National Institute for Health and Care Excellence

Final

Type 2 diabetes in adults: management (medicines update)

[F2.5] Evidence reviews for subsequent pharmacological management of type 2 diabetes – Appendix D4

NICE guideline

Evidence reviews underpinning recommendations 1.9.1 to 1.9.5, 1.10.1 to 1.18. 4, 1.19.1 to 1.19.3, 1.22.1 to 1.31.2 and recommendations for research in the NICE guideline

February 2026

Final

This evidence review was developed by NICE

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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.

222. Jardine, 2017

Bibliographic Reference	Jardine, Meg J; Mahaffey, Kenneth W; Neal, Bruce; Agarwal, Rajiv; Bakris, George L; Brenner, Barry M; Bull, Scott; Cannon, Christopher P; Charytan, David M; de Zeeuw, Dick; Edwards, Robert; Greene, Tom; Heerspink, Hiddo J L; Levin, Adeera; Pollock, Carol; Wheeler, David C; Xie, John; Zhang, Hong; Zinman, Bernard; Desai, Mehul; Perkovic, Vlado; The Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) Study Rationale, Design, and Baseline Characteristics.; American journal of nephrology; 2017; vol. 46 (no. 6); 462-472

222.1. Study details

Secondary publication of another included study- see primary study for details	CREDENCE trial. Perkovic, V., Jardine, M. J., Neal, B. et al. (2019) Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med 380(24): 2295-2306
Other publications associated with this study included in review	Sarraju, Ashish, Li, JingWei, Cannon, Christopher P et al. (2021) Effects of canagliflozin on cardiovascular, renal, and safety outcomes in participants with type 2 diabetes and chronic kidney disease according to history of heart failure: Results from the CREDENCE trial. American heart journal 233: 141-148
Trial name / registration number	CREDENCE trial. NCT02065791

223. Ji, 2016

Bibliographic Reference	Ji, L. N.; Pan, C. Y.; Lu, J. M.; Li, H.; Zhu, D. L.; Li, Q.; Li, Q. F.; Peng, Y. D.; Tian, H. M.; Yao, C.; Zhao, Z. G.; Wang, L.; Wang, B. H.; Efficacy and safety of combination therapy with vildagliptin and metformin versus metformin uptitration in Chinese patients with type 2 diabetes inadequately controlled with metformin monotherapy: a randomized, open-label, prospective study (VISION); Diabetes Obes Metab; 2016; vol. 18 (no. 8); 775-782

223.1. Study details

Other publications associated with this study included in review	Ji LN, Pan CY, Lu JM, Li H, Li Q, Li QF, Peng YD, Tian HM, Yao C, Zhao ZG, Zhang RY, Wang XL, Wang L; VISION Study Group. Efficacy and safety of combination therapy with vildagliptin and metformin versus metformin up-titration in Chinese patients with type 2 diabetes mellitus: study design and rationale of the vision study. Cardiovasc Diabetol. 2013 Aug 19;12:118. doi: 10.1186/1475-2840-12-118. PMID: 23958390; PMCID: PMC3766124.
Trial name / registration number	NCT01541956.
Study type	Randomised controlled trial (RCT)
Study location	127 medical centres in China
Study setting	No additional information
Study dates	NR
Sources of funding	Study funded by Novartis Pharmaceuticals. Two authors are also employees of Novartis Pharmaceuticals.
Inclusion criteria	Male and female Chinese T2DM patients (WHO/IDF criteria) aged >18 years with HbA1c levels ranging between 6.5% and 9.0% and BMI between 22 and 45 kg/m2 at visit 1 who have received metformin at a stable dose of 750–1000 mg daily for at least 12 weeks before screening will be enrolled in the study. The patients will be required to maintain their individual eating and exercise habits during the study, and to follow all the study requirements. Written informed consent will be obtained from each patient prior to enrolment.
Exclusion criteria	1. Pregnant or lactating women 2. Medical history of following diseases: • Type 1 diabetes mellitus or diabetes caused by pancreatic injury or secondary diabetes: Cushing syndrome or acromegaly

	• Acute complications of diabetes: ketoacidosis or non-ketotic hyperosmolar coma within the past 3 months • Acute infections within 4 weeks prior to the screening that may affect the efficacy and safety of the study • Any obvious diabetic complications such as symptomatic autonomic neuropathy, gastroparesis, worsening hyperglycemia in the absence of any comorbid illnesses, and conditions that may affect blood glucose • History of kidney disease or clinical diagnosis of renal insufficiency indicated by serum creatinine ≥132 μmol/L (≥1.5 mg/dL) in males, and ≥123 μmol/L (≥1.4 mg/dL) in females • History of a liver disease such as cirrhosis, hepatitis B, or hepatitis C (except carriers) or ALT, aspartate aminotransferase (AST) greater than 2 times the ULN or total bilirubin greater than 2 times the ULN • History of acute and chronic pancreatitis • Malignant tumor in the past 5 years, including leukemia and lymphoma (except for carcinoma in situ of the skin) • Torsades de pointes ventricular tachycardia or persistent, clinically relevant ventricular tachycardia or ventricular fibrillation or second-degree atrioventricular block (Mobitz type I and II) or third-degree atrioventricular block, or QTc prolongation (>500 ms) • Myocardial infarction, coronary artery bypass surgery or percutaneous coronary intervention, unstable angina, or stroke within the past 6 months • Congestive heart failure requiring medical treatment 3. Fasting plasma glucose >15 mmol/L (>270 mg/dL) at visit 1 4. Clinically significant thyroid-stimulating hormone levels outside the normal range at visit 1 5. Use of concomitant medications: • Other antihyperglycemic agents besides metformin within 12 weeks of visit 1 • Long-term glucocorticoids (>7 consecutive days of treatment) within 4 weeks of visit 1 • Treatment with growth hormone or similar drugs • Treatment with class Ia, Ib, or Ic, or class III antiarrhythmics • Treatment with any drug with known and frequent toxicity to a major organ system within the past 3 months

	6. Use of other investigational drugs at visit 1, or within 30 days or 5 half-lives of visit 1, whichever is longer 7. History of active substance abuse (including alcohol) within the past 2 years 8. Potentially unreliable patients or patients who, in the opinion of the investigator, are unsuitable for the stud
Recruitment / selection of participants	No additional information
Intervention(s)	Vildagliptin 50 mg (n=2573) Patients received 50 mg vildagliptin twice daily for 24 weeks
Cointervention	Metformin: All patients received background 500 mg metformin twice daily for 24 weeks
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Excluded “Congestive heart failure requiring medical treatment”, otherwise unclear. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Excluded “Myocardial infarction, coronary artery bypass surgery or percutaneous coronary intervention, unstable angina, or stroke within the past 6 months”, prior unclear. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	People without chronic kidney disease Study design paper states excluded "History of kidney disease or clinical diagnosis of renal insufficiency indicated by serum creatinine ≥132 µmol/L (≥1.5 mg/dL) in males, and ≥123 µmol/L (≥1.4 mg/dL) in females"
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	High dose metformin (n= 511) Patients received 500 mg metformin daily for 4 weeks and then up-titrated to 1000 mg twice daily for a further 20 weeks. Dose reduction/adjustment by 250 mg with a minimum dose of 500 mg twice daily was allowed for patients in the HDM arm who could not tolerate the GI symptoms after metformin up-titration at visit 3. Dose adjustment was not allowed after visit 4 (week 12).
Number of participants	3084
Duration of follow-up	24 weeks
Indirectness	NA
Method of analysis	ITT

Additional comments	Intention-to-treat (ITT) analysis will be performed. The full analysis set (FAS) will include all randomized patients who took the study drugs at least once and had at least 1 primary or secondary efficacy evaluation after baseline. For assessment of missing primary efficacy variables, the last observation carried forward (LOCF) technique will be used. The per-protocol set include ITT patients completing at least 22 weeks of treatment, and those who discontinued the study due to a poor therapeutic response (FPG >13.3 mmol/L [240 mg/dL]) after 12 weeks of treatment, provided they have no major protocol deviations and had a valid assessment of HbA1c levels within 7 days after their last dose of study drug.

223.2. Study arms

223.2.1. Vildagliptin (N = 2573)

Cointervention	Metformin: Patients received 500 mg metformin twice daily combined with vildagliptin for 24 weeks
Comparator	High dose metformin (n= 511) Patients received 500 mg metformin daily for 4 weeks and then titrated to 1000 mg twice daily for a further 20 weeks. Dose reduction/adjustment by 250 mg with a minimum dose of 500 mg twice daily was allowed for patients in the HDM arm who could not tolerate the GI symptoms after metformin up-titration at visit 3. Dose adjustment was not allowed after visit 4 (week 12).

Patients received 50 mg vildagliptin in addition to background metformin 500 mg twice daily for 24 weeks

223.2.2. Metformin (N = 511)

Cointervention	Metformin: Patients received 500 mg metformin twice daily combined with vildagliptin for 24 weeks
Comparator	High dose metformin (n= 511) Patients received 500 mg metformin daily for 4 weeks and then titrated to 1000 mg twice daily for a further 20 weeks. Dose reduction/adjustment by 250 mg with a minimum dose of 500 mg twice daily was allowed for patients in the HDM arm who could not tolerate the GI symptoms after metformin up-titration at visit 3. Dose adjustment was not allowed after visit 4 (week 12).

Patients initially received 500 mg metformin daily for four weeks and then up-titrated to 1000 mg daily for the remaining 20 weeks

223.3. Characteristics

223.3.1. Arm-level characteristics

Characteristic	Vildagliptin (N = 2573)	Metformin (N = 511)
% Male Vildagliptin + metformin n = 2501, High dose metformin n = 484 Sample size	n = 1361 ; % = 54.4	n = 240 ; % = 49.6
Mean age (SD) (Years (mean, SD)) Vildagliptin + metformin n = 2501, High dose metformin n = 484 Mean (SD)	56.5 (10.6)	56.2 (10.8)
Ethnicity Vildagliptin + metformin n = 2501, High dose metformin n = 484 Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of frailty Vildagliptin + metformin n = 2501, High dose metformin n = 484 Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed (Years (mean, SD)) Vildagliptin + metformin n = 2500, High dose metformin n = 484 Mean (SD)	4.3 (4.2)	4.1 (4.3)
Smoking status Vildagliptin + metformin n = 2501, High dose metformin n = 484 Sample size	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Vildagliptin + metformin n = 2501, High dose metformin n = 484 Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Vildagliptin + metformin n = 2501, High dose metformin n = 484 Sample size	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Vildagliptin (N = 2573)	Metformin (N = 511)
People with significant cognitive impairment Vildagliptin + metformin n = 2501, High dose metformin n = 484 Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Vildagliptin + metformin n = 2501, High dose metformin n = 484 Sample size	n = NR ; % = NR	n = NR ; % = NR
Number of people with obesity Vildagliptin + metformin n = 2501, High dose metformin n = 484 Sample size	n = NR ; % = NR	n = NR ; % = NR
Other antidiabetic medication used Vildagliptin + metformin n = 2501, High dose metformin n = 484 Sample size	n = NR ; % = NR	n = NR ; % = NR
Blood pressure-lowering medication used Vildagliptin + metformin n = 2501, High dose metformin n = 484 Sample size	n = NR ; % = NR	n = NR ; % = NR
Statins/lipid-lowering medication used Vildagliptin + metformin n = 2501, High dose metformin n = 484 Sample size	n = NR ; % = NR	n = NR ; % = NR
Other treatment being received Vildagliptin + metformin n = 2501, High dose metformin n = 484 Sample size	n = NR ; % = NR	n = NR ; % = NR

224. Ji, 2021

Bibliographic Reference	Ji, L.; Dong, X.; Li, Y.; Li, Y.; Lim, S.; Liu, M.; Ning, Z.; Rasmussen, S.; Skjoth, T. V.; Yuan, G.; Eliaschewitz, F. G.; Efficacy and safety of once-weekly semaglutide versus once-daily sitagliptin as add-on to metformin in patients with type 2 diabetes in SUSTAIN China: A 30-week, double-blind, phase 3a, randomized trial; Diabetes, Obesity & Metabolism; 2021; vol. 23 (no. 2); 404-414

224.1. Study details

Trial name / registration number	SUSTAIN CHINA / NCT03061214
Study type	Randomised controlled trial (RCT)
Study location	65 sites in Brazil, China, Hong Kong, Taiwan, Republic of Korea, South Africa and Ukraine
Study setting	No additional information
Study dates	NR
Sources of funding	Trial was funded by Novo Nordisk A/S Denmark. Multiple authors declare employment and funding from Novo Nordisk
Inclusion criteria	According to the trial protocol, an eligible patient was to meet all of the following inclusion criteria: 1. Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial 2. Male or female, age ≥ 18 years at the time of signing informed consent 3. (For Korea: Male or female, age above or equal to 19 years at the time of signing informed consent.) 4. Patients diagnosed with type 2 diabetes and on stable treatment in a period of 60 days prior to screening with metformin ≥ 1500 mg (or maximum tolerated dose ≥ 1000 mg). Stable is defined as unchanged medication and unchanged daily dose 5. HbA1c 7.0 – 10.5 % (53-91 mmol/mol) (both inclusive)
Exclusion criteria	1. Known or suspected hypersensitivity to trial product(s) or related products

	2. Previous participation in this trial. Participation is defined as informed consent 3. Female who is pregnant, breast-feeding or intends to become pregnant or is of childbearing potential not using an adequate contraceptive method throughout the trial including the 5-week follow-up period (adequate contraceptive measure as required by local regulation or practice) (China: Sterilisation, intrauterine device (IUD), oral contraceptives or barrier methods). (Brazil: For women who expressly declare free of the risk of pregnancy, either by not engaging in sexual activity or by having sexual activity with no birth potential risk, use of contraceptive method will not be mandatory). 4. Receipt of any investigational medicinal product within 90 days before screening (Brazil: Participation in other trials within one year prior to screening visit (V1) unless there is a direct benefit to the research patient at the Investigator´s discretion) 5. Any disorder which, in the opinion of the investigator, might jeopardise patient's safety or compliance with the protocol 6. Treatment with glucose lowering agent(s) other than stated in the inclusion criteria in a period of 60 days before screening. An exception is short-term treatment (≤7 days in total) with insulin in connection with inter-current illness 7. Use of non-herbal Chinese medicine or other non-herbal local medicine with unknown/unspecified content. Herbal traditional Chinese medicine or other local herbal medicines may, at the Investigator's discretion, be continued throughout the trial 8. History of pancreatitis (acute or chronic) 9. Screening calcitonin value ≥ 50 ng/L (pg/mL) 10. Personal or family history of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia syndrome type 2 (MEN 2) 11. Impaired renal function defined as eGFR < 60 ml/min/1.73 m2 per Modification of Diet in Renal Disease (MDRD) formula (4 variable version)
Recruitment / selection of participants	No additional information
Intervention(s)	Semaglutide 0.5mg + placebo (n=287) Semaglutide 1.0mg + placebo (n=290) Patients received either 0.5 mg or 1.0 mg semaglutide once weekly injections in the thigh, abdomen or upper arm, and were to be taken on the

	same day of the week irrespective of meals. Participants followed a fixed-dose escalation regimen starting from a dose of 0.25 mg and the dose doubled every 4 weeks until the maintenance dose was achieved. Doses were not to be changed during the trial after the semaglutide maintenance dose had been reached. Placebo were provided as tablets and were to be administered orally once-daily irrespective of meals.
Cointervention	Metformin: Metformin dose or dosing frequency was not changed during the treatment period of 30 weeks unless rescue medication was needed.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Excluded “heart failure (NYHA class IV)”, otherwise unclear. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Excluded “acute coronary or cerebrovascular event within 90 days before randomization”, 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 (estimated glomerular filtration rate [eGFR] < 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
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	NA
Comparator	Sitagliptin + placebo (n=290) Patients received once daily 100 mg sitagliptin and placebo for the 0.5 mg and 1.0 mg semaglutide
Number of participants	868
Duration of follow-up	35 weeks
Indirectness	NA
Method of analysis	ITT
Additional comments	The analyses of the confirmatory endpoints and other change from baseline endpoints were based on the full analysis set using data from the 'on-treatment without rescue medication' observation period in a mixed model for repeated measures. The model included all postbaseline measurements collected at scheduled visits up to and including week 30 data as dependent variables

224.2. Study arms

224.2.1. Semaglutide 0.5 mg (N = 288)

0.5 mg semaglutide was administered by once weekly subcutaneous injections on the same day of the week irrespective of meals for 30 weeks

224.2.2. Semaglutide 1.0 mg (N = 290)

1.0 mg Semaglutide was administered by once weekly subcutaneous injections on the same day of the week irrespective of meals for 30 weeks

224.2.3. Sitagliptin (100 mg) (N = 290)

100 mg sitagliptin was administered once daily orally

224.3. Characteristics

224.3.1. Arm-level characteristics

Characteristic	Semaglutide 0.5 mg (N = 288)	Semaglutide 1.0 mg (N = 290)	Sitagliptin (100 mg) (N = 290)
% Male Sample size	n = 160 ; % = 55.6	n = 154 ; % = 53.1	n = 185 ; % = 63.8
Mean age (SD) (Years (mean, SD)) Mean (SD)	53 (11.4)	53 (10.6)	53.1 (10.4)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Hispanic or Latino Sample size	n = 24 ; % = 8.3	n = 28 ; % = 9.7	n = 30 ; % = 10.3
Not hispanic or latino Sample size	n = 264 ; % = 91.7	n = 262 ; % = 90.3	n = 260 ; % = 89.7
Asian Sample size	n = 243 ; % = 84.4	n = 251 ; % = 86.6	n = 244 ; % = 84.1
White Sample size	n = 30 ; % = 10.4	n = 28 ; % = 9.7	n = 31 ; % = 10.7
Black or African American Sample size	n = 8 ; % = 2.8	n = 8 ; % = 2.8	n = 9 ; % = 3.1
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Semaglutide 0.5 mg (N = 288)	Semaglutide 1.0 mg (N = 290)	Sitagliptin (100 mg) (N = 290)
Time since type 2 diabetes diagnosed (Years (mean, SD)) Mean (SD)	6.3 (5.4)	6.7 (4.9)	6.1 (5.2)
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 = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Biguanides Sample size	n = 287 ; % = 99.7	n = 289 ; % = 99.7	n = 290 ; % = 100
Statins/lipid-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Statins Sample size	n = 91 ; % = 31.6	n = 92 ; % = 31.7	n = 91 ; % = 31.4
Other treatment being received Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Semaglutide 0.5 mg (N = 288)	Semaglutide 1.0 mg (N = 290)	Sitagliptin (100 mg) (N = 290)
Calcium-channel blockers Sample size	n = 53 ; % = 18.4	n = 49 ; % = 16.9	n = 57 ; % = 19.7
Anti-platelet drugs excl. heparin Sample size	n = 53 ; % = 18.4	n = 44 ; % = 15.2	n = 56 ; % = 19.3
ARBs Sample size	n = 56 ; % = 19.4	n = 50 ; % = 17.2	n = 46 ; % = 15.9
ACE inhibitors Sample size	n = 22 ; % = 7.6	n = 27 ; % = 9.3	n = 26 ; % = 9
Beta blockers Sample size	n = 22 ; % = 7.6	n = 33 ; % = 11.4	n = 18 ; % = 6.2
Herbal and traditional medicine Sample size	n = 19 ; % = 6.6	n = 22 ; % = 7.6	n = 17 ; % = 5.9

225. Ji, 2019

Bibliographic Reference	Ji, L.; Liu, Y.; Miao, H.; Xie, Y.; Yang, M.; Wang, W.; Mu, Y.; Yan, P.; Pan, S.; Lauring, B.; et, al.; Safety and efficacy of ertugliflozin in Asian patients with type 2 diabetes mellitus inadequately controlled with metformin monotherapy: VERTIS Asia; Diabetes Obes Metab; 2019; vol. 21 (no. 6); 1474-1482

225.1. Study details

Trial name / registration number	VERTIS Asia / NCT02630706
Study type	Randomised controlled trial (RCT)
Study location	Multicentre from China, Hong Kong, Republic of Korea, Philippines and Taiwan
Study setting	No additional information
Study dates	NR
Sources of funding	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., USA, in collaboration with Pfizer Inc., USA. A number of authors are employees of Merck Sharp and Dohme and Pfizer
Inclusion criteria	Asian men and women aged ≥18 years with T2DM (diagnosed in accordance with American Diabetes Association guidelines) inadequately controlled [HbA1c, 7.0-10.5% (53-91 mmol/mol) inclusive] with metformin monotherapy and with a BMI ≥18.0 kg/m2 . Participants who had received dual antihyperglycaemic agent (AHA) therapy, metformin monotherapy <1500 or ≥1500 mg/d for <8 weeks were required to adjust their background AHA therapy so that, at a second screening visit, they had received metformin monotherapy at ≥1500 mg/d for ≥8 weeks. To be eligible for study inclusion, these participants underwent a repeat HbA1c measurement for confirmation of HbA1c 7.0 to 10.5% (53-91 mmol/mol) inclusive. Participants were required to be receiving stable doses of BP and/or lipid-altering medications for ≥4 weeks prior to randomization.
Exclusion criteria	Key exclusion criteria included type 1 diabetes mellitus, history of ketoacidosis, eGFR <55 mL/min/ 1.73 m2 according to the 4-variable Modification of Diet in Renal Disease equation at screening, and <80% compliance (based on pill count) with the placebo run-in medication. Use of AHAs (other than those approved by the study protocol) was prohibited for the duration of the trial. Participants who had undergone bariatric surgery were also ineligible.

Recruitment / selection of participants	No additional information
Intervention(s)	Ertugliflozin 5 mg (n=170) Ertugliflozin 15 mg (n=170) Patients received either 5 mg or 15 mg oral ertugliflozin once daily for 26 weeks
Cointervention	Metformin: All patients remained on a stable dose of metformin throughout the trial
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 2: People with 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 “estimated glomerular filtration rate (eGFR) <55 mL/min/1.73 m2”, 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	NA
Comparator	Placebo (n=167) Patients received daily oral placebo in addition to their standard metformin dose
Number of participants	506
Duration of follow-up	26 weeks
Indirectness	NA
Method of analysis	ITT

225.2. Study arms

225.2.1. Ertugliflozin 5 mg (N = 170)

Patients received 5 mg ertugliflozin once daily for 26 weeks

225.2.2. Ertugliflozin 15 mg (N = 169)

Patients received 15 mg ertugliflozin once daily for 26 weeks

225.2.3. Placebo (N = 167)

Patients received once daily placebo for 26 weeks

225.3. Characteristics

225.3.1. Arm-level characteristics

Characteristic	Ertugliflozin 5 mg (N = 170)	Ertugliflozin 15 mg (N = 169)	Placebo (N = 167)
% Male Sample size	n = 95 ; % = 55.9	n = 98 ; % = 58	n = 88 ; % = 52.7
Mean age (SD) (Years (mean, SD)) Mean (SD)	56.1 (9)	56.3 (9.3)	56.9 (9)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Asian Sample size	n = 170 ; % = 100	n = 169 ; % = 100	n = 167 ; % = 100
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed (Years (mean, SD)) Mean (SD)	7 (5)	7.5 (5.1)	6.4 (5.1)
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	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Ertugliflozin 5 mg (N = 170)	Ertugliflozin 15 mg (N = 169)	Placebo (N = 167)
Sample size			
Number of people with obesity 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
Alpha-glucosidase inhibitor Sample size	n = 11 ; % = 6.5	n = 4 ; % = 2.4	n = 8 ; % = 4.8
Biguanides Sample size	n = 170 ; % = 100	n = 169 ; % = 100	n = 167 ; % = 100
DPP-4 inhibitor Sample size	n = 1 ; % = 0.6	n = 5 ; % = 3	n = 7 ; % = 4.2
Meglitinide Sample size	n = 11 ; % = 6.5	n = 5 ; % = 3	n = 7 ; % = 4.2
Sulfonlyurea Sample size	n = 34 ; % = 20	n = 34 ; % = 20.1	n = 30 ; % = 18
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

226. Ji, 2023

Bibliographic Reference	Ji, Linong; Lu, Yibin; Li, Qifu; Fu, Liujun; Luo, Yong; Lei, Tao; Li, Ling; Ye, Shandong; Shi, Bimin; Li, Xiyan; Meinicke, Thomas; Efficacy and safety of empagliflozin in combination with insulin in Chinese patients with type 2 diabetes and insufficient glycaemic control: A phase III, randomized, double-blind, placebo-controlled, parallel study.; Diabetes, obesity & metabolism; 2023

226.1. Study details

Other publications associated with this study included in review	
Trial name / registration number	NCT04233801
Study type	Randomised controlled trial (RCT)
Study location	24 centres in China
Study setting	No additional information
Study dates	April 2020 to March 2022
Sources of funding	Funded by Boehringer Ingelheim. Two of the authors are also employees of Boehringer Ingelheim.
Inclusion criteria	· Male or female patients aged 18–75 years at screening o Female patients of childbearing potential had to be ready and able to use highly effective methods of birth control per International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) M3 (R2) that resulted in a low failure rate of less than 1% per year when used consistently and correctly. A list of contraception methods meeting these criteria was provided in the patient information. · Chinese patients diagnosed with T2DM prior to screening · Patients on a stable treatment with premixed insulin ≥ 20 IU/day) or basal insulin (≥ 16 IU/day) for ≥ 12 weeks prior to enrolment, with or without up to two OADs o With maximum insulin dose of ≤ 1 unit/kg/day. Acceptable basal insulins had duration of action up to 24 h, such as insulin degludec, insulin

	glargine, insulin detemir or neutral protamine Hagedorn insulin. Acceptable premixed insulins could be once or twice daily posology only. The total insulin dose should not be changed by > 20% of the baseline value within the 12 weeks prior to randomisation. Both human insulin and insulin analogue were acceptable o If the patient was taking OADs, regimen had to be unchanged for ≥ 12 weeks prior to randomisation o If the patient was taking metformin, stable dose (≥ 1500 mg daily or maximum tolerated dose) had to be maintained for ≥ 12 weeks without dose adjustments prior to randomisation · Patients with HbA1c ≥ 7.5% and ≤ 11.0% at screening · Patients with fasting C-peptide > 0.5 ng/mL (> 166 pmol/L) at screening · Patients with 18.5 kg/m2 ≤ BMI ≤ 45 kg/m2 at screening · Patients with signed and dated written informed consent in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice (ICH-GCP) and local legislation prior to admission to the trial
Exclusion criteria	· Patients diagnosed with type 1 diabetes · Patients receiving MDI insulin or insulin pump treatment · Patients with eGFR < 45ml/min/1.73 m2 calculated based on Modification of Diet in Renal Disease (MDRD) formula · Patients with uncontrolled hyperglycaemia (glucose level > 13. 9 mmol/l) after an overnight fast during placebo run-in · Patients with severe hypoglycaemia episode (event requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions) within 6 months prior to screening · Patients with history of diabetic ketoacidosis or hyperosmolar non-kenotic coma · Patients with myocardial infarction, stroke or transient ischaemic attack within 3 months prior to screening · Patients who had bariatric surgery · Patients who had taken SGLT2 inhibitors within 12 weeks prior to screening · Patients who had been treated with anti-obesity drugs within 12 weeks prior to screening

	· Patients who had been treated with GLP-1 receptor agonists within 12 weeks prior to screening · Patients who had been treated with sulphonylureas if the patient is on premixed insulin within 12 weeks prior to screening · Patients with impaired hepatic function (serum alanine aminotransferase, aspartate aminotransferase or alkaline phosphatase > 3 times the upper limit of normal) at screening · Patients with contraindication to background antidiabetes medication according to the local label · Patients with disorders causing haemolysis or unstable red blood cells · Patients who had treatment with systemic steroids at the time of consent · Patients with change in dosage of thyroid hormones within 6 weeks prior to screening · Patients with alcohol or drug abuse within 12 weeks prior to screening · Patients with history of unstable or rapidly progressing renal disease · Patients with conditions of congenital renal glucosuria · Patients with known allergy or hypersensitivity to empagliflozin or other SGLT2 inhibitors · Patients with major surgery (major according to the investigator's assessment) performed within 12 weeks prior to randomisation or planned within 28 weeks after screening · Patients with any documented active or suspected malignancy or history of malignancy within 5 years prior to screening, except appropriately treated basal cell carcinoma of the skin or *in situ* carcinoma of uterine cervix · Patients not expected to comply with the protocol requirements or not expected to complete the trial as scheduled (e.g., chronic alcohol or drug abuse or any other condition that, in the investigator's opinion, made the patient an unreliable trial participant) · Patients who had previous enrolment in this trial · Patients who were enrolled in another investigational device or drug trial, or < 30 days since ending another investigational device or drug trial(s), or receiving other investigational treatment(s)

	· Female patients who were pregnant, nursing, or who planned to become pregnant while in the trial · Patients with any other clinical condition that would jeopardise patient's safety while participating in this clinical trial (e.g., frequent hypoglycaemic events on current therapy) in the opinion of the investigator
Recruitment / selection of participants	No additional information
Intervention(s)	Empagliflozin 10mg and 25 mg (n=73 + 73 = 146 total): Eligible patients were randomized to receive once-daily empagliflozin 10 or 25 mg as add-on therapy to stable insulin with or without up to two OADs for 24 weeks.
Cointervention	All patients received insulin and up to 2 oral antidiabetic therapies
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 "Patients with myocardial infarction, stroke or transient ischaemic attack 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 "Patients with eGFR < 45ml/min/1.73 m2; and patients with history of unstable or rapidly progressing renal disease", 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	
Comparator	Placebo (n=73): Patients were randomized (1:1:1) to receive once-daily placebo, as add-on therapy to stable insulin with or without up to two OADs for 24 weeks.
Number of participants	219
Duration of follow-up	24 weeks
Indirectness	No additional information
Method of analysis	Modified ITT
Additional comments	The modified intention-to-treat (mITT) set comprised all randomized patients who received at least one dose of treatment, had a baselineHbA1c assessment and at least one on-treatment HbA1c value. The per-protocol set (PPS) consisted of all patients in the mITT set who did not have important protocol deviations that may have had a distorting influence on the assessment of the primary endpoint. The treated set consisted of all patients who were randomized and received at least one dose of treatment. All efficacy endpoints were analysed on the mITT set, except for an additional analysis of the change in HbA1c from baseline after24 weeks of treatment based on the PPS to assess the impact of

	important protocol deviations. All safety endpoints were analysed for the treated set

226.2. Study arms

226.2.1. Empagliflozin 10 mg (N = 73)

Patients received once-daily empagliflozin 10 o, as add-on therapy to stable insulin with or without up to two OADs for 24 weeks.

226.2.2. Empagliflozin 25 mg (N = 73)

Patients receive once-daily empagliflozin 25 mg as add-on therapy to stable insulin with or without up to two OADs for 24 weeks.

226.2.3. Placebo (N = 73)

Patients received once-daily placebo as add-on therapy to stable insulin with or without up to two OADs for 24 weeks.

226.3. Characteristics

226.3.1. Arm-level characteristics

Characteristic	Empagliflozin 10 mg (N = 73)	Empagliflozin 25 mg (N = 73)	Placebo (N = 73)
% Male Sample size	n = 43 ; % = 58.9	n = 40 ; % = 54.8	n = 36 ; % = 49.3
Mean age (SD) (Years (mean, SD)) Mean (SD)	59.9 (7.7)	60.7 (9.1)	60.1 (8)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed (Years (mean, SD)) Mean (SD)	14.74 (7.01)	15.05 (7.45)	14.14 (7.26)
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Empagliflozin 10 mg (N = 73)	Empagliflozin 25 mg (N = 73)	Placebo (N = 73)
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 = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Metformin Sample size	n = 48 ; % = 65.8	n = 45 ; % = 61.6	n = 56 ; % = 76.7
Sulfonlyurea Sample size	n = 6 ; % = 8.2	n = 5 ; % = 6.8	n = 8 ; % = 11
Meglitinides Sample size	n = 6 ; % = 8.2	n = 3 ; % = 4.1	n = 1 ; % = 1.4
Alpha glucosidase inhibitors Sample size	n = 20 ; % = 27.4	n = 22 ; % = 30.1	n = 23 ; % = 31.5
Thiazolidinediones Sample size	n = 5 ; % = 6.8	n = 3 ; % = 4.1	n = 0 ; % = 0
DPP-4 inhibitor Sample size	n = 6 ; % = 8.2	n = 6 ; % = 8.2	n = 1 ; % = 1.4
Fixed dose combination; metformin + sitagliptin Sample size	n = 0 ; % = 0	n = 1 ; % = 1.4	n = 0 ; % = 0

Characteristic	Empagliflozin 10 mg (N = 73)	Empagliflozin 25 mg (N = 73)	Placebo (N = 73)
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

227. Ji, 2013

Bibliographic Reference	Ji, Li-Nong; Pan, Chang-Yu; Lu, Ju-Ming; Li, Hong; Li, Qiang; Li, Qi-Fu; Peng, Yong-De; Tian, Hao-Ming; Yao, Chen; Zhao, Zhi-Gang; Zhang, Ru-Ya; Wang, Xiang-Ling; Wang, Lei; Efficacy and safety of combination therapy with vildagliptin and metformin versus metformin up-titration in Chinese patients with type 2 diabetes mellitus: study design and rationale of the vision study.; Cardiovascular diabetology; 2013; vol. 12; 118

227.1. Study details

Secondary publication of another included study- see primary study for details	Parent study Ji 2016B Ji LN, Pan CY, Lu JM, Li H, Zhu DL, Li Q, Li QF, Peng YD, Tian HM, Yao C, Zhao ZG, Wang L, Wang BH; VISION Study Group. Efficacy and safety of combination therapy with vildagliptin and metformin versus metformin uptitration in Chinese patients with type 2 diabetes inadequately controlled with metformin monotherapy: a randomized, open-label, prospective study (VISION). Diabetes Obes Metab. 2016 Aug;18(8):775-82. doi: 10.1111/dom.12667. Epub 2016 May 18. PMID: 27406394.

228. Jiang, 2021

Bibliographic Reference	Jiang, Jianjia; Lin, Lu; Chen, Pin; Comparison of Dapaglifozin and Liraglutide in Patients with Poorly Controlled Type 2 Diabetes Mellitus: a 24-week, Open, Double-centered, Head to Head Trial.; Endocrine, metabolic & immune disorders drug targets; 2021; vol. 21 (no. 7); 1366-1374

228.1. 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)
Study location	2 sites in China
Study setting	Quanzhou First Hospital and Fuzong Clinical Medical College
Study dates	September 2017 to September 2018
Sources of funding	Funded by Fujian Provincial Department of Science and Technology
Inclusion criteria	Aged 18-75 years, met the 1999 WHO diabetes criteria, had been treated with stable doses of insulin glargine (>30 U/d), repaglinide (1 mg,3/d) and metformin (1500 mg/d) for over 3 months, with HbA1c level ranging from 7 to 9%, and BMI is 20-35 kg/m2
Exclusion criteria	Patients with type 1 diabetes mellitus, those with acute complications of diabetes mellitus, those with impaired liver and kidney function, those with definite severe cardiovascular and cerebrovascular diseases, pregnant or lactating women, those known or possibly allergic to liraglutide and/or dapagliflozin, and those with genital and urinary tract infections.

