Metformin Sample size	n = 50 ; % = 100	n = 50 ; % = 100
Blood pressure-lowering medication used	NR	NR

Characteristic	Dapagliflozin (N = 50)	Placebo (N = 50)
Nominal		
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

65. Iacobellis, 2017

Bibliographic Reference	Iacobellis, G.; Mohseni, M.; Bianco, S. D.; Banga, P. K.; Liraglutide causes large and rapid epicardial fat reduction; Obesity; 2017; vol. 25 (no. 2); 311-316

65.1. 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	NCT02014740
Study location	US - Report describes that screening occurred at the University of Miami
Study setting	Report describes that participants attended clinic visits
Study dates	Screening took place between January 2014 and January 2016
Sources of funding	Novo Nordisk
Inclusion criteria	• Type 2 diabetes • HbA1c ≤8% measured at least 1 month before the study • BMI ≥27 kg/m2, prior treatment with metformin only • Aged ≥18 and ≤65 years
Exclusion criteria	• Type 1 diabetes • Current use of insulin, other GLP-1 receptor agonists, dipeptidyl peptidase (DPP)-4 inhibitors, pramlintide, sulfonylureas, thiazolidinediones • History of diabetic ketoacidosis • History of diabetic macro- or microvascular complications • Known contraindications to liraglutide, such as previous history of pancreatitis or medullary thyroid carcinoma, personal or family history of multiple endocrine neoplasia type 2, renal or liver or heart

	failure, acute or chronic infective diseases, cancer or chemotherapy • Current use of systemic corticosteroids or in the 3 months prior to this study • Known or suspected allergy to liraglutide, excipients, or related products, • Pregnant, breast-feeding, or the intention of becoming pregnant
Recruitment / selection of participants	Patients were screened from those routinely referred to the Division of Endocrinology, Diabetes and Metabolism outpatient clinic at the University of Miami. Approximately 500 patients were screened.
Intervention(s)	Liraglutide up to 1.8 mg subcutaneous once daily. Starting dose was 0.6 mg for at least one week, with subsequent increments to 1.2 mg and to 1.8 mg (after at least 1 week on 1.2 mg). The liraglutide group participants had to achieve the final dose of 1.8 mg by at least 3 weeks from the starting dose. Participants who were unable to tolerate a dose of 1.8 mg were advised to lower the dose to 1.2 mg. Participants received full training and titration instructions from a registered nurse.
Cointervention	• The metformin regimen was continued. • Both groups received lifestyle and diabetes education • Patients in both groups were advised to continue with their usual dietary habits and physical activity
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Excluded heart failure
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Excluded “history of diabetic macro- or microvascular complications”, otherwise unclear. No patient had history or signs or symptoms of coronary artery disease (other criteria in protocol unclear)
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Excluded “renal failure”, otherwise unclear. 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 Inclusion criteria included "BMI≥27 kg/m2" and mean BMI was 37.8 (SD 7.3)
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	NA
Comparator	The metformin group was treated with metformin monotherapy for the duration of the study at the dosage from 500 mg twice daily to a maximum of 1,000 mg twice daily.
Number of participants	500 participants were screened to assess eligibility, and 95 participants were randomised. 54 participants were allocated to liraglutide on metformin, and 41 participants were randomised to remain on metformin monotherapy. In the liraglutide + metformin group, 6 participants were lost to follow-up, and 1 participant discontinued the intervention, meaning that 49 participants were analysed (90.7%). In the metformin monotherapy group, 4 participants were lost to follow-up and 1 discontinued intervention, meaning that 36 participants were analysed (87.8%).
Duration of follow-up	3 and 6 months
Indirectness	Directly applicable

Method of analysis	Not stated/unclear Although not stated, it appears that an available case analysis has been used, as the number of participants in the number of analysed participants matches the number of participants allocated to treatment minus those who were lost to follow-up or discontinued the intervention.
Additional comments	Power analyses were calculated based on change in the outcome of epicardial adipose tissue (EAT).

65.2. Study arms

65.2.1. Liraglutide (N = 54)

65.2.2. Control (N = 41)

65.3. Characteristics

65.3.1. Arm-level characteristics

Characteristic	Liraglutide (N = 54)	Control (N = 41)
% Male Sample size	n = 23 ; % = 41	n = 15 ; % = 37
Mean age (SD) Mean (SD)	50 (10)	52 (10)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 19 ; % = 35	n = 14 ; % = 27
Hispanic Sample size	n = 21 ; % = 39	n = 17 ; % = 41
Afro-American Sample size	n = 14 ; % = 26	n = 10 ; % = 24
Comorbidities Nominal	NR	NR