Recruitment / selection of participants	No additional information
Intervention(s)	Dapagliflozin (n=80) Patients received 10 mg oral dapagliflozin before breakfast for 24 weeks
Cointervention	Patients continued to receive the intensive treatment of metformin (1,500 mg/d), repaglinide (1 mg, 3/d) and glargine insulin (≥30U/d).
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Excluded “those with definite severe cardiovascular and cerebrovascular diseases”, otherwise unclear. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Excluded “those with definite severe cardiovascular and cerebrovascular diseases”, otherwise unclear. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Excluded “impaired liver and kidney 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 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	Liraglutide (n=80): Started with 0.6 mg, and added to 1.8 mg one week later, subcutaneous injection before bedtime for 24 weeks. Patients continued to receive the intensive treatment of metformin (1,500 mg/d), repaglinide (1 mg, 3/d) and glargine insulin (≥30U/d).
Number of participants	172
Duration of follow-up	24 weeks
Indirectness	NA
Method of analysis	Per protocol
Additional comments	The effects for the two groups before and after treatment were compared by student t test. The t test upon two independent samples was used for the comparison between the two groups, enumeration data are expressed by rate, $\chi 2$ test is adopted, and $P < 0.05$ was defined as being statistically significant. Given the results reported - most likely analysis is per protocol

228.2. Study arms

228.2.1. Dapagliflozin (N = 80)

Patients received 10 mg orally for 24 weeks

228.2.2. Liraglutide (N = 80)

Patients received 1.8 mg liraglutide as a subcutaneous injection for 24 weeks

228.3. Characteristics

228.3.1. Arm-level characteristics

Characteristic	Dapagliflozin (N = 80)	Liraglutide (N = 80)
% Male Dapagliflozin n = 79, Liraglutide n = 77 Sample size	n = 53 ; % = 67	n = 47 ; % = 61
Mean age (SD) (Years (mean, SD)) Dapagliflozin n = 79, Liraglutide n = 77 Mean (SD)	56.03 (10.02)	55.29 (10.53)
Ethnicity Dapagliflozin n = 79, Liraglutide n = 77 Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed (Years (mean, SD)) Dapagliflozin n = 79, Liraglutide n = 77 Mean (SD)	9.14 (6.07)	9.04 (6.11)
Smoking status Dapagliflozin n = 79, Liraglutide n = 77 Sample size	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Dapagliflozin n = 79, Liraglutide n = 77 Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Dapagliflozin n = 79, Liraglutide n = 77 Sample size	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Dapagliflozin (N = 80)	Liraglutide (N = 80)
People with significant cognitive impairment Dapagliflozin n = 79, Liraglutide n = 77 Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Dapagliflozin n = 79, Liraglutide n = 77 Sample size	n = NR ; % = NR	n = NR ; % = NR
Other antidiabetic medication used Dapagliflozin n = 79, Liraglutide n = 77 Sample size	n = NA ; % = NA	n = NA ; % = NA
Metformin Sample size	n = 79 ; % = 100	n = 77 ; % = 100
Repaglinide Sample size	n = 79 ; % = 100	n = 77 ; % = 100
Insulin glargine Sample size	n = 79 ; % = 100	n = 77 ; % = 100
Blood pressure-lowering medication used Dapagliflozin n = 79, Liraglutide n = 77 Sample size	n = NR ; % = NR	n = NR ; % = NR
Statins/lipid-lowering medication used Dapagliflozin n = 79, Liraglutide n = 77 Sample size	n = NR ; % = NR	n = NR ; % = NR
Other treatment being received Dapagliflozin n = 79, Liraglutide n = 77 Sample size	n = NR ; % = NR	n = NR ; % = NR

229. Jodar, 2020

Bibliographic Reference	Jodar, E; Michelsen, M; Polonsky, W; Rea, R; Sandberg, A; Vilsboll, T; Warren, M; Harring, S; Ziegler, U; Bain, S; Semaglutide improves health-related quality of life versus placebo when added to standard of care in patients with type 2 diabetes at high cardiovascular risk (SUSTAIN 6); Diabetes, Obesity and Metabolism; 2020; vol. 22 (no. 8); 1339-1347

229.1. Study details

Secondary publication of another included study- see primary study for details	SUSTAIN-6 trial. Primary publication: Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, Lingvay I, Rosenstock J, Seufert J, Warren ML, Woo V, Hansen O, Holst AG, Pettersson J, Vilsbøll T; SUSTAIN-6 Investigators. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med. 2016 Nov 10;375(19):1834-1844. doi: 10.1056/NEJMoa1607141. Epub 2016 Sep 15. PMID: 27633186. ID: 11795735
Other publications associated with this study included in review	NA
Trial name / registration number	SUSTAIN 6 / NCT01720446
Study location	See primary publication
Study setting	See primary publication
Study dates	See primary publication
Sources of funding	See primary publication
Inclusion criteria	See primary publication
Exclusion criteria	See primary publication

Recruitment / selection of participants	See primary publication
Intervention(s)	See primary publication
Population subgroups	See primary publication
Comparator	See primary publication
Number of participants	See primary publication
Duration of follow-up	See primary publication SF-36 completed at randomisation, 56 weeks and 104 weeks.
Indirectness	See primary publication
Method of analysis	ITT
Additional comments	Primary publication reports ITT analysis. For SF-36 outcomes, observed values used and missing values imputed using a mixed model for repeated measurements.

229.2. Study arms

229.2.1. Semaglutide (0.5 mg + 1.0 mg) (N = 1648)

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

229.2.2. Placebo (0.5 mg + 1.0 mg) (N = 1649)

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

230. Jonker, 2010

Bibliographic Reference	Jonker, J T; Lamb, H J; van der Meer, R W; Rijzewijk, L J; Menting, L J; Diamant, M; Bax, J J; de Roos, A; Romijn, J A; Smit, J W A; Pioglitazone compared with metformin increases pericardial fat volume in patients with type 2 diabetes mellitus.; The Journal of clinical endocrinology and metabolism; 2010; vol. 95 (no. 1); 456-60

230.1. Study details

Secondary publication of another included study- see primary study for details	Parent study van der Meer 2009 van der Meer RW, Rijzewijk LJ, de Jong HW, Lamb HJ, Lubberink M, Romijn JA, Bax JJ, de Roos A, Kamp O, Paulus WJ, Heine RJ, Lammertsma AA, Smit JW, Diamant M. Pioglitazone improves cardiac function and alters myocardial substrate metabolism without affecting cardiac triglyceride accumulation and high-energy phosphate metabolism in patients with well-controlled type 2 diabetes mellitus. Circulation. 2009 Apr 21;119(15):2069-77. doi: 10.1161/CIRCULATIONAHA.108.803916. Epub 2009 Apr 6. PMID: 19349323.

231. Jonker, 2010

Bibliographic Reference	Jonker, Jacqueline T; Wang, Yanan; de Haan, Willeke; Diamant, Michaela; Rijzewijk, Luuk J; van der Meer, Rutger W; Lamb, Hildo J; Tamsma, Jouke T; de Roos, Albert; Romijn, Johannes A; Rensen, Patrick C N; Smit, Johannes W A; Pioglitazone decreases plasma cholesteryl ester transfer protein mass, associated with a decrease in hepatic triglyceride content, in patients with type 2 diabetes.; Diabetes care; 2010; vol. 33 (no. 7); 1625-8

231.1. Study details

Secondary publication of another included study- see primary study for details	Parent study van der Meer 2009 van der Meer RW, Rijzewijk LJ, de Jong HW, Lamb HJ, Lubberink M, Romijn JA, Bax JJ, de Roos A, Kamp O, Paulus WJ, Heine RJ, Lammertsma AA, Smit JW, Diamant M. Pioglitazone improves cardiac function and alters myocardial substrate metabolism without affecting cardiac triglyceride accumulation and high-energy phosphate metabolism in patients with well-controlled type 2 diabetes mellitus. Circulation. 2009 Apr 21;119(15):2069-77. doi: 10.1161/CIRCULATIONAHA.108.803916. Epub 2009 Apr 6. PMID: 19349323.

232. Joubert, 2021

Bibliographic Reference	Joubert, M.; Opigez, V.; Pavlikova, B.; Peyro Saint Paul, L.; Jeandidier, N.; Briant, A. R.; Parienti, J. J.; Reznik, Y.; Efficacy and safety of exenatide as add-on therapy for patients with type 2 diabetes with an intensive insulin regimen: A randomized double-blind trial; Diabetes, Obesity & Metabolism; 2021; vol. 23 (no. 2); 374-381

232.1. 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	EXEPUMP [NCT01140893]
Study type	Randomised controlled trial (RCT)
Study location	Not clear, likely to be France
Study setting	NR
Study dates	NR
Sources of funding	AstraZeneca
Inclusion criteria	• Aged 35-70 years old • T2D diagnosed for at least 12 months • IIR (CSII or MDI) with insulin analogues for at least 6 months • HbA1c 7.5-10% • BMI 25-45 kg/m2 • Stable body weight (≤10% variation) during the last 3 months • Oral hypoglycemic agents (OHA) had to be interrupted at least two months prior to randomization

Exclusion criteria	• Active macro- or microvascular diabetic complications, especially those with proliferative retinopathy or with estimated glomerular filtration < 50 mL/min • Treatments that especially addressed weight loss and corticosteroid therapy were not permitted during the study. • Pregnancy/breastfeeding, history of confirmed pancreatitis and documented gastroparesis
Recruitment / selection of participants	NR
Intervention(s)	Subcutaneous (SC) injections of exenatide (5 µg BID) or matched placebo for the first month. Treatment was titrated thereafter to 10 µg BID for the 5 remaining months of the study, unless secondary effects prompted investigators to maintain the lower dose.
Cointervention	• In order to avoid hypoglycaemic episodes, an insulin retro titration protocol was applied at the introduction of the study treatment and when the study drug was titrated from 5 to 10 µg BID. • At the beginning of the study and during each visit, investigators promoted a healthy lifestyle, including a balanced diet and regular physical activity. • Patients were required to perform study drug injections 15 to 60 minutes before breakfast and dinner (or before lunch and dinner if they normally skipped the morning meal). • Injections were performed SC into habitual areas (upper arms, buttocks, abdomen, lower back or thighs) using a rechargeable injection pen provided by the manufacturer, as specified in the product leaflet. • Each study drug administration was recorded by the patient in a logbook diary In addition, regular information concerning hypoglycaemic symptoms and treatment was provided to patients. • Telephone calls were planned on a weekly basis during the first month, and after study drug titration to 10 µg BID, in order to readjust insulin doses in both arms of the study in a “treat to target” approach (fasting self-monitoring of blood glucose [SMBG] target: 70-130 mg/dL; 2-hour post-meal target: 120-180 mg/dL). 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. Baseline characteristics give breakdown by CAD, cerebral artery disease and PAD, overlap unclear but likely to be mixed.

Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	People without chronic kidney disease <20% had CKD
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	NA
Comparator	Subcutaneous (SC) injections of matched placebo

Number of participants	46 participants were randomised and 28 were allocated to exenatide and 18 were allocated to placebo.
Duration of follow-up	6 months
Indirectness	Directly applicable
Method of analysis	Not stated/unclear HbA1c, weight change, and BMI data were analysed with a covariance analysis. For HbA1c, data were missing at 6 months for 2 participants, and LOCF was used.
Additional comments	It appears that initially 38 participants were initially randomised (26 to exenatide and 12 to placebo. It then appears that 2 participants were later further allocated to exenatide and 6 were allocated to placebo.

232.2. Study arms

232.2.1. Exenatide (N = 28)

232.2.2. Placebo (N = 18)

232.3. Characteristics

232.3.1. Arm-level characteristics

Characteristic	Exenatide (N = 28)	Placebo (N = 18)
Mean age (SD) Mean (SD)	61 (7)	58 (8)
Ethnicity Nominal	NR	NR
Comorbidities Sample size	n = NA ; % = NA	n = NA ; % = NA
Retinopathy Sample size	n = 4 ; % = 14	n = 3 ; % = 17
Chronic kidney disease	n = 5 ; % = 18	n = 1 ; % = 6

Characteristic	Exenatide (N = 28)	Placebo (N = 18)
Sample size		
Neuropathy Sample size	n = 6 ; % = 21	n = 6 ; % = 33
Coronary artery disease Sample size	n = 10 ; % = 36	n = 6 ; % = 33
Cerebral artery disease Sample size	n = 2 ; % = 7	n = 1 ; % = 6
Peripheral artery disease Sample size	n = 7 ; % = 25	n = 3 ; % = 17
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed Mean (SD)	7.1 (6.1)	5.8 (5.5)
Cardiovascular risk factors Nominal	NR	NR
Smoking status Nominal	NR	NR
Alcohol consumption Nominal	NR	NR
Presence of severe mental illness Nominal	NR	NR
People with significant cognitive impairment Nominal	NR	NR
People with a learning disability Nominal	NR	NR
Number of people with obesity Nominal	NR	NR
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Exenatide (N = 28)	Placebo (N = 18)
Other antidiabetic medication used Mean (SD)	NA (NA)	NA (NA)
Insulin pump Sample size	n = 21 ; % = 75	n = 16 ; % = 89
Insulin pump Mean (SD)	NA (NA)	NA (NA)
Daily insulin dose/bodyweight Sample size	n = NA ; % = NA	n = NA ; % = NA
Daily insulin dose/bodyweight Mean (SD)	1.22 (0.73)	1.05 (0.35)
Blood pressure-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Beta-blockers Sample size	n = 13 ; % = 46	n = 7 ; % = 39
ACEI/ARB Sample size	n = 27 ; % = 96	n = 12 ; % = 67
Diuretics Sample size	n = 17 ; % = 61	n = 6 ; % = 33
Other antihypertensive drugs Sample size	n = 14 ; % = 50	n = 4 ; % = 22
Statins/lipid-lowering medication used Statins Sample size	n = 23 ; % = 82	n = 13 ; % = 72
Other treatment being received Platelet aggregation inhibitors Sample size	n = 20 ; % = 71	n = 8 ; % = 44

233. Kadowaki, 2017

Bibliographic Reference	Kadowaki, T.; Inagaki, N.; Kondo, K.; Nishimura, K.; Kaneko, G.; Maruyama, N.; Nakanishi, N.; Iijima, H.; Watanabe, Y.; Gouda, M.; Efficacy and safety of canagliflozin as add-on therapy to teneligliptin in Japanese patients with type 2 diabetes mellitus: Results of a 24-week, randomized, double-blind, placebo-controlled trial; Diabetes Obes Metab; 2017; vol. 19 (no. 6); 874-882

233.1. Study details

Trial name / registration number	NCT02354235
Study type	Randomised controlled trial (RCT)
Study location	Mulitcentre
Study setting	No additional information
Study dates	NR
Sources of funding	Mitsubishi Tanabe Pharma Corporation. Numerous authors declare funding and honoraria from multiple pharmaceutical companies
Inclusion criteria	Japanese patients with T2DM, aged 20 to 75 years, who had undergone a diet and exercise regimen and had received teneligliptin 20 mg monotherapy once daily for at least 8 weeks prior to initiation of the run-in period were enrolled. Patients using antidiabetic drugs other than teneligliptin were also eligible, providing the other antidiabetic drug was withdrawn for an 8-week washout period; that is, they used only teneligliptin for at least 8 weeks before the run-in period. Other inclusion criteria were HbA1c ≥ 7.0% and < 10.5% at initiation of the run-in period and by week 2 of the run-in period, with a difference of ≤0.5% in HbA1c between those time points, and fasting plasma glucose of ≤270 mg/dL at initiation of the run-in period.
Exclusion criteria	Diagnosis of type 1 diabetes mellitus or diabetes caused by pancreatic disorder or secondary diabetes (e.g., associated with acromegaly or Cushing syndrome) Insulin required for control of blood glucose Hereditary glucose–galactose malabsorption or renal diabetes Concomitant anorexia or bulimia Extremely low-carbohydrate diet

	Concomitant urinary tract/genital infection History of abdominal surgery or ileus Poorly controlled hypertension (systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥100 mmHg) Treatment for arrhythmia History of ventricular tachycardia or ventricular fibrillation Findings by standard 12-lead electrocardiogram at rest of paroxysmal tachycardia, atrioventricular block, sick sinus syndrome, ventricular fibrillation, QTc prolongation Heart failure (New York Heart Association class III or IV) Myocardial infarction, congestive heart failure, unstable angina, cerebrovascular disorder (excluding lacunar infarction) within 6 months before the run-in period History of transient ischemic attacks or brain infarction with clear neurological symptoms Complications of arteriosclerosis obliterans (Fontaine Class III or IV) Serious diabetic complications (proliferative retinopathy, Stage 4 or later diabetic nephropathy, or serious diabetic neuropathy) Alcohol addiction (pure alcohol ≥60 g/day intake every day) Serious concurrent liver or kidney disease (e.g., requiring hospitalization for treatment or for which surgery is indicated) Estimated glomerular filtration rate <45 mL/min/1.73 m2 Alanine aminotransferase or aspartate aminotransferase levels ≥2.5 times the upper limit of normal Malignant tumour (except patients without recurrence for ≥5 years, even with a past history of malignant tumour) Previous canagliflozin treatment Patients with contraindications as listed on the package insert for CANAGLU® Patients with contraindications as listed on the package insert for TENELIA® Females who may become pregnant or male who do not agree to use birth control during the study period.

	Females who are or may be pregnant or are nursing. Patients who have participated in other clinical studies and have been prescribed other study drugs within 8 weeks (56 days) prior to the first day of the run-in period, or patients who are currently participating in other studies.
Recruitment / selection of participants	No additional information
Intervention(s)	Canagliflozin (n=70) Canagliflozin 100 mg was administered orally once daily before breakfast for 24 weeks.
Cointervention	Teneligliptin Patients received 20 mg teneligliptin orally once daily before breakfast for 24 week treatment period in addition to canagliflozin. After the treatment period, patients were observed for an additional 2 weeks (post-treatment observation period), during which they continued to receive teneligliptin 20 mg orally once daily before breakfast
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 Excluded “Myocardial infarction, congestive heart failure, unstable angina, cerebrovascular disorder (excluding lacunar infarction) 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 “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 category at baseline	Not stated/unclear
Population subgroups	NA
Comparator	Placebo (n=68) Patients received oral placebo for 24 week treatment period Patients also received 20 mg teneligliptin orally once daily before breakfast for 24 week treatment period in addition to placebo
Number of participants	138
Duration of follow-up	26 weeks; 24 week treatment period plus an additional 2 weeks post-treatment observation period
Indirectness	NA
Method of analysis	ITT

Additional comments	Efficacy was analysed using the full analysis set. For measurements at the end of the treatment period, descriptive statistics, change from baseline to end of treatment period for each group, 95% confidence interval (CI) of the mean for each group, between-group difference (T + C − T + P group) and 95% CI of the difference were calculated. The impact of the baseline measurement on changes in each efficacy endpoint was determined by analysis of covariance using the baseline measurement as the covariate. For the primary endpoint, the least square mean (LS mean) and standard error (SE) of the LS mean were calculated for each group. The point estimate of the between-group difference in LS mean (T + C group − T+P group) as well as the SE, 95% CI and P value were also calculated. Safety analysis was performed on the safety analysis set, which included all randomized patients except those who did not receive any dose of canagliflozin or placebo in combination with teneligliptin during the treatment period or patients for whom no safety data were collected after randomization.

233.2. Study arms

233.2.1. Canagliflozin (N = 70)

Patients received 100 mg canagliflozin orally once daily before breakfast in addition to 20 mg teneligliptin also administered orally once daily before breakfast

233.2.2. Placebo (N = 68)

Patients received oral placebo once daily before breakfast in addition to 20 mg teneligliptin also administered orally once daily before breakfast

233.3. Characteristics

233.3.1. Arm-level characteristics

Characteristic	Canagliflozin (N = 70)	Placebo (N = 68)
% Male Sample size	n = 54 ; % = 77.1	n = 53 ; % = 77.9
Mean age (SD) (Years (mean, SD)) Mean (SD)	58.4 (8.9)	56 (9.5)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Canagliflozin (N = 70)	Placebo (N = 68)
Time since type 2 diabetes diagnosed (Years (mean, SD)) Mean (SD)	8.34 (7.74)	6.5 (3.89)
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 = NR ; % = NR	n = NR ; % = NR
Blood pressure-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Statins/lipid-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR

234. Kadowaki, 2011

Bibliographic Reference	Kadowaki, T.; Namba, M.; Imaoka, T.; Yamamura, A.; Goto, W.; Boardman, M. K.; Sowa, H.; Improved glycemic control and reduced bodyweight with exenatide: A double-blind, randomized, phase 3 study in Japanese patients with suboptimally controlled type 2 diabetes over 24 weeks; J Diabetes Invest; 2011; vol. 2 (no. 3); 210-7

234.1. 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	NCT00577824
Study type	Randomised controlled trial (RCT)
Study location	Japan
Study setting	Report states that study was carried out in 23 centres - no further information was given
Study dates	NR
Sources of funding	Amylin Pharmaceuticals and Eli Lilly and Company
Inclusion criteria	• Between 20 and 75 years-of-age and had been diagnosed with type 2 diabetes mellitus • Body weight ≥ 50 kg • Treated with SU monotherapy, combination therapy with SU and BG, or SU and TZD without any dose change for 90 days before screening. • Patients on alpha-glucosidase inhibitors or short-acting insulin secretion inducers at the time of screening could be included in the present study but had to be discontinued and washed-out for a period of 2–3 weeks.

	• Patients had inadequate glycaemic control, as shown by HbA1c ≥ 7.0% and ≤ 10.0% at screening.
Exclusion criteria	• Treatment with any exogenous insulin or drug directly affecting gastrointestinal motility within 90 days before screening • A clinically significant gastrointestinal disorder or hepatic disorder • Serum creatinine ≥1.5 mg/dL in men or ≥ 1.4 mg/dL in women • Fasting plasma glucose (FPG) ≥ 250 mg/dL or casual blood glucose ≥ 350 mg/dL or at least one episode of severe hypoglyacemia. • Female patients of childbearing age were excluded if they were pregnant at the time of enrolment, intended to become pregnant during the study, had not practiced a reliable method of birth control for 90 days before screening or did not agree to continue practicing a reliable method of birth control during the study.
Recruitment / selection of participants	211 patients were screened and 181 fulfilled inclusion/exclusion criteria.
Intervention(s)	• Exenatide 5 ug b.i.d subcutaneous injection • Exenatide 10 ug b.i.d subcutaneous injection- participants received 5 ug b.i.d for the first 4 weeks followed by 10 ug twice daily for the last 20 weeks [Patients were instructed to self-administer randomised study drug into the abdomen within 60 min before their morning and evening meals.]
Cointervention	Randomised treatment was received in addition to oral therapy.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics
Strata 2: People with 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 subcutaneous [Patients were instructed to self-administer randomised study drug into the abdomen within 60 min before their morning and evening meals.]
Number of participants	Of 72 participants allocated to exenatide 5 ug, 65 participants completed, 6 discontinued due to adverse events and 1 discontinued due to protocol violation. Of 73 participants allocated exenatide 10 ug, 72 participants received at least one dose, 53 participants completed, 18 discontinued due to adverse events and 1 discontinued due to protocol violation. Of 36 participants allocated to placebo, 35 received one dose of placebo, 34 completed and 1 discontinued due to adverse events.

Duration of follow-up	24 weeks
Indirectness	Directly applicable
Method of analysis	Not stated/unclear Data are presented for the full analysis set (FAS), which includes all randomized patients who received at least one dose of study drug who had post-baseline data available. Change in HbA1c was evaluated by analysis of of covariance with treatment group as a factor and baseline HbA1c as the covariate and comparison with the placebo carried out with t-test using lease square (Ls) mean.
Additional comments	The study also included an open-label extension period to 52 weeks, however, this was not included as it was an extension study.

234.2. Study arms

234.2.1. Exenatide 5 ug (N = 72)

234.2.2. Exenatide 10 ug (N = 73)

234.2.3. Placebo (N = 36)

234.3. Characteristics

234.3.1. Arm-level characteristics

Characteristic	Exenatide 5 ug (N = 72)	Exenatide 10 ug (N = 73)	Placebo (N = 36)
% Male Characteristics reported for participants who received at lease one study dose. Exenatide 10 ug n=72, placebo n=35 Sample size	n = 49 ; % = 68.1	n = 49 ; % = 68.1	n = 24 ; % = 68.6
Mean age (SD) Mean (SD)	58.5 (9.3)	59.4 (9.8)	56.3 (11.4)

Characteristic	Exenatide 5 ug (N = 72)	Exenatide 10 ug (N = 73)	Placebo (N = 36)
Ethnicity Nominal	NR	NR	NR
Comorbidities Nominal	NR	NR	NR
Presence of frailty Nominal	NR	NR	NR
Time since type 2 diabetes diagnosed Sample size	n = 12.2 ; % = 6.3	n = 11.6 ; % = 7	n = 12.4 ; % = 6.5
Cardiovascular risk factors Nominal	NR	NR	NR
Smoking status Nominal	NR	NR	NR
Alcohol consumption Nominal	NR	NR	NR
Presence of severe mental illness Nominal	NR	NR	NR
People with significant cognitive impairment Nominal	NR	NR	NR
People with a learning disability Nominal	NR	NR	NR
Number of people with obesity Nominal	NR	NR	NR
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
SU alone Sample size	n = 4 ; % = 5.6	n = 8 ; % = 11.1	n = 3 ; % = 8.6
SU + alpha-GI Sample size	n = 1 ; % = 1.4	n = 4 ; % = 5.6	n = 3 ; % = 8.6

Characteristic	Exenatide 5 ug (N = 72)	Exenatide 10 ug (N = 73)	Placebo (N = 36)
SU + BG Sample size	n = 33 ; % = 45.8	n = 27 ; % = 37.5	n = 14 ; % = 40
SU + BG + alpha-GI Sample size	n = 22 ; % = 30.6	n = 13 ; % = 18.1	n = 9 ; % = 25.7
SU + BG + meglitinide derivative Sample size	n = 0 ; % = 0	n = 1 ; % = 1.4	n = 0 ; % = 0
SU + TZD Sample size	n = 6 ; % = 8.3	n = 12 ; % = 16.7	n = 4 ; % = 11.4
SU + TZD + alpha-GI Sample size	n = 6 ; % = 8.3	n = 7 ; % = 9.7	n = 2 ; % = 5.7
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

235. Kaku, 2009

Bibliographic Reference	Kaku, K.; Efficacy and safety of therapy with metformin plus pioglitazone in the treatment of patients with type 2 diabetes: a double-blind, placebo-controlled, clinical trial; Curr Med Res Opin; 2009; vol. 25 (no. 5); 1111-9

235.1. 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 000001110
Study type	Randomised controlled trial (RCT)
Study location	Japan
Study setting	The report states that the study was performed in 25 centres throughout Japan - no further details were reported
Study dates	NR
Sources of funding	Takeda Pharmaceutical Co., Ltd
Inclusion criteria	• Male or female outpatients with type 2 diabetes • Aged ≥20 and <65 years • Treated with diet and exercise but no antidiabetic drugs other than metformin • Following the 12-week observation period, participants had HbA1c of ≥6.5 and <10%
Exclusion criteria	• Patients with type 1 diabetes • Impaired hepatic function • Renal insufficiency

	• Cardiac failure • Other serious heart disease • Cerebrovascular disease • Patients with other conditions that could potentially require hospitalization such as cancer, severe lung, gastrointestinal, pancreatic, or haematological disorders. • Patients with a history of lactic acidosis/ketoacidosis/diabetic coma (or precoma within the preceding 26 weeks) • History of drug (including alcohol) dependency • Drugs which might affect glycaemic control were not permitted
Recruitment / selection of participants	236 participants were screened and following a 12-week observation period where participants received treatment with metformin, 169 participants were deemed eligible and were randomised.
Intervention(s)	Pioglitazone - participants received 15 mg pioglitazone once daily before or after breakfast for 12 weeks. Providing the drug regimen was well tolerated, pioglitazone dosage was increased to 30 mg once daily from weeks 13 to 28.
Cointervention	During the 12-week observation period, participants received metformin 500 or 750 mg/day, and the dosage was maintained throughout the study. In the pioglitazone + metformin arm, 46 participants received 500 mg/day and 37 participants received 750 mg/day during observation and treatment. In the metformin only arm, 46 participants received 500 mg/day and 40 participants received 750 mg/day during observation and treatment.
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Excluded cardiac failure
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Excluded “serious heart disease, cerebrovascular disease”, otherwise unclear. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Excluded “renal insufficiency”, otherwise unclear. No information in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and	Not stated/unclear

high cardiovascular risk	
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	NA
Comparator	Placebo for a period of 12 weeks
Number of participants	Of 83 participants allocated to pioglitazone, 9 participants withdrew from the study. Of 86 participants allocated to placebo, 7 participants withdrew from the study.
Duration of follow-up	28 weeks
Indirectness	Directly applicable
Method of analysis	Not stated/unclear Report states that a 'full analysis set' assessment (FAS) of efficacy was performed in patients receiving ≥1 dose of pioglitazone, and that tolerability was assessed in the 'safety analysis set' which comprised all patients who had taken ≥1 dose of study medication. The last

	measurement before discontinuation or on completion of the protocol was considered the end-of-treatment measurement.
Additional comments	NA

235.2. Study arms

235.2.1. Pioglitazone + Metformin (N = 83)

235.2.2. Placebo + Metformin (N = 86)

235.3. Characteristics

235.3.1. Arm-level characteristics

Characteristic	Pioglitazone + Metformin (N = 83)	Placebo + Metformin (N = 86)
% Male Sample size	n = 55 ; % = 66.3	n = 49 ; % = 57
Mean age (SD) Mean (SD)	52 (8.6)	53 (7.5)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	4.5 (3.7)	5.6 (5)
Cardiovascular risk factors Nominal	NR	NR

Characteristic	Pioglitazone + Metformin (N = 83)	Placebo + Metformin (N = 86)
Smoking status Sample size	n = NA ; % = NA	n = NA ; % = NA
Never Sample size	n = 35 ; % = 42.2	n = 36 ; % = 41.9
Active Sample size	n = 31 ; % = 37.3	n = 28 ; % = 32.6
Previous Sample size	n = 17 ; % = 20.5	n = 22 ; % = 26.6
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 Number of participants on metformin therapy before trial Sample size	n = 58 ; % = 70	n = 66 ; % = 77
Blood pressure-lowering medication used Nominal	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

236. Kaku, 2019

Bibliographic Reference	Kaku, K.; Araki, E.; Tanizawa, Y.; Ross Agner, B.; Nishida, T.; Ranthe, M.; Inagaki, N.; Superior efficacy with a fixed-ratio combination of insulin degludec and liraglutide (IDegLira) compared with insulin degludec and liraglutide in insulin-naive Japanese patients with type 2 diabetes in a phase 3, open-label, randomized trial; Diab Obes Metab; 2019; vol. 21 (no. 12); 2674-2683

236.1. 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	NCT02607306
Study type	Randomised controlled trial (RCT)
Study location	Japan
Study setting	Hospital
Study dates	11/2015 - 12/2017
Sources of funding	Novo Nordisk funded medical writing and editorial support. Two Novo Nordisk employees also provided review and input to the manuscript.
Inclusion criteria	• Male or female Japanese subjects, age at least 20 years at the time of signing informed consent • Type 2 diabetes subjects (diagnosed clinically) at least 6 months prior to screening • HbA1c (glycosylated haemoglobin) 7.0-11.0 % (both inclusive) by central laboratory analysis, with the aim of a median of 8.3%. When approximately 50% of the randomised subjects have a HbA1c above 8.3%, the remaining subjects randomised must have a HbA1c below or equal to 8.3%; or when approximately 50% of the

	randomised subjects have a HbA1c below or equal to 8.3%, the remaining subjects randomised must have a HbA1c above 8.3% • BMI above or equal to 20 kg/m^2 • Subjects on stable therapy with one oral antidiabetic (defined as unchanged medication and unchanged dose) for at least 60 days (metformin, a-GI, TZD, SU, SGLT2i or glinide) prior to screening according to approved Japanese labelling
Exclusion criteria	• Previous treatment with insulin (except for short-term treatment in connection with intercurrent illness including gestational diabetes) • Treatment with any medication for the indication of diabetes or obesity other than stated in the inclusion criteria in a period of 60 days before screening • Anticipated initiation or change in concomitant medications in excess of 14 days known to affect weight or glucose metabolism • Impaired liver function, defined as alanine aminotransferase or aspartate aminotransferase equal to or above 2.5 times upper limit of normal • Renal impairment eGFR below 60mL/min/1.73m^2 as per Chronic Kidney Disease Epidemiology Collaboration • Screening calcitonin equal to or above 50 ng/L • History of pancreatitis (acute or chronic) • Personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2. • Subjects presently classified as being in New York Heart Association Class IV
Recruitment / selection of participants	Participants in Japan with uncontrolled type 2 diabetes on oral antidiabetic medication were recruited and randomised 1:1:1 via a centralized allocation system using a web response system to one of the three treatments.
Intervention(s)	Insulin degludec/liraglutide (IDegLira) administered once daily, subcutaneously Doses were 10 dose steps of IDegLira (10 U degludec +0.36 mg liraglutide) and adjusted twice weekly in increments of ±2 U. The maximum dose of IDegLira was 50 dose steps, which delivers the maximum licensed liraglutide dose for diabetes (50 U degludec/1.8 mg liraglutide).
Cointervention	Metformin, alpha-glucosidase inhibitors, thiazolidinediones, sulphonylureas, SGLT2 inhibitors, glinides. Pre-trial oral antidiabetic treatment continued unchanged at pre-trial doses; in some cases, for safety reasons, the dose could be reduced at the discretion of the investigator.
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 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	Degludec administered once daily, subcutaneously Recommended starting dose was 10U and doses were adjusted twice weekly in increments of ±2 U. There was no maximum dose for degludec. Liraglutide administered once daily, subcutaneously Liraglutide was initiated at 0.3 mg and increased by 0.3 mg each week over a 6-week period up to the maximum dose of 1.8 mg. Temporary dose reductions for <1 week were only allowed for safety reasons.
Number of participants	N = 819
Duration of follow-up	52 weeks
Indirectness	No additional information.
Method of analysis	ITT Not stated/unclear
Additional comments	The authors mention ITT and completer case analysis was used.

236.2. Study arms

236.2.1. Insulin degludec/liraglutide once daily (N = 275)

Administered subcutaneously.

236.2.2. Degludec once daily (N = 271)

Administered subcutaneously.

236.2.3. Liraglutide once daily (N = 273)

Administered subcutaneously.

236.3. Characteristics

236.3.1. Study-level characteristics

Characteristic	Study (N = 819)
Japanese No of events	n = 819 ; % = 100

236.3.2. Arm-level characteristics

Characteristic	Insulin degludec/liraglutide once daily (N = 275)	Degludec once daily (N = 271)	Liraglutide once daily (N = 273)
% Male No of events	n = 194 ; % = 70.5	n = 195 ; % = 72	n = 192 ; % = 70.3
Mean age (SD) (years) Mean (SD)	56.9 (10.2)	57.8 (9.9)	56.8 (10.1)
Presence of frailty Nominal	NR	NR	NR
Smoking status Nominal	NR	NR	NR
Alcohol consumption Nominal	NR	NR	NR
Presence of severe mental illness Nominal	NR	NR	NR
People with significant cognitive impairment Nominal	NR	NR	NR
People with a learning disability Nominal	NR	NR	NR
Number of people with obesity Nominal	NR	NR	NR

Characteristic	Insulin degludec/liraglutide once daily (N = 275)	Degludec once daily (N = 271)	Liraglutide once daily (N = 273)
Metformin No of events	n = 47 ; % = 17.1	n = 46 ; % = 17	n = 47 ; % = 17.2
Alpha-glucosidase inhibitor No of events	n = 41 ; % = 14.9	n = 40 ; % = 14.8	n = 41 ; % = 15
Thiazolidinediones No of events	n = 43 ; % = 15.6	n = 43 ; % = 15.9	n = 42 ; % = 15.4
Sulphonylureas No of events	n = 43 ; % = 15.6	n = 42 ; % = 15.5	n = 42 ; % = 15.4
SGLT2 inhibitor No of events	n = 61 ; % = 22.2	n = 61 ; % = 22.5	n = 61 ; % = 22.3
Glinides No of events	n = 40 ; % = 14.5	n = 39 ; % = 14.4	n = 40 ; % = 14.7
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

237. Kaku, 2010

Bibliographic Reference	Kaku, K; Rasmussen, M F; Clauson, P; Seino, Y; Improved glycaemic control with minimal hypoglycaemia and no weight change with the once-daily human glucagon-like peptide-1 analogue liraglutide as add-on to sulphonylurea in Japanese patients with type 2 diabetes.; Diabetes, obesity & metabolism; 2010; vol. 12 (no. 4); 341-7

237.1. Study details

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	Seino, Y., Rasmussen, M. F., Nishida, T. et al. (2011) Glucagon-like peptide-1 analog liraglutide in combination with sulfonylurea safely improves blood glucose measures vs sulfonylurea monotherapy in japanese patients with type 2 diabetes: Results of a 52-week, randomized, multicenter trial. J Diabetes Invest 2(4): 280-286
Trial name / registration number	NCT00395746
Study type	Randomised controlled trial (RCT)
Study location	Japan
Study setting	Report states that study was carried out in 49 centres in Japan - no further information reported
Study dates	NR
Sources of funding	Novo Nordisk Pharmaceuticals Ltd
Inclusion criteria	• Japanese men and women • ≥20 years of age • T2DM currently treated with an SU [glibenclamide (1.25–10 mg), glicazide (40–160 mg) or glimepiride (1–6 mg)] for > 8 weeks • HBA1c levels ranging from 7.0 to <10% • Body mass index (BMI) <35.0 kg/m2

Exclusion criteria	• Treated with insulin within 12 week • Were receiving or expecting to receive systemic corticosteroids • Had known hypoglycaemia unawareness or recurrent major hypoglycaemia • Impaired renal or hepatic function • Significant cardiovascular disease (heart failure, coronary artery disease or uncontrolled hypertension) • Non-stabilized proliferative retinopathy or maculopathy
Recruitment / selection of participants	There was a 4-week (± 7 day) run-in/screening period preceded randomisation.
Intervention(s)	• Liraglutide 0.6 mg/day once daily • Liraglutide 0.9 mg/day once daily [There was a 2-week dose escalation period where 2-week dose escalation period where daily liraglutide doses were up-titrated from 0.3 mg/day (50µl) to 0.6 mg/day (100 µl) after the first week, with an additional increase to 0.9 mg/day (150 µl) for the 0.9 mg cohort after the second week. During the 22-week maintenance period, liraglutide was injected once daily in the morning or evening subcutaneously into the upper arm, thigh or abdomen.
Cointervention	Subjects continued on their current SU therapies throughout the trial.
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 “significant cardiovascular disease (coronary artery disease or uncontrolled hypertension)”, otherwise unclear. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Study excluded "impaired renal or hepatic function" no further details
Strata 4: People with type 2 diabetes mellitus and high	Not stated/unclear

cardiovascular risk	
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	NA
Comparator	Placebo
Number of participants	308 people were screened, 264 participants were randomised and exposed to treatment, 241 completed the trial at 24-weeks. At 52 weeks, in placebo, liraglutide 0.6 mg and liraglutide 0.9 mg arms, 75%, 88.6%, and 95.5% of participants completed the study. Most participants who withdrew did so as a result of ineffective therapy in the placebo group. No patients in the liraglutide 0.9 mg group dropped out due to ineffective therapy.
Duration of follow-up	24 weeks and 52 weeks
Indirectness	Directly applicable
Method of analysis	Not stated/unclear 95% CI for the mean difference (each liraglutide - placebo) was calculated by analysis of variance (ANOVA) model with treatment group and pre-trial SU as fixed effects and corresponding baseline value as covariate. The

	last observation carried forward (LOCF) approach was used for subjects who had at least one valid post-baseline measurement. Furthermore, each end-point was summarized using summary statistics by visit and treatment group.
Additional comments	The first 24 weeks were double-blind, and this was followed by a 28-week open-label period.