Characteristic	Liraglutide (N = 54)	Control (N = 41)
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed Mean (SD)	3.7 (3.4)	3.6 (3.5)
Cardiovascular risk factors Nominal	NR	NR
Smoking status Nominal	NR	NR
Alcohol consumption Nominal	NR	NR
Presence of severe mental illness Nominal	NR	NR
People with significant cognitive impairment Nominal	NR	NR
People with a learning disability Nominal	NR	NR
Number of people with obesity Nominal	NR	*empty data*
Other antidiabetic medication used Metformin Sample size	n = 54 ; % = 100	n = 41 ; % = 100
Blood pressure-lowering medication used Nominal	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

66. Iijima, 2023

Bibliographic Reference	Iijima, Takahiro; Shibuya, Makoto; Ito, Yuzuru; Terauchi, Yasuo; Effects of switching from liraglutide to semaglutide or dulaglutide in patients with type 2 diabetes: A randomized controlled trial.; Journal of diabetes investigation; 2023; vol. 14 (no. 6); 774-781

66.1. Study details

Trial name / registration number	UMIN000040044
Study location	Yokosuka Kyosai Hospital in Japan
Study setting	No additional information
Study dates	NR
Sources of funding	NR
Inclusion criteria	(i) patients who were older than 20 years at the time of registration (regardless of sex), (ii) patients diagnosed with type 2 diabetes, (iii) patients being treated with liraglutide (0.6 or 0.9 mg), (iv) patients who had not been treated with a new diabetes drug for more than 3 months, and (v) patients who agreed to participate in this study.
Exclusion criteria	(i) patients with severe liver damage (up to three times the upper limit of the normal levels of aspartate transaminase (AST) and alanine transaminase (ALT) recorded within 28 days before enrollment); (ii) patients with severe congestive heart failure and acute heart failure; (iii) patients being treated with steroids; (iv) patients with a history of diabetic ketoacidosis or diabetic coma within the past 6 months; (v) patients with cancer currently undergoing treatment; (vi) patients who received surgery and had a severe infectious disease along with severe trauma before and after surgery; (vii) patients with contraindications or allergic reactions to the study drugs; (viii) patients who were pregnant, possibly pregnant, or lactating during the treatment period; (ix) patients who had participated in a clinical trial concurrently within 3 months before inclusion in this study; and (x) patients who were deemed to be inappropriate for inclusion in the study at the discretion of the doctor.
Recruitment / selection of participants	Patient were recruited from September 2020 to March 2022
Intervention(s)	Semaglutide (n=16) Patients received 0.25 mg of semaglutide for 4 weeks, followed by 0.5 mg using a dedicated single-use pen injector with a fixed injection for 26 weeks

Cointervention	NA
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
Comparator	Dulaglutide (n=16) Patients received 0.75mg dulaglutide for 26 weeks
Number of participants	32
Duration of follow-up	26 weeks
Indirectness	NA
Method of analysis	ITT
Additional comments	Little details on analysis but appears to be iTT

66.2. Study arms

66.2.1. Semaglutide (N = 16)

Patients received 0.25 mg of semaglutide for 4 weeks, followed by 0.5 mg using a dedicated single-use pen injector with a fixed injection for 26 weeks

66.2.2. Dulaglutide (N = 16)

Patients received 0.75mg dulaglutide for 26 weeks

66.3. Characteristics

66.3.1. Arm-level characteristics

Characteristic	Semaglutide (N = 16)	Dulaglutide (N = 16)
% Male Sample size	n = 11 ; % = 68.8	n = 15 ; % = 93.8
Mean age (SD) (Years (mean, SD)) Mean (SD)	61.5 (11.2)	62.7 (12)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed (Years (mean, SD)) Mean (SD)	12.3 (11.2)	13.4 (10.6)
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Prior Liraglutide Use Sample size	n = 16 ; % = 100	n = 16 ; % = 100
Metformin Sample size	n = 13 ; % = 81.25	n = 11 ; % = 68.75
Metformin + SGLT2 inhibitor Sample size	n = 0 ; % = 0	n = 2 ; % = 12.5

Characteristic	Semaglutide (N = 16)	Dulaglutide (N = 16)
Insulin degludec + Metfromin + SGLT2 Sample size	n = 1 ; % = 6.25	n = 0 ; % = 0
Insuln glargine Sample size	n = 0 ; % = 0	n = 1 ; % = 6.25
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

67. Ikonomidis, 2020

Bibliographic Reference	Ikonomidis, I.; Pavlidis, G.; Thymis, J.; Birba, D.; Kalogeris, A.; Kousathana, F.; Kountouri, A.; Balampanis, K.; Parissis, J.; Andreadou, I.; Katogiannis, K.; Dimitriadis, G.; Bamias, A.; Iliodromitis, E.; Lambadiari, V.; Effects of Glucagon-Like Peptide-1 Receptor Agonists, Sodium-Glucose Cotransporter-2 Inhibitors, and Their Combination on Endothelial Glycocalyx, Arterial Function, and Myocardial Work Index in Patients With Type 2 Diabetes Mellitus After 12-Month Treatment; Journal of the American Heart Association; 2020; vol. 9 (no. 9); e015716

67.1. 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	NCT03878706
Study type	Randomised controlled trial (RCT)
Study location	Study reports that recruitments was conducted at Attikon Hospital in Athens, Greece
Study setting	Report states that participants were recruited from the Cardiometabolic outpatient clinic of Attikon hospital outpatient clinic, however, it wasn't clear where the study took place.
Study dates	NR
Sources of funding	Report states there were no sources of funding
Inclusion criteria	Subjects with T2D who were at high or very high cardiovascular risk. High cardiovascular risk patients were considered all subjects with T2DM and a calculated systematic coronary risk estimation =5% and <10%, whereas very high cardiovascular risk patients were considered subjects with T2DM and target organ damage or with a major risk factor, such as smoking,

	marked hypercholesterolemia, or marked hypertension (a calculated systematic coronary risk estimation =10%).
Exclusion criteria	• Malignancies • Chronic inflammatory disease • Chronic kidney disease (estimated glomerular filtration rate <60 mL/min per 1.73 m2 for a period of at least 90 days) • Liver failure • Peripheral vascular disease • Retinopathy
Recruitment / selection of participants	Patients were recruited from the Cardiometabolic outpatient clinic of Attikon hospital outpatient clinic
Intervention(s)	Basal insulin dose between 10 and 50 IU. Basal insulin was titrated according to the American Diabetes Association and the European Association for the Study of Diabetes to reach fasting glucose target without hypoglycaemia. Liraglutide 1.8 mg once daily as a subcutaneous injection with a weekly dose escalation as instructed by the Summary of Product Characteristics Empagliflozin 25 mg once daily orally Combination of liraglutide and empagliflozin therapies
Cointervention	Metformin
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear LVEF <55% was 46%. Otherwise unclear.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Recruited people at high cardiovascular risk (a calculated systematic coronary risk estimation ≥5% and <10%) or very high cardiovascular risk (target organ damage or with a major risk factor, such as smoking, marked hypercholesterolemia, or marked hypertension (a calculated systematic coronary risk estimation ≥10%)). Excluded PAD. Baseline characteristics show 34% had CAD, but history of stroke unclear.
Strata 3: People with type 2	People without chronic kidney disease

diabetes mellitus and chronic kidney disease	Excluded CKD as classified by study (estimated glomerular filtration rate <60 mL/min per 1.73 m2 for a period of at least 90 days)
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	People at higher risk of developing cardiovascular disease Report states that "patients were at high or very high cardiovascular risk" and "high cardiovascular risk patients were considered all subjects with T2DM and a calculated systematic coronary risk estimation =5% and <10%, whereas very high cardiovascular risk patients were considered subjects with T2DM and target organ damage or with a major risk fac tor, such as smoking, marked hypercholesterolemia, or marked hypertension (a calculated systematic coronary risk estimation =10%)
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear

Population subgroups	NA
Comparator	NA
Number of participants	180 participants were included with 40 participants randomised to each arm. 20 participants did not complete the study (insulin = 5, liraglutide = 5, empagliflozin = 5, combination = 5)
Duration of follow-up	4 and 12 months
Indirectness	Directly applicable
Method of analysis	ITT All analyses were intention to treat. ANOVA (general linear model) for repeated measurements was applied (1) for measurements of the examined markers at baseline and 4 and 12 months after treatment used as a within-subject factor and (2) for the effects of treatment, as a between-subject factor (insulin, GLP-1RA, SGLT-2i, and combination GLP-1RA and SGLT-2i).
Additional comments	NA