237.2. Study arms

237.2.1. Liraglutide 0.6 mg (N = 88)

237.2.2. Liraglutide 0.9 mg (N = 88)

237.2.3. Placebo (N = 88)

237.3. Characteristics

237.3.1. Arm-level characteristics

Characteristic	Liraglutide 0.6 mg (N = 88)	Liraglutide 0.9 mg (N = 88)	Placebo (N = 88)
% Male Sample size	n = 53 ; % = 60.2	n = 59 ; % = 67	n = 57 ; % = 64.8
Mean age (SD) Mean (SD)	59.1 (10.3)	61.3 (11)	58.6 (9.7)
Ethnicity Nominal	NR	NR	NR
Comorbidities Concomitant illness Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Yes Sample size	n = 86 ; % = 97.7	n = 87 ; % = 98.9	n = 88 ; % = 100
No	n = 2 ; % = 2.3	n = 1 ; % = 1.1	n = 0 ; % = 0

Characteristic	Liraglutide 0.6 mg (N = 88)	Liraglutide 0.9 mg (N = 88)	Placebo (N = 88)
Sample size			
Presence of frailty Nominal	NR	NR	NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	9.3 (5.8)	11.6 (7.7)	10.1 (7.3)
Cardiovascular risk factors Nominal	NR	NR	NR
Smoking status Nominal	NR	NR	NR
Alcohol consumption Nominal	NR	NR	NR
Presence of severe mental illness Nominal	NR	NR	NR
People with significant cognitive impairment Nominal	NR	NR	NR
People with a learning disability Nominal	NR	NR	NR
Number of people with obesity Nominal	NR	NR	NR
Other antidiabetic medication used Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Glibenclamide Sample size	n = 20 ; % = 22.7	n = 21 ; % = 23.9	n = 20 ; % = 22.7
Gliclazide Sample size	n = 7 ; % = 8	n = 6 ; % = 6.8	n = 6 ; % = 6.8
Glimepiride	n = 61 ; % = 69.3	n = 61 ; % = 69.3	n = 62 ; % = 70.5

Characteristic	Liraglutide 0.6 mg (N = 88)	Liraglutide 0.9 mg (N = 88)	Placebo (N = 88)
Sample size			
Blood pressure-lowering medication used Nominal	NR	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR	NR
Other treatment being received Nominal	NR	NR	NR

238. Kanazawa, 2010

Bibliographic Reference	Kanazawa, I.; Yamaguchi, T.; Yano, S.; Yamamoto, M.; Yamauchi, M.; Kurioka, S.; Sugimoto, T.; Baseline atherosclerosis parameter could assess the risk of bone loss during pioglitazone treatment in type 2 diabetes mellitus; Osteoporos Int; 2010; vol. 21 (no. 12); 2013-8

238.1. Study details

Secondary publication of another included study- see primary study for details	
Other publications associated with this study included in review	Kanazawa 2011 Kanazawa I, Yamamoto M, Yamaguchi T, Sugimoto T. Effects of metformin and pioglitazone on serum pentosidine levels in type 2 diabetes mellitus. Exp Clin Endocrinol Diabetes. 2011 Jun;119(6):362-5. doi: 10.1055/s-0030-1267953. Epub 2011 Apr 6. PMID: 21472665.
Trial name / registration number	UMIN 000001997
Study type	Randomised controlled trial (RCT)
Study location	Shimane University Hospital, Japan
Study setting	No additional information
Study dates	Patients enrolled from 1November 2006 to 1 January 2008
Sources of funding	Supported by the Alumni Association of Shimane University School of Medicine and from the Ministry of Science, Education and Culture of Japan
Inclusion criteria	Patients who visited Shimane University Hospital for treatment of type 2 diabetes. All women had been without spontaneous menstrual cycle for more than 1 year
Exclusion criteria	(1) Patients with hepatic or renal dysfunction or nutritional derangements, (2) who had taken TZDs or metformin, and (3) who had taken drugs known to influence bone and calcium metabolism, such as vitamin D, bisphosphonate, or estrogen up until the time of the study.

Recruitment / selection of participants	No additional information
Intervention(s)	Pioglitazone (n=22) Pioglitazone 15–30 mg was orally administered once daily for 12 months
Cointervention	Patients had also been receiving insulin, sulfonylurea, and alpha-glucosidase inhibitors. All prescription medications of each patient were not changed during 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 Excluded “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	NA
Comparator	Metformin (n = 23) Metformin (250 mg) was two or three times after meal (500–750 mg/day) Patients had also been receiving insulin, sulfonylurea, and alpha-glucosidase inhibitors. All prescription medications of each patient were not changed during the study
Number of participants	45
Duration of follow-up	12 months
Indirectness	NA
Method of analysis	Not stated/unclear
Additional comments	Data were expressed as mean ± SD. Student's t tests were used for comparison between two groups, paired t tests for comparison of mean values within groups, $\chi 2$ tests for nominal scale, and correlation and multiple regression analysis for the relationships between two parameters. All analyses were carried out using the statistical computer program StatView

238.2. Study arms

238.2.1. Pioglitazone (N = 22)

Pioglitazone 15–30 mg was orally administered once daily for 12 months

238.2.2. Metformin (N = 23)

250 mg Metformin was orally administered 2 or 3 times after meals (500 -75 mg/day) for 12 months

238.3. Characteristics

238.3.1. Arm-level characteristics

Characteristic	Pioglitazone (N = 22)	Metformin (N = 23)
% Male Sample size	n = 14 ; % = 63.6	n = 13 ; % = 56.5
Mean age (SD) (Years (mean, SD)) Mean (SD)	67 (10)	66 (10)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed (Years (mean, SD)) Mean (SD)	14 (9)	12 (11)
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

Characteristic	Pioglitazone (N = 22)	Metformin (N = 23)
Insulin Sample size	n = 12 ; % = 54.5	n = 13 ; % = 56.5
Sulfonylurea Sample size	n = 6 ; % = 27.3	n = 5 ; % = 21.7
Alpha glucosidase inhibitors Sample size	n = 3 ; % = 13.6	n = 2 ; % = 8.7
Blood pressure-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Statins/lipid-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR

239. Kaneto, 2020

Bibliographic Reference	Kaneto, Hideaki; Takami, Akane; Spranger, Robert; Amano, Atsushi; Watanabe, Daisuke; Niemoeller, Elisabeth; Efficacy and safety of insulin glargine/lixisenatide fixed-ratio combination (iGlarLixi) in Japanese patients with type 2 diabetes mellitus inadequately controlled on basal insulin and oral antidiabetic drugs: The LixiLan JP-L randomized clinical trial.; Diabetes, obesity & metabolism; 2020; vol. 22suppl4; 3-13

239.1. 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	LixiLan JP-L [NCT02752412]
Study type	Randomised controlled trial (RCT)
Study location	Japan
Study setting	NR
Study dates	NR
Sources of funding	Sanofi
Inclusion criteria	• Japanese adult patients with HbA1c ≥7.5% (58.5 mmol/mol) and ≤9.5% (80.3 mmol/mol) • Had been diagnosed with T2DM for more than 1 year • HbA1c had been inadequately controlled by the use of 1 or 2 OADs (Acceptable OADs included metformin, sulfonylureas, a-glucosidase inhibitors, glinides, DPP-4 inhibitors, and sodium-glucose co-transporter 2 inhibitors) plus basal insulin for at least 3 months prior to screening

	• Stable insulin dose up to 15 U/day for at least 1 month prior to screening
Exclusion criteria	NR
Recruitment / selection of participants	There was an initial 14-week screening period with a 12-week run-in period where all OADs except metformin were discontinued and metformin therapy was initiated if not already used. Existing treatment with basal insulin was continued or switched to iGlar and was optimised to reach fasting self-monitored plasma glucose (SMPG) levels ≤8.9 mmol/L. At the end of the run-in period, participants with an HbA1c ≥7.5% and ≤9.5%, average SMPG ≤8.9 mmol/L, average iGlar dose ≥5 U/day and ≤14 U/day, metformin dose ≥750 mg/day, and no signs of pancreatic disease were randomised.
Intervention(s)	iGlarLixi was self-administered using a subcutaneous pen injector. Participants were instructed to inject before breakfast. The starting dose of iGlarLixi was based on the dose used on the day before randomisation and was ≥5 U/5mcg and ≥10 U/10mcg. Following titration, the maximum dose was ≥20 U/20mcg.
Cointervention	Both treatments were titrated once a week during the 26-week treatment period to achieve a fasting SMPG of 4.4 to 5.6 mmol/L (80-100 mg/dL) while avoiding hypoglycemia. If a higher daily dose was needed to maintain HbA1c below 8.5% (69.4 mmol/mol) after week 12, the maximum dose was maintained and initiation of rescue therapy with a rapid-acting insulin glulisine was recommended. Metformin was maintained at a stable dose throughout treatment after randomization unless there was a safety issue related to its use.
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 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear

Subgroup 2: Onset of type 2 diabetes mellitus	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	iGlar was self-administered using a subcutaneous pen injector. Injections could be given either before breakfast or at bedtime, but at about the same time every day.
Number of participants	906 participants were screened, and 512 participants were randomised. Of 255 participants allocated to iGlarLixi, 245 completed the 26-treatment period and 10 discontinued. Of 257 participants allocated to iGlar, 244 participants completed the treatment period, and 13 participants discontinued treatment.
Duration of follow-up	26 weeks
Indirectness	Directly applicable
Method of analysis	Modified ITT All participants who were exposed to at least one dose of study drug and had a baseline assessment and one post-baseline assessment of any efficacy variable irrespective of compliance. Participants underwent efficacy analyses according to the treatment they were randomised. Other Safety analyses included any randomised participants who had received one or more doses of the study drug. Participants underwent safety analyses according to the treatment received.
Additional comments	Open-label study

239.2. Study arms

239.2.1. iGlarLixi (N = 255)

239.2.2. Insulin glargine (N = 257)

239.3. Characteristics

239.3.1. Arm-level characteristics

Characteristic	iGlarLixi (N = 255)	Insulin glargine (N = 257)
Mean age (SD) Mean (SD)	59.4 (10.5)	60.2 (10.4)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	11.86 (7.5)	12.02 (7.27)
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

Characteristic	iGlarLixi (N = 255)	Insulin glargine (N = 257)
People with a learning disability Nominal	NR	NR
Number of people with obesity Nominal	NR	NR
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Using one oral antidiabetic drug at screening Sample size	n = 140 ; % = 54.9	n = 145 ; % = 56.4
Using two oral antidiabetic drugs at screening Sample size	n = 115 ; % = 45.1	n = 112 ; % = 43.6
Biguanide use at screening Sample size	n = 204 ; % = 80	n = 210 ; % = 81.7
Blood pressure-lowering medication used Nominal	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR
% Female (n (%)) Sample size	n = 96 ; % = 37.6	n = 110 ; % = 42.8
Insulin glargline 100 U/mL Sample size	n = 137 ; % = 53.7	n = 128 ; % = 49.8
Insulin glargine 300 U/mL Sample size	n = 37 ; % = 14.5	n = 46 ; % = 17.9
Insulin degludec Sample size	n = 80 ; % = 31.4	n = 82 ; % = 31.9
Insulin detemir Sample size	n = 1 ; % = 0.4	n = 1 ; % = 0.4

Characteristic	iGlarLixi (N = 255)	Insulin glargine (N = 257)
Other Sample size	n = 0 ; % = 0	n = 0 ; % = 0
Daily dose (mg) of metformin at baseline (n (%)) Sample size	n = NR ; % = NR	n = NR ; % = NR
<750 Sample size	n = 0 ; % = 0	n = 1 ; % = 0.4
>=750 to <=1500 Sample size	n = 238 ; % = 93.3	n = 234 ; % = 91.1

240. Kang, 2021

Bibliographic Reference	Kang, C.; Qiao, Q.; Tong, Q.; Bai, Q.; Huang, C.; Fan, R.; Wang, H.; Kaliannan, K.; Wang, J.; Xu, J.; Effects of exenatide on urinary albumin in overweight/obese patients with T2DM: a randomized clinical trial; Scientific Reports; 2021; vol. 11 (no. 1); 20062

240.1. 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	ChiCTR-IPR-17010825
Study type	Randomised controlled trial (RCT) Double-blind active-controlled parallel group randomised trial
Study location	Chongqing, China
Study setting	Outpatient
Study dates	03/2017 to 12/2017
Sources of funding	Supported by Project 2014YLC20 of the Xinqiao Hospital, and Project ctstc2015shmszx120014 and ctstc2015jcsf10003 of the Chongqing Science and Technology Commission.
Inclusion criteria	• Aged 18-65 years inclusive • Newly diagnosed with type 2 diabetes within past 3-mo • HbA1c 6.5–7.5% inclusive • BMI≥24 kg/m2 • Systolic blood pressure 90-120 mmHg inclusive, and diastolic blood pressure 60-90 mmHg • If taking them, willing to stop taking ACE inhibitors and angiotensin receptor blockers for duration of trial

Exclusion criteria	• Diagnosis of the following diseases/treatment for:
	  ○ Cancer
	  ○ Cardiovascular
	  ○ Gastrointestinal
	  ○ Respiratory
	  ○ Kidney or liver
	• Inability to understand or comply with instructions due to: eating disorders, psychological disorders or cognitive deficit
	• Lactating, pregnancy, or planning pregnancy before the end of the intervention
	• Any severe illness not otherwise specified that would interfere with the participant
	• Current smoker
	• Alcoholism
	• Attending another clinical trial
	• Lack of informed consent
	• Judgment of the investigator that an individual is ineligible for inclusion in the study.

Recruitment / selection of participants	Participants recruited from endocrinology department and randomised 1:1, using computer-generated randomisation list and sealed envelopes, to exenatide or insulin glargine. Participants, investigators and sponsor's clinical team blinded to allocation. Participants asked to have average protein intake of 0.8-1.2 g/kg/day 3 days before clinic visit and refrain from vigorous physical activity, alcohol, caffeine or nicotine 24h before visit.
Intervention(s)	• Exenatide 20 mcg daily Subcutaneous injection of exenatide 5 mcg twice daily, before breakfast and dinner, for 4 weeks, then up-titrated to 10 mcg twice daily for remaining 20 weeks.
Cointervention	All participants continued to receive their background antidiabetic treatment (metformin, sulphonylurea or both) during trial.
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Excluded cardiovascular disease diagnosis or treatment;
Strata 2: People with atherosclerotic cardiovascular disease	People without atherosclerotic cardiovascular diseases Excluded cardiovascular disease diagnosis or treatment;
Strata 3: People with type 2 diabetes mellitus and	People without chronic kidney disease Excluded kidney disease diagnosis or treatment;

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 Inclusion criteria: BMI>=24 kg/m2 (Chinese definition of obesity is >=28 kg/m2
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Comparator	• Insulin glargine Subcutaneous injection of insulin glargine once daily for 24 weeks.
Number of participants	N=159
Duration of follow-up	24 weeks
Indirectness	None

Method of analysis	ITT ITT analysis for all outcomes, missing data strategy unclear

240.2. Study arms

240.2.1. Exenatide 10/20 mcg daily (N = 79)

Subcutaneous injection of exenatide 5/10 mcg twice daily, for 24 weeks, in addition to background antidiabetic drugs.

240.2.2. Insulin glargine (N = 80)

Subcutaneous insulin glargine injection once daily for 24 weeks, in addition to background antidiabetic drugs.

240.3. Characteristics

240.3.1. Arm-level characteristics

Characteristic	Exenatide 10/20 mcg daily (N = 79)	Insulin glargine (N = 80)
% Male Sample size	n = 42 ; % = 53.16	n = 45 ; % = 56.25
Mean age (SD) (years) Mean (SD)	49.37 (8.43)	47.63 (9.65)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed (years) Median (IQR)	3 (1 to 5)	3 (2 to 4)
Cardiovascular risk factors Nominal	NR	NR

Characteristic	Exenatide 10/20 mcg daily (N = 79)	Insulin glargine (N = 80)
Smoking status Current smoker Sample size	n = 0 ; % = 0	n = 0 ; % = 0
Alcohol consumption Nominal	NR	NR
Presence of severe mental illness Nominal	NR	NR
People with significant cognitive impairment Sample size	n = 0 ; % = 0	n = 0 ; % = 0
People with a learning disability Sample size	n = 0 ; % = 0	n = 0 ; % = 0
Number of people with obesity Nominal	NR	NR
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Metformin + sulphonylurea Sample size	n = 42 ; % = 53.16	n = 48 ; % = 60
Metformin only Sample size	n = 27 ; % = 34.18	n = 20 ; % = 25
Sulphonylurea only Sample size	n = 10 ; % = 12.66	n = 12 ; % = 15
Blood pressure-lowering medication used Sample size	n = 0 ; % = 0	n = 0 ; % = 0
Statins/lipid-lowering medication used Sample size	n = 15 ; % = 18.99	n = 17 ; % = 21.25
Other treatment being received Nominal	NR	NR

241. Kawamori, 2018

Bibliographic Reference	Kawamori, R.; Haneda, M.; Suzaki, K.; Cheng, G.; Shiki, K.; Miyamoto, Y.; Solimando, F.; Lee, C.; Lee, J.; George, J.; Empagliflozin as add-on to linagliptin in a fixed-dose combination in Japanese patients with type 2 diabetes: glycaemic efficacy and safety profile in a 52-week, randomized, placebo-controlled trial; Diab Obes Metab; 2018; vol. 20 (no. 9); 2200-2209

241.1. Study details

Trial name / registration number	NCT02453555
Study type	Randomised controlled trial (RCT)
Study location	40 sites in Japan
Study setting	No additional information
Study dates	May 2015 and March 2017
Sources of funding	Funded by Boehringer Ingelheim and Eli Lilly and Company. Boehringer Ingelheim International GmbH and Nippon Boehringer Ingelheim Co. Ltd were involved in the study design, data collection, data analysis and preparation of the manuscript. A number of authors are employees of Boehringer Ingelheim and others disclose receiving multiple honoraria and funding grants from numerous pharmaceutical companies
Inclusion criteria	Male and female adults (≥20 years) with a BMI ≤ 40.0 kg/m2 and a diagnosis of T2DM who had been on a diet and exercise regimen for ≥12 weeks and were either treatment-naive or using a stable dosage of one OAD (sulfonylurea up to half the maximum approved dosage) for ≥12 weeks (≥18 weeks for thiazolidinedione); OADs (except linagliptin) were discontinued at screening. Required HbA1c levels at screening were ≥ 8.0% and ≤ 10.5% for treatment-naive patients, ≥7.5% and ≤10.5% for OAD-pretreated (except linagliptin) patients, and ≥7.5% and ≤10.0% for linagliptin-pretreated patients.
Exclusion criteria	Uncontrolled hyperglycaemia, defined as FPG > 270 mg/dL (>15 mmol/L; mmol/L = [mg/dL]/18) during the open-label period (confirmed by two measurements); acute coronary syndrome, stroke or transient ischemic attack within 3 months; treatment with insulin, GLP-1 agonists, anti-obesity drugs or any other treatment leading to unstable body weight within 12 weeks before informed consent; indication of liver disease (alanine aminotransferase, aspartate aminotransferase or alkaline phosphatase >3 × upper limit of normal); and estimated glomerular filtration rate (eGFR) < 45 mL/min/1.73 m2

Recruitment / selection of participants	No additional information
Intervention(s)	Empagliflozin (n=182) Patients with HbA1c ≥7.5% and ≤10.0% after ≥16 weeks of Linagliptin monotherapy received 10 mg Empagliflozin for 52 weeks. Patients with HbA1c ≥ 7.0% at Week 24 received 25 mg Empagliflozin All study drugs were taken orally once daily in the morning
Cointervention	Linagliptin Patients received 5 mg Linagliptin for 16 weeks prior to randomisation and continued for 52 weeks post randomisation
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 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) < 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	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 (n=93) Oral placebo was taken for all patients for 2 weeks prior to randomisation and continued for 52 weeks for those patients in the placebo arm Patients received 5 mg linagliptin for 16 weeks prior to randomisation and continued for 52 weeks post randomisation All drugs were taken orally once daily in the morning
Number of participants	275
Duration of follow-up	52 weeks
Indirectness	NA
Method of analysis	ITT
Additional comments	The primary endpoint was analysed using a restricted maximum likelihood-based mixed-model repeated measures (MMRM) approach in all randomized patients who received ≥1 dose of study drug and underwent both baseline and ≥1 on-treatment HbA1c assessment during the 24-week double-blind period. The model included treatment, baseline renal function, prior OAD use, visit and visit-by treatment interaction as fixed effects, and baseline HbA1c as a linear covariate. The model was used to estimate differences in means between treatment groups and their 95% confidence

	intervals (CI). Missing data were handled implicitly by the model (observed cases) rather than by imputation. Data obtained after use of rescue medication were treated as missing values. Other continuous efficacy endpoints were analysed using the same MMRM model, with the respective baseline parameter as an additional covariate. Safety was analysed in randomized patients who received ≥1 dose of study drug and was presented using descriptive statistics.

241.2. Study arms

241.2.1. Empagliflozin (N = 182)

Patients received 10 mg or 25 mg empagliflozin as an add on to 5 mg Linagliptin for 52 weeks

241.2.2. Placebo (N = 93)

Patients received placebo plus 5 mg linagliptin for 52 weeks

241.3. Characteristics

241.3.1. Arm-level characteristics

Characteristic	Empagliflozin (N = 182)	Placebo (N = 93)
% Male Sample size	n = 142 ; % = 78	n = 72 ; % = 77.4
Mean age (SD) (Years (mean, SD)) Mean (SD)	60 (9.9)	59.8 (10.8)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed (Years (mean, SD)) Mean (SD)	9 (7.2)	8.7 (6.1)
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Empagliflozin (N = 182)	Placebo (N = 93)
Sample size		
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR
Pre-treated with 1 oral antidiabetic excluding linagliptin Sample size	n = 58 ; % = 31.9	n = 30 ; % = 32.3
Pre-treated with linagliptin Sample size	n = 112 ; % = 61.5	n = 57 ; % = 61.3
Blood pressure-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Statins/lipid-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR

242. Kellerer, 2022

Bibliographic Reference	Kellerer, M.; Kaltoft, M. S.; Lawson, J.; Nielsen, L. L.; Strojek, K.; Tabak, Ö; Jacob, S.; Effect of once-weekly semaglutide versus thrice-daily insulin aspart, both as add-on to metformin and optimized insulin glargine treatment in participants with type 2 diabetes (SUSTAIN 11): a randomized, open-label, multinational, phase 3b trial; Diabetes, obesity & metabolism; 2022; vol. 24 (no. 9); 1788-1799

242.1. 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	SUSTAIN 11/NCT03689374
Study type	Randomised controlled trial (RCT) Open-label active-controlled randomised trial
Study location	International (21 countries: Bosnia-Herzegovina, Bulgaria, Croatia, Czech Republic, Estonia, Germany, Greece, Hungary, India, Latvia, Lithuania, Macedonia, Poland, Portugal, Romania, Serbia, Slovakia, Slovenia, South Africa, Spain, and Turkey)
Study setting	Outpatient
Study dates	10/2018 to 10/2019
Sources of funding	Funded by Novo Nordisk A/S
Inclusion criteria	• Age ≥18 years • Diagnosed with type 2 diabetes (T2D)≥180 days prior to screening • HbA1c>7.5 to ≤10.0% • Treated with basal insulin once or twice daily for ≥90 days prior to screening

	• Stable daily metformin dose 90 days prior to screening (≥1,500 mg to ≤3,000 mg or maximum tolerated or effective dose) with or without one additional oral antihyperglycemic drug (a sulphonylurea, meglitinide, DPP-4 inhibitor or an alpha-glucosidase inhibitor) • Need and willingness to undergo treatment intensification with the study drugs with aim to reach an HbA1c of 6.5-7.5% inclusive
Exclusion criteria	• Any disorder that, in investigator's opinion, might jeopardize a participant's safety • History or presence of acute or chronic pancreatitis • Myocardial infarction, stroke, hospitalization for unstable angina or transient ischemic attack within 180 days prior to screening • Presence of NYHA Class IV heart failure • Planned coronary, carotid or peripheral artery revascularization known on the day of screening • Treatment with any medication for indication of diabetes or obesity other than stated in the inclusion criteria within the past 90 days prior screening (short-term bolus insulin treatment for a maximum of 14 days prior to screening was allowed) • Uncontrolled and potentially unstable diabetic retinopathy or maculopathy within the past 90 days prior to run-in phase • eGFR<30mL/min/1.73 m2 • Presence of history of malignant neoplasms within 5 years prior of screening (basal and squamous cell skin cancer and any carcinoma *in situ* were allowed)
Recruitment / selection of participants	After 2 week screening period, eligible participants had 12 week run-in period, 52 week treatment period, and 5 week follow up period. At start of run-in, participants were transferred from their existing basal insulin treatments to insulin glargine U100 once daily. Self-measured plasma glucose profiles used to optimize insulin glargine dose during run-in period and treatment period. Metformin was continued (1500-3000 mg or max tolerated dose) for duration of trial unless safety concerns but additional oral antidiabetic drugs were discontinued. Participants who had HbA1c >7.5 to ≤10% at end of run-in period, were randomised 1:1 to semaglutide (dose escalation as per label) or insulin aspart.
Intervention(s)	• Semaglutide 1 mg weekly Subcutaneous injection of semaglutide 1 mg once weekly for 52 weeks, in addition to insulin glargine and stable metformin dose.
Cointervention	• Insulin glargine U100 daily • Metformin 1500-3000 mg All participants received subcutaneous injection of insulin glargine U100 once daily and oral metformin 1500-3000 mg daily or maximum tolerated dose) for duration of trial.
Strata 1: People with type 2 diabetes	Not stated/unclear Excluded "New York Heart Association Class IV heart failure", otherwise unclear. No information in baseline characteristics.

mellitus and heart failure	
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Excluded “Myocardial infarction, stroke, hospitalization for unstable angina or transient ischemic attack within the past 180 days prior to screening”, prior unclear. No information in baseline characteristics. Baseline characteristics give some breakdown but not overall CVD.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/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	Mixed population At baseline, ~20% of participants had formal diagnosis of obesity in medical history; 58% of participants had BMI>30 kg/m2
Subgroup 5: eGFR category at baseline	eGFR ≥30mL/min/1.73m2 Exclusion criteria: eGFR<30 mL/min/1.73m2. Note that at randomisation 5 participants had eGFR <30 mL/min/1.73 m2.
Subgroup 6: Albuminuria	Not stated/unclear

category at baseline	
Population subgroups	
Comparator	• Insulin aspart 100 U/ml thrice daily Subcutaneous injection of insulin aspart (IAsp) 100 U/ml three times daily for 52 weeks, in addition to insulin glargine and stable metformin dose.
Number of participants	N=1748
Duration of follow-up	52 weeks + 5 week safety period follow up
Indirectness	None
Method of analysis	ITT ITT (full analysis set) population used for efficacy outcomes with multiple imputation for missing data Modified ITT Safety analysis included all randomised participants who received at least one study drug dose
Additional comments	

242.2. Study arms

242.2.1. Semaglutide 1 mg weekly (N = 874)

Subcutaneous injection of semaglutide 1 mg once weekly for 52 weeks, in addition to metformin.

242.2.2. Insulin aspart 100 U/ml thrice daily (N = 874)

Subcutaneous injection of insulin aspart 100 U/ml three times daily for 52 weeks, in addition to metformin.

242.3. Characteristics

242.3.1. Arm-level characteristics

Characteristic	Semaglutide 1 mg weekly (N = 874)	Insulin aspart 100 U/ml thrice daily (N = 874)
% Male Sample size	n = 445 ; % = 50.9	n = 449 ; % = 51.4
Mean age (SD) (years) Mean (SD)	60.8 (9.4)	61.5 (9.5)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Asian Sample size	n = 176 ; % = 20.1	n = 166 ; % = 19
Black or African American Sample size	n = 21 ; % = 2.4	n = 14 ; % = 1.6
Other Sample size	n = 3 ; % = 0.3	n = 3 ; % = 0.3
White Sample size	n = 674 ; % = 77.1	n = 691 ; % = 79.1
Hispanic or Latino Sample size	n = 23 ; % = 2.6	n = 22 ; % = 2.5
Not hispanic or latino Sample size	n = 851 ; % = 97.4	n = 852 ; % = 97.5
Comorbidities Data for macroangiopathy includes peripheral vascular disease Sample size	n = NA ; % = NA	n = NA ; % = NA
Non-alcoholic fatty liver disease Sample size	n = 88 ; % = 10.1	n = 93 ; % = 10.6
Benign prostatic hyperplasia Sample size	n = 48 ; % = 5.5	n = 52 ; % = 5.9

Characteristic	Semaglutide 1 mg weekly (N = 874)	Insulin aspart 100 U/ml thrice daily (N = 874)
History of diabetic retinopathy Sample size	n = 146 ; % = 16.7	n = 131 ; % = 15
History of diabetic neuropathy Sample size	n = 258 ; % = 29.5	n = 249 ; % = 28.5
History of diabetic nephropathy Sample size	n = 109 ; % = 12.5	n = 85 ; % = 9.7
History of macroangiopathy Sample size	n = 114 ; % = 13	n = 100 ; % = 11.4
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	13.4 (6.8)	13.4 (6.5)
Cardiovascular risk factors Dyslipidaemia, hyperlipidaemia, and hypercholesterolaemia classification according to formal diagnosis listed in medical history and not lab lipid assessments Sample size	n = NA ; % = NA	n = NA ; % = NA
Hypertension Sample size	n = 690 ; % = 78.9	n = 686 ; % = 78.5
Dyslipidaemia Sample size	n = 246 ; % = 28.1	n = 266 ; % = 30.4
Hyperlipidaemia Sample size	n = 235 ; % = 26.9	n = 220 ; % = 25.2
Hypercholesterolaemia Sample size	n = 69 ; % = 7.9	n = 64 ; % = 7.3
Alcohol consumption Nominal	NR	NR
Presence of severe mental illness Nominal	NR	NR

Characteristic	Semaglutide 1 mg weekly (N = 874)	Insulin aspart 100 U/ml thrice daily (N = 874)
People with significant cognitive impairment Nominal	NR	NR
People with a learning disability Nominal	NR	NR
Number of people with obesity Obesity classification required formal diagnosis of obesity listed in medical history rather than BMI assessment; ~58% of participants in trial had BMI>30 kg/m2 Sample size	n = 175 ; % = 20	n = 188 ; % = 21.5
eGFR mL/min/1.73m2 Sample size	n = NA ; % = NA	n = NA ; % = NA
Normal (>=90) Sample size	n = 533 ; % = 61	n = 549 ; % = 62.8
Mild impairment (60 to <90) Sample size	n = 282 ; % = 32.3	n = 272 ; % = 31.1
Moderate impairment (30 to <60) Sample size	n = 55 ; % = 6.3	n = 52 ; % = 5.9
Severe impairment (15 to <30) Sample size	n = 3 ; % = 0.3	n = 1 ; % = 0.1
End-stage impairment (<15) Sample size	n = 1 ; % = 0.1	n = 0 ; % = 0

243. Kendall, 2005

Bibliographic Reference	Kendall, D. M.; Riddle, M. C.; Rosenstock, J.; Zhuang, D.; Kim, D. D.; Fineman, M. S.; Baron, A. D.; Effects of exenatide (exendin-4) on glycemic control over 30 weeks in patients with type 2 diabetes treated with metformin and a sulfonylurea; Diabetes Care; 2005; vol. 28 (no. 5); 1083-91

243.1. 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	Exendin-4/registration number not reported
Study type	Randomised controlled trial (RCT) Double-blind, placebo-controlled randomised trial
Study location	USA (91 sites)
Study setting	Outpatient
Study dates	05/2002 to 08/2003
Sources of funding	Supported by Amylin Pharmaceuticals, CA, USA and Eli Lilly, IN, USA.
Inclusion criteria	• Screening FPG<13.3 mmol/L • BMI 27-45 kg/m2 inclusive • HbA1c 7.5-11% inclusive • Receiving metformin≥1500 mg/day and at least maximally effective sulphonylurea dose for 3-mo before screening • Stable weight (±10%) for 3-mo before screening • No clinically relevant abnormal lab test values (>25% outside normal lab values)

	• If female, then postmenopausal, surgically sterile or using contraceptives for at least 3-mo before screening and during trial
Exclusion criteria	• Clinically significant medical condition • Use of thiazolidinediones, meglitinides, alpha-glucosidase inhibitors, exogenous insulin, or weight loss drugs within 3-mo of screening • Use of corticosteroids, drugs known to affect gastrointestinal motility, transplantation medication or any other investigational drug
Recruitment / selection of participants	Potential participants underwent 4 week single-blind lead-in period with placebo injections twice daily. Eligible participants then randomised 1:1:1:1, stratified by HbA1c (<9%; ≥9%), to exenatide 10 mcg twice daily, exenatide 5 mcg twice daily, placebo for exenatide 10 mcg twice daily, or placebo for exenatide 5 mcg twice daily. After randomisation, 4 week titration period then 26 weeks maintenance period. Participants could be withdrawn from trial if: there was HbA1c increase of 1.5% from baseline at any visit or HbA1c≥11.5% at week 18 or 24; or FPG>13.3 mmol/L on two consecutive study visits from weeks 18-24 or if fingerstick FPG>14.4 mmol/L for at least 2 weeks from weeks 18-24 (not secondary to identifiable illness or pharmacological treatment).
Intervention(s)	• Exenatide 20 mcg daily • Exenatide 10 mcg daily Subcutaneous injection of exenatide 10 mcg twice daily or 5 mcg daily, in abdomen 15 min before morning and evening meals, for 30 weeks, in addition to metformin and a sulphonylurea. Exenatide dose started at 5 mcg twice daily for 4 weeks in both arms, before increase to 10 mcg twice daily in 10 mcg twice daily arm.
Cointervention	• Metformin • Sulphonylurea All participants continued their pre-study metformin dose. To standardize sulphonylurea use, participants were also randomised within each arm 1:1 to maximally effective dose group (4 mg/day glimepiride, 20mg/day glipizide, 10 mg/day glipizide XL,10 mg/day glibenclamide [glyburide], 6mg/day micronized glibenclamide, 350mg/day chlorpropamide, 500 mg/day tolazamide, or 1,500 mg/day tolbutamide) or to minimum recommended dose group (1 mg/day glimepiride, 5 mg/day glipizide, 5 mg/day glipizide XL, 1.25 mg/day glibenclamide, 0.75 mg/day micronized glibenclamide, 100 mg/day chlorpropamide, 100 mg/day tolazamide, or 250 mg/day tolbutamide). Assignment to sulphonylurea group was not blinded. Sulphonylurea dose could be reduced by 50% during treatment phase if one documented hypoglycaemia event or two undocumented suspected events; in case of further hypoglycaemia events, further 50% reductions (including cessation) permitted. In minimum sulphonylurea group, if majority of FPG readings >6.9 mmol/L up to 12 weeks, sulphonyluirea use could be doubled. No further escalation permitted in this group after 12 weeks.

Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear

Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Comparator	• Placebo for exenatide 20 mcg daily • Placebo for exenatide 10 mcg daily Matched placebo with volumes equal to exenatide arms for 30 weeks.
Number of participants	N=734
Duration of follow-up	30 weeks
Indirectness	None
Method of analysis	Modified ITT mITT LOCF analysis (all randomised participants who received at least one dose of study drug) for all efficacy and safety outcomes

243.2. Study arms

243.2.1. Exenatide 20 mcg daily (N = 241)

Subcutaneous injection of exenatide 10 mcg twice daily for 30 weeks, in addition to stable metformin and sulphonylurea.

243.2.2. Exenatide 10 mcg daily (N = 245)

Subcutaneous injection of exenatide 5 mcg twice daily for 30 weeks, in addition to stable metformin and sulphonylurea.

243.2.3. Placebo (N = 247)

Matching placebo subcutaneous injection twice daily for 30 weeks, in addition to stable metformin and sulphonylurea. Note that this was a 4-arm trial with 2 placebo arms. Reported data in article is for combined placebo arms.