67.2. Study arms

67.2.1. Insulin (N = 40)

67.2.2. Liraglutide (N = 40)

67.2.3. Empagliflozin (N = 40)

67.2.4. Liraglutide + Empagliflozin (N = 40)

67.3. Characteristics

67.3.1. Arm-level characteristics

Characteristic	Insulin (N = 40)	Liraglutide (N = 40)	Empagliflozin (N = 40)	Liraglutide + Empagliflozin (N = 40)
% Male Sample size	n = 28 ; % = 70	n = 27 ; % = 67.5	n = 30 ; % = 75	n = 30 ; % = 75
Mean age (SD) Mean (SD)	57 (10)	57 (9)	58 (10)	58 (9)
Ethnicity Nominal	NR	NR	NR	NR
Comorbidities Coronary artery disease Sample size	n = 14 ; % = 35	n = 13 ; % = 32.5	n = 13 ; % = 32.5	n = 14 ; % = 35
Presence of frailty Nominal	NR	NR	NR	NR
Time since type 2 diabetes diagnosed Median (IQR)	6.7 (1 to 9)	5.9 (1 to 8)	6.6 (1 to 11)	6.8 (2 to 12)
Cardiovascular risk factors Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Hypertension Sample size	n = 24 ; % = 60	n = 24 ; % = 60	n = 24 ; % = 60	n = 25 ; % = 62.5
Dyslipaemia Sample size	n = 40 ; % = 100	n = 40 ; % = 100	n = 40 ; % = 100	n = 40 ; % = 100
Family history of CAD Sample size	n = 12 ; % = 30	n = 11 ; % = 27.5	n = 15 ; % = 37.5	n = 13 ; % = 32.5
Smoking status Sample size	n = 15 ; % = 37.5	n = 17 ; % = 42.5	n = 16 ; % = 40	n = 16 ; % = 40
Alcohol consumption Nominal	NR	NR	NR	NR

Characteristic	Insulin (N = 40)	Liraglutide (N = 40)	Empagliflozin (N = 40)	Liraglutide + Empagliflozin (N = 40)
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 Metformin Sample size	n = 29 ; % = 72.5	n = 25 ; % = 62.5	n = 27 ; % = 67.5	n = 28 ; % = 70
Blood pressure-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Beta-blockers Sample size	n = 18 ; % = 45	n = 19 ; % = 47.5	n = 21 ; % = 52.5	n = 20 ; % = 50
Calcium-channel blockers Sample size	n = 10 ; % = 25	n = 9 ; % = 22.5	n = 10 ; % = 25	n = 20 ; % = 50
ACEI or ARB Sample size	n = 20 ; % = 50	n = 19 ; % = 47.5	n = 21 ; % = 52.5	n = 20 ; % = 50
Diuretics Sample size	n = 6 ; % = 15	n = 5 ; % = 12.5	n = 8 ; % = 20	n = 9 ; % = 22.5
Aldosterone antagonists Sample size	n = 1 ; % = 2.5	n = 2 ; % = 5	n = 1 ; % = 2.5	n = 3 ; % = 7.5

Characteristic	Insulin (N = 40)	Liraglutide (N = 40)	Empagliflozin (N = 40)	Liraglutide + Empagliflozin (N = 40)
Statins/lipid-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Statins Sample size	n = 40 ; % = 100	n = 40 ; % = 100	n = 40 ; % = 100	n = 40 ; % = 100
Fibrates Sample size	n = 2 ; % = 5	n = 2 ; % = 5	n = 3 ; % = 7.5	n = 3 ; % = 7.5
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Antiplatelet medications Sample size	% = 35	n = 13 ; % = 32.5	n = 15 ; % = 37.5	n = 15 ; % = 37.5

68. Inagaki, 2012

Bibliographic Reference	Inagaki, N.; Atsumi, Y.; Oura, T.; Saito, H.; Imaoka, T.; Efficacy and safety profile of exenatide once weekly compared with insulin once daily in Japanese patients with type 2 diabetes treated with oral antidiabetes drug(s): results from a 26-week, randomized, open-label, parallel-group, multicenter, noninferiority study; Clin Ther; 2012; vol. 34 (no. 9); 1892-908

68.1. Study details

Trial name / registration number	NCT00935532
Study type	Randomised controlled trial (RCT)
Study location	Japan
Study setting	No additional information
Study dates	NR
Sources of funding	Eli Lilly and Company and Amylin Pharmaceuticals Inc. Three authors are employees of Eli Lilly, two others have have received funding or honoraria from multiple pharmaceutical companies
Inclusion criteria	Eligible patients were aged ≥20 years with a diagnosis of type 2 diabetes mellitus based on the disease diagnostic criteria described by the WHO. Patients were required to have insufficient glucose control at screening (for patients not receiving an SU, HbA1c between 7.1% and 11.0%,; for patients receiving an SU, HbA1c between 7.1% and 10.0%), BMI >18 kg/m2 and <35 kg/m2 , inclusive; and a history of stable weight (not varying by >5% for at least 90 days before screening). Patients were to have been treated with a stable dose regimen of BG alone, BG + TZD, BG + SU, or BG + TZD + SU for 90 days before screening; the stable dose must have been within the dose range from the minimum maintenance dose to the maximum approved dose. Patients receiving an SU had to discontinue SU treatment from week -2. Patients treated with BG alone or BG + TZD plus α-glucosidase inhibitors or rapid-acting insulin secretagogues at the same dose for 90 days could be included in the study but were required to discontinue the -glucosidase inhibitors or rapid-acting insulin secretagogues from week -2. Female patients of child-bearing potential were required to have a negative serum pregnancy test result at screening and agree to use a reliable method of birth control during the study.
Exclusion criteria	Exclusion criteria included FSG >250 mg/dL or occasional serum glucose >350 mg/dL at screening, >2 episodes of hypoglycaemia requiring another person's support within 180 days before screening, and treatment for >2 consecutive weeks with insulin, dipeptidyl peptidase -4 inhibitors, or GLP-1 analogues within 90 days before screening.