243.3. Characteristics

243.3.1. Arm-level characteristics

Characteristic	Exenatide 20 mcg daily (N = 241)	Exenatide 10 mcg daily (N = 245)	Placebo (N = 247)
% Male Sample size	n = 143 ; % = 59.3	n = 145 ; % = 59.2	n = 138 ; % = 55.9
Mean age (SD) (years) Mean (SD)	55 (10)	55 (9)	56 (10)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Asian Sample size	n = 7 ; % = 2.9	n = 7 ; % = 2.9	n = 4 ; % = 1.6
Black Sample size	n = 28 ; % = 11.6	n = 25 ; % = 10.2	n = 30 ; % = 12.1
Hispanic Sample size	n = 40 ; % = 16.6	n = 39 ; % = 15.9	n = 39 ; % = 15.8
Native American Sample size	n = 2 ; % = 0.8	n = 0 ; % = 0	n = 1 ; % = 0.4
Other Sample size	n = 4 ; % = 1.7	n = 5 ; % = 2	n = 4 ; % = 1.6
White Sample size	n = 160 ; % = 66.4	n = 169 ; % = 69	n = 169 ; % = 68.4
Comorbidities Nominal	NR	NR	NR
Presence of frailty Nominal	NR	NR	NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	8.7 (6.4)	8.7 (5.9)	9.4 (6.2)
Cardiovascular risk factors Nominal	NR	NR	NR

Characteristic	Exenatide 20 mcg daily (N = 241)	Exenatide 10 mcg daily (N = 245)	Placebo (N = 247)
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

244. Kesavadev, 2017

Bibliographic Reference	Kesavadev, J.; Pillai, P. B. S.; Shankar, A.; Krishnan, G.; Jothydev, S.; Sitagliptin 100 mg vs glimepiride 1-3 mg as an add-on to insulin and metformin in type 2 diabetes (SWIM); Endocrine connections; 2017; vol. 6 (no. 8); 748-757

244.1. 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	NCT01341717
Study type	Randomised controlled trial (RCT) Open-label, parallel-group active-controlled randomised trial
Study location	Kerala, India
Study setting	Outpatient
Study dates	02/2012 to 05/2014
Sources of funding	Funded by grant from Merck & Co., Inc.
Inclusion criteria	• Diagnosis of type 2 diabetes • Aged 25-60 years inclusive • Stable metformin dose of ≥1000 mg daily and >10IU total daily dose of biphasic or basal insulin • HbA1c 7.3-8.5% inclusive
Exclusion criteria	• Type 1 diabetes • BMI>40 kg/m2 • History of pancreatitis

	• Creatinine clearance ≤50 mL/min • Chronic liver and kidney diseases • Serum glutamate transaminase and prothrombin time ≥2.5× upper limit of normal • Uncontrolled thyroid disorders • Cardiac failure • Hemochromatosis • Autoimmune disorders • Taking systemic corticosteroids • Using acarbose, pioglitazone or short-acting insulin analogue during run-in phase
Recruitment / selection of participants	Eligible participants randomised 1:1 using computer-generated stratified block design (by gender) to glimepiride or sitagliptin, with sealed envelope for allocation concealment. Compliance to optimal diet, exercise, and treatment with metformin and insulin, as well as stable treatment with statin and antihypertensive use monitored during run-in period (duration not reported) before receiving treatment. After randomisation, 6 week titration period followed by 18 week maintenance period. Participants continued to receive concurrent lipid-lowering agents, antihypertensive agents and other medications without change.
Intervention(s)	• Glimepiride 1-3 mg daily Oral glimepiride 1-3 mg daily for 24 weeks, in addition to stable dose of metformin and biphasic or basal insulin. During titration period (6 weeks after randomisation), glimepiride was titrated every 2 weeks by 1 mg to maximum of 3 mg daily.
Cointervention	• Metformin • Insulin All participants received oral metformin (median dose of 1000 mg) daily and insulin for duration of trial. Insulin was titrated with target FPG 70-125 mg/dL without hypoglycaemia. Total daily dose of insulin was reduced by 20% during 6 week titration period following randomisation and held constant (or reduced in case of hypoglycaemia).
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Exclusion criteria: cardiac 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	People without chronic kidney disease Excluded creatinine clearance ≤50 mL/min, chronic liver and kidney diseases

diabetes mellitus and chronic kidney disease	
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	
Comparator	• Sitagliptin 100 mg daily Oral sitagliptin 100 mg daily for 24 weeks, in addition to stable dose of metformin and biphasic or basal insulin.
Number of participants	N=440

Duration of follow-up	24 weeks
Indirectness	None
Method of analysis	Per protocol PPA for primary analysis of HbA1c, weight and BMI. Modified ITT mITT analysis (all randomised participants who received at least one doe of study drug) for safety outcomes

244.2. Study arms

244.2.1. Glimepiride 1-3 mg daily (N = 221)

Oral glimepiride 1-3 mg daily for 24 weeks, in addition to stable dose of metformin and biphasic or basal insulin.

244.2.2. Sitagliptin 100 mg daily (N = 219)

Oral sitagliptin 100 mg daily for 24 weeks, in addition to stable dose of metformin and biphasic or basal insulin.

244.3. Characteristics

244.3.1. Arm-level characteristics

Characteristic	Glimepiride 1-3 mg daily (N = 221)	Sitagliptin 100 mg daily (N = 219)
% Male Sample size	n = 113 ; % = 51.13	n = 103 ; % = 47.03
Mean age (SD) (years) Mean (SD)	50.11 (7.83)	51.09 (6.58)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR

Characteristic	Glimepiride 1-3 mg daily (N = 221)	Sitagliptin 100 mg daily (N = 219)
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	15.67 (7.2)	14.96 (7.33)
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 = NA ; % = NA	n = NA ; % = NA
Basal insulin Sample size	n = 108 ; % = 48.9	n = 116 ; % = 53
Biphasic insulin Sample size	n = 113 ; % = 51.1	n = 103 ; % = 47
Blood pressure-lowering medication used Nominal	NR	NR

Characteristic	Glimepiride 1-3 mg daily (N = 221)	Sitagliptin 100 mg daily (N = 219)
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

245. Khaloo, 2019

Bibliographic Reference	Khaloo, P.; Asadi Komeleh, S.; Alemi, H.; Mansournia, M. A.; Mohammadi, A.; Yadegar, A.; Afarideh, M.; Esteghamati, S.; Nakhjavani, M.; Esteghamati, A.; Sitagliptin vs. pioglitazone as add-on treatments in patients with uncontrolled type 2 diabetes on the maximal dose of metformin plus sulfonylurea; J Endocrinol Invest; 2019; vol. 42 (no. 7); 851-857

245.1. 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	NCT03125694
Study type	Randomised controlled trial (RCT) Open-label, active-controlled, parallel-group, randomised trial.
Study location	Vali-Asr Hospital, Tehran, Iran
Study setting	Outpatient
Study dates	02/2015 to 04/2017
Sources of funding	Reports that study did not "receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors"
Inclusion criteria	• Type 2 diabetes diagnosis • Aged 25-70 years inclusive • HbA1c 7-11% inclusive • At least 6 months treatment with metformin 2000 mg daily (500 mg four times daily) and advised maximum dose of gliclazide 240 mg daily.

Exclusion criteria	• Cardiovascular disease (including myocardial infarction, unstable angina, history of revascularization procedure or cerebrovascular accident) or uncontrolled hypertension • eGFR< 60 ml/min/1.73 m2 (CKD–EPI equation) • Treatment with corticosteroids or other drugs interfering with glucose metabolism • Any history of malignant disease, active infectious disease or history of infectious disease in the last 6 months • Documented diagnosis of interstitial or obstructive lung disease
Recruitment / selection of participants	Eligible participants assigned 1:1 to groups using randomisation software. Participants instructed to continue existing lifestyle during trial and were withdrawn if any severe adverse events experienced (including hypoglycaemia, heart failure and hepatic failure).
Intervention(s)	• Pioglitazone 30 mg daily Oral pioglitazone 30 mg daily for 52 weeks, in addition to metformin and gliclazide.
Cointervention	• Metformin 2000 mg daily • Gliclazide 240 mg daily All participants also received oral metformin 500 mg four times daily and oral gliclazide 80 mg three times daily for 52 weeks.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics
Strata 2: People with atherosclerotic cardiovascular disease	People without atherosclerotic cardiovascular diseases Excluded "cardiovascular disease (including myocardial infarction, unstable angina, history of revascularization procedure or cerebrovascular accident) or uncontrolled hypertension"
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Excluded “estimated glomerular filtration rate (eGFR)<60 ml/ min/1.73 m2> < 60 ml/ min/1.73 m2”, 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 5: eGFR category at baseline	eGFR ≥30mL/min/1.73m2 Exclusion criteria: eGFR<60 mL/min/1.73 m2 (CKD-EPI equation)
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Comparator	• Sitagliptin 100 mg daily Oral sitagliptin 100 mg daily for 52 weeks, in addition to metformin and gliclazide.
Number of participants	N=250
Duration of follow-up	52 weeks
Indirectness	None
Method of analysis	Modified ITT mITT LOCF analysis (all randomised participants who received at least one study drug dose, and had baseline and at least one post-baseline hbA1c measurement) for all outcomes.

245.2. Study arms

245.2.1. Pioglitazone 30 mg daily (N = 125)

Oral pioglitazone 30 mg daily for 52 weeks, in addition to metformin and gliclazide.

245.2.2. Sitagliptin 100 mg daily (N = 125)

Oral sitagliptin 100 mg daily for 52 weeks, in addition to metformin and gliclazide.

245.3. Characteristics

245.3.1. Arm-level characteristics

Characteristic	Pioglitazone 30 mg daily (N = 125)	Sitagliptin 100 mg daily (N = 125)
% Male Significant difference at baseline Sample size	n = 39 ; % = 41.5	n = 55 ; % = 58.5
Mean age (SD) (years) Mean (SD)	62.7 (8.2)	60.8 (8.1)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed (years) Significant difference at baseline Mean (SD)	14.3 (6.9)	11.3 (6.2)
Cardiovascular risk factors Nominal	NR	NR
Smoking status Nominal	NR	NR
Alcohol consumption Nominal	NR	NR
Presence of severe mental illness Nominal	NR	NR

Characteristic	Pioglitazone 30 mg daily (N = 125)	Sitagliptin 100 mg daily (N = 125)
People with significant cognitive impairment Nominal	NR	NR
People with a learning disability Nominal	NR	NR
Number of people with obesity Nominal	NR	NR
Other antidiabetic medication used Nominal	NR	NR
Blood pressure-lowering medication used Nominal	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

Baseline characteristics is for completers only, PIOG group, N=110 and SITA group, N=112.

246. Khan, 2022

Bibliographic Reference	Khan, A.; Khan, I. A.; Abidi, H.; Ahmed, M.; Comparison of empagliflozin and vildagliptin for efficacy and safety in type 2 diabetes mellitus in the Pakistani population; Frontiers in endocrinology; 2022; vol. 13; 926633

246.1. 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	NCT05359432
Study type	Randomised controlled trial (RCT) Open-label, parallel-group, active-controlled randomised trial
Study location	Karachi, Pakistan
Study setting	Primary Care centres
Study dates	11/2020 to 11/2021
Sources of funding	Sponsored by Primary Care Diabetes Association, Pakistan
Inclusion criteria	• Aged 30-65 years • Type 2 diabetes diagnosis • HbA1c level >7% • Metformin monotherapy fixed dose of 1500 mg/day for at least 3 months prior to trial, with lifestyle modifications • BMI 18-45 kg/m2 inclusive • eGFR≥60 mL/min/1.73 m2
Exclusion criteria	• Pregnancy or planning to conceive in following 6 months

	• Diagnosis of type 1 diabetes or diabetes resulting from specific causes, or advanced diabetic complications • Any other terminal disease • Participating in other trials on SGLT or DPP4 inhibitors • On insulin therapy or oral glucose-lowering drugs other than metformin
Recruitment / selection of participants	Participants recruited from two primary care centres were randomised 1:1 using computer-generated sequence to groups. Lifestyle modifications were maintained. All study drugs were titrated starting with low dose and intensified as needed. Participants were followed up every month to 24 weeks.
Intervention(s)	• Empagliflozin 10/20 mg daily Oral empagliflozin 10 mg once or twice daily for 24 weeks, in addition to stable metformin dose.
Cointervention	• Metformin 1500 mg daily All participants also received metformin tablet 1500 mg daily for duration of trial.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	People without atherosclerotic cardiovascular diseases Not an inclusion/exclusion criteria. <1% had CVD
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Excluded “eGFR levels ≤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
Subgroup 5: eGFR category at baseline	eGFR ≥30mL/min/1.73m2 Inclusion criteria: eGFR≥60 mLmin/1.723m3
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Comparator	• Vildagliptin 50/100 mg daily Oral vildagliptin 50 mg once or twice daily for 24 weeks, in addition to stable metformin dose.
Number of participants	N=120
Duration of follow-up	24 weeks
Indirectness	None
Method of analysis	Modified ITT Appears to be mITT completer analysis excluding participants who were lost to follow up or discontinued trial.
Additional comments	Appears to be completer analysis excluding participants who were lost to follow up or discontinued trial.

246.2. Study arms

246.2.1. Empagliflozin 10/20 mg daily (N = 60)

Oral empagliflozin 10 mg once or twice daily for 24 weeks, in addition to metformin.

246.2.2. Vildagliptin 50/100 mg daily (N = 60)

Oral vildagliptin 50 mg once or twice daily for 24 weeks, in addition to metformin.

246.3. Characteristics

246.3.1. Arm-level characteristics

Characteristic	Empagliflozin 10/20 mg daily (N = 60)	Vildagliptin 50/100 mg daily (N = 60)
% Male Sample size	n = 28 ; % = 46.7	n = 21 ; % = 35
Mean age (SD) Mean (SD)	52.3 (7.6)	49.4 (9.5)
Comorbidities Sample size	n = NA ; % = NA	n = NA ; % = NA
Hypertension Sample size	n = 33 ; % = 55	n = 30 ; % = 50
Cardiovascular disease Sample size	n = 1 ; % = 0.8	n = 0 ; % = 0
Arthritis Sample size	n = 2 ; % = 1.7	n = 0 ; % = 0
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed Nominal	NR	NR
Cardiovascular risk factors Nominal	NR	NR

Characteristic	Empagliflozin 10/20 mg daily (N = 60)	Vildagliptin 50/100 mg daily (N = 60)
Smoking status Sample size	n = 16 ; % = 26.7	n = 8 ; % = 13.3
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

Reported percentage data not reliable, have assumed that sample size data is correct.

247. Kim, 2020

Bibliographic Reference	Kim, J. M.; Kim, S. S.; Kim, J. H.; Kim, M. K.; Kim, T. N.; Lee, S. H.; Lee, C. W.; Park, J. Y.; Kim, E. S.; Lee, K. J.; et, al.; Efficacy and safety of pioglitazone versus glimepiride after metformin and alogliptin combination therapy: A randomized, open-label, multicenter, parallel-controlled study; Diabetes Metabol J; 2020; vol. 44 (no. 1); 67-77

247.1. 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	NCT02426294
Study type	Randomised controlled trial (RCT)
Study location	Korea
Study setting	Medical centres
Study dates	03/2015 - 04/2018
Sources of funding	This study was funded by Takeda Pharmaceuticals Korea Co.
Inclusion criteria	Patients with inadequately controlled T2DM (glycosylated haemoglobin [HbA1c] of 7.5% to <10%) were considered eligible if they had consistently received metformin plus alogliptin for ≥3 months before randomization, were 19 to 80 years old, and had a body mass index (BMI) of 18.5 to 35 kg/m2.
Exclusion criteria	Type 1 diabetes mellitus, heart failure or history of heart failure (New York Heart Association Class III or IV), major cardiovascular disorders (e.g., myocardial infarction, cardiovascular intervention, stroke, and transient

	ischaemic attack) during the last 6 months, renal or hepatic dysfunction (creatinine clearance <50 mL/min or elevated levels of aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, or total bilirubin to ≥2.5 x the upper normal limit), and pregnancy, breastfeeding, or unwillingness to use appropriate contraceptive measures (for women of reproductive age).
Recruitment / selection of participants	Participants were selected form eight Korean centres. Participants were randomly assigned to receive either pioglitazone (15 mg/day) or glimepiride (2 mg/day) in addition to their current treatment using metformin plus alogliptin. After 12 weeks of treatment, the doses could be adjusted to 30 mg/day for pioglitazone or 4 mg/day for glimepiride, based on the investigator's decision.
Intervention(s)	Pioglitazone 15 mg daily After 12 weeks of treatment, the doses could be adjusted to 30 mg daily.
Cointervention	Metformin + alogliptin
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Excluded "heart failure or history of heart failure (New York Heart Association Class III or IV)", otherwise unclear. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Excluded "major cardiovascular disorders (e.g., myocardial infarction, cardiovascular intervention, stroke, and transient ischemic attack) during the last 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 "renal dysfunction (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	Not stated/unclear

moderate or severe frailty	
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Comparator	Glimepiride 2 mg daily After 12 weeks of treatment, the doses could be adjusted to 4 mg/day based on the investigator's decision.
Number of participants	N=135
Duration of follow-up	26 weeks
Indirectness	
Method of analysis	Modified ITT
Additional comments	ITT population was defined as participants who were exposed to at least one dose and then underwent at least one post-baseline assessment.

247.2. Study arms

247.2.1. Pioglitazone 15 mg daily (N = 69)

Administered orally

247.2.2. Glimepiride 2 mg daily (N = 66)

Administered orally

247.3. Characteristics

247.3.1. Arm-level characteristics

Characteristic	Pioglitazone 15 mg daily (N = 69)	Glimepiride 2 mg daily (N = 66)
% Male No of events	n = 34 ; % = 49.3	n = 30 ; % = 45.5
Mean age (SD) Mean (SD)	60.7 (9.1)	58.5 (10.4)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed Mean (SD)	10.6 (8.2)	9.7 (6.7)
Smoking status Nominal	NR	NR
Alcohol consumption Nominal	NR	NR
Presence of severe mental illness Nominal	NR	NR
People with significant cognitive impairment Nominal	NR	NR

Characteristic	Pioglitazone 15 mg daily (N = 69)	Glimepiride 2 mg daily (N = 66)
People with a learning disability Nominal	NR	NR
Number of people with obesity Nominal	NR	NR
Alogliptin No of events	n = 69 ; % = 100	n = 66 ; % = 100
Metformin No of events	n = 69 ; % = 100	n = 66 ; % = 100
Blood pressure-lowering medication used Nominal	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

248. Kim, 2018

Bibliographic Reference	Kim, Jong-Dai; Park, Cheol-Young; Cha, Bong-Yun; Ahn, Kyu Jeung; Kim, In Joo; Park, Kyong Soo; Lee, Hyung Woo; Min, Kyung-Wan; Won, Jong Chul; Chung, Min Young; Kim, Jae-Taek; Kang, Jun Goo; Park, Sung-Woo; Comparison of Adherence to Glimepiride/Metformin Sustained Release Once-daily Versus Glimepiride/Metformin Immediate Release BID Fixed-combination Therapy Using the Medication Event Monitoring System in Patients With Type 2 Diabetes.; Clinical therapeutics; 2018; vol. 40 (no. 5); 752-761e2

248.1. Study details

Trial name / registration number	NCT01620489
Study type	Randomised controlled trial (RCT)
Study location	11 centres in the Republic of Korea
Study setting	No additional information
Study dates	NR
Sources of funding	HANDOK Pharmaceuticals
Inclusion criteria	Type 2 diabetic outpatients diagnosed up to 3 months before the study, aged 18 to 75 years, treated with 44 mg of glimepiride and 1000 mg of metformin for 42 weeks, body mass index <40 kg/m2 , and HbA1c level <9.0%.
Exclusion criteria	Type 1 diabetes, need for insulin therapy, a history of acute metabolic complications (e.g., diabetic ketoacidosis), significant renal disease (serum creatinine level 41.5 mg/dL in men and 1.4 mg/dL in women), liver cirrhosis or chronic active hepatitis, New York Heart Association functional class III and IV heart failure, unstable angina pectoris, symptomatic infection, a history of allergy to glimepiride or metformin, corticosteroid use, drug or alcohol use, and any conditions requiring the help of others for drug administration (e.g., manual disability, serious visual defect). Women who were pregnant or breastfeeding were also excluded.
Recruitment / selection of participants	No additional information
Intervention(s)	Glimepiride + Metformin sustained release (GM-SR) (n=86)

	Patients randomised to the GM-SR group received 4mg Glimepiride and 1000 mg Metformin as 2 tablets to be taken once daily between 5:00am and 9:00am for 24 weeks
Cointervention	65.1% of patients receiving GM-SR received an additional oral antidiabetic medication maintained at the same dosage throughout the study
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure
Strata 2: People with atherosclerotic cardiovascular disease	Mixed population Around 60% had CVD
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Excluded “significant renal disease (serum creatinine level >1.5 mg/dL in men and 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	Glimepiride + Metformin immediate release (GM-IR) (n=82) Patients randomised to the GM-IR arm received a daily dose 4 mg Glimepiride and 1000 mg Metformin as 2 mg Glimepiride and 500 mg Metformin taken twice daily between 6:00 and 8:00 AM and between 6:00 and 8:00 PM for 24 weeks 52.4% of patients received concomitant oral antidiabetic medication
Number of participants	168
Duration of follow-up	25 weeks; 24 week treatment period plus an additional for any new adverse drug reactions
Indirectness	NA
Method of analysis	ITT
Additional comments	168 patients constituted the intention-to-treat set and were analysed for baseline characteristics, adherence, and safety. Of these, 53 patients were excluded from the efficacy analysis, The remaining 115 patients constituted the per-protocol set.

248.2. Study arms

248.2.1. Glimepiride + metformin sustained release (N = 86)

4 mg Glimepiride and 100 mg Metformin sustained release was received as two tablets to be taken once daily for 24 weeks

248.2.2. Glimepiride + metformin immediate release (N = 82)

2 mg Glimepiride and 500 mg Metformin immediate release was received twice daily (total dose 4 mg and 1000 mg) for 24 weeks

248.3. Characteristics

248.3.1. Arm-level characteristics

Characteristic	Glimepiride + metformin sustained release (N = 86)	Glimepiride + metformin immediate release (N = 82)
% Male Sample size	n = 40 ; % = 46.5	n = 40 ; % = 48.8
Mean age (SD) (Years (mean, SD)) Mean (SD)	57.4 (9.9)	58.2 (9.3)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed (Years (mean, SD)) Mean (SD)	10.3 (7.1)	10.5 (6.6)
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

Characteristic	Glimepiride + metformin sustained release (N = 86)	Glimepiride + metformin immediate release (N = 82)
Any concomitant OADs except metformin and SU Sample size	n = 31 ; % = 36	n = 28 ; % = 34.1
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

249. Kimura, 2023

Bibliographic Reference	Kimura, Tomohiko; Katakura, Yukino; Shimoda, Masashi; Kawasaki, Fumiko; Yamabe, Mizuho; Tatsumi, Fuminori; Matsuki, Michihiro; Iwamoto, Yuichiro; Anno, Takatoshi; Fushimi, Yoshiro; Kamei, Shinji; Kimura, Yukiko; Nakanishi, Shuhei; Mune, Tomoatsu; Kaku, Kohei; Kaneto, Hideaki; Comparison of clinical efficacy and safety of weekly glucagon-like peptide-1 receptor agonists dulaglutide and semaglutide in Japanese patients with type 2 diabetes: Randomized, parallel-group, multicentre, open-label trial (COMING study).; Diabetes, obesity & metabolism; 2023

249.1. Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.
Trial name / registration number	University Hospital Medical Information Network: UMIN000044264
Study type	Randomised controlled trial (RCT)
Study location	Japan
Study setting	Outpatient follow-up.
Study dates	Japan 2021-April 2022.
Sources of funding	Supported by Research Project Grants from the Kawasaki Medical School (R03B-058 and R04B-009).
Inclusion criteria	Japanese patients with type 2 diabetes mellitus aged at least 20 years who initiated treatment with a GLP-1RA; receiving no oral antidiabetic or receiving drug(s) (sulfonylureas [up to 2mg or glimepiride, 1.25mg of glibenclamide and 40mg of gliclazide per day], glinide, metformin, thiazolidinedione, alpha-glucosidase inhibitor, SGLT2 inhibitor and DPP-4 inhibitor) at a stable daily dose at least for 12 weeks before screening;

	people receiving DPP-4 inhibitors discontinued DPP-4 inhibitors when GLP-1RA was started.
Exclusion criteria	No additional information.
Recruitment / selection of participants	No additional information.
Intervention(s)	Dulaglutide N=59 Dulaglutide 0.75mg/week for 24 weeks.
Cointervention	Concomitant therapy: No other antidiabetic drugs were changed. All people received a diet and exercise brief. Majority of people were receiving another antidiabetic medication before entering the study.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	People with chronic kidney disease Based on urinary ACR being >30mg/g Cr.
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	Mixed population 29% NAFLD at baseline
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	Semaglutide N=61 Semaglutide 0.25mg/week for 4-6 weeks, increased to 0.5mg and then could be increased up to 1mg. Overall treatment duration of 24 weeks.
Number of participants	120
Duration of follow-up	24 weeks
Indirectness	None. Note that although some participants may have not been receiving oral glucose-lowering agents at baseline, ~84% participants were receiving metformin (biguanide) treatment.
Method of analysis	ITT
Additional comments	No additional information.

249.2. Study arms

249.2.1. Dulaglutide (N = 59)

Dulaglutide 0.75mg/week for 24 weeks. Concomitant therapy: No other antidiabetic drugs were changed. All people received a diet and exercise brief. Majority of people were receiving another antidiabetic medication before entering the study.

249.2.2. Semaglutide (N = 61)

Semaglutide 0.25mg/week for 4-6 weeks, increased to 0.5mg and then could be increased up to 1mg. Overall treatment duration of 24 weeks. Concomitant therapy: No other antidiabetic drugs were changed. All people received a diet and exercise brief. Majority of people were receiving another antidiabetic medication before entering the study.

249.3. Characteristics

249.3.1. Arm-level characteristics

Characteristic	Dulaglutide (N = 59)	Semaglutide (N = 61)
% Male Sample size	n = 29 ; % = 55	n = 30 ; % = 56
Mean age (SD) (years) Mean (SD)	62.7 (11.4)	62.7 (10.1)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR
Ischaemic heart disease Sample size	n = 4 ; % = 7.5	n = 1 ; % = 1.9
Cerebrovascular disease Sample size	n = 7 ; % = 13.2	n = 5 ; % = 9.3
Peripheral arterial disease Sample size	n = 1 ; % = 1.9	n = 0 ; % = 0
Neuropathy Sample size	n = 6 ; % = 22.6	n = 7 ; % = 42.6
Simple retinopathy Sample size	n = 5 ; % = 11.4	n = 5 ; % = 11.4

Characteristic	Dulaglutide (N = 59)	Semaglutide (N = 61)
Preproliferative retinopathy Sample size	n = 0 ; % = 0	n = 1 ; % = 2.3
Proliferative retinopathy Sample size	n = 1 ; % = 2.3	n = 1 ; % = 2.3
Stage 1 nephropathy Sample size	n = 34 ; % = 65.4	n = 25 ; % = 46.3
Stage 2 nephropathy Sample size	n = 17 ; % = 32.7	n = 21 ; % = 38.9
Stage 3 nephropathy Sample size	n = 1 ; % = 1.9	n = 7 ; % = 13
Stage 4 or more nephropathy Sample size	n = 0 ; % = 0	n = 1 ; % = 1.9
Dyslipidaemia Sample size	n = 53 ; % = 100	n = 51 ; % = 94.4
Hypertension Sample size	n = 48 ; % = 90.6	n = 45 ; % = 83.3
Presence of frailty Sample size	n = NA ; % = NA	n = NA ; % = NA
Time since type 2 diabetes diagnosed (years) Mean (SD)	13.2 (7)	14.6 (7.8)
Cardiovascular risk factors Sample size	n = NR ; % = NR	n = NR ; % = NR
Heart rate Sample size	n = NR ; % = NR	n = NR ; % = NR
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Dulaglutide (N = 59)	Semaglutide (N = 61)
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
DPP-4 inhibitor Sample size	n = 37 ; % = 69.8	n = 44 ; % = 81.5
Sulfonylurea Sample size	n = 10 ; % = 18.9	n = 14 ; % = 25.9
Glinide Sample size	n = 6 ; % = 11.3	n = 6 ; % = 11.1
Biguanide Sample size	n = 44 ; % = 83	n = 46 ; % = 85.2
Thiazolidine Sample size	n = 15 ; % = 28.3	n = 12 ; % = 22.2
SGLT2 inhibitor Sample size	n = 29 ; % = 54.7	n = 40 ; % = 74.1
Alpha-glucosidase inhibitor Sample size	n = 3 ; % = 5.7	n = 1 ; % = 1.9
Blood pressure-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
ARB Sample size	n = 25 ; % = 47.2	n = 30 ; % = 55.6

Characteristic	Dulaglutide (N = 59)	Semaglutide (N = 61)
ACE inhibitor Sample size	n = 2 ; % = 3.8	n = 0 ; % = 0
CCB Sample size	n = 16 ; % = 30.2	n = 29 ; % = 53.7
Diuretic Sample size	n = 1 ; % = 1.9	n = 1 ; % = 1.9
Beta-blocker Sample size	n = 2 ; % = 3.8	n = 6 ; % = 11.1
Alpha-blocker Sample size	n = 1 ; % = 1.9	n = 1 ; % = 1.9
MRA Sample size	n = 1 ; % = 1.9	n = 3 ; % = 5.6
Statins/lipid-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Statin Sample size	n = 38 ; % = 71.7	n = 39 ; % = 72.2
Fibrate Sample size	n = 1 ; % = 1.9	n = 3 ; % = 5.6
SPPARMalpha Sample size	n = 5 ; % = 9.4	n = 5 ; % = 9.3
Ezetimib Sample size	n = 7 ; % = 13.2	n = 2 ; % = 3.7
Other treatment being received Sample size	n = NA ; % = NA	n = NA ; % = NA

250. Kinoshita, 2020

Bibliographic Reference	Kinoshita, T.; Shimoda, M.; Nakashima, K.; Fushimi, Y.; Hirata, Y.; Tanabe, A.; Tatsumi, F.; Hirukawa, H.; Sanada, J.; Kohara, K.; et, al.; Comparison of the effects of three kinds of glucose-lowering drugs on non-alcoholic fatty liver disease in patients with type 2 diabetes: a randomized, open-label, three-arm, active control study; J Diabetes Invest; 2020

250.1. 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	UMIN000021291
Study type	Randomised controlled trial (RCT) Open-label, parallel-group, active-controlled randomised trial
Study location	Japan (7 hospitals)
Study setting	Outpatient
Study dates	10/2015 to 12/2016
Sources of funding	Supported in part by Research Project Grant 29G-002, Kawasaki Medical School, Japan.
Inclusion criteria	• Aged≥20 years-old • HbA1c≥6.5% • BMI≥22 kg/m2 • ALT≥25 units/L (men) or ≥17 units/L (women) at screening • Stable dose of antidiabetic drugs≥1.5 months before screening • Non-alcoholic fatty liver disease (defined as liver-to-spleen L/S ratio <1.0 using computer tomography)

Exclusion criteria	• Alcohol use (>30 g/day for men,>20 g/day for women) • Previous treatment during the past 3 months with insulin, SGLT2 inhibitor, thiazolidinediones or sulfonylurea • Diabetic coma • Renal dysfunction (eGFR<45 mL/min) • Cardiac failure • Liver diseases (viral hepatitis, alcoholic hepatitis, autoimmune liver disease or liver cirrhosis) • Use of steroid and/or immuno-suppressants • Pregnancy or possible pregnancy and/or breast-feeding • Researcher deemed an individual inappropriate as a study participant • Did not visit the hospital for≥1 month and/or only <70% medication compliance
Recruitment / selection of participants	Participants recruited from 7 hospitals in Japan with screening visit, 6 weeks before randomisation, and then randomised 1:1:1 using computer-generated block randomisation table, and allocated using computer-generated random allocation sequence by epidemiologist not aware of study protocol. Enrolment and assignment carried out by investigator not involved in treatment/data collection. Participants continued background antidiabetic drug therapy for duration of trial.
Intervention(s)	• Pioglitazone 7.5-15 mg daily Oral pioglitazone 7.5-15 mg daily, at discretion of investigator, for 28 weeks, in addition to background antidiabetic drug therapy.
Cointervention	• Background antidiabetic drug therapy All participants continued with their background drug therapy for duration of trial.
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Excluded cardiac 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 “renal dysfunction (estimate glomerular filtration rate <45 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	People with non-alcoholic fatty liver disease
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	eGFR ≥30mL/min/1.73m2 Exclusion criteria: eGFR<45 mL/min/1.73 m2
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Comparator	• Glimepiride 0.5-1 mg daily • Dapagliflozin 5 mg daily Oral glimepiride 0.5-1 mg daily, at discretion of investigator, for 28 weeks, in addition to background antidiabetic drug therapy. Oral dapagliflozin 5 mg daily for 28 weeks, in addition to background antidiabetic drug therapy.
Number of participants	N=110
Duration of follow-up	28 weeks

Indirectness	None
Method of analysis	Modified ITT mITT completer analysis for all outcomes

250.2. Study arms

250.2.1. Pioglitazone 7.5-15 mg daily (N = 36)

Oral pioglitazone 7.5-15 mg daily for 24 weeks, in addition to background anti-diabetic drugs.

250.2.2. Glimepiride 0.5-1 mg daily (N = 34)

Oral glimepiride 0.5-1 mg daily for 24 weeks, in addition to background anti-diabetic drugs.

250.2.3. Dapagliflozin 5 mg daily (N = 40)

Oral dapagliflozin 5 mg daily for 24 weeks, in addition to background anti-diabetic drugs.

250.3. Characteristics

250.3.1. Arm-level characteristics

Characteristic	Pioglitazone 7.5-15 mg daily (N = 36)	Glimepiride 0.5-1 mg daily (N = 34)	Dapagliflozin 5 mg daily (N = 40)
% Male Sample size	n = 15 ; % = 45.5	n = 15 ; % = 45.5	n = 15 ; % = 46.9
Mean age (SD) (years) Mean (SE)	59 (1.9)	58 (2.3)	58.7 (1.6)
Ethnicity Nominal	NR	NR	NR
Comorbidities Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Neuropathy	n = 9 ; % = 25.8	n = 4 ; % = 12.5	n = 4 ; % = 12.9

Characteristic	Pioglitazone 7.5-15 mg daily (N = 36)	Glimepiride 0.5-1 mg daily (N = 34)	Dapagliflozin 5 mg daily (N = 40)
Sample size			
Retinopathy Sample size	n = 2 ; % = 6.3	n = 2 ; % = 6.1	n = 2 ; % = 6.7
Nephropathy Sample size	n = 9 ; % = 27.3	n = 6 ; % = 18.2	n = 7 ; % = 21.9
Presence of frailty Nominal	NR	NR	NR
Time since type 2 diabetes diagnosed Mean (SE)	7.9 (0.8)	7.2 (1)	6.6 (0.9)
Cardiovascular risk factors Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Hypertension Sample size	n = 25 ; % = 75	n = 21 ; % = 64.3	n = 23 ; % = 70.4
Cerebrovascular diseases Sample size	n = 2 ; % = 6.5	n = 0 ; % = 0	n = 0 ; % = 0
Ischemic heart disease Sample size	n = 0 ; % = 0	n = 0 ; % = 0	n = 1 ; % = 3.1
Dyslipidemia Sample size	n = 30 ; % = 90	n = 31 ; % = 92.6	n = 28 ; % = 86.7
Hyperuricaemia Sample size	n = 10 ; % = 30.1	n = 9 ; % = 28.6	n = 6 ; % = 18.2
Smoking status Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Current smoker Sample size	n = 3 ; % = 9.4	n = 7 ; % = 21.9	n = 10 ; % = 31.3
Non-smoker Sample size	n = 24 ; % = 71.9	n = 21 ; % = 62.5	n = 16 ; % = 50

Characteristic	Pioglitazone 7.5-15 mg daily (N = 36)	Glimepiride 0.5-1 mg daily (N = 34)	Dapagliflozin 5 mg daily (N = 40)
Ex-smoker Sample size	n = 6 ; % = 18.7	n = 5 ; % = 15.6	n = 6 ; % = 18.8
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
Alpha glucosidase inhibitors Sample size	n = 4 ; % = 12.1	n = 3 ; % = 9.1	n = 5 ; % = 15.6
DPP4-inhibitors Sample size	n = 21 ; % = 63.6	n = 26 ; % = 78.8	n = 18 ; % = 56.3
Glinides Sample size	n = 0 ; % = 0	n = 0 ; % = 0	n = 1 ; % = 3.1
GLP-1 receptor agonists Sample size	n = 0 ; % = 0	n = 0 ; % = 0	n = 1 ; % = 3.1
Blood pressure-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
ARB or ACE inhibitor	n = 14 ; % = 42.4	n = 11 ; % = 33.3	n = 9 ; % = 28.1

Characteristic	Pioglitazone 7.5-15 mg daily (N = 36)	Glimepiride 0.5-1 mg daily (N = 34)	Dapagliflozin 5 mg daily (N = 40)
Sample size			
Statins/lipid-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Statins Sample size	n = 22 ; % = 66.7	n = 21 ; % = 63.6	n = 22 ; % = 68.8
Fibrates Sample size	n = 2 ; % = 6.1	n = 5 ; % = 15.2	n = 2 ; % = 6.3
Other treatment being received Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Ursodeoxycholic acid Sample size	n = 1 ; % = 3	n = 2 ; % = 6.1	n = 1 ; % = 3.1
Eicosapentaenoic acid Sample size	n = 1 ; % = 3	n = 1 ; % = 3	n = 1 ; % = 3.1

Baseline characteristics are for the following number of participants: PIOG, N=33; GLIM, N=33; and DAPA, N=32

251. Kirkman, 2024

Bibliographic Reference	Kirkman, M Sue; Tripputi, Mark; Krause-Steinrauf, Heidi; Bebu, Ionut; AbouAssi, Hiba; Burch, Henry; Duran-Valdez, Elizabeth; Florez, Hermes; Garvey, W Timothy; Hsia, Daniel S; Salam, Maamoun; Pop-Busui, Rodica; 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; 2024

251.1. 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]

252. Kohan, 2014

Bibliographic Reference	Kohan, D. E.; Fioretto, P.; Tang, W.; List, J. F.; Long-term study of patients with type 2 diabetes and moderate renal impairment shows that dapagliflozin reduces weight and blood pressure but does not improve glycemic control; Kidney Int; 2014; vol. 85 (no. 4); 962-971

252.1. Study details

Trial name / registration number	Bristol-Myers Squibb and AstraZeneca-supported study is also known as Study MB102029 and is registered with ClinicalTrials.gov, number NCT00663260
Study type	Randomised controlled trial (RCT)
Study location	111 sites in United States, Argentina, Canada, India, Mexico, Peru, Italy, Australia, France, Spain, Denmark, Puerto Rico, and Singapore.
Study setting	NR
Study dates	19 June 2008 to 21 May 2009
Sources of funding	Bristol-Myers Squibb and AstraZeneca-supported study
Inclusion criteria	Male and female patients ≥18 years with T2DM and inadequate glycemic control defined as HbA1c ≥7.0 and ≤11.0%; moderate renal impairment (eGFR values of 30 to 59 ml/min per 1.73 m2) and body mass index ≤45.0 kg/m2. Stable antidiabetic regimen was defined as diet and exercise therapy alone or in combination with a regimen of any approved antidiabetic medication(s), including insulin, in which either doses of oral antidiabetic medications, exenatide, or pramlintide had not changed during 6 weeks before enrolment, or doses of long-acting insulin or intermediate-acting insulin had not varied by >20% during 6 weeks before enrolment.
Exclusion criteria	Aspartate or alanine aminotransferases >3.0 times the upper limit of normal, serum total bilirubin >2.0 mg/dl, history of diabetes insipidus or diabetic ketoacidosis or hyperosmolar nonketotic coma, uncontrolled hypertension defined as systolic blood pressure ≥180 mm Hg and/or diastolic blood pressure ≥110 mm Hg, or specified cardiovascular/vascular diseases within 6 months of enrolment visit. Renal exclusion criteria included the need for hemodialysis or renal replacement therapy, history of rapidly progressing renal disease, lupus nephritis, renal or systemic vasculitis, renal artery stenosis, renal transplant, or hepatic disease.
Recruitment / selection of participants	NR
Intervention(s)	Dapagliflozin 5mg or 10mg