Recruitment / selection of participants	No additional information
Intervention(s)	Exenatide (n=215) 2mg Exenatide administered by self subcutaneous injection for 26 weeks.
Cointervention	Biguanide or biguanide + thiazolidine derivative at the pre-study 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 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	Not stated/unclear

fatty liver disease	
Subgroup 4: People with obesity	Mixed population ~59% have BMI>=25 kg/m2 (obesity definition in Japan)
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	No additional information
Comparator	Insulin glargine (n=212) Patients in the insulin glargine treatment group received insulin glargine, given once daily (before bedtime) by subcutaneous injection. Both treatments were self-injected, and patients in the exenatide QW treatment group were provided training on how to prepare and inject exenatide. The dose of insulin glargine was started at 4 U and adjusted to achieve a target fasting blood glucose level of 100 mg/dL. Insulin glargine was not administered the day before the week 26 study visit to avoid an increased risk of hypoglycemia at switching to exenatide QW. All patients continued their OAD treatment of BG or BG TZD, at the pre-study dose, throughout the study.
Number of participants	427
Duration of follow-up	26 weeks
Method of analysis	Modified ITT
Additional comments	Change in HbA1c from baseline to end point was evaluated by using an ANCOVA model with treatment group,

68.2. Study arms

68.2.1. 2 mg Exenatide QW (N = 215)

2 mg Exenatide was administered once weekly by self subcutaneous injection for 26 weeks

68.2.2. Insulin glargine (N = 212)

Once daily insulin glargine administered before bedtime by subcutaneous injection for 26 weeks

68.3. Characteristics

68.3.1. Arm-level characteristics

Characteristic	2 mg Exenatide QW (N = 215)	Insulin glargine (N = 212)
% Male Sample size	n = 142 ; % = 66	n = 148 ; % = 69.8
Mean age (SD) (Years (mean, SD)) Mean (SD)	57.07 (10.44)	56.44 (11.16)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed (Years (mean, SD)) Mean (SD)	8.86 (6.06)	9.21 (5.99)
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR
Number of people with obesity Sample size	n = 124 ; % = 57.7	n = 127 ; % = 59.9
Biguanide Sample size	n = 145 ; % = 67	n = 142 ; % = 67

Characteristic	2 mg Exenatide QW (N = 215)	Insulin glargine (N = 212)
Biguanide + thiazolidine derivative Sample size	n = 70 ; % = 32.6	n = 70 ; % = 33
Pretreatment with a sulfonylurea Sample size	n = 129 ; % = 60	n = 126 ; % = 59.4
Blood pressure-lowering medication used No of events	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

69. Inagaki, 2013

Bibliographic Reference	Inagaki, N.; Watada, H.; Murai, M.; Kagimura, T.; Gong, Y.; Patel, S.; Woerle, H. J.; Linagliptin provides effective, well-tolerated add-on therapy to pre-existing oral antidiabetic therapy over 1year in Japanese patients with type 2 diabetes; Diabetes Obes Metab; 2013; vol. 15 (no. 9); 833-843

69.1. Study details

Trial name / registration number	NCT01204294
Study type	Randomised controlled trial (RCT)
Study location	43 centres in Japan
Study setting	No additional information
Study dates	15 September 2010 and 6 January 2012
Sources of funding	Medical writing funded by Boehringer Ingelheim. Five of the authors are employed by Boehringer Ingelheim. Authors declare multiple funding from numerous pharmaceutical companies
Inclusion criteria	The study enrolled male and female patients, aged ≥20 years, with T2DM and inadequate glycaemic control (defined as HbA1c ≥7.0–≤10.5% at visit 1), despite a diet and exercise regimen and treatment with one oral antidiabetic drug (OAD) (biguanide, glinide, glitazone, SU or A-GI). The concomitant OAD and dosing schedule was required to be unchanged for 10 weeks before the informed consent; for glitazone therapy, this period was 18 weeks
Exclusion criteria	A BMI >40 kg/m2; myocardial infarction, stroke, transient ischaemic attack or pulmonary embolism within 12 weeks before the informed consent; impaired hepatic function (serum alanine aminotransferase, aspartate aminotransferase or alkaline phosphatase levels above three times the upper limit of normal); renal failure [defined as eGFR <30 ml/min (glinide, glitazone and SU groups) or eGFR <60 ml/min (biguanide group)]; known hypersensitivity to the investigational product or other concomitant OADs; current treatment with systemic steroids at the time of informed consent, or change in dosage of thyroid hormones within 6 weeks before informed consent, or treatment with anti-obesity drugs within 12 weeks before informed consent and premenopausal women who were nursing or pregnant or at risk of becoming pregnant
Recruitment / selection of participants	No additional information
Intervention(s)	Linagliptin (n=228) Patients received 5 mg as a single once daily dose for 52 weeks

Cointervention	Patients received either sulphonylurea or alpha-glucosidase inhibitor
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 Excluded “myocardial infarction, stroke, transient ischaemic attack or pulmonary embolism within 12 weeks before the informed consent”, prior unclear. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Excluded “; renal failure [defined as eGFR < 30 ml/min (glinide, glitazone and SU groups) or eGFR < 60 ml/min (biguanide group)]”, otherwise unclear. Baseline characteristics give eGFR categories but not CKD diagnosis.
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	Patients were split by background medication of either sulphonylurea or alpha-glucosidase inhibitor
Comparator	Metformin (n=124) Patients received twice or thrice daily doses of metformin, up to 2250 mg/day
Number of participants	352
Duration of follow-up	52 weeks
Indirectness	No additional information
Additional comments	The full analysis set (FAS) was defined, according to the intent-to-treat principle, as patients who had received at least one dose of study drug and had an HbA1c measurement at baseline and at one or more time points after starting a treatment period. This was the primary analysis set for the efficacy evaluation.

69.2. Study arms

69.2.1. Linagliptin 5mg (N = 228)

Patients received 5 mg linagliptin once daily for 52 weeks

69.2.2. Metformin (N = 124)

Patients received up metformin either twice or thrice daily, up to 2250 mg per day

69.3. Characteristics

69.3.1. Arm-level characteristics

Characteristic	Linagliptin 5mg (N = 228)	Metformin (N = 124)
% Male Linagliptin n= 185, metformin n=124 Sample size	n = 128 ; % = 69.2	n = 86 ; % = 69.4
Mean age (SD) (Years (mean, SD)) Linagliptin n= 185, metformin n=124 Mean (SD)	60.7 (11)	60.3 (10.5)
Ethnicity Linagliptin n= 185, metformin n=124 Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed Linagliptin n= 185, metformin n=124 Mean (SD)	NR (NR)	NR (NR)
Smoking status Linagliptin n= 185, metformin n=124 Sample size	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Linagliptin n= 185, metformin n=124 Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Linagliptin n= 185, metformin n=124 Sample size	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Linagliptin n= 185, metformin n=124 Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Linagliptin n= 185, metformin n=124 Sample size	n = NR ; % = NR	n = NR ; % = NR
Number of people with obesity Linagliptin n= 185, metformin n=124 Sample size	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Linagliptin 5mg (N = 228)	Metformin (N = 124)
Sulfonlyureas Sample size	n = 124 ; % = 67	n = 63 ; % = 50.9
Alpha glucosidase inhibitors Sample size	n = 61 ; % = 33	n = 61 ; % = 49.2
Blood pressure-lowering medication used Linagliptin n= 185, metformin n=124 Sample size	n = NR ; % = NR	n = NR ; % = NR
Statins/lipid-lowering medication used Linagliptin n= 185, metformin n=124 Sample size	n = NR ; % = NR	n = NR ; % = NR
Other treatment being received Linagliptin n= 185, metformin n=124 Sample size	n = NR ; % = NR	n = NR ; % = NR

70. Inagaki, 2016

Bibliographic Reference	Inagaki, Nobuya; Araki, Eiichi; Oura, Tomonori; Matsui, Akiko; Takeuchi, Masakazu; Tanizawa, Yukio; The combination of dulaglutide and biguanide reduced bodyweight in Japanese patients with type 2 diabetes.; Diabetes, obesity & metabolism; 2016; vol. 18 (no. 12); 1279-1282

70.1. Study details

Secondary publication of another included study- see primary study for details	Araki E, Inagaki N, Tanizawa Y, Oura T, Takeuchi M, Imaoka T. Efficacy and safety of once-weekly dulaglutide in combination with sulphonylurea and/or biguanide compared with once-daily insulin glargine in Japanese patients with type 2 diabetes: a randomized, open-label, phase III, non-inferiority study. Diabetes Obes Metab. 2015 Oct;17(10):994-1002. doi: 10.1111/dom.12540.