Cointervention	A 7-day lead-in period included diet and exercise counselling, which continued throughout the study. Pre-enrolment antidiabetic regimen continued. During the first 24 weeks (short-term period), patients received rescue medication (any approved antidiabetic agent except metformin) if FPG 4270 mg/dl (weeks 4–6), 4240 mg/dl (weeks 6–12), or 4200 mg/dl (weeks 12–24). Patients completing the first 24 weeks were eligible to continue into an additional 28-week (long-term) period and were eligible to receive rescue medication if HbA1c 48.0%. Patients completing the first 52 weeks (the short-term plus long-term periods) were eligible to continue into the extension period (an additional 52 weeks) and received rescue medication if HbA1c 47.5% (weeks 52–76) and 47.0% (weeks 76–104).
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 “specified cardiovascular/vascular diseases within 6 months of enrolment visit”, prior unclear. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	People with chronic kidney disease Recruited people with moderate renal impairment (eGFR values of 30 to 59 ml/min per 1.73 m2). All had CKD as defined by the study (this was based on eGFR, but was study-classified). Study classifies as either stage 2, 3A, 3B, or 4 CKD. Renal exclusion criteria included the need for hemodialysis or renal replacement therapy, history of rapidly progressing renal disease, lupus nephritis, renal or systemic vasculitis, renal artery stenosis, renal transplant, or hepatic 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	Not stated/unclear

2 diabetes mellitus	
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Mixed population Reports the proportion of people with BMI ≥30 kg/m2 (65%)
Subgroup 5: eGFR category at baseline	eGFR ≥30mL/min/1.73m2
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	
Comparator	Placebo
Number of participants	252
Duration of follow-up	104 weeks
Indirectness	None
Method of analysis	Modified ITT

252.2. Study arms

252.2.1. Dapagliflozin 5mg (N = 83)

252.2.2. Dapagliflozin 10mg (N = 85)

252.2.3. Placebo (N = 184)

252.3. Characteristics

252.3.1. Arm-level characteristics

Characteristic	Dapagliflozin 5mg (N = 83)	Dapagliflozin 10mg (N = 85)	Placebo (N = 184)
% Male Sample size	n = 55 ; % = 66.3	n = 56 ; % = 65.9	n = 53 ; % = 63.1
Mean age (SD) Mean (SD)	66 (8.9)	68 (7.7)	67 (8.6)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 65 ; % = 78.3	n = 77 ; % = 90.6	n = 69 ; % = 82.1
African-American Sample size	n = 7 ; % = 8.4	n = 4 ; % = 4.7	n = 1 ; % = 1.2
Asian Sample size	n = 4 ; % = 4.8	n = 3 ; % = 3.5	n = 6 ; % = 7.1
Other Sample size	n = 7 ; % = 8.4	n = 1 ; % = 1.2	n = 8 ; % = 9.5
Comorbidities Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Diabetic nephropathy Sample size	n = 61 ; % = 73.5	n = 58 ; % = 68.2	n = 60 ; % = 71.4
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed Mean (SD)	16.9 (9)	18.2 (10.1)	15.7 (9.5)
Cardiovascular risk factors Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Dapagliflozin 5mg (N = 83)	Dapagliflozin 10mg (N = 85)	Placebo (N = 184)
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Mean (SD)	NR (NR)	NR (NR)	NR (NR)
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Number of people with obesity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
BMI >30 kg/m2 Sample size	n = 59 ; % = 71.1	n = 54 ; % = 63.5	n = 50 ; % = 59.5
eGFR mL/min/1.73m2 Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
CKD Stage 4 (eGFR <30ml/min per 1.73 m2) Sample size	n = 4 ; % = 4.8	n = 2 ; % = 2.4	n = 4 ; % = 4.8
CKD Stage 3B (eGFR 30+ and <45ml/min per 1.73 m2) Sample size	n = 41 ; % = 49.4	n = 47 ; % = 55.3	n = 34 ; % = 40.5
CKD Stage 3A (eGFR 45+ and <60ml/min per 1.73 m2) Sample size	n = 35 ; % = 42.2	n = 33 ; % = 38.8	n = 41 ; % = 48.8
CKD Stage 2 (eGFR 60+ ml/min per 1.73 m2) Sample size	n = 3 ; % = 3.6	n = 3 ; % = 3.5	n = 5 ; % = 6
Other antidiabetic medication used	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Dapagliflozin 5mg (N = 83)	Dapagliflozin 10mg (N = 85)	Placebo (N = 184)
Sample size			
Insulin based Sample size	n = 54 ; % = 65.1	n = 55 ; % = 64.7	n = 55 ; % = 65.5
Sulfonlyurea based Sample size	n = 21 ; % = 25.3	n = 21 ; % = 24.7	n = 21 ; % = 25
Thiazolidinedione based Sample size	n = 1 ; % = 1.2	n = 2 ; % = 2.4	n = 1 ; % = 1.2
Other Sample size	n = 7 ; % = 8.4	n = 7 ; % = 8.2	n = 7 ; % = 8.3
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

253. Komorizono, 2020

Bibliographic Reference	Komorizono, Y.; Hosoyamada, K.; Imamura, N.; Kajiya, S.; Hashiguchi, Y.; Ueyama, N.; Shinmaki, H.; Koriyama, N.; Tsukasa, M.; Kamada, T.; Metformin increase versus added linagliptin in nonalcoholic liver disease and type 2 diabetes: An analysis of J-LINK study; Diabetes, obesity & metabolism; 2020

253.1. Study details

Trial name / registration number	J-LINK / UMIN000014864
Study type	Randomised controlled trial (RCT)
Study location	10 medical institutions in Kagoshima, Japan
Study setting	No additional information
Study dates	July 2014 and September 2017
Sources of funding	Boehringer Ingelheim and Eli Lilly Company
Inclusion criteria	Patients aged 20–75 years who had been clinically diagnosed with NAFLD and T2DM with HbA1c levels between 6.0% and 8.5% were included in the study if they had been treated with metformin at a stable dose of ≤ 750 mg/day or had not received metformin. NAFLD was diagnosed through liver brightness on ultrasound (US) examination. Thus, the presence of HS was defined through the detection of a bright liver echo pattern; i.e., fine, packed, and high amplitude echoes, with consequent brightness of the liver, increase in liver–kidney contrast, and possible evidence of vascular blurring and deep attenuation signs.1,2 Additional eligible patients for the study included those with a daily alcohol intake < 20 g/day for men or < 10 g/day for women, prothrombin time-international normalized ratio (PT-INR) < 1.7, serum albumin > 3.5 g/dL, total bilirubin < 1.5 mg/dL, and estimated glomerular filtration rate (eGFR) ≥ 50
Exclusion criteria	T1DM or secondary diabetes mellitus; any history of liver disease including hepatitis B, hepatitis C, autoimmune hepatitis, primary biliary cholangitis, or alpha-1 antitrypsin deficiency; a diagnosis of congestive heart failure (New York Heart Association Functional Classification III–IV); serum alanine transaminase (ALT) or aspartate transaminase (AST) levels ≥ 5.0 times the upper limit of reference values at each institution; serum creatinine level ≥ 5.0 times the upper limit of reference values at each institution; or pregnant or trying to become pregnant.
Recruitment / selection of participants	No additional information

Intervention(s)	Linagliptin (n =25) Patients received 5 mg linagliptin once daily for 52 weeks
Cointervention	Metformin Patients received 750 mg daily oral Metformin
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure
Strata 2: People with atherosclerotic cardiovascular disease	People without atherosclerotic cardiovascular diseases
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	People without chronic kidney disease
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	People with non-alcoholic fatty liver disease

Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	All included individuals have NAFLD
Comparator	Metformin (n=25) Patients received up to 1500 mg Metformin twice or three times daily for 52 weeks
Number of participants	50
Duration of follow-up	52 weeks
Indirectness	NA
Method of analysis	ITT
Additional comments	The safety endpoint was evaluated from the treated set population, which included all patients who were randomized and had at least one safety information at week 4 or hereafter. The efficacy endpoints were evaluated from the full analysis set population, which included all patients who had at least one CT data at baseline or week 52.

253.2. Study arms

253.2.1. Linagliptin (N = 25)

Patients received 5 mg oral linagliptin once daily added to 750 mg daily metformin for 52 weeks

253.2.2. Metformin (N = 25)

Patients received oral metformin up to 1500 mg twice or three times daily for 52 weeks

253.3. Characteristics

253.3.1. Arm-level characteristics

Characteristic	Linagliptin (N = 25)	Metformin (N = 25)
% Male Linagliptin n = 24, Metformin n = 25 Sample size	n = 10 ; % = 41.7	n = 9 ; % = 36
Mean age (SD) (Years (mean, SD)) Linagliptin n = 24, Metformin n = 25 Mean (SD)	49.4 (10.8)	55.6 (10.2)
Ethnicity Linagliptin n = 24, Metformin n = 25 Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed Linagliptin n = 24, Metformin n = 25 Sample size	n = NR ; % = NR	n = NR ; % = NR
Smoking status Linagliptin n = 24, Metformin n = 25 Sample size	n = 5 ; % = 21.7	n = 0 ; % = 0
Alcohol consumption Linagliptin n = 24, Metformin n = 25 Sample size	n = 6 ; % = 25	n = 7 ; % = 28
Presence of severe mental illness Linagliptin n = 24, Metformin n = 25 Sample size	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Linagliptin n = 24, Metformin n = 25 Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Linagliptin n = 24, Metformin n = 25 Sample size	n = NR ; % = NR	n = NR ; % = NR
Other antidiabetic medication used Linagliptin n = 24, Metformin n = 25 Sample size	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Linagliptin (N = 25)	Metformin (N = 25)
Blood pressure-lowering medication used Linagliptin n = 24, Metformin n = 25 Sample size	n = NR ; % = NR	n = NR ; % = NR
Statins/lipid-lowering medication used Linagliptin n = 24, Metformin n = 25 Sample size	n = NR ; % = NR	n = NR ; % = NR
Other treatment being received Linagliptin n = 24, Metformin n = 25 Sample size	n = NR ; % = NR	n = NR ; % = NR

254. Kooy, 2009

Bibliographic Reference	Kooy, A.; Jager, J.; Lehert, P.; Bets, D.; Wulffelé, M. G.; Donker, A. J.; Stehouwer, C. D.; Long-term effects of metformin on metabolism and microvascular and macrovascular disease in patients with type 2 diabetes mellitus; Arch Intern Med; 2009; vol. 169 (no. 6); 616-25

254.1. Study details

Other publications associated with this study included in review	Wulffelé MG, Kooy A, Lehert P, Bets D, Ogterop JC, Borger van der Burg B, Donker AJ, Stehouwer CD. Combination of insulin and metformin in the treatment of type 2 diabetes. Diabetes Care. 2002 Dec;25(12):2133-40. doi: 10.2337/diacare.25.12.2133. PMID: 12453950. de Jager J, Kooy A, Schalkwijk C, van der Kolk J, Lehert P, Bets D, Wulffelé MG, Donker AJ, Stehouwer CD. Long-term effects of metformin on endothelial function in type 2 diabetes: a randomized controlled trial. J Intern Med. 2014 Jan;275(1):59-70. doi: 10.1111/joim.12128. Epub 2013 Sep 16. PMID: 23981104.
Trial name / registration number	HOME / NCT00375388
Study type	Randomised controlled trial (RCT)
Study location	3 sites in the Netherlands
Study setting	Out-patient clinics of 3 non-academic hospitals
Study dates	NR
Sources of funding	Supported by grants from Altana; Lifescan; E. Merck/Sante´; Merck, Sharpe, & Dohme; and Novo Nordisk
Inclusion criteria	Patients with T2DM aged between 30 and 80 years who had received a diagnosis of diabetes after 25 years of age, had never had an episode of ketoacidosis, and whose blood glucose–lowering treatment had previously consisted of oral agents but now exclusively consisted of insulin or a combination of insulin and metformin
Exclusion criteria	Pregnant women and women trying to become pregnant, patients with a Cockroft-Gault–estimated creatinine clearance <50 ml/min or low plasma cholinesterase (reference value, ≥3.5 units/l), and patients with congestive heart failure (New York Heart Association class III/IV) or other serious medical or psychiatric diseases.

Recruitment / selection of participants	No additional information
Intervention(s)	Metformin (n=196) Patients were supplied with boxes of 850 mg tablets of metformin; all patients successfully increased the dose from one table to 3 tablets per day if tolerated. The first tablet was taken at bedtime, the second at breakfast, and the third at dinner for 4.3 years
Cointervention	Insulin: All patients were treated with insulin four times daily or twice daily preceding breakfast and dinner. Individual titration took place according to good clinical practice to reach the target glucose levels and to prevent hypoglycemia. The nurse specialized in diabetes care, and if necessary, gave advice to adjust the insulin dose or try another insulin mixture or injection schedule (e.g., four times instead of twice daily). The adjustments of the insulin dose took place in “small steps,” changing the dose by ≤4 units per injection. If the target values for glycemic control were difficult to reach, the study nurse consulted the principal investigator for advice to optimize the insulin therapy. This intensive glucose-monitoring and insulin adjustment scheme was continued during the whole trial.
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Excluded "patients with congestive heart failure (New York Heart Association class III/IV)", otherwise unclear. Baseline characteristics: no people had HF at baseline.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Not an inclusion/exclusion criteria. Around 30% had "diabetic CV complications", unclear if definition consistent with review protocol. CV disease history in baseline characteristics consists of micro and macrovascular disease. Also given by breakdown of specific CV events at baseline (i.e. MI, stroke separately), overlap unclear so unable to calculation overall proportion.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Excluded "a Cockroft-Gault–estimated creatinine clearance <50 ml/min", 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
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	NA
Comparator	Placebo (n=194) Patients were supplied with boxes of placebo tablets; all patients increased the dose from one table to 3 tablets per day. The first tablet was taken at bedtime, the second at breakfast, and the third at dinner for 4.3 years. All patients were treated with insulin four times daily or twice daily preceding breakfast and dinner. Individual titration took place according to good clinical practice to reach the target glucose levels and to prevent hypoglycemia. The nurse specialized in diabetes care, and if necessary, gave advice to adjust the insulin dose or try another insulin mixture or injection schedule (e.g., four times instead of twice daily). The adjustments of the insulin dose took place in “small steps,” changing the dose by ≤4 units per injection. If the target values for glycemic control were difficult to reach, the study nurse consulted the principal investigator for advice to optimize the insulin therapy. This intensive glucose-monitoring and insulin adjustment scheme was continued during the whole trial.

Number of participants	390
Duration of follow-up	4.3 years
Indirectness	NA
Method of analysis	ITT
Additional comments	

254.2. Study arms

254.2.1. Metformin (N = 196)

Patients received 850 mg metformin up to a maximum of two tablets per day added to insulin therapy for 4.3 years

254.2.2. Placebo (N = 194)

Patients received placebo tablets to be added to insulin therapy for 4.3 years

254.3. Characteristics

254.3.1. Arm-level characteristics

Characteristic	Metformin (N = 196)	Placebo (N = 194)
% Male Sample size	n = 81 ; % = 41.3	n = 97 ; % = 50
Mean age (SD) (Years (mean, SD)) Mean (SD)	64 (10)	59 (11)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed (Years (mean, SD)) Mean (SD)	14 (9)	12 (8)

Characteristic	Metformin (N = 196)	Placebo (N = 194)
Smoking status Currently smoking at baseline Sample size	n = 38 ; % = 19	n = 59 ; % = 30
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR
Blood pressure-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
BP-lowering drugs Sample size	n = 93 ; % = 47	n = 75 ; % = 39
Statins/lipid-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Lipid-lowering drugs Sample size	n = 32 ; % = 16	n = 31 ; % = 16
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR

255. Kosiborod, 2024

Bibliographic Reference Kosiborod MN; Petrie MC; Borlaug BA; Butler J; Davies MJ; Hovingh GK; Kitzman DW; Møller DV; Treppendahl MB; Verma S; Jensen TJ; Liisberg K; Lindegaard ML; Abhayaratna W; Ahmed FZ; Ben-Gal T; Chopra V; Ezekowitz JA; Fu M; Ito H; Lelonek M; Melenovský V; Merkely B; Núñez J; Perna E; Schou M; Senni M; Sharma K; van der Meer P; Von Lewinski D; Wolf D; Shah SJ; ; Semaglutide in Patients with Obesity-Related Heart Failure and Type 2 Diabetes.; The New England journal of medicine; 2024; vol. 390 (no. 15)

255.1. 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	STEP-HFpEF DM trial / NCT04916470
Study type	Randomised controlled trial (RCT)
Study location	108 sites in 16 countries in Asia, Europe and North and South America
Study setting	NR
Study dates	June 15 2021 to August 19 2022
Sources of funding	Novo Nordisk
Inclusion criteria	1. Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial. 2. Male or female, age above or equal to 18 years at the time of signing informed consent (above or equal to 20 years for Japan) 3. BMI ≥ 30.0 kg/m2 . 4. NYHA Class II-IV. 5. LVEF ≥ 45% at screening.

	6. No hospitalisations due to heart failure between screening (V1) and randomisation (V2). 7. Able to perform the 6MWT at screening with a minimum distance of 100 metres. 8. KCCQ clinical summary score < 90 at screening. 9. At least one of the following: a. Mean pulmonary wedge pressure ≥15 mmHg or left ventricular end diastolic pressure (LVEDP) ≥15 mmHg documented during catheterisation at rest or pulmonary artery (PA) diastolic pressure measured by implantable monitor ≥15 mmHg or pulmonary wedge pressure or LVEDP ≥25 mmHg documented during catheterisation at exercise. b. If BMI < 35.0: NT-proBNP ≥ 220 pg/mL (for patients with sinus rhythm) or NT[1]proBNP ≥660 pg/mL (for patients with persistent/permanent atrial fibrillation); if BMI ≥ 35.0: NT-proBNP ≥ 125 pg/mL (for patients with sinus rhythm) or NT[1]proBNP ≥ 375 pg/mL (for patients with persistent/permanent atrial fibrillation) at screening (NT-proBNP analysed by the central laboratory) in combination with at least one of the following (documented by echocardiography within 12 months prior to or at screening): i. Septal é < 7cm/sec or lateral é < 10 cm/sec or average E/é ≥ 15 ii. PA systolic pressure >35mmHg iii. Left atrial (LA) enlargement (LA width ≥3.8 cm or LA length ≥ 5.0cm or LA area ≥ 20.0cm2 or LA volume ≥ 55mL or LA volume index ≥ 29mL/m2) iv. LV hypertrophy with septal thickness or posterior wall thickness ≥1.2cm c. Hospitalisation with a primary diagnosis of decompensated heart failure which required intravenous loop diuretic treatment, within the previous 12 months incombination with at least two of the following (documented by echocardiography within 12 months prior to or at screening): i. Septal é < 7cm/sec or lateral é < 10cm/sec or average E/é ≥ 15 ii. PA systolic pressure > 35mmHg iii. LA enlargement (LA width ≥ 3.8cm or LA length ≥ 5.0cm or LA area ≥ 20.0cm2 or LA volume ≥ 55mL or LA volume index ≥ 29mL/m2) iv. LV hypertrophy with septal thickness or posterior wall thickness ≥ 1.2cm v. Ongoing use of diuretic therapy for at least 30 days prior to screening 10. Diagnosed with T2D ≥ 90 days prior to the day of screening. 11. Subject treated with diet, exercise, and/or antidiabetic treatment* according to local label in stable dosing for at least 30 days prior to screening: o *OAD(s): unchanged drug(s), dose and dosing frequency o *Insulin(s): unchanged regimen (basal, basal+bolus, premix combination) with stable total daily insulin dose as judged by the investigator 12. HbA1c of ≤ 10.0% as measured at the screening visit.
Exclusion criteria	Cardiovascular-related: 1. Myocardial infarction, stroke, hospitalisation for heart failure, unstable angina pectoris or transient ischemic attack within 30 days prior to the day of screening. 2. Systolic blood pressure > 160 mmHg at screening. 3. Planned coronary, carotid or peripheral artery revascularization. 4. Any other condition judged by the investigator to be the primary cause of dyspnoea (such as heart failure due to restrictive cardiomyopathy or infiltrative conditions (e.g. amyloidosis), hypertrophic obstructive cardiomyopathy, primary pulmonary arterial hypertension, chronic obstructive pulmonary disease, right heart failure due to pulmonary disease, complex congenital heart disease, anaemia, or more than moderate heart valve disease). Obesity-related:

	5. Bariatric surgery prior to screening or planned bariatric surgery within the trial time course. 6. A self-reported change in body weight > 5 kg (11 lbs) within 90 days before screening irrespective of medical records. Glycaemia-related: 7. History of type 1 diabetes (history of gestational diabetes is allowed). 8. Treatment with any GLP-1 receptor agonist within 90 days prior to the day of screening. 9. Uncontrolled and potentially unstable diabetic retinopathy or maculopathy. Verified by a fundus examination performed within 90 days prior to screening or in the period between screening and randomisation. Pharmacological pupil-dilation is a requirement unless using a digital fundus photography camera specified for non-dilated examination. 10. Recurrent severe hypoglycaemic episodes within the last year as judged by the investigator. 11. Treatment with continuous subcutaneous insulin infusion General health and safety: 12. Personal or first-degree relative(s) history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma. 13. Presence of acute pancreatitis within the last 180 days prior to screening. 14. History or presence of chronic pancreatitis.
Recruitment / selection of participants	NR
Intervention(s)	Semaglutide (N = 310) Participants received once weekly subcutaneous semaglutide for 52 weeks initiated at a dose of 0.25 mf for 4 weeks until the maintenance dose of 2.4 mg was reached by week 16.
Cointervention	Patients were receiving metformin (71.9%), SGLT2i (32.8%), sulfonylureas (17.5%), DPP-4i (14.9%) and insulin (20.8%)
Strata 1: People with type 2 diabetes mellitus and heart failure	People with heart failure
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear
Strata 3: People with type 2 diabetes mellitus and chronic	Not stated/unclear

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	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 (n=306) Patients received placebo once weekly for 52 weeks
Number of participants	616
Duration of follow-up	52 weeks with a five week follow-up period

Indirectness	NA
Method of analysis	ITT
Additional comments	NA

255.2. Study arms

255.2.1. Semaglutide (N = 310)

Patients received a weekly does of 2.4 mg subcutaneous semaglutide for 52 weeks

255.2.2. Placebo (N = 306)

Patients received weekly subcutaneous placebo

255.3. Characteristics

255.3.1. Arm-level characteristics

Characteristic	Semaglutide (N = 310)	Placebo (N = 306)
% Male Sample size	n = 182 ; % = 58.7	n = 161 ; % = 52.6
Mean age (SD) (years (mean)) Mean (SD)	NR (NR)	NR (NR)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Ethnicity - Asian Sample size	n = 45 ; % = 14.5	n = 31 ; % = 10.1
Ethnicity - Black Sample size	n = 13 ; % = 4.2	n = 5 ; % = 1.6
Ethnicity - white Sample size	n = 251 ; % = 81	n = 268 ; % = 87.6
Ethnicity - Other Sample size	n = 1 ; % = 0.3	n = 2 ; % = 0.7
Time since type 2 diabetes diagnosed (Years (mean, SD)) Mean (SD)	NR (NR)	NR (NR)
Smoking status No of events	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
Other antidiabetic medication used - Metformin Sample size	n = 235 ; % = 75.8	n = 208 ; % = 68
Other antidiabetic medication used - SGLT2 inhibitor Sample size	n = 107 ; % = 34.5	n = 95 ; % = 31
Other antidiabetic medication used - DPP-4 inhibitor Sample size	n = 55 ; % = 17.7	n = 37 ; % = 12.1
Other antidiabetic medication used - Sulfonlyurea Sample size	n = 57 ; % = 18.4	n = 51 ; % = 16.7
Other antidiabetic medication used - Insulin Sample size	n = 53 ; % = 17.1	n = 75 ; % = 24.5
Other treatment being received - Diuretic Sample size	n = 246 ; % = 79.4	n = 252 ; % = 82.4
Other treatment being received - Loop diuretic Sample size	n = 186 ; % = 60	n = 187 ; % = 61.1
Other treatment being received - Thiazide Sample size	n = 42 ; % = 13.5	n = 43 ; % = 14.1
Other treatment being received - MRA Sample size	n = 105 ; % = 33.9	n = 95 ; % = 31
Other treatment being received - ACEI/ARB/ARNI Sample size	n = 249 ; % = 80.3	n = 253 ; % = 82.7
Other treatment being received - Beta blocker Sample size	n = 257 ; % = 82.9	n = 253 ; % = 82.7

256. Kothny, 2013

Bibliographic Reference	Kothny, W.; Foley, J.; Kozlovski, P.; Shao, Q.; Gallwitz, B.; Lukashevich, V.; Improved glycaemic control with vildagliptin added to insulin, with or without metformin, in patients with type 2 diabetes mellitus; Diabetes Obes Metab; 2013; vol. 15 (no. 3); 252-7

256.1. Study details

Trial name / registration number	NR
Study type	Randomised controlled trial (RCT)
Study location	Multicentre trial conducted in Europe, Asia, Australia and Central America
Study setting	No additional information
Study dates	NR
Sources of funding	Novartis Pharmaceuticals corporation for which two authors are also employees. A number of authors declare honoraria for multiple pharmaceutical companies
Inclusion criteria	Patients with T2DM who were being treated with stable insulin doses ≤1 U/kg/day (long-acting, intermediate-acting or premixed) with or without stable concomitant metformin treatment (≥1500 mg or maximally tolerated dose) for at least 12 weeks. Eligible patients were 18–80 years of age and had HbA1c values ≥7.5% and ≤11% and fasting plasma glucose levels (FPG) <15 mmol/l.
Exclusion criteria	Patients were excluded if they had an acute metabolic condition (such as ketoacidosis), acute or chronic liver disease, a myocardial infarction, coronary artery bypass surgery, percutaneous coronary intervention, stroke or transient ischaemic attack within the previous 6 months, unstable angina within the previous 3 months or a current heart failure diagnosis (New York Heart Association class III or IV)
Recruitment / selection of participants	No additional information
Intervention(s)	Vildagliptin (n=228) Patients received 50 mg daily oral vildagliptin for 24 weeks
Cointervention	Insulin Insulin doses had to be maintained within 10% of baseline during the trial unless insulin dose adjustments were required for safety reasons.

Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Exclusion criteria statement about heart failure diagnosis (NYHA class III-IV).
Strata 2: People with atherosclerotic cardiovascular disease	People without atherosclerotic cardiovascular diseases Exclusion criteria statement for people who had a myocardial infarction, coronary artery bypass surgery, a percutaneous coronary intervention, stroke or transient ischaemic attack in the previous 6 months or unstable angina in the previous 3 months
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with 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=221) Patients received oral placebo for 24 weeks. Insulin doses had to be maintained within 10% of baseline during the trial unless insulin dose adjustments were required for safety reasons.
Number of participants	449
Duration of follow-up	24 weeks
Indirectness	NR
Method of analysis	ACA
Additional comments	The change from baseline in HbA1c at week 24, was compared between vildagliptin and placebo using an analysis of covariance with treatment, region, metformin use and insulin type as classification variables, and baseline HbA1c as a covariate. This comparison was performed on the full analysis Set (including all randomised patients who received at least one dose of study drug and had at least one postbaseline efficacy measurement) as well as the two subgroups of patients with/without concomitant metformin within FAS. The last observation carried forward (LOCF) method was used to handle missing data because of early discontinuation or data censoring. Safety data were summarized descriptively by treatment. Hypoglycaemic incidences were compared between treatments using a chi-squared test. All available data were included in analysis for safety assessment.

256.2. Study arms

256.2.1. Vildagliptin 50 mg daily (N = 228)

Patients received 50 mg oral vildaglitpin daily for 24 weeks

256.2.2. Placebo (N = 221)

Patients received oral placebo for 24 weeks

256.3. Characteristics

256.3.1. Arm-level characteristics

Characteristic	Vildagliptin 50 mg daily (N = 228)	Placebo (N = 221)
% Male Sample size	n = 109 ; % = 47.8	n = 115 ; % = 52
Mean age (SD) (Years (mean, SD)) Mean (SD)	59.3 (9.9)	59.1 (10.1)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 116 ; % = 50.9	n = 116 ; % = 52.5
Asian Sample size	n = 87 ; % = 38.2	n = 86 ; % = 38.9
Other Sample size	n = 25 ; % = 11	n = 19 ; % = 8.6
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed (Years (mean, SD)) Mean (SD)	12.9 (6.9)	13.2 (7.9)
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Vildagliptin 50 mg daily (N = 228)	Placebo (N = 221)
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
Insulin Immediate-acting Sample size	n = 39 ; % = 17.1	n = 35 ; % = 15.8
Insulin Long-acting Sample size	n = 52 ; % = 22.8	n = 51 ; % = 23.1
Insulin Premixed Sample size	n = 137 ; % = 60.1	n = 135 ; % = 61.1
Metformin Sample size	n = 139 ; % = 61	n = 137 ; % = 62
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

257. Kothny, 2012

Bibliographic Reference	Kothny, W; Shao, Q; Groop, P-H; Lukashevich, V; One-year safety, tolerability and efficacy of vildagliptin in patients with type 2 diabetes and moderate or severe renal impairment.; Diabetes, obesity & metabolism; 2012; vol. 14 (no. 11); 1032-9

257.1. Study details

Secondary publication of another included study- see primary study for details	Lukashevich 2011 Lukashevich V, Schweizer A, Shao Q, Groop PH, Kothny W. Safety and efficacy of vildagliptin versus placebo in patients with type 2 diabetes and moderate or severe renal impairment: a prospective 24-week randomized placebo-controlled trial. Diabetes Obes Metab. 2011 Oct;13(10):947-54. doi: 10.1111/j.1463-1326.2011.01467.x. PMID: 21733061.

258. Kothny, 2015

Bibliographic Reference	Kothny, Wolfgang; Lukashevich, Valentina; Foley, James E; Rendell, Marc S; Schweizer, Anja; Comparison of vildagliptin and sitagliptin in patients with type 2 diabetes and severe renal impairment: a randomised clinical trial.; Diabetologia; 2015; vol. 58 (no. 9); 2020-6

258.1. Study details

Secondary publication of another included study- see primary study for details	N/A
Other publications associated with this study included in review	N/A
Trial name / registration number	NCT00616811
Study type	Randomised controlled trial (RCT)
Study location	6 centres in Brazil and 81 centres in the US
Study setting	Outpatient setting
Study dates	January 2008 and October 2010
Sources of funding	Novartis Pharma
Inclusion criteria	• Age 18 to85 years • BMI 18 to 42 kg/m2 • HbA1c 6.5 to10.0% (48 to 86 mmol/mol) • Type 2 diabetes either untreated (no glucose lowering medication in the past 8 weeks) or treated with a stable dose of sulfonylurea, thiazolidinedione, meglitinide or insulin, as monotherapy or in combination (for at least 4 weeks) • Severe RI (estimated GFR [eGFR] by the Modification of Diet in Renal Disease [MDRD] formula <30 ml min-1 [1.73 m]-2

Exclusion criteria	• History of renal transplant, significant cardiovascular history within 6 months • Liver disease, abnormal liver function tests (alanine transaminase [ALT] >2× upper limit of normal [ULN], aspartate transaminase >2× ULN or total bilirubin >2× ULN and/or direct bilirubin >ULN) • Any treatment that is contraindicated (i.e. metformin) in the severe RI population. The initial protocol excluded patients undergoing any dialysis, but it was subsequently amended to remove this restriction to facilitate recruitment.
Recruitment / selection of participants	503 patients were assessed for eligibility, and a total of 355 were excluded prior to randomisation. The trial targeted enrolling a population of approximately 33% elderly women as a patient population considered more vulnerable. Patients were randomised following a 2-week single-blind placebo run-in.
Intervention(s)	• Vildagliptin (50 mg once daily) • Sitagliptin (25 mg once daily) [One pill a day orally before breakfast]
Cointervention	Patients continued their initial background treatment throughout the study if applicable. Rescue medication (insulin addition or intensification) could be administered on or after week 4 if fasting plasma glucose (FPG) was >15 mmol/l, after week 8 if FPG >13.3 mmol/l and after week 16 if FPG >12.2 mmol/l. Efficacy data were censored at the start of rescue 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 “significant cardiovascular history within 6 months”, prior unclear. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and	People with chronic kidney disease Recruited people with "severe renal impairment (estimated GFR [eGFR] by the Modification of Diet in Renal Disease [MDRD] formula <30 ml min−1 [1.73 m]−2)"

chronic kidney disease	
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Mixed population
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	N/A
Comparator	N/A
Number of participants	148 participants were randomised.
Duration of follow-up	24 weeks

Indirectness	Directly applicable - The population did include participants who were treatment naïve. However, the baseline characteristics table shows that only 3 participants in the vildagliptin group (3.6%), and 1 participant in the sitagliptin group (1.5%), and therefore, this is deemed unlikely to affect the overall results.
Method of analysis	ITT Although not explicitly stated, it is likely that the analysis was ITT. The report states: "Adjusted mean changes from baseline to endpoint (with last observation carried forward) were compared between treatments using an ANCOVA model, with the baseline value as the covariate, and background therapy, pooled centre and treatment as the classification variables... Efficacy data were censored at the start of rescue medication... Safety analyses were performed on all collected data regardless of rescue medication."
Additional comments	None

258.2. Study arms

258.2.1. Vildagliptin (N = 83)

258.2.2. Sitagliptin (N = 65)

258.3. Characteristics

258.3.1. Study-level characteristics

Characteristic	**Study (N = 148)**
Comorbidities Nominal	NR
Presence of frailty Nominal	NR
Cardiovascular risk factors Nominal	NR
Smoking status Nominal	NR

Characteristic	Study (N = 148)
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
Number of people with obesity Nominal	NR
Blood pressure-lowering medication used Nominal	NR
Statins/lipid-lowering medication used n calculated by analyst Sample size	n = 130 ; % = 88
Antihypertensives Sample size	n = 141 ; % = 95
Platelet aggregation inhibitors Sample size	n = 89 ; % = 60

258.3.2. Arm-level characteristics

Characteristic	Vildagliptin (N = 83)	Sitagliptin (N = 65)
% Male Sample size	n = 42 ; % = 50.6	n = 29 ; % = 44.6
Mean age (SD) Mean (SD)	66.7 (8.8)	66.9 (9.6)
White Sample size	n = 51 ; % = 61.4	n = 40 ; % = 61.5
Black	n = 19 ; % = 22.9	n = 15 ; % = 23.1

Characteristic	Vildagliptin (N = 83)	Sitagliptin (N = 65)
Sample size		
Hispanic or Latino Sample size	n = 10 ; % = 12	n = 7 ; % = 10.8
Other Sample size	n = 3 ; % = 3.6	n = 3 ; % = 4.6
Time since type 2 diabetes diagnosed Mean (SD)	18.2 (10.4)	20.3 (10)
None Sample size	n = 3 ; % = 3.6	n = 1 ; % = 1.5
Any Sample size	n = 80 ; % = 96.4	n = 64 ; % = 98.5
Insulin monotherapy Sample size	n = 45 ; % = 54.2	n = 45 ; % = 69.2
Insulin + sulfonylurea Sample size	n = 11 ; % = 13.3	n = 7 ; % = 10.8
Insulin + thiazolidinedione Sample size	n = 7 ; % = 8.4	n = 2 ; % = 3.1
Sulfonylurea monotherapy Sample size	n = 9 ; % = 10.8	n = 7 ; % = 10.8
Other Sample size	n = 8 ; % = 9.6	n = 3 ; % = 4.5

259. Kovacs, 2014

Bibliographic Reference	Kovacs, C. S.; Seshiah, V.; Swallow, R.; Jones, R.; Rattunde, H.; Woerle, H. J.; Broedl, U. C.; Empagliflozin improves glycaemic and weight control as add-on therapy to pioglitazone or pioglitazone plus metformin in patients with type 2 diabetes: A 24-week, randomized, placebo-controlled trial; Diabetes Obes Metab; 2014; vol. 16 (no. 2); 147-158

259.1. Study details

Other publications associated with this study included in review	Kovacs 2015: Kovacs CS, Seshiah V, Merker L, Christiansen AV, Roux F, Salsali A, Kim G, Stella P, Woerle HJ, Broedl UC; EMPA-REG EXTEND™ PIO investigators. Empagliflozin as Add-on Therapy to Pioglitazone With or Without Metformin in Patients With Type 2 Diabetes Mellitus. Clin Ther. 2015 Aug;37(8):1773-88.e1. doi: 10.1016/j.clinthera.2015.05.511. Epub 2015 Jun 29. PMID: 26138864.
Trial name / registration number	EMPA-REG PIO / NCT012100001
Study type	Randomised controlled trial (RCT)
Study location	69 centres in 8 countries (Canada, China, Greece, India, Philippines, Thailand, Ukraine and USA)
Study setting	No additional information
Study dates	NR
Sources of funding	Boehringer Ingelheim and Eli Lilly. A number of authors are employees of Boehringer Ingelheim
Inclusion criteria	Patients with T2DM aged ≥18 years (and ≤65 years in India) with a body mass index ≤45 kg/m2 and HbA1c ≥7 and ≤10% at screening were eligible for this trial if they were on a diet and exercise regimen and, for ≥12 weeks prior to randomization, had been receiving unchanged doses of pioglitazone monotherapy (≥30 mg/day, or the maximum tolerated dose, or the maximum dose according to the local label) or pioglitazone plus metformin (≥1500 mg/day, or maximum tolerated dose or maximum dose according to the local label) Patients who completed 24 weeks of treatment and who still did not contravene the exclusion criteria for the initial study could elect to continue double-blind treatment for 52 weeks in an extension study.

Exclusion criteria	Key exclusion criteria included uncontrolled hyperglycaemia (plasma glucose >13.3 mmol/l after an overnight fast during a 2-week open-label placebo run-in period and confirmed by a second measurement), severe renal impairment [estimated glomerular filtration rate (eGFR) <30 ml/min/1.73 m2 using the Modification of Diet in Renal Disease (MDRD) equation], contraindication to pioglitazone and/or metformin according to the local label, or indication of liver disease (serum alanine aminotransferase, aspartate aminotransferase or alkaline phosphatase >3 × upper limit of normal) prior to randomization. Patients were also excluded if they had acute coronary syndrome, stroke or a transient ischaemic attack within 3 months of consent, were receiving anti-obesity drugs within 3 months of consent, had undergone bariatric surgery within 2 years, were receiving systemic steroids at the time of consent, had a change in the dose of thyroid hormones within 6 weeks of consent, or had any uncontrolled endocrine disorder except T2DM.
Recruitment / selection of participants	No additional information
Intervention(s)	Empagliflozin 10 mg (n=165) Empagliflozin 25 mg (n=168) Patients received once daily empagliflozin 10 mg or 25 mg for an initial 24 weeks, extending to 53 weeks
Cointervention	Pioglitazone or pioglitazone plus 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 “acute coronary syndrome, stroke or a transient ischaemic attack within 3 months of consent”, prior unclear. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Excluded “severe renal impairment [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 (n=165) Patients received placebo for 24 weeks as add-on to pioglitazone or pioglitazone plus metformin
Number of participants	498
Duration of follow-up	76 weeks
Indirectness	NA

Method of analysis	ITT
Additional comments	The analysis was undertaken using data from the full analysis set (FAS), which comprised all patients who received ≥1 dose of study medication and had a baseline HbA1c value. Values observed after a patient started rescue therapy were set to missing and imputed using the last observation carried forward (LOCF) method TO NOTE: For safety outcomes (hypoglycaemia and death) the authors state that "Median exposure was 12.8 months in the placebo group compared with 17.7 and 17.6 months in the empagliflozin 10mg and 25mg groups, respectively". Therefore a overall median value has been used for the timepoints for hypoglycaemia and death in the results spreadsheet. This has been reflected in the Risk of Bias scoring

259.2. Study arms

259.2.1. Empagliflozin 10 mg (N = 165)

Patients received once daily empagliflozin 10 mg for 24 weeks

259.2.2. Empagliflozin 25 mg (N = 168)

Patients received once daily empagliflozin 25 mg for 24 weeks

259.2.3. Placebo (N = 165)

Patients received placebo therapy for 24 weeks

259.3. Characteristics

259.3.1. Arm-level characteristics

Characteristic	Empagliflozin 10 mg (N = 165)	Empagliflozin 25 mg (N = 168)	Placebo (N = 165)
% Male Sample size	n = 83 ; % = 50.3	n = 85 ; % = 50.6	n = 73 ; % = 44.2

Characteristic	Empagliflozin 10 mg (N = 165)	Empagliflozin 25 mg (N = 168)	Placebo (N = 165)
Mean age (SD) (Years (mean, SD)) Mean (SD)	54.7 (9.9)	54.2 (8.9)	54.6 (10.5)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Asian Sample size	n = 91 ; % = 55.2	n = 94 ; % = 56	n = 103 ; % = 62.4
White Sample size	n = 69 ; % = 41.8	n = 68 ; % = 40.5	n = 60 ; % = 36.4
Black/African-American Sample size	n = 4 ; % = 2.4	n = 6 ; % = 3.6	n = 1 ; % = 0.6
American indian / Alaska native Sample size	n = 1 ; % = 0.6	n = 0 ; % = 0	n = 1 ; % = 0.6
Time since type 2 diabetes diagnosed Mean (SD)	NR (NR)	NR (NR)	NR (NR)
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Number of people with obesity	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Empagliflozin 10 mg (N = 165)	Empagliflozin 25 mg (N = 168)	Placebo (N = 165)
Sample size			
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Pioglitazone Sample size	n = 40 ; % = 24.2	n = 41 ; % = 24.4	n = 41 ; % = 24.8
Pioglitazone + Metformin Sample size	n = 125 ; % = 75.8	n = 127 ; % = 75.6	n = 124 ; % = 75.2
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

260. Kovacs, 2015

Bibliographic Reference	Kovacs, Christopher S; Seshiah, Veeraswamy; Merker, Ludwig; Christiansen, Anita Vedel; Roux, Flavien; Salsali, Afshin; Kim, Gabriel; Stella, Peter; Woerle, Hans-Juergen; Broedl, Uli C; Empagliflozin as Add-on Therapy to Pioglitazone With or Without Metformin in Patients With Type 2 Diabetes Mellitus.; Clinical therapeutics; 2015; vol. 37 (no. 8); 1773-88e1

260.1. Study details

Secondary publication of another included study- see primary study for details	Parent study Kovacs 2014 Kovacs CS, Seshiah V, Swallow R, Jones R, Rattunde H, Woerle HJ, Broedl UC; EMPA-REG PIO™ trial investigators. Empagliflozin improves glycaemic and weight control as add-on therapy to pioglitazone or pioglitazone plus metformin in patients with type 2 diabetes: a 24-week, randomized, placebo-controlled trial. Diabetes Obes Metab. 2014 Feb;16(2):147-58. doi: 10.1111/dom.12188. Epub 2013 Aug 22. PMID: 23906415.

261. Koyama, 2014

Bibliographic Reference	Koyama, H.; Tanaka, S.; Monden, M.; Morioka, T.; Fukumoto, S.; Mori, K.; Emoto, M.; Shoji, T.; Fukui, M.; Fujii, H.; Nishizawa, Y.; Inaba, M.; Comparison of effects of pioglitazone and glimepiride on plasma soluble RAGE and RAGE expression in peripheral mononuclear cells in type 2 diabetes: Randomized controlled trial (PioRAGE); Atherosclerosis; 2014; vol. 234 (no. 2); 329-334

261.1. 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	UMIN000002055
Study location	Japan
Study setting	Single centre trial. Report states that participants were recruited from the Diabetes Center of Osaka City University Hospital, however, no further information was reported.
Study dates	NR
Sources of funding	Ministry of Education, Culture, Sports, Science and Technology, Japan.
Inclusion criteria	• Diagnosis of type 2 diabetes • Age 20 to 80 years • Hemoglobin A1c 6.4 to 10.3% • Participants naive to glucose-lowering therapy at screening or taking 2.0 mg/day or less glimepiride (or the equivalent dosage of another sulfonylurea; gliclazide 20-80 mg/day, glibenclamide 1.25-5.0 mg/day, or nateglinide or mitiglynide) [abstract states that 63 diabetic patients being treated with sulfonyylurea or with nateglinide or metiglynide]

Exclusion criteria	• Use of insulin • Current pregnancy or planning on becoming pregnant during the study period • Chronic heart failure, liver cirrhosis, malignancies, or serum creatinine ≥2.0 mg/dL
Recruitment / selection of participants	Participants were recruited from patients being treated at the Diabetes Centre of Osaka City University Hospital
Intervention(s)	• Pioglitazone 15 mg (all 27 patients in the pioglitazone group started with a 15 mg dose, of whom 16 patients were increased to 30 mg at 24 weeks) • Glimepiride 0.5 to 2 mg (doses chosen by physician according to pre-registered treatment - 1 patient started with 0.5 mg, 22 with 1 mg, and 7 patients with 2 mg. At 24 weeks, 2 patients were being treated with 0.5 mg, 17 with 1 mg, and 11 with 2 mg) [Doses could be increased every 4 weeks to achieve HbA1c less than 7.4%]
Cointervention	Physicians were asked not to alter any other drugs that may affect blood pressure, lipids and platelet function.
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Exclusion criteria for chronic heart failure
Strata 2: People with atherosclerotic cardiovascular disease	People without atherosclerotic cardiovascular diseases 14% of people had previous 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	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	Of 31 participants allocated to pioglitazone, 27 completed the trial period. Of 32 participants allocated to glimepiride, 30 participants completed the trial period.
Duration of follow-up	12 and 24 weeks
Indirectness	Directly applicable
Method of analysis	Per protocol Described as participants wo completed the trial period.
Additional comments	NA

261.2. Study arms

261.2.1. Pioglitazone (N = 31)

261.2.2. Glimepiride (N = 32)

261.3. Characteristics

261.3.1. Arm-level characteristics

Characteristic	Pioglitazone (N = 31)	Glimepiride (N = 32)
% Male Baseline characteristics reported for completers only (pioglitazone n=27, glimepiride n=30) Sample size	n = 20 ; % = 74.1	n = 20 ; % = 66.7
Mean age (SD) Baseline characteristics reported for completers only (pioglitazone n=27, glimepiride n=30) Mean (SE)	64.6 (2)	65.2 (1.7)
Ethnicity Nominal	NR	NR
Comorbidities Baseline characteristics reported for completers only (pioglitazone n=27, glimepiride n=30) Sample size	n = NA ; % = NA	n = NA ; % = NA
Hypertension Sample size	n = 11 ; % = 40.7	n = 14 ; % = 46.7
Dyslipidemia Sample size	n = 18 ; % = 66.7	n = 21 ; % = 70
Past cardiovascular disease Sample size	n = 3 ; % = 11.1	n = 5 ; % = 16.7
Presence of frailty Nominal	NR	NR

Characteristic	Pioglitazone (N = 31)	Glimepiride (N = 32)
Time since type 2 diabetes diagnosed Baseline characteristics reported for completers only (pioglitazone n=27, glimepiride n=30) Range	1 to 40	1 to 30
Time since type 2 diabetes diagnosed Baseline characteristics reported for completers only (pioglitazone n=27, glimepiride n=30) Mean (SD)	8 (*empty data*)	6 (*empty data*)
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 ACEI or ARB use - Baseline characteristics reported for completers only (pioglitazone n=27, glimepiride n=30) Sample size	n = 5 ; % = 18.5	n = 8 ; % = 26.7
Statins/lipid-lowering medication used Baseline characteristics reported for completers only (pioglitazone n=27, glimepiride n=30) Sample size	n = 9 ; % = 33.3	n = 10 ; % = 33.3

Characteristic	Pioglitazone (N = 31)	Glimepiride (N = 32)
Other treatment being received Anti-platelet drug use - Baseline characteristics reported for completers only (pioglitazone n=27, glimepiride n=30) Sample size	n = 6 ; % = 22.2	n = 6 ; % = 20

262. Krobot, 2012

Bibliographic Reference	Krobot, Karl J; Ferrante, Shannon Allen; Davies, Michael J; Seck, Thomas; Meininger, Gary E; Williams-Herman, Debora; Kaufman, Keith D; Goldstein, Barry J; Lower risk of hypoglycemia with sitagliptin compared to glipizide when either is added to metformin therapy: a pre-specified analysis adjusting for the most recently measured HbA(1c) value.; Current medical research and opinion; 2012; vol. 28 (no. 8); 1281-7

262.1. Study details

Secondary publication of another included study- see primary study for details	Nauck 2007B
Other publications associated with this study included in review	

263. Langenfeld, 2005

Bibliographic Reference	Langenfeld, M. R.; Forst, T.; Hohberg, C.; Kann, P.; Lubben, G.; Konrad, T.; Pioglitazone decreases carotid intima-media thickness independently of glycaemic control in patients with type 2 diabetes mellitus. Results from a controlled randomized study; Circulation; 2005; vol. 111; 2525-2531

263.1. Study details

Secondary publication of another included study- see primary study for details	No
Other publications associated with this study included in review	None
Trial name / registration number	Not reported
Study type	Randomised controlled trial (RCT) Open-label, active-controlled RCT
Study location	Germany
Study setting	Outpatient
Study dates	Not reported but in or before 2004
Sources of funding	Unrestricted grant from Takeda Pharma GmbH, Germany
Inclusion criteria	• Aged 40-75 years • Type 2 diabetes diagnosis • Previous treatment with oral anti-diabetic agents • HbA1c 6.6-9.9% inclusive • No significant hepatic (ALT>2.5 times gender-specific normal value) or renal (serum creatinine>1.2 mg/dL) disease • Absence of congestive heart failure (NYHA class II to IV) • No cigarette smoking at the time of randomization and during previous 6 months

	• No known carotid artery stenosis.
Exclusion criteria	
Recruitment / selection of participants	Eligible participants recruited from one centre after one screening visit. Participants provided with individual medical advice to optimise glycaemic control (HbA1c <7%) at start and for duration of trial. Participants consecutively randomised to pioglitazone or glimepiride. Other oral anti-diabetic treatment (including sulphonylurea but not metformin) permitted in pioglitazone group; any other oral treatment permitted in glimepiride group except for thiazolidinediones.
Intervention(s)	• Pioglitazone 45 mg daily Oral pioglitazone 45 mg daily for 24 weeks, in addition to background oral anti-diabetic therapy.
Cointervention	• Background oral anti-diabetic therapy Other oral anti-diabetic treatment (including sulphonylurea but not metformin) permitted in pioglitazone group; any other oral treatment permitted in glimepiride group except for thiazolidinediones.
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Exclusion criteria for NYHA class II-IV heart failure
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Exclusion criteria based on creatinine but no statement on CKD explicitly
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	• Glimepiride 1-6 mg daily titrated Oral glimepiride 1-6 mg daily titrated for 24 weeks, in addition to background oral anti-diabetic therapy.
Number of participants	N=192 randomised (N=173 per protocol population; N=162 completers)
Duration of follow-up	24 weeks
Indirectness	None
Method of analysis	Per protocol Not explicitly stated but results reported for per protocol population (all randomised participants with no major protocol violations)

263.2. Study arms

263.2.1. Pioglitazone 45 mg daily (N = 92)

Oral pioglitazone 45 mg daily for 24 weeks, in addition to background anti-diabetic drug therapy.

263.2.2. Glimepiride 1-6 mg daily (N = 87)

Oral glimepiride 1-6 mg daily titrated for 24 weeks, in addition to background anti-diabetic drug therapy.

263.3. Characteristics

263.3.1. Arm-level characteristics

Characteristic	Pioglitazone 45 mg daily (N = 92)	Glimepiride 1-6 mg daily (N = 87)
% Male Sample size	n = 55 ; % = 61.8	n = 52 ; % = 61.9
Mean age (SD) Mean (SD)	62 (8)	63 (7)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Other Sample size	n = 1 ; % = 1.1	n = 3 ; % = 3.6
White Sample size	n = 88 ; % = 98.9	n = 81 ; % = 96.4
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed Mean (SD)	7.4 (7.9)	6.9 (6.5)
Cardiovascular risk factors Nominal	NR	NR
Smoking status Sample size	n = 0 ; % = 0	n = 0 ; % = 0

Characteristic	Pioglitazone 45 mg daily (N = 92)	Glimepiride 1-6 mg daily (N = 87)
Alcohol consumption Nominal	NR	NR
Presence of severe mental illness Nominal	NR	NR
People with significant cognitive impairment Nominal	NR	NR
People with a learning disability Nominal	NR	NR
Number of people with obesity Nominal	NR	NR
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Monotherapy Sample size	n = 58 ; % = 65.2	n = 53 ; % = 63.1
Combination therapy Sample size	n = 31 ; % = 34.8	n = 31 ; % = 36.9
Blood pressure-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
ACE-inhibitor or ARB at start of trial Sample size	n = 52 ; % = 58.4	n = 41 ; % = 48.8
ACE-inhibitor or ARB at end of trial Sample size	n = 54 ; % = 60.7	n = 43 ; % = 51.2
Statins/lipid-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Statins at start of trial Sample size	n = 18 ; % = 20.2	n = 13 ; % = 15.5

Characteristic	Pioglitazone 45 mg daily (N = 92)	Glimepiride 1-6 mg daily (N = 87)
Statins at end of trial Sample size	n = 29 ; % = 32.8	n = 13 ; % = 15.5
Other treatment being received Sample size	n = NA ; % = NA	n = NA ; % = NA
Antiplatelet therapy at start Sample size	n = 25 ; % = 28.1	n = 26 ; % = 31
Antiplatelet therapy at end Sample size	n = 35 ; % = 39.3	n = 34 ; % = 40.5

Baseline characteristics are for per protocol population, Pioglitazone, N=89 and Glimepiride, N=84.

264. Lavalle-Gonzalez, 2013

Bibliographic Reference	Lavalle-Gonzalez, F. J.; Januszewicz, A.; Davidson, J.; Tong, C.; Qiu, R.; Canovatchel, W.; Meininger, G.; Efficacy and safety of canagliflozin compared with placebo and sitagliptin in patients with type 2 diabetes on background metformin monotherapy: A randomised trial; Diabetologia; 2013; vol. 56 (no. 12); 2582-2592

264.1. Study details

Trial name / registration number	NCT01106677
Study type	Randomised controlled trial (RCT)
Study location	169 centres in 22 countries
Study setting	No additional information
Study dates	April 2010 and August 2012
Sources of funding	Janssen Research & Development, LLC. Numerous authors declare honoraria and funding from multiple pharmaceutical companies
Inclusion criteria	Men and women with type 2 diabetes, aged ≥18 and ≤80 years, who had inadequate glycaemic control (HbA1c ≥7.0% [53 mmol/mol] and ≤10.5% [91 mmol/mol]) and who were on stable metformin therapy (≥2,000 mg/day [or ≥1,500 mg/day if unable to tolerate higher dose]) for ≥8 weeks and had fasting plasma glucose (FPG) <15 mmol/l at week−2 and fasting fingerstick glucose ≥6.1 mmol/l and <15 mmol/l on day 1. Participants on metformin immediate-release (IR) monotherapy at protocol-specified doses at screening directly entered the placebo run-in period. Those on metformin extended release (XR), metformin IR or XR at below protocol-specified doses or metformin plus sulfonylurea underwent a metformin IR dose titration/dose stable and, if applicable, a sulfonylurea washout period of up to 10 weeks, followed by the placebo run-in period.
Exclusion criteria	Repeated FPG and/or fasting self-monitored blood glucose (SMBG) ≥15.0 mmol/l during the pretreatment phase; history of type 1 diabetes, cardiovascular disease (including myocardial infarction, unstable angina, revascularisation procedure or cerebrovascular accident) in the 3 months before screening or uncontrolled hypertension; treatment with a peroxisome proliferator-activated receptor γ agonist, insulin, another SGLT2 inhibitor or any other AHA (except metformin as monotherapy or in combination with a sulfonylurea) in the 12 weeks before screening; or estimated glomerular filtration rate (eGFR) <55 ml min−1 (1.73 m2) −1 (or <60 ml min−1 [1.73 m2] −1 if based upon restriction in local label) or serum creatinine ≥124 µmol/l (men) or ≥115 µmol/l (women)

Recruitment / selection of participants	No additional information
Intervention(s)	Sitagliptin (n=366) Patients received 100 mg sitagliptin once daily for 52 weeks Canagliflozin 100 mg (n=368) Patients received 100 mg canagliflozin once daily for 52 weeks Canagliflozin 300 mg (n=367) Patients received 300 mg canagliflozin once daily for 52 weeks
Cointervention	Metformin: All patients received immediate release metformin as background therapy
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear
Strata 2: People with atherosclerotic cardiovascular disease	People without atherosclerotic cardiovascular diseases Exclusion criteria based on cardiovascular disease, including myocardial infarction, unstable angina, revascularisation procedure or cerebrovascular accident in the 3 months before screening
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Exclusion criteria based on eGFR and creatinine but otherwise no clear statement
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	NA
Comparator	Placebo (n=183) Patients received placebo once daily for 26 weeks
Number of participants	1284
Duration of follow-up	52 weeks
Indirectness	NA
Method of analysis	Modified ITT
Additional comments	Primary efficacy analysis was performed in the modified intent-to-treat (mITT) population (randomised participants who received ≥1 dose of study drug) using a last observation carried forward (LOCF) approach. Primary efficacy analyses were performed in the mITT population according to randomised treatment assignment using LOCF to impute missing data; for participants who received rescue therapy, the last post-baseline value before rescue was used. Safety analyses were performed in the same

	population according to the predominant treatment received; in this study, the mITT and safety populations were identical. PLEASE NOTE; The data for this study has been split into 26 weeks for comparisons of cana and sita v placebo and (labelled 2013A) and 52 weeks for cana v sita (labelled 2013B)

264.2. Study arms

264.2.1. Placebo (N = 183)

Patients received placebo once daily for 26 weeks

264.2.2. Sitagliptin (N = 366)

Patients received 100 mg sitagliptin daily for 52 weeks

264.2.3. Canagliflozin 100 mg (N = 368)

Patients received 100 mg canagliflozin daily for 52 weeks

264.2.4. Canagliflozin 300 mg (N = 367)

Patients received 300 mg canagliflozin daily for 52 weeks

264.3. Characteristics

264.3.1. Arm-level characteristics

Characteristic	Placebo (N = 183)	Sitagliptin (N = 366)	Canagliflozin 100 mg (N = 368)	Canagliflozin 300 mg (N = 367)
% Male Sample size	n = 94 ; % = 51.4	n = 172 ; % = 47	n = 174 ; % = 47.3	n = 165 ; % = 45
Mean age (SD) (Years (mean, SD)) Mean (SD)	55.3 (9.8)	55.5 (9.6)	55.5 (9.4)	55.3 (9.2)

Characteristic	Placebo (N = 183)	Sitagliptin (N = 366)	Canagliflozin 100 mg (N = 368)	Canagliflozin 300 mg (N = 367)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 129 ; % = 70.5	n = 264 ; % = 72.1	n = 252 ; % = 68.5	n = 256 ; % = 69.8
Black or African American Sample size	n = 3 ; % = 1.6	n = 13 ; % = 3.6	n = 16 ; % = 4.3	n = 13 ; % = 3.5
Asian Sample size	n = 30 ; % = 16.4	n = 41 ; % = 11.2	n = 51 ; % = 13.9	n = 60 ; % = 16.3
Other Includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, multiple and other Sample size	n = 21 ; % = 11.5	n = 48 ; % = 13.1	n = 49 ; % = 13.3	n = 38 ; % = 10.4
Time since type 2 diabetes diagnosed (Years (mean, SD)) Mean (SD)	6.8 (5.3)	6.8 (5.2)	6.7 (5.4)	7.1 (5.4)
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Placebo (N = 183)	Sitagliptin (N = 366)	Canagliflozin 100 mg (N = 368)	Canagliflozin 300 mg (N = 367)
Other antidiabetic medication used Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Blood pressure-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Statins/lipid-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR

265. Ledesma, 2019

Bibliographic Reference	Ledesma, G.; Umpierrez, G. E.; Morley, J. E.; Lewis-D'Agostino, D.; Keller, A.; Meinicke, T.; van der Walt, S.; von Eynatten, M. R.; Efficacy and safety of linagliptin to improve glucose control in older people with type 2 diabetes on stable insulin therapy: a randomized trial; Diabetes Obes Metab; 2019

265.1. 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	NCT02240680
Study type	Randomised controlled trial (RCT) Double-blind, parallel group, active-controlled randomised trial
Study location	International (16 countries: Australia, Colombia, Denmark, Finland, Germany, Greece, Ireland, Japan, Mexico, New Zealand, Poland, Romania,South Africa, Spain, UK and USA)
Study setting	Outpatient
Study dates	02/2014 to 11/2016
Sources of funding	Supported by Boehringer Ingelheim and Eli Lilly & Co. and the Diabetes Alliance.
Inclusion criteria	• Aged ≥60 years-old • Treated with basal insulin(stratified by <40 IU/day and ≥40 IU/day) maintained at a stable (i.e., unchanged) dose for ≥4 weeks prior to randomization • HbA1c level 7.0–10.0% inclusive • BMI≤45 kg/m2 • Permitted basal insulin or biosimilar were either intermediate-acting formulations (insulin neutral protamine Hagedorn [NPH insulin];

	insulin lispro protamine), or long-acting formulations (insulin degludec; insulin detemir; insulin glargine) • The only permitted additional glucose-lowering therapies were metformin and/or alpha-glucosidase inhibitors, administered at a stable dose for 12 weeks prior to randomization
Exclusion criteria	• Type 1 diabetes mellitus • Currently treated with any glucose-lowering therapies not included in the permitted list or any anti-obesity medication • Depression or cognitive impairment • Acute coronary syndrome • Indication of liver disease • History of cancer or bariatric surgery • Treatment with additional glucose-lowering therapies (excluding metformin and/or alpha-glucosidase inhibitors) administered at a stable dose for 12-weeks prior to randomization
Recruitment / selection of participants	Participants recruited from 16 countries and were screened and underwent 1 week placebo run-in period. Participants randomised 1:1 using computer-generated random sequence and third-party phone/web--based system, stratified based on screening hBa1c (<8.5%; ≥8.5%) and daily insulin dose at end of run-in period (<40IU vs ≥40 IU). Participants, clinical staff and investigators analyzing trial data were blinded to treatment for duration of trial.
Intervention(s)	• Linagliptin 20 mg daily Oral linagliptin 5 mg four times daily for 24 weeks, in addition to stable basal insulin therapy.
Cointervention	• Basal insulin All participants continued their insulin therapy for duration of trial.
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 Debatably the eGFR categories could put the majority of the population into a CKD category, but with the absence of any other evidence it is difficult to say.

Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	
Comparator	• Placebo Matching placebo for 24 weeks, in addition to stable basal insulin therapy.
Number of participants	N=302
Duration of follow-up	24 weeks
Indirectness	None

Method of analysis	ITT ITT LOCF analysis for all outcomes
Additional comments	

265.2. Study arms

265.2.1. Linagliptin 20 mg daily (N = 151)

Oral linagliptin 5 mg four times daily for 24 weeks, in addition to stable basal insulin therapy.

265.2.2. Placebo (N = 151)

Matching placebo for 24 weeks, in addition to stable basal insulin therapy.

265.3. Characteristics

265.3.1. Arm-level characteristics

Characteristic	Linagliptin 20 mg daily (N = 151)	Placebo (N = 151)
% Male Sample size	n = 92 ; % = 60.9	n = 91 ; % = 60.3
Mean age (SD) (years) Mean (SD)	72.3 (5.1)	72.5 (5.6)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Asian Sample size	n = 52 ; % = 34.4	n = 52 ; % = 34.4
Other Sample size	n = 15 ; % = 10	n = 18 ; % = 12
White Sample size	n = 84 ; % = 55.6	n = 81 ; % = 53.6

Characteristic	Linagliptin 20 mg daily (N = 151)	Placebo (N = 151)
Comorbidities Sample size	n = NA ; % = NA	n = NA ; % = NA
Microvascular disease Sample size	n = 70 ; % = 46.4	n = 84 ; % = 55.6
Diabetic retinopathy Sample size	n = 38 ; % = 25.2	n = 30 ; % = 19.9
Diabetic nephropathy Sample size	n = 36 ; % = 23.8	n = 41 ; % = 27.2
Diabetic neuropathy Sample size	n = 32 ; % = 21.2	n = 51 ; % = 33.8
Diabetic foot Sample size	n = 6 ; % = 4	n = 5 ; % = 3.3
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed Sample size	n = NA ; % = NA	n = NA ; % = NA
Less than 1 year Sample size	n = 3 ; % = 2	n = 2 ; % = 1.4
More than 1 year to 5 years Sample size	n = 7 ; % = 4.7	n = 8 ; % = 5.4
More than 5 to 10 years Sample size	n = 26 ; % = 17.4	n = 24 ; % = 16.3
More than 10 to 15 years Sample size	n = 39 ; % = 26.2	n = 33 ; % = 22.4
More than 15 years Sample size	n = 74 ; % = 49.7	n = 80 ; % = 54.4
Cardiovascular risk factors Sample size	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Linagliptin 20 mg daily (N = 151)	Placebo (N = 151)
Macrovascular disease without hypertension Sample size	n = 56 ; % = 37.1	n = 53 ; % = 35.1
Coronary artery disease Sample size	n = 44 ; % = 29.1	n = 43 ; % = 28.5
Peripheral artery occlusive disease Sample size	n = 9 ; % = 6	n = 13 ; % = 8.6
Cerebrovascular disease Sample size	n = 17 ; % = 11.3	n = 8 ; % = 5.3
Hypertension Sample size	n = 128 ; % = 84.8	n = 115 ; % = 76.2
Hyperlipidemia Sample size	n = 114 ; % = 75.5	n = 112 ; % = 74.2
Smoking status Nominal	NR	NR
Alcohol consumption Nominal	NR	NR
Presence of severe mental illness Nominal	NR	NR
People with significant cognitive impairment Sample size	n = 0 ; % = 0	n = 0 ; % = 0
People with a learning disability Sample size	n = 0 ; % = 0	n = 0 ; % = 0
Number of people with obesity Nominal	NR	NR
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Insulin monotherapy Sample size	n = 45 ; % = 30.2	n = 38 ; % = 25.9

Characteristic	Linagliptin 20 mg daily (N = 151)	Placebo (N = 151)
Insulin + metformin Sample size	n = 88 ; % = 59.1	n = 92 ; % = 62.6
Insulin + alpha-glucosidase inhibitor Sample size	n = 5 ; % = 3.4	n = 6 ; % = 4.1
Insulin + metformin + alpha-glucosidase inhibitor Sample size	n = 8 ; % = 5.4	n = 11 ; % = 7.5
Insulin + metformin + a sulphonylurea Sample size	n = 3 ; % = 2	n = 0 ; % = 0
Blood pressure-lowering medication used Nominal	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR

266. Lee, 2022

Bibliographic Reference	Lee, C. H.; Wu, M. Z.; Lui, Dt- W.; Chan, Ds- H.; Fong, Ch- Y.; Shiu, Sw- M.; Wong, Y.; Lee, Ac- H.; Lam, Jk- Y.; Woo, Y. C.; et, al.; Comparison of Serum Ketone Levels and Cardiometabolic Efficacy of Dapagliflozin versus Sitagliptin among Insulin-Treated Chinese Patients with Type 2 Diabetes Mellitus; Diabetes & metabolism journal; 2022

266.1. 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	DISTINCTION/NCT03959501
Study type	Randomised controlled trial (RCT) Open-label, active-controlled, randomised trial
Study location	Hong Kong, P.R. of China
Study setting	Outpatient
Study dates	08/2017 to 10/202
Sources of funding	Supported in part by funding from AstraZeneca, and from Endowment Fund awarded to Dr K.C.-B. Tan.
Inclusion criteria	• Type 2 diabetes diagnosis • Aged 21-75 years inclusive • BMI 21-40 kg/m2 inclusive • HbA1c 8-10.5% inclusive • Receiving stable (+/- <10% change in total daily dose for at least 3 months before trial) single or two dose insulin therapy (intermediate-acting human insulin; pre-mixed human insulin, or insulin analogues) with or without metformin

Exclusion criteria	• Type 1 diabetes mellitus • History of ketoacidosis • Concurrent use of sulphonylurea or loop diuretics • Prior use of SGLT2 or DPP-4 inhibitors or GLP-1 RAs in preceding 3 months • History of intolerance to SGLT2 or DPP-4 inhibitors • eGFR< 45 mL/min/1.73 m2 (CKD-EPI equation) • History of acute or chronic pancreatitis, benign or malignant pancreatic tumours, bladder cancer, • Severe liver disease with elevated plasma alanine aminotransferase (ALT) ≥ 5 times the upper limit of normal • Active or history of malignancy in the preceding 5 years, • Hospitalization for acute illness in preceding 3 months before enrolment. • Severe mental disorder • Pregnancy or breastfeeding
Recruitment / selection of participants	Participants recruited from Diabetes clinic of Queen Mary Hospital, Hong Kong and eligible people were block randomised 1:1, using computer-based allocation schedule, to groups. All participants remained on preexisting insulin dose for 12 weeks (unless hypoglycaemia events); after 12 weeks insulin was titrated to achieve fasting and pre-prandial blood glucose 4-7 mmol/L inclusive.
Intervention(s)	• Dapagliflozin 10 mg daily Oral dapagliflozin 10 mg daily for 24 weeks, in addition to insulin therapy.
Cointervention	• Insulin • Metformin All participants received insulin for duration of trial. First 12 weeks insulin dose remained same, then titrated to achieve fasting and preprandial blood glucose 4-7 mmol/L inclusive. Although trial recruited people on insulin with or without metformin, all participants received background metformin.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear A minority of people had a coronary artery disease or stroke, but unclear whether the same people had those events (putting it into people without ACD) or different people (putting it into mixed).
Strata 3: People with type 2 diabetes	Not stated/unclear Exclusion criteria based on eGFR but no explicit statement about CKD

mellitus and chronic kidney disease	
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	eGFR ≥30mL/min/1.73m2 Exclusion criteria: eGFR<45 mL/min/1.73 m2 (CKD-EPI equation)
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Comparator	• Sitagliptin 100 mg daily Oral sitagliptin 100 mg daily for 24 weeks, in addition to insulin therapy.
Number of participants	N=60
Duration of follow-up	24 weeks
Indirectness	None

Method of analysis	ITT ITT analysis for all outcomes with LOCF for missing data

266.2. Study arms

266.2.1. Dapagliflozin 10 mg daily (N = 30)

Oral dapagliflozin 10 mg daily for 24 weeks, in addition to background insulin therapy.

266.2.2. Sitagliptin 100 mg daily (N = 30)

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

266.3. Characteristics

266.3.1. Arm-level characteristics

Characteristic	Dapagliflozin 10 mg daily (N = 30)	Sitagliptin 100 mg daily (N = 30)
% Male Sample size	n = 16 ; % = 53.3	n = 20 ; % = 66.7
Mean age (SD) (years) Mean (SD)	56.9 (10.7)	60.6 (7.03)
Ethnicity Nominal	NR	NR
Comorbidities Sample size	n = NA ; % = NA	n = NA ; % = NA
Sight-threatening diabetic retinopathy Sample size	n = 2 ; % = 6.7	n = 3 ; % = 10
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	17.1 (9.56)	19.3 (8.5)

Characteristic	Dapagliflozin 10 mg daily (N = 30)	Sitagliptin 100 mg daily (N = 30)
Cardiovascular risk factors Sample size	n = NA ; % = NA	n = NA ; % = NA
Hypertension Sample size	n = 24 ; % = 80	n = 25 ; % = 83.3
Coronary heart disease Sample size	n = 4 ; % = 13.3	n = 4 ; % = 13.3
Stroke Sample size	n = 2 ; % = 6.7	n = 2 ; % = 6.7
Smoking status History of smoking Sample size	n = 12 ; % = 40	n = 12 ; % = 40
Alcohol consumption Nominal	NR	NR
Presence of severe mental illness Sample size	n = 0 ; % = 0	n = 0 ; % = 0
People with significant cognitive impairment Nominal	NR	NR
People with a learning disability Nominal	NR	NR
Number of people with obesity Nominal	NR	NR
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Metformin Sample size	n = 30 ; % = 100	n = 30 ; % = 100
Pioglitazone Sample size	n = 4 ; % = 13.3	n = 5 ; % = 16.7

Characteristic	Dapagliflozin 10 mg daily (N = 30)	Sitagliptin 100 mg daily (N = 30)
Blood pressure-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Angiotensin-converting enzyme inhibitors Sample size	n = 15 ; % = 50	n = 16 ; % = 53.3
Angiotensin II receptor blockers Sample size	n = 8 ; % = 27.7	n = 8 ; % = 26.7
Statins/lipid-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Statins Sample size	n = 19 ; % = 63.3	n = 24 ; % = 80
Fibrates Sample size	n = 0 ; % = 0	n = 3 ; % = 10
Other treatment being received Sample size	n = NA ; % = NA	n = NA ; % = NA
Aspirin Sample size	n = 8 ; % = 26.7	n = 8 ; % = 26.7

267. Lee, 2013

Bibliographic Reference	Lee, H. W.; Lee, H. C.; Kim, B. W.; Yang, M. J.; Park, J. S.; Oh, J. H.; Choi, J. H.; Cha, K. S.; Hong, T. J.; Kim, S. P.; Song, S.; Park, J. H.; Effects of low dose pioglitazone on restenosis and coronary atherosclerosis in diabetic patients undergoing drug eluting stent implantation; Yonsei Med J; 2013; vol. 54 (no. 6); 1313-1320

267.1. Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.
Trial name / registration number	No additional information.
Study type	Randomised controlled trial (RCT)
Study location	South Korea
Study setting	Hospital
Study dates	10/2009 to 07/2011
Sources of funding	This study was supported by a grant from the Korean Heath Technology R&D Project, Ministry of Health and Welfare, Republic of Korea (A070001).
Inclusion criteria	• A known medical history or they were newly diagnosed with type 2 diabetes mellitus and symptomatic ischemic heart disease with an angiographically significant coronary lesion and who had undergone percutaneous coronary intervention with drug eluting stents (DES). • For the diagnosis of type 2 diabetes mellitus, patients had to meet the criteria of 1) fasting plasma glucose level >126 mg/dL, 2) known medical history of type 2 diabetes mellitus and 3) glycosylated hemoglobin level >7 mg/dL.