71. Jabbour, 2020

Bibliographic Reference	Jabbour, S. A.; Frias, J. P.; Ahmed, A.; Hardy, E.; Choi, J.; Sjostrom, C. D.; Guja, C.; Efficacy and Safety Over 2 Years of Exenatide Plus Dapagliflozin in the DURATION-8 Study: A Multicenter, Double-Blind, Phase 3, Randomized Controlled Trial; Diabetes Care; 2020; vol. 43 (no. 10); 2528-2536

71.1. Study details

Secondary publication of another included study- see primary study for details	Primary article with 28-wk results: • Frías, J. P., Guja, C., Hardy, E., Ahmed, A., Dong, F., Öhman, P., & Jabbour, S. A. (2016). Exenatide once weekly plus dapagliflozin once daily versus exenatide or dapagliflozin alone in patients with type 2 diabetes inadequately controlled with metformin monotherapy (DURATION-8): a 28 week, multicentre, double-blind, phase 3, randomised controlled trial. *The lancet Diabetes & endocrinology*, *4*(12), 1004-1016.
Other publications associated with this study included in review	52-wk results reported in: • Jabbour SA, Frías JP, Hardy E, et al. Safety and efficacy of exenatide once weekly plus dapagliflozin once daily versus exenatide or dapagliflozin alone in patients with type 2 diabetes inadequately controlled with metformin monotherapy: 52-week results of the DURATION-8 randomized controlled trial. Diabetes Care 2018;41:2136–2146
Trial name / registration number	DURATION-8/NCT02229396
Study type	Randomised controlled trial (RCT)

71.2. Study arms

71.2.1. Exenatide 2 mg weekly + Dapagliflozin 10 mg daily (N = 231)

71.2.2. Exenatide 2 mg weekly (N = 231)

71.2.3. Dapagliflozin 10 mg daily (N = 233)

72. Jabbour, 2014

Bibliographic Reference	Jabbour, S. A.; Hardy, E.; Sugg, J.; Parikh, S.; Dapagliflozin is effective as add-on therapy to sitagliptin with or withoutmetformin: A 24-Week, multicenter, randomized, double-blind, placebo-controlled study; Diabetes Care; 2014; vol. 37 (no. 3); 740-750

72.1. Study details

Trial name / registration number	NCT00984867
Study type	Randomised controlled trial (RCT)
Study location	Conducted in Argentina, Germany, Mexico, Poland, UK and the US
Study setting	No additional information
Study dates	No additional information
Sources of funding	Funded by AstraZeneca and Bristol-Myers Squibb. A number of authors are stockholders and/or employees of AstraZeneca. Primary author belongs to speakers' bureaus for Eli Lilly and Company and Amlyn.
Inclusion criteria	Adult patients (≥18 years) with type 2 diabetes were eligible for inclusion. An upper age limit was imposed for those receiving metformin where local label restrictions applied. HbA1c values between 7.7% (61 mmol/mol) and 10.5% (91 mmol/mol) were required for individuals not receiving a DPP-4 inhibitor at enrollment and between 7.2% (55 mmol/mol) and 10.0% (86 mmol/mol) for those receiving a DPP-4 inhibitor. Prior to randomization, HbA1c values were required to be between 7.0% (53 mmol/mol) and 10.0% (86 mmol/mol) for all patients.
Exclusion criteria	Individuals with type 1 diabetes or FPG >270 mg/dL (15.0 mmol/L) were excluded, as were pregnant or breast-feeding women and patients receiving metformin with a calculated creatinine clearance ,60 mL/min or serum creatinine values ≥1.5 mg/dL for men or ≥1.4 mg/dL for women. Patients not treated with metformin and with a baseline calculated creatinine clearance <50 mL/min were excluded. At enrolment, individuals with SBP ≥170 mmHg and/or diastolic BP ≥110 mmHg were excluded.
Recruitment / selection of participants	Patients were required to have an SBP <160 mmHg and/or a diastolic BP <100 mmHg at randomisation
Intervention(s)	Dapagliflozin (n= 225) Patients received 10 mg dapagliflozin daily orally for an initial 24 double blind study and a further 24 as an add on.
Cointervention	Sitagliptin ± metformin:

	All patients received open-label oral sitagliptin 100 mg once daily for the 10-week dose-stabilization period, the 2-week placebo lead-in period, the 24-week double-blind treatment period, and the 24-week extension period. Patients in stratum 2 received open-label oral metformin immediate release 500-mg tablets (≥1,500 mg/day)
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	No additional information
Comparator	Placebo: Patients received daily placebo orally for an initial 24 double blind study and a further 24 as an add on. All patients received open-label oral sitagliptin 100 mg once daily for the 10-week dose-stabilization period, the 2-week placebo lead-in period, the 24-week double-blind treatment period, and the 24-week extension period. Patients in stratum 2 received open-label oral metformin immediate release 500-mg tablets (≥1,500 mg/day)
Number of participants	451
Duration of follow-up	initial 24 week double blind study with additional 24 week extension
Indirectness	No additional information
Additional comments	The data were analysed for the overall study population and for each stratum separately. Efficacy data were analysed with a full analysis set (FAS) that included all randomized individuals who took at least one dose of double-blind study medication and had a non-missing baseline value and one or more postbaseline efficacy values for one or more efficacy variables. The safety set comprised patients who took one or more doses of double-blind study medication