	• For glycemic control, all kinds of diabetic medication were allowed, including insulin. • Coronary artery disease included one-vessel or multi-vessel disease, a vessel length of less than 50 mm and a vessel diameter from 2.5 mm to 4 mm with de novo lesion, diffuse long lesion and ostial lesion.
Exclusion criteria	• Patients who were already taking pioglitazone or patients with bifurcated (>2 mm) lesion, chronic total obstruction lesion, left main lesion, liver and renal dysfunction, left ventricular (LV) dysfunction (LV ejection fraction <40%) at the time of percutaneous coronary intervention or previous myocardial infarction (MI) in the previous 6 weeks before intervention.
Recruitment / selection of participants	Patients with type 2 diabetes and coronary artery disease.
Intervention(s)	Pioglitazone 15 mg once daily orally administered
Cointervention	Patients n(%) were taking the following treatments for managing their type 2 diabetes and coronary artery disease: Pioglitazone arm: insulin (11.7%), metformin (36.7%), glimepride (60.0%), sulfonylurea (5.0%), α-glycosidase inhibitor (1.7%), cilostazol (28.3%), clopidogrel (98.3%), statins (73.3%) Control arm: insulin (8.2%), metformin (32.8%), glimepride (62.3%), sulfonylurea (1.6%), α-glycosidase inhibitor (3.3%), cilostazol (32.8%), clopidogrel (100%), statins (73.8%)
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Exclusion criteria for the echocardiographic features of heart failure (LV ejection fraction <40% etc.)
Strata 2: People with atherosclerotic cardiovascular disease	People with atherosclerotic cardiovascular diseases Inclusion criteria
Strata 3: People with type 2 diabetes	Not stated/unclear Exclusion criteria about a lack of renal dysfunction but no explicit mention of chronic kidney disease

mellitus and chronic kidney disease	
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	No additional information.
Comparator	Placebo once daily orally administered
Number of participants	N=121
Duration of follow-up	12 months

Indirectness	No additional information.
Method of analysis	Not stated/unclear
Additional comments	All patients completed follow-up (N=121) and were included in the analysis for 12-month follow-up lipid profiles and HbA1c values.

267.2. Study arms

267.2.1. Pioglitazone 15 mg (N = 60)

Administered orally, once daily

267.2.2. Placebo (N = 61)

Administered orally, once daily

267.3. Characteristics

267.3.1. Arm-level characteristics

Characteristic	Pioglitazone 15 mg (N = 60)	Placebo (N = 61)
% Male No of events	n = 43 ; % = 71.7	n = 46 ; % = 75.4
Mean age (SD) (years) Mean (SD)	60.3 (9.53)	61.9 (8.75)
Ethnicity Nominal	NR	NR
Stable angina pectoris No of events	n = 16 ; % = 26.7	n = 15 ; % = 24.6
Unstable angina pectroisis No of events	n = 12 ; % = 20	n = 16 ; % = 26.2
NSTEMI No of events	n = 10 ; % = 16.7	n = 12 ; % = 19.7

Characteristic	Pioglitazone 15 mg (N = 60)	Placebo (N = 61)
STEMI No of events	n = 22 ; % = 36.7	n = 17 ; % = 27.9
Hypertension No of events	n = 33 ; % = 55	n = 36 ; % = 59
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	6.03 (7.05)	5.5 (6.44)
Smokers No of events	n = 30 ; % = 50	n = 30 ; % = 40.2
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
Insulin No of events	n = 7 ; % = 11.7	n = 5 ; % = 8.2
Metformin No of events	n = 22 ; % = 36.7	n = 20 ; % = 32.8
Glimepiride No of events	n = 36 ; % = 60	n = 38 ; % = 62.3
Sulfonylurea No of events	n = 3 ; % = 5	n = 1 ; % = 1.6

Characteristic	Pioglitazone 15 mg (N = 60)	Placebo (N = 61)
Alpha-glucosidase inhibitor No of events	n = 1 ; % = 1.7	n = 2 ; % = 3.3
Blood pressure-lowering medication used Nominal	NR	NR
Statin No of events	n = 44 ; % = 73.3	n = 45 ; % = 73.8
Clopidogrel No of events	n = 59 ; % = 98.3	n = 60 ; % = 100
Previous PCI (percutaneous coronary intervention) No of events	n = 15 ; % = 25	n = 8 ; % = 13.1

268. Leiter, 2014

Bibliographic Reference	Leiter, L. A.; Cefalu, W. T.; De Bruin, T. W. A.; Gause-Nilsson, I.; Sugg, J.; Parikh, S. J.; Dapagliflozin added to usual care in individuals with type 2 diabetes mellitus with preexisting cardiovascular disease: A 24-week, multicenter, randomized, double-blind, placebo-controlled study with a 28-week extension; J Am Geriatr Soc; 2014; vol. 62 (no. 7); 1252-1262

268.1. 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	
Trial name / registration number	NCT01042977
Study type	Randomised controlled trial (RCT)
Study location	Conducted in 173 centres in the United States, Canada, Australia, Chile, Argentina, and five European countries (not specified)
Study setting	Hospital setting
Study dates	October 2009 - July 2011
Sources of funding	Funded by Astra Zeneca and Bristol-Myers Squibb
Inclusion criteria	Participants with uncontrolled type 2 diabetes mellitus (HbA1c 7.0–10.0%) and preexisting CVD were randomised 1:1 to receive once-daily dapagliflozin 10 mg or matched placebo in addition to their preexisting, stable background treatment; participants were not permitted to have been taking rosiglitazone for at least 8 weeks before enrolment.
Exclusion criteria	• Type 1 diabetes mellitus; use of rosiglitazone or three or more oral antihyperglycemic drugs; symptoms of poorly controlled diabetes such as marked polyuria, polydipsia, and/or >10% weight loss, fasting plasma glucose (FPG) >270 mg/dL;

	• Cardiovascular events within 2 months of enrolment; New York Association class IV congestive heart failure; unstable or acute congestive heart failure; systolic blood pressure (BP) ≥160 mmHg and/or diastolic BP ≥100 mmHg at randomisation; • Calculated creatinine clearance <60 mL/min; urine albumin: creatinine ratio >1,800 mg/g; history of unstable or rapidly progressing renal disease.
Recruitment / selection of participants	Participants were studied as part of a 24-week, multicentre, randomized, double-blind , age-stratified placebo-controlled phase III study.
Intervention(s)	Dapagliflozin 10 mg daily, administered orally
Cointervention	Patients used the following concomitant medications: ACE-I/ARB, loop diuretics, beta-blockers, acetylsalicylic acid, lipid-reducing agents.
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Exclusion criteria for NYHA class IV congestive heart failure and unstable or acute congestive heart failure
Strata 2: People with atherosclerotic cardiovascular disease	People with atherosclerotic cardiovascular diseases Inclusion criteria
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Exclusion criteria for history of unstable or rapidly progressing renal disease but not statement about chronic kidney disease that doesn't fall into this category
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	Placebo once daily, administered orally
Number of participants	N=964
Duration of follow-up	52 weeks
Indirectness	
Method of analysis	ITT
Additional comments	

268.2. Study arms

268.2.1. Dapagliflozin 10 mg (N = 480)

Administered orally, once daily

268.2.2. Placebo (N = 482)

Administered orally, once daily

268.3. Characteristics

268.3.1. Arm-level characteristics

Characteristic	Dapagliflozin 10 mg (N = 480)	Placebo (N = 482)
% Male No of events	n = 321 ; % = 67	n = 323 ; % = 67
Mean age (SD) (years) Mean (SD)	63.9 (7.6)	63.6 (7)
Ethnicity Nominal	NR	NR
Congestive heart failure No of events	n = 86 ; % = 17.9	n = 66 ; % = 13.7
Hypertension No of events	n = 446 ; % = 92.9	n = 447 ; % = 92.7
Coronary heart disease No of events	n = 359 ; % = 74.8	n = 377 ; % = 78.2
Stroke or TIA No of events	n = 105 ; % = 21.9	n = 84 ; % = 17.4
Peripheral artery disease No of events	n = 15 ; % = 3.1	n = 19 ; % = 3.9
Time since type 2 diabetes diagnosed Mean (SD)	13.5 (8.2)	13 (8.4)
Smoking status Nominal	NR	NR
Alcohol consumption	NR	NR

Characteristic	Dapagliflozin 10 mg (N = 480)	Placebo (N = 482)
Nominal		
Presence of severe mental illness Nominal	NR	NR
People with significant cognitive impairment Nominal	NR	NR
People with a learning disability Nominal	NR	NR
Number of people with obesity Nominal	NR	NR
Oral antihyperglycaemic agent No of events	n = 188 ; % = 39.2	n = 192 ; % = 39.8
Oral antihyperglycaemic agent + Insulin No of events	n = 203 ; % = 42.3	n = 190 ; % = 39.4
Insulin No of events	n = 89 ; % = 18.5	n = 100 ; % = 20.7
ACE inhibitor or ARB No of events	n = 403 ; % = 83.6	n = 400 ; % = 82.8
Loop diuretic No of events	n = 113 ; % = 23.4	n = 96 ; % = 19.9
Beta-blocker No of events	n = 359 ; % = 74.5	n = 351 ; % = 72.7
Lipid-reducing agent No of events	n = 411 ; % = 85.3	n = 400 ; % = 82.8
Acetylsalicylic acid No of events	n = 350 ; % = 72.6	n = 342 ; % = 70.8

269. Leiter, 2015

Bibliographic Reference	Leiter, Lawrence A; Yoon, Kun-Ho; Arias, Pablo; Langslet, Gisle; Xie, John; Balis, Dainius A; Millington, Dawn; Vercruysse, Frank; Canovatchel, William; Meininger, Gary; Canagliflozin provides durable glycemic improvements and body weight reduction over 104 weeks versus glimepiride in patients with type 2 diabetes on metformin: a randomized, double-blind, phase 3 study.; Diabetes care; 2015; vol. 38 (no. 3); 355-64

269.1. Study details

Secondary publication of another included study- see primary study for details	Cefalu, W. T., Leiter, L. A., Yoon, K. H., Arias, P., Niskanen, L., Xie, J., ... & Meininger, G. (2013). Efficacy and safety of canagliflozin versus glimepiride in patients with type 2 diabetes inadequately controlled with metformin (CANTATA-SU): 52 week results from a randomised, double-blind, phase 3 non-inferiority trial. *The Lancet*, *382*(9896), 941-950.
Other publications associated with this study included in review	See Cefalu 2013
Trial name / registration number	CANTATA-SU/NCT00968812
Study type	Randomised controlled trial (RCT) Double-blind parallel group RCT

269.2. Study arms

269.2.1. Glimepiride 6 mg or 8 mg daily (N = 482)

Oral glimepiride up-titrated to 6 mg or 8 mg daily for 24 months (12 months followed by 12 month extension period) in addition to stable metformin dose.

269.2.2. Canagliflozin 100 mg daily (N = 483)

Oral canagliflozin 100 mg daily for 24 months (12 months followed by 12 month extension period) in addition to stable metformin dose.

269.2.3. Canagliflozin 300 mg daily (N = 485)

Oral canagliflozin 300 mg daily for 24 months (12 months followed by 12 month extension period) in addition to stable metformin dose.

270. Li, 2014

Bibliographic Reference	Li, C. J.; Yu, Q.; Yu, P.; Zhang, Q. M.; Ding, M.; Liu, X. J.; Yu, D. M.; Efficacy and safety comparison of add-on therapy with liraglutide, saxagliptin and vildagliptin, all in combination with current conventional oral hypoglycemic agents therapy in poorly controlled Chinese type 2 diabetes; Exp Clin Endocrinol Diabetes; 2014; vol. 122 (no. 8); 469-76

270.1. Study details

Trial name / registration number	NR
Study type	Randomised controlled trial (RCT)
Study location	Metabolic Disease Hospital of Tianjin Medical University
Study setting	Out-patient setting
Study dates	March 2012 to April 2013
Sources of funding	NR
Inclusion criteria	The study enrolled male and non-pregnant female subjects, aged 18–75 years, with type 2 diabetes for > 6 months and < 10 years, treated with a stable dose of metformin or sulfonylureas (SUs) for monotherapy, or dual therapy combined metformin with sulfonylurea or α-glucosidase inhibitors or Thiazolidinediones (TZDs), or a triple therapy combined metformin with SUs and α-glucosidase inhibitors for a minimum of 3 months prior to screening. Inclusion criteria included HbA1c of 7–10 %, body mass index (BMI) 23–35 kg/m 2 , and the willingness and ability to perform self-monitoring of blood glucose and to provide written informed consent. Women participating in the study agreed to remain abstinent or use an acceptable method of birth control during the study.
Exclusion criteria	Exclusion criteria included alanine aminotransferase or aspartate aminotransferase more than 2.5 times the upper limit of normal, TSH greater than the upper limit of normal, serum creatinine ≥ 133 μmol/L for men or ≥ 124 μmol/L for women. Further exclusion criteria included currently use of any systemic or topical treatment with drugs known to influence glucose metabolism or weight (systemic glucocorticoids, nonselective β-sympathetic blockers, and weight-loss drugs within 3 months of randomization), uncontrolled hypertension, anemia, recurrent hypoglycemia or self-reported inability to recognize hypoglycemia, a history of malignancy or clinically important haematological disorder that required disease-specific treatment, a personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2, history of laser treatment for proliferative retinopathy within 6 months, history of New York Heart Association Class III or IV heart failure,

	cardiac surgery, or myocardial infarction within 12 months, or a history of drug or alcohol abuse
Recruitment / selection of participants	No additional information
Intervention(s)	Liraglutide (n=68) Liraglutide was to be administered subcutaneously at a dose of 0.6 mg in the morning for 1 week followed by an increase to 1.2 mg once daily for the next 23 weeks Saxagliptin (n=68) Saxagliptin was taken 5 mg once daily in the morning,
Cointervention	Patients remained on their previous therapy which included metformin or sulfonylureas (SUs) for monotherapy, or dual therapy combined metformin with sulfonylurea or α-glucosidase inhibitors or Thiazolidinediones, or a triple therapy combined metformin with SUs and α-glucosidase inhibitors
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
Comparator	Vildagliptin (n=67) Vildagliptin was taken orally at a dose of 50 mg twice daily before the breakfast and dinner.
Number of participants	203
Duration of follow-up	24 weeks
Indirectness	
Method of analysis	Per protocol
Additional comments	Detail on statistical analysis is sparse however data are only presented for patients that completed study and therefore presumption is per protocol analysis

270.2. Study arms

270.2.1. Liraglutide (N = 68)

Patients received liraglutide administered subcutaneously at a dose of 0.6 mg in the morning for 1 week followed by an increase to 1.2 mg once daily for the next 23 weeks.

270.2.2. Saxagliptin (N = 68)

Patients received 5mg saxagliptin once daily in the morning for 24 weeks

270.2.3. Vildagliptin (N = 67)

Patients received vildagliptin orally at a dose of 50 mg twice daily before the breakfast and dinner for 24 weeks

270.3. Characteristics

270.3.1. Arm-level characteristics

Characteristic	Liraglutide (N = 68)	Saxagliptin (N = 68)	Vildagliptin (N = 67)
% Male Liraglutide n = 61, Saxagliptin n = 60, Vildaglitpin n = 57 Sample size	n = 36 ; % = 52.9	n = 39 ; % = 57.4	n = 34 ; % = 50.7
Mean age (SD) (Years (mean, SD)) Liraglutide n = 61, Saxagliptin n = 60, Vildaglitpin n = 57 Mean (SD)	47.9 (10.8)	47 (11.3)	46.4 (9.8)
Ethnicity Liraglutide n = 61, Saxagliptin n = 60, Vildagliptin n = 57 Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed (Years (mean, SD)) Liraglutide n = 61, Saxagliptin n = 60, Vildagliptin n = 57 Mean (SD)	5.8 (2.8)	5.4 (2.7)	5.4 (2.2)

Characteristic	Liraglutide (N = 68)	Saxagliptin (N = 68)	Vildagliptin (N = 67)
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Other antidiabetic medication used Liraglutide n = 61, Saxagliptin n = 60, Vildagliptin n = 57 Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Metformin monotherapy Sample size	n = 7 ; % = 11.5	n = 9 ; % = 15	n = 6 ; % = 10.5
Sulfonylureas monotherapy Sample size	n = 4 ; % = 6.6	n = 5 ; % = 8.3	n = 7 ; % = 12.3
metformin + sulfonylureas Sample size	n = 17 ; % = 27.9	n = 14 ; % = 23.3	n = 15 ; % = 26.3
metformin + alpha glucosidase inhibitors Sample size	n = 4 ; % = 6.6	n = 6 ; % = 10	n = 3 ; % = 5.3
metformin + thiazolidinedione Sample size	n = 5 ; % = 8.2	n = 7 ; % = 11.7	n = 6 ; % = 10.5
sulfonylureas + alpha glucosidase inhibitors Sample size	n = 8 ; % = 13.1	n = 5 ; % = 8.3	n = 5 ; % = 8.8
metformin + sulfonylureas + alpha glucosidase inhibitors Sample size	n = 16 ; % = 26.2	n = 14 ; % = 23.3	n = 15 ; % = 26.3

Characteristic	Liraglutide (N = 68)	Saxagliptin (N = 68)	Vildagliptin (N = 67)
Blood pressure-lowering medication used Liraglutide n = 61, Saxagliptin n = 60, Vildagliptin n = 57 Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Statins/lipid-lowering medication used Liraglutide n = 61, Saxagliptin n = 60, Vildagliptin n = 57 Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Other treatment being received (Liraglutide n = 61, Saxagliptin n = 60, Vildagliptin n = 57) Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR

271. Li, 2014

Bibliographic Reference	Li, Chun-Jun; Liu, Xiao-Juan; Bai, Lian; Yu, Qian; Zhang, Qiu-Mei; Yu, Pei; Yu, De-Min; Efficacy and safety of vildagliptin, Saxagliptin or Sitagliptin as add-on therapy in Chinese patients with type 2 diabetes inadequately controlled with dual combination of traditional oral hypoglycemic agents.; Diabetology & metabolic syndrome; 2014; vol. 6; 69

271.1. Study details

Trial name / registration number	NR
Study type	Randomised controlled trial (RCT)
Study location	Tianjin. China
Study setting	Tianjin Medical University
Study dates	Patients recruited between January 2012 and January 2013
Sources of funding	Supported by the National Nature Science Foundation of China and grants from Tianjin Health Bureau Technology Fund
Inclusion criteria	Patients with T2DM aged 18–70 inadequately controlled by dual combination of traditional oral hypoglycemic agents with HbA1c of 7.5–10.0% and BMI of 22.5–30 kg/m2 were eligible for enrolment. Patients were required to have been treated with metformin and another oral hypoglycemic agent (glimepiride, acarbose, or pioglitazone) for at least 12 weeks and be on a stable recommended dose.
Exclusion criteria	Patients were excluded if they had a history of type 1 diabetes mellitus or diabetes due to pancreatic injury or secondary forms of diabetes, any acute metabolic diabetic complications such as ketoacidosis or hyperosmolar state (coma) within past 6 months, myocardial infarction, unstable angina or coronary artery bypass surgery within past 6 months. Patients with congestive heart failure, liver disease such as cirrhosis or chronic active hepatitis or with any of the following laboratory abnormalities at Visit 1 were also excluded: ALT or AST > 2 times the upper limit of normal (ULN), total bilirubin > 2 times ULN, serum creatinine levels [men: ≥ 1.5 mg/dl (132 μmol/l); women: ≥ 1.4 mg/dl (123 μmol/l)] or thyroid-stimulating hormone beyond the normal range, fasting triglycerides > 500 mg/dl (5.6 mmol/l)
Recruitment / selection of participants	Patients were recruited from the Metabolic Disease Hospital of Tianjin Medical University between Jan 2012 and Jan 2013.

Intervention(s)	Saxagliptin (n = 71) Patients received 5 mg saxagliptin daily for 24 weeks as an add on to their current dual therapy
Cointervention	Patients were receiving dual therapy of either metformin plus glimepiride, metformin with acarbose or metformin plus pioglitazone
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Exclusion criteria for congestive heart failure.
Strata 2: People with atherosclerotic cardiovascular disease	People without atherosclerotic cardiovascular diseases Exclusion criteria for myocardial infarction, unstable angina or coronary artery bypass surgery within the past 6 months.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Exclusion criteria based on creatinine level but no statement specifically about CKD.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
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	Vildagliptin (n = 69) Patients received 50 mg vildagliptin twice daily (100 mg per day) for 24 weeks as an add on to their current dual therapy Sitagliptin (n = 68) Patients received 100 mg vildagliptin once daily for 24 weeks as an add on to their current dual therapy All patients were receiving dual therapy of either metformin plus glimepiride, metformin with acarbose or metformin plus pioglitazone
Number of participants	208
Duration of follow-up	24 weeks
Indirectness	NA
Method of analysis	Per protocol
Additional comments	A total of 208 patients were randomized, and 190 patients comprised the full analysis set.

271.2. Study arms

271.2.1. Saxagliptin (N = 71)

Patients received 5 mg sitagliptin once daily for 24 weeks

271.2.2. Vildagliptin (N = 69)

Patients received 50 mg vildagliptin twice daily for 24 weeks

271.2.3. Sitagliptin (N = 68)

Patients received 100 mg sitagliptin once daily for 24 weeks

271.3. Characteristics

271.3.1. Arm-level characteristics

Characteristic	Saxagliptin (N = 71)	Vildagliptin (N = 69)	Sitagliptin (N = 68)
% Male Saxagliptin n = 66, Vildagliptin n = 63, Sitagliptin n = 61 Sample size	n = 39 ; % = 59	n = 37 ; % = 59	n = 33 ; % = 54
Mean age (SD) (Years (mean, SD)) Saxagliptin n = 66, Vildagliptin n = 63, Sitagliptin n = 61 Mean (SD)	46.5 (10.7)	44.8 (8.5)	48.6 (11.3)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed 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

Characteristic	Saxagliptin (N = 71)	Vildagliptin (N = 69)	Sitagliptin (N = 68)
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Metformin + Glimepiride Saxagliptin n = 66, Vildagliptin n = 63, Sitagliptin n = 61 Sample size	n = 26 ; % = 40	n = 26 ; % = 41	n = 25 ; % = 41
Metformin + acarbose Saxagliptin n = 66, Vildagliptin n = 63, Sitagliptin n = 61 Sample size	n = 22 ; % = 33	n = 20 ; % = 32	n = 20 ; % = 33
Metformin + Pioglitazone Sample size	n = 18 ; % = 27	n = 17 ; % = 27	n = 16 ; % = 26
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

272. Li, 2014

Bibliographic Reference	Li, Chun-Jun; Zhang, Jing-Yun; Yu, De-Min; Zhang, Qiu-Mei; Adding glimepiride to current insulin therapy increases high-molecular weight adiponectin levels to improve glycemic control in poorly controlled type 2 diabetes.; Diabetology & metabolic syndrome; 2014; vol. 6 (no. 1); 41

272.1. 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	Tianjin, China
Study setting	Outpatient setting of the Metabolic Disease Hospital of Tianjin Medical University
Study dates	NR
Sources of funding	National Nature Science Foundation of China, Tianjin Health Bureau Technology, Science and Technology Development Foundation of Tianjin Advanced College
Inclusion criteria	Participants with type 2 diabetes as defined by Chinese Diabetes Association and HbA1c exceeding 8%, who have been treated with a large dosage of insulin (daily insulin dose more than 40 units) for at least 6 months.
Exclusion criteria	• Hepatic injury (serum alanine or aspartate aminotransferase 2.5 of more times the upper-normal range) • Congestive heart failure (NYHA Class III or IV) • Renal damage (serum creatinine above 2.0 mg/dl)

	• Already receiving sulfonylureas or insulin sensitizers such as TZDs within 6 months prior to the recruitment.
Recruitment / selection of participants	Eligible subjects were explained the goals and risk of the study and gave their written informed consent before beginning the study.
Intervention(s)	Glimepiride (Amaryl, Sanofi Aventis) initiated at the minimum dosage 1 mg once daily and then titrated up to 4 mg daily until the glycaemic control target
Cointervention	Continuation of base therapy.
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Exclusion criteria for congestive heart failure (NYHA class III or IV)
Strata 2: People with atherosclerotic cardiovascular disease	People with atherosclerotic cardiovascular diseases 82% had cardiovascular disease
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	People with chronic kidney disease Based on nephropathy (80% had nephropathy)
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear

Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Mixed population 75% of population with abdominal obesity
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Mixed population
Population subgroups	N/A
Comparator	Insulin with doses increased to reach the glycaemic control target.
Number of participants	56 participants
Duration of follow-up	12 and 24 weeks
Indirectness	Directly applicable
Method of analysis	Not stated/unclear The type of analysis was unclear. The methods section states that changes in HbA1C were studies using the repeated measurements ANOVA with treatment as a grouping factor.
Additional comments	None

272.2. Study arms

272.2.1. Glimepiride (N = 29)

272.2.2. Insulin (N = 27)

272.3. Characteristics

272.3.1. Study-level characteristics

Characteristic	Study (N = 56)
Number of people with obesity Abdominal obesity - n calculated by analyst Sample size	n = 42 ; % = 75

272.3.2. Arm-level characteristics

Characteristic	Glimepiride (N = 29)	Insulin (N = 27)
% Male % calculated by analyst Sample size	n = 15 ; % = 51.7	n = 13 ; % = 48.1
Mean age (SD) Mean (SD)	56.8 (12.3)	56.3 (12.4)
Ethnicity Nominal	NR	NR
Hypertension Sample size	n = 22 ; % = 75.9	n = 21 ; % = 77.8
Simple diabetic retinopathy Sample size	n = 17 ; % = 58.6	n = 16 ; % = 61.5
Proliferative diabetic retinopathy Sample size	n = 10 ; % = 34.5	n = 9 ; % = 34.6
Nephropathy (normo-albuminuria) Sample size	n = 6 ; % = 20.7	n = 5 ; % = 19.2
Nephropathy (micro-albuminuria) Sample size	n = 14 ; % = 48.3	n = 14 ; % = 53.8
Nephropathy (macro-albuminuria) Sample size	n = 9 ; % = 31	n = 8 ; % = 30.8
Cardiovascular disease Sample size	n = 5 ; % = 17.2	n = 5 ; % = 19.2

Characteristic	Glimepiride (N = 29)	Insulin (N = 27)
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed Mean (SD)	15.6 (5.7)	15.4 (6.2)
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
Alpha glucosidase inhibitors Sample size	n = 2 ; % = 69	n = 1 ; % = 3.8
Metformin Sample size	n = 13 ; % = 44.8	n = 14 ; % = 53.8
Blood pressure-lowering medication used Nominal	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

273. Li, 2017

Bibliographic Reference	Li, F.; Shen, Y.; Sumn, R; Zhang, D; Jin, X.; Zhai, X.; Chen, M; Su, X.; Wu, J; Ye, L; Ma, J; Effects of vildagliptin add-on insulin therapy on nocturnal glycemic variations in uncontrolled type 2 diabetes; Diabetes Ther; 2017; vol. 8 (no. 5); 1111-1122

273.1. 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	NCT01582230
Study type	Randomised controlled trial (RCT)
Study location	China
Study setting	Hospital
Study dates	June 2012 - April 2013
Sources of funding	Science and Technology Support Program of Jiangsu Province (CN) (no. BL2014010) and by the China Postdoctoral Science Foundation (no. 2015M581829).
Inclusion criteria	• Patients with confirmed diagnosis of Type 2 diabetes mellitus by standard criteria • C-peptide >0.6 ng/ml (>0.20 nmol/L). • Uncontrolled Type 2 diabetes defined as HbA1c ≥7.5 to ≤11% • Treatment with stable, once or twice daily doses (maximum dose of < 1 unit/kg/day) of basal (long-acting, intermediate-acting) insulin alone or pre-mixed insulin for at least 12 weeks prior to Visit 1. Stable is defined as ±10% of the Visit 1 dose during the previous 12 weeks

	• Patients receiving metformin must be on a stable dose of metformin (at least 1500 mg daily or a maximally tolerated dose) for at least 12 weeks prior to screening period • BMI ≥20 to ≤40 kg/m2
Exclusion criteria	• FPG ≥240 mg/dl (13.3 mmol/L) at visit 1 • Pregnant or lactating women • Acute metabolic diabetes complications such as ketoacidosis or hyperosmolar state (coma) within the past 6 months • Current diagnosis of congestive heart failure (NYHA III or IV). • Myocardial infarction (MI) within the past 6 months • Liver disease such as cirrhosis or chronic active hepatitis
Recruitment / selection of participants	Patients with uncontrolled type 2 diabetes were recruited from a university hospital in China. Baseline parameters were collected from all subjects 4 days prior to randomisation. The trial included a 2-week screening period and a 24-week treatment period.
Intervention(s)	Vildagliptin administered orally, twice daily.
Cointervention	Insulin +/- metformin
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 2 people had coronary heart disease
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear

Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	eGFR ≥30mL/min/1.73m2
Subgroup 6: Albuminuria category at baseline	A2 (ACR 30-300 mg/g or 3-30mg/mmol)
Comparator	Placebo administered orally, twice daily.
Number of participants	N = 33
Duration of follow-up	24-week follow-up period.
Indirectness	
Method of analysis	Not stated/unclear
Additional comments	

273.2. Study arms

273.2.1. Vildagliptin 50 mg twice daily (N = 17)

Administered orally

273.2.2. Placebo twice daily (N = 16)

Administered orally

273.3. Characteristics

273.3.1. Study-level characteristics

Characteristic	Study (N = 33)
Time since type 2 diabetes diagnosed (years) Mean (SD)	12 (7.8)

273.3.2. Arm-level characteristics

Characteristic	Vildagliptin 50 mg twice daily (N = 17)	Placebo twice daily (N = 16)
% Male No of events	n = 6 ; % = 35	n = 9 ; % = 56
Mean age (SD) (year) Mean (SD)	58.9 (9)	59.9 (7.7)
Ethnicity Nominal	NR	NR
Hypertension No of events	n = 4 ; % = 24	n = 3 ; % = 19
Hyperlipidemia No of events	n = 3 ; % = 18	n = 1 ; % = 6
Coronary heart disease No of events	n = 1 ; % = 6	n = 1 ; % = 6
Presence of frailty Nominal	NR	NR
Smoking status Nominal	NR	NR
Alcohol consumption	NR	NR

Characteristic	Vildagliptin 50 mg twice daily (N = 17)	Placebo twice daily (N = 16)
Nominal		
Presence of severe mental illness Nominal	NR	NR
People with significant cognitive impairment Nominal	NR	NR
People with a learning disability Nominal	NR	NR
Number of people with obesity Nominal	NR	NR
Basal insulin No of events	n = 6 ; % = 35	n = 6 ; % = 38
Pre-mixed insulin analogue No of events	n = 11 ; % = 65	n = 10 ; % = 63
Basal insulin + metformin No of events	n = 4 ; % = 24	n = 6 ; % = 38
Pre-mixed insulin analogue + metformin No of events	n = 7 ; % = 41	n = 4 ; % = 25

274. Lind, 2015

Bibliographic Reference	Lind, M.; Hirsch, I. B.; Tuomilehto, J.; Dahlqvist, S.; Ahren, B.; Torffvit, O.; Attvall, S.; Ekelund, M.; Filipsson, K.; Tengmark, B. O.; Sjoberg, S.; Pehrsson, N. G.; Liraglutide in people treated for type 2 diabetes with multiple daily insulin injections: randomised clinical trial (MDI Liraglutide trial); BMJ; 2015; vol. 351; h5364

274.1. 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	Design and methods for this study are published in the following paper (Lind 2015): "Design and methods of a randomised double-blind trial of adding liraglutide to control HbA1c in patients with type 2 diabetes with impaired glycaemic control treated with multiple daily insulin injections (MDI-Liraglutide trial)" Primary care diabetes; 2015; vol. 9 (no. 1); 15-22. Ahmadi 2019: "Effect of liraglutide on anthropometric measurements, sagittal abdominal diameter and adiponectin levels in people with type 2 diabetes treated with multiple daily insulin injections: evaluations from a randomized trial (MDI-liraglutide study 5)." Obesity science & practice; 2019; vol. 5 (no. 2); 130-140.
Trial name / registration number	MDI-liraglutide/EudraCT 2012-001941-42
Study type	Randomised controlled trial (RCT)
Study location	Sweden
Study setting	Outpatient clinic and primary care unit
Study dates	02/2013 - 08/2014
Sources of funding	Novo Nordisk provided financial support and study drugs but did not play a role in the design and execution of the trial.

Inclusion criteria	• Adult patients over 18 years of age and less than 80 years of age • HbA1c greater than or equal to 7.5% (NGSP standard = DCCT standard) = 58 mmol/mol (IFCC standard) and less than or equal to 11.5% = 102mmol/mol • Treated with multiple daily insulin injections defined as separate basal and mealtime insulin components, including at least two daily mealtime insulin doses for at least the last 6 months • Treated with/without metformin as only diabetes therapy apart from insulin • Fasting C-peptide of 0.10 nmol/l or greater (ref. 0.25–1.0 nmol/l) • BMI greater than 27.5 kg/m2 and less than 45 kg/m2
Exclusion criteria	• Fasting glucose less than 6.0mmol/l (108mg/dl) or greater than 15.0 mmol/l (270mg/dl) • Unstable cardiovascular disease, NYHA Class II or greater heart failure, new symptoms of cardiovascular disease • Proliferative diabetic retinopathy or clinically significant macula oedema. Retinal photograph should not be older than 3 years • Systemic glucocorticoid treatment during the last 3 months, however, patients using systemic corticoid treatment only for substitution of cortisol deficiency (physiologic doses) such as Addisons Disease, do not need to be excluded • Acute coronary syndrome, stroke, coronary artery intervention or myocardial infarction during the previous 6 months • Creatinine greater than 150 umol/l • Liver transaminases greater than double of the normal reference interval • Treatment with other oral antidiabetic agents than metformin during the previous 3 months • Treatment with GLP-1 receptor agonists within 90 days of screening • Severe psychiatric disorder (untreated severe depression, schizophrenia, dementia or severe alcohol or drug abuse) • Frequent non-severe hypoglycaemia (greater than 2 times per week) or any severe hypoglycaemia during the previous month • Hypoglycaemic unawareness • Current cancer or diagnosis of cancer in the previous 5 years (except basal cell skin cancer or squamous cell skin cancer) • Personal history of non-familial thyroid carcinoma or multiple endocrine neoplasia syndrome type 2 (MEN2) • Screening calcitonin values greater than 14.6 pmol/l • Blood pressure greater than 160/100mmHg • Need for continuous use of paracetamol. During the 3 periods of 7 days with CGM, paracetamol cannot be used. Alternative pain killers can be substituted if plausible because paracetamol is the only medication influencing CGM results • History of chronic or acute pancreatitis • Inflammatory bowel disease

Recruitment / selection of participants	After a maximum run-in period of eight weeks, participants were randomised to either subcutaneous liraglutide or placebo. The composition of the placebo was the same as for liraglutide but with the absence of the active pharmaceutical ingredient. The study was double blinded and patients were randomly allocated 1:1 to liraglutide or placebo.
Intervention(s)	Liraglutide 0.6 mg during week 1, 1.2 mg during week 2, and 1.8 mg during week 3 onwards. Patients chose when to administer the drug during the day and they were supposed to use the same timing each day during the trial.
Cointervention	Metformin + Insulin
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Excluded NYHA Class II or greater heart failure
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Excluded "unstable cardiovascular disease and new symptoms of cardiovascular disease", but unclear if excluded all atherosclerotic CVD. Excluded "acute coronary syndrome, stroke, coronary artery intervention or myocardial infarction during the previous 6 months", unclear prior to this. Baseline characteristics give CV complications separately, unable to determine number of people who had CV disease.
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	
Comparator	Placebo Patients chose when to administer the drug during the day and they were supposed to use the same timing each day during the trial
Number of participants	N=124
Duration of follow-up	24 weeks
Indirectness	
Method of analysis	Per protocol ITT
Additional comments	Dexcom G4 PLATINUM (San Diego, CA) continuous glucose monitoring system was used to carry out masked continuous glucose monitoring during one week of the eight week run-in period, week 12 of the trial, and one of the two final weeks of the follow-up period of 24 weeks. Rescue therapy primarily consisted of the investigator helping in increasing the insulin doses, while continuing with liraglutide/placebo until glycaemic

	control was improved. Measurements taken after rescue therapy were excluded from the efficacy analyses.