72.2. Study arms

72.2.1. Dapagliflozin 10 mg (N = 225)

Dapagliflozin 10 mg was administered orally daily for a 24 week double blind and a 24 week extension period

72.2.2. Placebo (N = 226)

Placebo was administered orally daily for 24 week double blind and a 24 week extension period

72.3. Characteristics

72.3.1. Arm-level characteristics

Characteristic	Dapagliflozin 10 mg (N = 225)	Placebo (N = 226)
% Male Dapagliflozin n = 223, Placebo n = 224 Sample size	n = 127 ; % = 57	n = 118 ; % = 52.7
Mean age (SD) (Years (mean, SD)) Dapagliflozin n = 223, Placebo n = 224 Mean (SD)	54.8 (10.4)	55 (10.2)
White Sample size	n = 161 ; % = 72.2	n = 171 ; % = 76.3
Black Sample size	n = 11 ; % = 4.9	n = 6 ; % = 2.7
Asian Sample size	n = 2 ; % = 0.9	n = 2 ; % = 0.9
Other Sample size	n = 49 ; % = 22	n = 45 ; % = 20.1
Time since type 2 diabetes diagnosed (Years (mean, SD)) Dapagliflozin n = 223, Placebo n = 224 Mean (SD)	5.7 (4.87)	5.64 (5.4)
Smoking status Dapagliflozin n = 223, Placebo n = 224 Sample size	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Dapagliflozin n = 223, Placebo n = 224 Sample size	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Dapagliflozin 10 mg (N = 225)	Placebo (N = 226)
Presence of severe mental illness Dapagliflozin n = 223, Placebo n = 224 Sample size	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Dapagliflozin n = 223, Placebo n = 224 Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Dapagliflozin n = 223, Placebo n = 224 Sample size	n = NR ; % = NR	n = NR ; % = NR
Number of people with obesity Dapagliflozin n = 223, Placebo n = 224 Sample size	n = NR ; % = NR	n = NR ; % = NR
Other antidiabetic medication used Dapagliflozin n = 223, Placebo n = 224 Sample size	n = NA ; % = NA	n = NA ; % = NA
Sitagliptin Sample size	n = 110 ; % = 49.3	n = 111 ; % = 49.6
Sitagliptin + Metformin Sample size	n = 113 ; % = 50.7	n = 113 ; % = 50.4
Blood pressure-lowering medication used Dapagliflozin n = 223, Placebo n = 224 Sample size	n = NR ; % = NR	n = NR ; % = NR
Statins/lipid-lowering medication used Dapagliflozin n = 223, Placebo n = 224 Sample size	n = NR ; % = NR	n = NR ; % = NR
Other treatment being received Dapagliflozin n = 223, Placebo n = 224 Sample size	n = NR ; % = NR	n = NR ; % = NR

73. Jabbour, 2018

Bibliographic Reference	Jabbour, Serge A; Frias, Juan P; Hardy, Elise; Ahmed, Azazuddin; Wang, Hui; Ohman, Peter; Guja, Cristian; Safety and Efficacy of Exenatide Once Weekly Plus Dapagliflozin Once Daily Versus Exenatide or Dapagliflozin Alone in Patients With Type 2 Diabetes Inadequately Controlled With Metformin Monotherapy: 52-Week Results of the DURATION-8 Randomized Controlled Trial.; Diabetes care; 2018; vol. 41 (no. 10); 2136-2146

73.1. Study details

Secondary publication of another included study- see primary study for details	Primary article, 28-wk results in: • Frías, J. P., Guja, C., Hardy, E., Ahmed, A., Dong, F., Öhman, P., & Jabbour, S. A. (2016). Exenatide once weekly plus dapagliflozin once daily versus exenatide or dapagliflozin alone in patients with type 2 diabetes inadequately controlled with metformin monotherapy (DURATION-8): a 28 week, multicentre, double-blind, phase 3, randomised controlled trial. *The lancet Diabetes & endocrinology*, *4*(12), 1004-1016.
Other publications associated with this study included in review	2-yr results reported in: • Jabbour, S. A., Frías, J. P., Ahmed, A., Hardy, E., Choi, J., Sjöström, C. D., & Guja, C. (2020). Efficacy and safety over 2 years of exenatide plus dapagliflozin in the DURATION-8 study: a multicenter, double-blind, phase 3, randomized controlled trial. *Diabetes Care*, *43*(10), 2528-2536.
Trial name / registration number	DURATION-8/NCT02229396
Study type	Randomised controlled trial (RCT)

73.2. Study arms

73.2.1. Exenatide 2 mg weekly + Dapagliflozin 10 mg daily (N = 231)

73.2.2. Exenatide 2 mg weekly (N = 231)

73.2.3. Dapagliflozin 10 mg daily (N = 233)