274.2. Study arms

274.2.1. Liraglutide 0.6 mg - 1.8 mg daily (N = 64)

Administered subcutaneously at the same time each day

274.2.2. Placebo (N = 60)

Administered subcutaneously at the same time each day

274.3. Characteristics

274.3.1. Arm-level characteristics

Characteristic	Liraglutide 0.6 mg - 1.8 mg daily (N = 64)	Placebo (N = 60)
% Male No of events	n = 40 ; % = 62.5	n = 40 ; % = 66.7
Mean age (SD) (years) Mean (SD)	40 (62.5)	40 (66.7)
Hispanic or Latino No of events	n = 2 ; % = 3.1	n = 0 ; % = 0
Non-hispanic or non-latino No of events	n = 62 ; % = 96.9	n = 60 ; % = 100
American Indian or Alaska Native No of events	n = 1 ; % = 1.6	n = 0 ; % = 0
White No of events	n = 63 ; % = 98.4	n = 60 ; % = 100
Previous myocardial infarction No of events	n = 6 ; % = 9.4	n = 10 ; % = 16.7
Previous stroke % No of events	n = 1 ; % = 1.6	n = 0 ; % = 0

Characteristic	Liraglutide 0.6 mg - 1.8 mg daily (N = 64)	Placebo (N = 60)
Previous percutaneous coronary intervention No of events	n = 5 ; % = 7.8	n = 8 ; % = 13.3
Previous coronary bypass surgery No of events	n = 5 ; % = 7.8	n = 7 ; % = 11.7
Previous photocoagulation No of events	n = 10 ; % = 15.6	n = 14 ; % = 23.3
Previous amputation No of events	n = 0 ; % = 0	n = 1 ; % = 1.7
Previous foot (or leg) ulcer No of events	n = 3 ; % = 4.7	n = 4 ; % = 6.7
Current foot (or leg) ulcer No of events	n = 0 ; % = 0	n = 0 ; % = 0
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed Mean (SD)	17.3 (7.6)	17 (8.1)
Never smoker % No of events	n = 27 ; % = 42.2	n = 22 ; % = 36.7
Former smoker No of events	n = 29 ; % = 45.3	n = 31 ; % = 51.7
Current smoker No of events	n = 8 ; % = 12.5	n = 7 ; % = 11.7
Alcohol consumption Nominal	NR	NR
Presence of severe mental illness Nominal	NR	NR
People with significant cognitive impairment Nominal	NR	NR

Characteristic	Liraglutide 0.6 mg - 1.8 mg daily (N = 64)	Placebo (N = 60)
People with a learning disability Nominal	NR	NR
Number of people with obesity Nominal	NR	NR
Metformin No of events	n = 44 ; % = 68.8	n = 44 ; % = 73.3
Insulin No of events	n = 64 ; % = 100	n = 60 ; % = 100
Blood pressure-lowering medication used Nominal	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

275. Lind, 2015

Bibliographic Reference	Lind, Marcus; Hirsch, Irl B; Tuomilehto, Jaakko; Dahlqvist, Sofia; Torffvit, Ole; Pehrsson, Nils-Gunnar; Design and methods of a randomised double-blind trial of adding liraglutide to control HbA1c in patients with type 2 diabetes with impaired glycaemic control treated with multiple daily insulin injections (MDI-Liraglutide trial).; Primary care diabetes; 2015; vol. 9 (no. 1); 15-22

275.1. Study details

Secondary publication of another included study- see primary study for details	Parent paper Lind 2015 (population strata details there) "Liraglutide in people treated for type 2 diabetes with multiple daily insulin injections: randomised clinical trial (MDI Liraglutide trial)" BMJ; 2015; vol. 351; h5364.
Other publications associated with this study included in review	Other publication (Ahmadi 2019): "Effect of liraglutide on anthropometric measurements, sagittal abdominal diameter and adiponectin levels in people with type 2 diabetes treated with multiple daily insulin injections: evaluations from a randomized trial (MDI-liraglutide study 5)" Obesity science & practice; 2019; vol. 5 (no. 2); 130-140.
Trial name / registration number	NCT02113332

275.2. Study arms

275.2.1. Liraglutide 0.6 mg - 1.8 mg daily (N = 64)

Administered subcutaneously at the same time each day.

275.2.2. Placebo (N = 60)

Administered subcutaneously at the same time each day.

276. Lingvay, 2019

Bibliographic Reference	Lingvay, I.; Catarig, A. M.; Frias, J. P.; Kumar, H.; Lausvig, N. L.; le Roux, C. W.; Thielke, D.; Viljoen, A.; McCrimmon, R. J.; Efficacy and safety of once-weekly semaglutide versus daily canagliflozin as add-on to metformin in patients with type 2 diabetes (SUSTAIN 8): a double-blind, phase 3b, randomised controlled trial; Lancet Diabetes Endocrinol; 2019; vol. 7 (no. 11); 834-844

276.1. 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	SUSTAIN 8/NCT03136484
Study type	Randomised controlled trial (RCT)
Study location	The trial was conducted in 111 centres in 11 countries: US Argentina Brazil Canada India Ireland Lebanon Malaysia

	Mexico Sweden United Kingdom
Study setting	Hospitals and specialised research centres.
Study dates	03/2017 to 11/2018
Sources of funding	Novo Nordisk
Inclusion criteria	• Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial. • Male or female, age above or equal to 18 years at the time of signing informed consent. • Diagnosed with type 2 diabetes mellitus (T2D). • HbA1c of 7.0-10.5% (53-91 mmol/mol, both inclusive). • Stable daily dose of metformin (≥1500 mg or maximum tolerated dose as documented in the subject medical record and in compliance with current local label) for at least 90 days prior to the day of screening.
Exclusion criteria	• History or presence of pancreatitis (acute/chronic). • History of diabetic ketoacidosis, myocardial infarction, stroke, hospitalisation for unstable angina, or transient ischaemic attack ≤180 days prior to screening, and Class IV heart failure.
Recruitment / selection of participants	Patients with type 2 diabetes uncontrolled on metformin therapy were screened by investigators at 111 centres (hospitals and specialised research centres) in 11 countries. Eligible patients were randomly assigned to receive semaglutide 1.0 mg once weekly by subcutaneous injection or canagliflozin once daily, orally.
Intervention(s)	Semaglutide 1.0 mg once daily administered subcutaneously
Cointervention	Metformin Rescue medication was permitted and the choice was at the investigator's discretion. The most commonly used rescue medication was sulphonylurea (25 [86%] of 29 patients in the semaglutide group; 19 [70%] of 27 patients in the canagliflozin group).
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Exclusion criteria for class IV heart failure, otherwise unclear

Strata 2: People with atherosclerotic cardiovascular disease	People without atherosclerotic cardiovascular diseases Exclusion criteria for people with myocardial infarction, stroke, hospitalisation for unstable angina or transient ischaemic attack in the 180 days before screening
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Mixed population Around 30% with mild-moderate renal impairment 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	Mixed population
Subgroup 6: Albuminuria category at baseline	Not stated/unclear

Population subgroups	
Comparator	Canagliflozin 300 mg once daily administered orally
Number of participants	N=788
Duration of follow-up	52 weeks
Indirectness	No additional information.
Method of analysis	ITT Modified ITT
Additional comments	Full analysis population included all patients randomly assigned to treatment. Safety analysis included a population of all patients exposed to at least one dose of trial drug.

276.2. Study arms

276.2.1. Semaglutide 1.0 mg once weekly (N = 394)

Administered subcutaneously

276.2.2. Canagliflozin 300 mg once daily (N = 394)

Administered orally

276.3. Characteristics

276.3.1. Arm-level characteristics

Characteristic	Semaglutide 1.0 mg once weekly (N = 394)	Canagliflozin 300 mg once daily (N = 394)
% Male No of events	n = 223 ; % = 56.6	n = 201 ; % = 51
Mean age (SD) Mean (SD)	55.7 (11.1)	57.5 (10.7)

Characteristic	Semaglutide 1.0 mg once weekly (N = 394)	Canagliflozin 300 mg once daily (N = 394)
American Indian or Alaska Native No of events	n = 1 ; % = 0.3	n = 3 ; % = 0.8
Asian No of events	n = 62 ; % = 15.7	n = 63 ; % = 16
Black or African American No of events	n = 28 ; % = 7.1	n = 30 ; % = 7.6
White No of events	n = 297 ; % = 75.4	n = 290 ; % = 73.6
Other No of events	n = 6 ; % = 1.5	n = 7 ; % = 1.8
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	7.5 (5.9)	7.2 (5.4)
Smoking status Nominal	NR	NR
Alcohol consumption Nominal	NR	NR
Presence of severe mental illness Nominal	NR	NR
People with significant cognitive impairment Nominal	NR	NR
People with a learning disability Nominal	NR	NR
Number of people with obesity Nominal	NR	NR

Characteristic	Semaglutide 1.0 mg once weekly (N = 394)	Canagliflozin 300 mg once daily (N = 394)
Albumin creatinine ratio Nominal	NR	NR
eGFR ≥90 mL/min per 1·73 m² No of events	n = 285 ; % = 72	n = 275 ; % = 70
eGFR ≥60 to <90 mL/min per 1·73 m² No of events	n = 107 ; % = 27	n = 117 ; % = 30
eGFR ≥30 to <60 mL/min per 1·73 m² No of events	n = 2 ; % = 1	n = 2 ; % = 1
eGFR ≥15 to <30 mL/min OR eGFR <15 mL/min per 1·73 m² No of events	n = 0 ; % = 0	n = 0 ; % = 0
Biguanides (metformin) No of events	n = 394 ; % = 100	n = 394 ; % = 100
Insulin and analogues for injection No of events	n = 1 ; % = 0.3	n = 0 ; % = 0
Other treatment being received Nominal	NR	NR

277. Lingvay, 2016

Bibliographic Reference	Lingvay, Ildiko; Perez Manghi, Federico; Garcia-Hernandez, Pedro; Norwood, Paul; Lehmann, Lucine; Tarp-Johansen, Mads Jeppe; Buse, John B; Effect of Insulin Glargine Up-titration vs Insulin Degludec/Liraglutide on Glycated Hemoglobin Levels in Patients With Uncontrolled Type 2 Diabetes: The DUAL V Randomized Clinical Trial.; JAMA; 2016; vol. 315 (no. 9); 898-907

277.1. 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	NCT01952145
Study type	Randomised controlled trial (RCT)
Study location	Patients were recruited from 10 countries: Argentina Australia Greece Hungary Mexico Russia Slovakia South Africa

	Spain United States
Study setting	Hospital
Study dates	09/2013 - 11/2014
Sources of funding	Novo Nordisk
Inclusion criteria	• Adults (aged ≥18 years) with type 2 diabetes • HbA1c level of 7% to 10% (inclusive), • Taking a stable dose of glargine (total daily dose, 20-50 U, inclusive, allowing individual fluctuations of ±10% for at least 56 days prior to screening) • Stable daily dosing of metformin (≥1500 mg or maximum tolerated dose), • BMI ≤ 40 and able to adhere to the protocol
Exclusion criteria	• Any use of oral antidiabetic agents (except for metformin) within 90 days prior to Visit 1 (screening) • Current use of any drug (except metformin and insulin glargine) or anticipated change in concomitant medication, which in the investigator's opinion could interfere with the glucose metabolism (e.g. systemic corticosteroids) • Previous and/or current treatment with any insulin regimen other than basal insulin, e.g. prandial or pre-mixed insulin (short term treatment due to intercurrent illness including gestational diabetes is allowed at the discretion of the investigator) • Previous and/or current treatment with GLP-1 receptor agonists (e.g. exenatide, liraglutide) • Impaired liver function, defined as ALAT ≥ 2.5 times upper normal range • Impaired renal function defined as serum-creatinine ≥133µmol/L (≥1.5 mg/dL) for males and ≥ 125 µmol/L (1.4 mg/dL) for females, or as allowed according to local contraindications for metformin • Screening calcitonin ≥ 50 ng/L • Personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2 (MEN2) • History of chronic pancreatitis or idiopathic acute pancreatitis
Recruitment / selection of participants	Patients with type 2 diabetes from 10 countries were recruited and randomised 1:1 to insulin degludec/liraglutide or insulin glargine.
Intervention(s)	Insulin degludec/liraglutide 50 U/1.8 mg once daily administered by subcutaneous injection.

Cointervention	Insulin glargine + metformin
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Exclusion criteria for congestive heart failure (NYHA class III-IV)
Strata 2: People with atherosclerotic cardiovascular disease	People without atherosclerotic cardiovascular diseases Exclusion criteria for unstable angina, cerebral stroke and/or myocardial infarction within the past 26 weeks and/or planned coronary, carotid or peripheral artery revascularisation procedures
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Exclusion criteria for impaired renal function based on creatinine but no clear statement on CKD
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear

Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Comparator	Insulin glargine administered once daily by subcutaneous injection with twice-weekly titration to a glucose target of 72 - 90 mg/dL.
Number of participants	N=557
Duration of follow-up	26-week follow-up
Indirectness	
Method of analysis	ITT
Additional comments	

277.2. Study arms

277.2.1. Insulin Degludec/Liraglutide 50 U/1.8 mg once daily (N = 278)

Administered by subcutaneous injection

277.2.2. Insulin glargine once daily (N = 279)

Administered by subcutaneous injection

277.3. Characteristics

277.3.1. Arm-level characteristics

Characteristic	Insulin Degludec/Liraglutide 50 U/1.8 mg once daily (N = 278)	Insulin glargine once daily (N = 279)
% Male	n = 143 ; % = 51	n = 137 ; % = 49

Characteristic	Insulin Degludec/Liraglutide 50 U/1.8 mg once daily (N = 278)	Insulin glargine once daily (N = 279)
No of events		
Mean age (SD) (years) Mean (SD)	58.4 (9.8)	59.1 (9.3)
Hispanic or Latino No of events	n = 107 ; % = 38.5	n = 133 ; % = 47.7
Not hispanic or latino % No of events	n = 171 ; % = 61.5	n = 146 ; % = 52.3
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	11.64 (7.44)	11.33 (6.59)
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
Renin angiotensin system blockers No of events	n = 182 ; % = 65.5	n = 177 ; % = 63.4
Calcium channel blockers No of events	n = 54 ; % = 19.4	n = 58 ; % = 20.8

Characteristic	Insulin Degludec/Liraglutide 50 U/1.8 mg once daily (N = 278)	Insulin glargine once daily (N = 279)
Beta-blockers No of events	n = 74 ; % = 26.6	n = 83 ; % = 29.7
Diuretic No of events	n = 25 ; % = 9	n = 19 ; % = 6.8
Statins No of events	n = 122 ; % = 43.9	n = 128 ; % = 45.9
Fibrates No of events	n = 22 ; % = 7.9	n = 23 ; % = 8.2

278. Liu, 2013

Bibliographic Reference	Liu, S. C.; Chien, K. L.; Wang, C. H.; Chen, W. C.; Leung, C. H.; Efficacy and safety of adding pioglitazone or sitagliptin to patients with type 2 diabetes insufficiently controlled with metformin and a sulfonylurea; Endocr Pract; 2013; vol. 19 (no. 6); 980-988

278.1. 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	NCT01195090
Study type	Randomised controlled trial (RCT)
Study location	Taiwan
Study setting	Hospital
Study dates	September 2009 - September 2011
Sources of funding	The study was supported by the Mackay Memorial Hospital. The sponsor of the study was not directly involved in study design.
Inclusion criteria	
Exclusion criteria	• Patients were excluded if they had type 1 diabetes • Insulin use within 12 weeks of the screening visit, any contraindications for the use of pioglitazone or sitagliptin, impaired renal function (serum creatinine >1.4 mg/dL), alanine aminotransferase or aspartate aminotransferase levels >2.5 times the upper limit of normal • Current or planned pregnancy, or lactation

Recruitment / selection of participants	Eligible patients were recruited to a prospective, randomized, open-label, parallel group study and randomised in a 1:1 ratio. The randomisation was performed using an interactive voice response system that used a permuted-block size of 6.
Intervention(s)	Pioglitazone 30 mg daily, administered orally
Cointervention	Antidiabetic medication: metformin, glimepiride, and gliclazide. Patients were allowed to continue using antihypertensive and lipid-lowering agents if they had been taking a stable dose for at least 10 weeks before entry into the study and the same doses were maintained during the entire study.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear

Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	
Comparator	Sitagliptin 100 mg daily, administered orally
Number of participants	N = 120
Duration of follow-up	24-week
Indirectness	
Method of analysis	Modified ITT
Additional comments	All patients included had received at least 1 dose of study medication and had HbA1c recorded at baseline and at least once after baseline were included in the ITT. All patients who had taken at least 1 dose of study medication were included in the safety analysis.

278.2. Study arms

278.2.1. Pioglitazone 30 mg daily (N = 60)

Administered orally

278.2.2. Sitagliptin 100 mg daily (N = 60)

Administered orally

278.3. Characteristics

278.3.1. Arm-level characteristics

Characteristic	Pioglitazone 30 mg daily (N = 60)	Sitagliptin 100 mg daily (N = 60)
% Male No of events	n = 23 ; % = 38	n = 22 ; % = 37
Mean age (SD) (years) Mean (SD)	58.1 (8.3)	60.1 (8.9)
Ethnicity Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	7.8 (3.9)	7.8 (4.3)
Smoking status Nominal	NR	NR
Alcohol consumption Nominal	NR	NR
Presence of severe mental illness Nominal	NR	NR
People with a learning disability Nominal	NR	NR

Characteristic	Pioglitazone 30 mg daily (N = 60)	Sitagliptin 100 mg daily (N = 60)
Number of people with obesity Nominal	NR	NR
Metformin No of events	n = 60 ; % = 100	n = 60 ; % = 100
Glimepiride No of events	n = 55 ; % = 92	n = 54 ; % = 90
Gliclazide No of events	n = 5 ; % = 8	n = 6 ; % = 10

279. Liu, 2021

Bibliographic Reference	Liu, S. C.; Lee, C. C.; Chuang, S. M.; Sun, F. J.; Zeng, Y. H.; Comparison of efficacy and safety of empagliflozin vs linagliptin added to premixed insulin in patients with uncontrolled type 2 diabetes: A randomized, open-label study; Diabetes & Metabolism; 2021; vol. 47 (no. 3); 101184

279.1. Study details

Trial name / registration number	NCT03458715
Study type	Randomised controlled trial (RCT)
Study location	Single centre
Study setting	NR
Study dates	21 September 2017 to 20 September 2018
Sources of funding	NR
Inclusion criteria	Patients aged 20–70 years with inadequately controlled T2DM (HbA1c > 7%) despite a regimen of premixed insulin twice daily, with or without OADs, were enrolled in the study
Exclusion criteria	type 1 diabetes; pregnancy; diabetic ketoacidosis; urinary tract infection (UTI); pancreatitis < 6 months prior to enrolment; estimated glomerular filtration rate (eGFR) < 45 mL/ min/1.73 m2 ; investigational drug use; treatment with anti-obesity drugs or glucagon-like peptide-1 receptor agonists (GLP-1RAs) 3 months prior to enrolment; and non-compliance with follow-up visits.
Recruitment / selection of participants	No additional information
Intervention(s)	Linagliptin (n=53) Patients received 5 mg Linagliptin for 24 weeks
Cointervention	Insulin ± OAD Throughout the study, premixed insulin doses were kept within 10% unless insulin up-titration (defined as a 10% increase from baseline) was clinically indicated (if a patient had a confirmed glucose level > 300 mg/dL in a randomly performed measurement or showed symptoms of hyperglycaemia). Otherwise, no dose modification of either the study

	medication or OAD was allowed. Only insulin could be reduced if two or more self-monitored blood glucose levels were ≤80 mg/dL Throughout the entire study, patients maintained the same OAD dose as was used prior to 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. Results states: "Most of the patients recruited for the study had normal kidney function (mean eGFR: 83.9 ± 34.9 mL/min/1.73 m2 in the linagliptin group, and 81.4 ± 26.7 mL/min/1.73 m2 in the empagliflozin group)", but no percentages given.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear

Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	NA
Comparator	Empagliflozin (n=53) Patients received 25 mg Empagliflozin for 24 weeks in addition to premixed insulin Insulin ± OAD Throughout the study, premixed insulin doses were kept within 10% unless insulin up-titration (defined as a 10% increase from baseline) was clinically indicated (if a patient had a confirmed glucose level > 300 mg/dL in a randomly performed measurement or showed symptoms of hyperglycaemia). Otherwise, no dose modification of either the study medication or OAD was allowed. Only insulin could be reduced if two or more self-monitored blood glucose levels were ≤80 mg/dL Throughout the entire study, patients maintained the same OAD dose as was used prior to the study
Number of participants	106
Duration of follow-up	24 weeks
Indirectness	NA
Method of analysis	ITT
Additional comments	Efficacy analyses were performed using the full analysis set, defined as all patients who received at least one dose of the study medication and had at least one post-baseline value ≥1 for efficacy variables measured during the treatment period. In addition, the safety analysis set, defined as all patients who received at least one dose of the study medication, was used for analyses of safety variables

279.2. Study arms

279.2.1. Linagliptin (N = 53)

Patients received 5 mg Linagliptin for 24 weeks in addition to background premixed insulin regimen

279.2.2. Empagliflozin (N = 53)

Patients received 25 mg Empagliflozin for 24 weeks in addition to background premixed insulin regimen

279.3. Characteristics

279.3.1. Arm-level characteristics

Characteristic	Linagliptin (N = 53)	Empagliflozin (N = 53)
% Male Sample size	n = 15 ; % = 28.3	n = 26 ; % = 49.1
Mean age (SD) (Years (mean, SD)) Mean (SD)	59.1 (10.2)	58 (10.4)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed (Years (mean, SD)) Mean (SD)	11.1 (6.2)	12.6 (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	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Linagliptin (N = 53)	Empagliflozin (N = 53)
Sample size		
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Insulin Sample size	n = 53 ; % = 100	n = 53 ; % = 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

280. Liutkus, 2010

Bibliographic Reference	Liutkus, J.; Rosas Guzman, J.; Norwood, P.; Pop, L.; Northrup, J.; Cao, D.; Trautmann, M.; A placebo-controlled trial of exenatide twice-daily added to thiazolidinediones alone or in combination with metformin; Diabetes Obes Metab; 2010; vol. 12 (no. 12); 1058-65

280.1. Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.
Trial name / registration number	No additional information.
Study type	Randomised controlled trial (RCT)
Study location	Conducted at 28 sites in the following countries: Canada Mexico Romania South Africa United states
Study setting	Conducted at 28 sites but setting was not reported.
Study dates	No additional information.
Sources of funding	This study was sponsored by Amylin Pharmaceuticals, Inc. and Eli Lilly and Company.

Inclusion criteria	• HbA1c levels ≥7.1% and ≤10.0% • BMI ≥25 kg/m2 and ≤45 kg/m2 • a history of stable body weight not varying by >10% for at least 3 months.
Exclusion criteria	• Experienced more than 3 episodes of severe (major) hypoglycaemia within 6 months prior to screening; • Were treated with any prescription drug to promote weight loss within 3 months • Were treated for longer than 1 week with exogenous insulin within 2 months • Were treated with any excluded medications—sulphonylureas, meglitinides, alpha-glucosidase inhibitors, dipeptidyl peptidase-4 inhibitors or pramlintide acetate within 3 months.
Recruitment / selection of participants	Participants ≥ 18 years of age with suboptimal glycaemic control while taking stable doses of TZD therapy for 120 days or combined metformin and TZD therapy for at least 90 days were recruited and randomised 2:1 to add exenatide twice daily or placebo twice daily to their thiazolidinediones or thiazolidinediones + metformin therapy.
Intervention(s)	Exenatide twice daily (5 mcg for first 4 weeks, 10 mcg thereafter) Administered subcutaneously before morning and evening meals.
Cointervention	Metformin + thiazolidinedione (pioglitazone/rosiglitazone) or thiazolidinedione (pioglitazone/rosiglitazone) alone. Medications for the treatment of high blood pressure were stable with respect to the treatment regimen, and blood pressure was adequately controlled for 4 weeks prior to screening. No changes to the regimen of lipid-lowering agents were allowed within 6 weeks of screening.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear

Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	
Comparator	Placebo administered by injection subcutaneously twice daily. Placebo volume equivalent to exenatide volume were injected in the upper arm, thigh or abdomen within 60 min before morning and evening meals.
Number of participants	N=165
Duration of follow-up	26-week

Indirectness	
Method of analysis	ITT
Additional comments	The analysis included all randomised participants who received at least one dose of study drug.

280.2. Study arms

280.2.1. Exenatide 10 mcg twice daily (N = 111)

Administered by subcutaneous injection before morning and evening meals

280.2.2. Placebo (N = 54)

Administered by subcutaneous injection before morning and evening meals

280.3. Characteristics

280.3.1. Arm-level characteristics

Characteristic	Exenatide 10 mcg twice daily (N = 111)	Placebo (N = 54)
% Male No of events	n = 67 ; % = 60	n = 31 ; % = 57
Mean age (SD) Mean (SD)	55 (8)	54 (9)
African-American No of events	n = 8 ; % = 7	n = 3 ; % = 6
Caucasian No of events	n = 63 ; % = 57	n = 33 ; % = 61
Asian No of events	n = 2 ; % = 2	n = 0 ; % = 0
Hispanic No of events	n = 38 ; % = 34	n = 18 ; % = 33

Characteristic	Exenatide 10 mcg twice daily (N = 111)	Placebo (N = 54)
Time since type 2 diabetes diagnosed (years) Mean (SD)	6.3 (4.2)	6.4 (4.6)
Smoking status Nominal	NR	NR
Alcohol consumption Nominal	NR	NR
Presence of severe mental illness Nominal	NR	NR
People with significant cognitive impairment Nominal	NR	NR
People with a learning disability Nominal	NR	NR
Number of people with obesity Nominal	NR	NR
Metformin + pioglitazone/rosiglitazone No of events	n = 105 ; % = 95	n = 52 ; % = 96
Pioglitazone/rosiglitazone No of events	n = 6 ; % = 5	n = 2 ; % = 4
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

281. Ljunggren, 2012

Bibliographic Reference	Ljunggren, O; Bolinder, J; Johansson, L; Wilding, J; Langkilde, A M; Sjostrom, C D; Sugg, J; Parikh, S; Dapagliflozin has no effect on markers of bone formation and resorption or bone mineral density in patients with inadequately controlled type 2 diabetes mellitus on metformin.; Diabetes, obesity & metabolism; 2012; vol. 14 (no. 11); 990-9

281.1. Study details

Secondary publication of another included study- see primary study for details	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	Grandy 2014, Bolinder 2014
Trial name / registration number	NCT00855166

282. Ludvik, 2018

Bibliographic Reference	Ludvik, B.; Frías, J. P.; Tinahones, F. J.; Wainstein, J.; Jiang, H.; Robertson, K. E.; García-Pérez, L. E.; Woodward, D. B.; Milicevic, Z.; Dulaglutide as add-on therapy to SGLT2 inhibitors in patients with inadequately controlled type 2 diabetes (AWARD-10): a 24-week, randomised, double-blind, placebo-controlled trial; Lancet Diabetes Endocrinol; 2018; vol. 6 (no. 5); 370-381

282.1. Study details

Secondary publication of another included study- see primary study for details	AWARD-10. Parent paper
Other publications associated with this study included in review	NA
Trial name / registration number	NCT02597049
Study type	Randomised controlled trial (RCT)
Study location	Austria, Czechia, Germany, Hungary, Israel, Mexico, Puerto Rico, Spain, United States
Study setting	Unspecified clinical setting: 40 clinical sites
Study dates	December 2015 - February 2017
Sources of funding	Eli Lilly and Company
Inclusion criteria	• Have type 2 diabetes mellitus (based on the World Health Organization's [WHO] diagnostic criteria) • Have been treated with an SGLT2 inhibitor, with or without metformin, for at least 3 months prior to study entry (minimum required doses for that period for allowed SGLT2 inhibitors: empagliflozin 10 mg, dapagliflozin 5 or 10 mg [per country-specific label], canagliflozin 100 mg); minimum required dose for metformin, if used, is ≥1500 mg/day and must be reached (or highest tolerated

	dose which is acceptable with documented gastrointestinal [GI] intolerability) Daily doses of all allowed oral antihyperglycemia agent (OAMs) must have been stable for at least 12 weeks (±3 days) prior to randomization (study enrolment); daily doses of SGLT2 inhibitor and metformin, if used, will be considered stable during this period if: • all prescribed daily doses were in the range between the minimum required dose and maximum-approved dose per country-specific label; and • >90% of prescribed daily doses were equal to the dose at randomization • Have HbA1c ≥7.0% and ≤9.5% at study entry and approximately 1 week prior to randomization • Have body mass index (BMI) ≤45 kilograms per meter squared (kg/m^2) and agree to not initiate a diet and/or exercise program during the study with the intent of reducing body weight other than the lifestyle and dietary measures for diabetes treatment
Exclusion criteria	• Have type 1 diabetes mellitus • Have been treated with any other OAMs (other than SGLT2 inhibitors and metformin), glucagon-like peptide-1 receptor agonist (GLP-1 RA), pramlintide or insulin 3 months prior to study entry, or between study entry and randomization; or initiate metformin between study entry and randomization; short-term use of insulin for acute care (≤14 days) during the 3-month period prior to entry is not exclusionary • Have any condition that is a contraindication for use of the GLP-1 RA class or the SGLT2 inhibitor class (per country-specific labels) at study entry or develop such condition between study entry and randomization • Have acute or chronic hepatitis, signs and symptoms of any other liver disease other than nonalcoholic fatty liver disease (NAFLD), or alanine transaminase (ALT) level >2.5 times the upper limit of the reference range, as determined by the central laboratory at study entry; participants with NAFLD are eligible for participation in this trial • Had chronic or acute pancreatitis any time prior to study entry • Estimated glomerular filtration rate (eGFR) <45 millilitres(mL)/minute/1.73m^2, calculated by the Chronic Kidney Disease-Epidemiology (CKD-EPI) equation, as determined by the central laboratory at study entry and confirmed at lead in • Have any self or family history of type 2A or type 2B multiple endocrine neoplasia (MEN 2A or 2B) in the absence of known C-cell hyperplasia (this exclusion includes participants with a family history of MEN 2A or 2B, whose family history for the syndrome is rearranged during transfect [RET]-negative; the only exception for this exclusion will be for participants whose family members with MEN 2A or 2B have a known RET mutation and the potential participant for the study is negative for the RET mutation)

	• Have any self or family history of medullary C-cell hyperplasia, focal hyperplasia, carcinoma (including sporadic, familial, or part of MEN 2A or 2B syndrome) • Have a serum calcitonin ≥20 picograms/mL as determined by the central laboratory at study entry
Recruitment / selection of participants	Eligible adult patients (≥18 years) had inadequately controlled type 2 diabetes (HbA1c concentration ≥7·0% [53 mmol/mol] and ≤9·5% [80 mmol/mol]), a BMI of 45 kg/m² or less, and had been taking a commercially available SGLT2 inhibitor with or without metformin (≥1500 mg/day, as tolerated) for at least 3 months.
Intervention(s)	Experimental: 1.5 mg Dulaglutide Experimental: 0.75 mg Dulaglutide
Cointervention	SGLT2 inhibitor (all) with or without Metformin
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Exclusion criteria for a recent cardiovascular event but not explicit as to what this means
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 Eligible to participate, but not clear how many did
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	eGFR ≥30mL/min/1.73m2 Exclusion criteria: eGFR<45 mL/min/1.73m2 (CKD-EPI)
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	none
Comparator	Placebo Comparator: Placebo Placebo given SC once a week for 24 weeks.
Number of participants	424 patients were randomly assigned to receive dulaglutide 1·5 mg (n=142), dulaglutide 0·75 mg (n=142), or placebo (n=140)
Duration of follow-up	24 weeks
Indirectness	None
Method of analysis	Modified ITT
Additional comments	all randomly assigned patients who received at least one injected dose of study drug

282.2. Study arms

282.2.1. dulaglutide 1·5 mg (N = 142)

1.5 milligrams (mg) given subcutaneously (SC) once a week, stratified for baseline HbA1c concentration, metformin use, and dose of SGLT2 inhibitor (low vs high)

282.2.2. dulaglutide 0·75 mg (N = 142)

0·75 mg given SC once a week, stratified for baseline HbA1c concentration, metformin use, and dose of SGLT2 inhibitor (low vs high)

282.2.3. placebo (N = 140)

placebo SC once weekly,

282.3. Characteristics

282.3.1. Arm-level characteristics

Characteristic	Dulaglutide 1·5 mg (N = 142)	Dulaglutide 0·75 mg (N = 142)	Placebo (N = 140)
% Male Nominal	54	49	47
Mean age (SD) Mean (SD)	56.17 (9.26)	58.55 (9.14)	57.1 (9.56)
Native American/Alaskan Nominal	1	1	3
Asian Nominal	0	1	0
Black Nominal	2	2	4
Multiple Nominal	8	6	4
White Nominal	89	90	89

Characteristic	Dulaglutide 1·5 mg (N = 142)	Dulaglutide 0·75 mg (N = 142)	Placebo (N = 140)
Hispanic or Latino Nominal	36	31	31
Not reported Nominal	1	0	1
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Presence of frailty Nominal	NR	NR	NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	9.21 (5.74)	10.05 (6.56)	8.87 (6.13)
HbA1c (%) Mean (SD)	8.04 (0.65)	8.04 (0.61)	8.05 (0.66)
Cardiovascular risk factors Nominal	NR	NR	NR
Systolic Mean (SD)	129.7 (14.48)	130.35 (15.66)	130.57 (13.74)
Diastolic Mean (SD)	77.1 (8.96)	76.55 (9.98)	78.36 (9.46)
Smoking status Nominal	NR	NR	NR
Alcohol consumption Mean (SD)	NR (NR)	NR (NR)	NR (NR)
Presence of severe mental illness Nominal	NR	NR	NR
People with significant cognitive impairment Nominal	NR	NR	NR

Characteristic	Dulaglutide 1·5 mg (N = 142)	Dulaglutide 0·75 mg (N = 142)	Placebo (N = 140)
People with a learning disability Nominal	NR	NR	NR
Weight Mean (SD)	92.87 (19.73)	91.07 (20.99)	90.07 (20.99)
BMI Mean (SD)	32.87 (5.56)	32.77 (6.27)	32.39 (4.98)
Number of people with obesity Nominal	NR	NR	NR
Other antidiabetic medication used (%) Nominal	NA	NA	NA
Metformin use Nominal	94	96	96
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

283. Ludvik, 2021

Bibliographic Reference	Ludvik, B.; Giorgino, F.; Jodar, E.; Frias, J. P.; Fernandez Lando, L.; Brown, K.; Bray, R.; Rodriguez, A.; Once-weekly tirzepatide versus once-daily insulin degludec as add-on to metformin with or without SGLT2 inhibitors in patients with type 2 diabetes (SURPASS-3): a randomised, open-label, parallel-group, phase 3 trial; Lancet; 2021; vol. 398 (no. 10300); 583-598

283.1. 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-3 (NCT03882970)
Study type	Randomised controlled trial (RCT)
Study location	Multinational - Argentina, Austria, Greece, Hungary, Italy, Poland, Puerto Rico, Romania, South Korea, Spain, Taiwan, Ukraine, USA
Study setting	Medical research centres and hospitals
Study dates	April 2019 - January 2021
Sources of funding	Conducted by employees and shareholders of Eli Lilly and Company
Inclusion criteria	≥18 years of age Insulin naïve Type 2 diabetes that was inadequately controlled on metformin alone or in combination with an SGLT2 inhibitor for at least 3 months before screening

	BMI ≥25 kg.m2 and ≤5% weight fluctuation in the past 3 months
Exclusion criteria	Type 1 diabetes History of pancreatitis , proliferative diabetic retinopathy or maculopathy eGFR <45 mL/min per 1.73 m2
Recruitment / selection of participants	No additional information
Intervention(s)	Following a 1-week screening and 2-week run-in period, participants allocated to the intervention arms received 5, 10 or 15 mg tirzepatide once per week, administered via subcutaneous injection. The initial treatment dose was 2.5 mg for the first 4 weeks, with increases of 2.5 mg per 4 weeks until the allocated treatment dose had been reached. If intolerable gastrointestinal symptoms or events (e.g., nausea, diarrhoea, vomiting) occurred and persisted when the dose was increased despite mitigating measures (eating smaller meals, symptomatic medications, temporary interruption of treatment by omitting one dose) the investigator could decide to continue treatment at a lower tolerated dose (5 or 10 mg). De-escalation was not allowed in the 5 mg arm. Participants who had their dose de-escalated remained on the tolerated dose for the duration of the study. De-escalation was not allowed after the 24-week escalation period. *Three study intervention arms containing 5, 10 and 15 mg tirzepatide combined for this review*
Cointervention	Initiation of new antihyperglycaemic medications (other than study drugs and background metformin and SGLT-1 inhibitors) during the study was only allowed for rescue therapy for persistent hyperglycaemia on the basis of prespecified criteria or after early study drug discontinuation. GLP-1 receptor agonists, DPP-4 inhibitors, and pramlintide were prohibited medications and were not allowed as rescue therapies. No other basal insulins were allowed throughout the study, except for the tirzepatide groups as rescue therapy.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear
Strata 2: People with	Not stated/unclear

atherosclerotic cardiovascular disease	
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with 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	Insulin Degludec: Following a 1-week screening and 2-week run-in period, participants allocated to the comparator received insulin degludec, administered once daily via subcutaneous injection with a prefilled pen containing 3 mL (U100/mL). The initial dose of insulin was 10 U per day, titrated weekly to achieve a fasting glucose of <5.0 mmol/L following a treat-to-target algorithm based on the median value of the last three self-monitored blood glucose values. Investigators could decide on insulin adjustments that deviated from the algorithm if there were safety concerns. Initiation of new antihyperglycaemic medications (other than study drugs and background metformin and SGLT-1 inhibitors) during the study was only allowed for rescue therapy for persistent hyperglycaemia on the basis of prespecified criteria or after early study drug discontinuation. GLP-1 receptor agonists, DPP-4 inhibitors, and pramlintide were prohibited medications and were not allowed as rescue therapies. No other basal insulins were allowed throughout the study, except for the tirzepatide groups as rescue therapy.
Number of participants	1444 randomised 359 received 5 mg tirzepatide, 333 completed 361 received 10 mg tirzepatide, 321 completed 359 received 15 mg tirzepatide, 340 completed 365 received insulin degludec, 331 completed
Duration of follow-up	52 weeks
Indirectness	None
Method of analysis	Modified ITT
Additional comments	None

283.2. Study arms

283.2.1. Tirzepatide (N = 1079)

5, 10 or 15 mg tirzepatide per day *Three study arms examining different doses combined for this review*

283.2.2. Insulin degludec (N = 365)

283.3. Characteristics

283.3.1. Arm-level characteristics

Characteristic	Tirzepatide (N = 1079)	Insulin degludec (N = 365)
% Male Sample size	n = 589 ; % = 55	n = 213 ; % = 59
Mean age (SD) (years) Mean (SD)	57.4 (10)	57.5 (10.1)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
American Indian or Alaska Native Sample size	n = 2 ; % = 0	n = 2 ; % = 1
Asian Sample size	n = 59 ; % = 5	n = 17 ; % = 5
Black or African American Sample size	n = 33 ; % = 3	n = 11 ; % = 3
Multiple Sample size	n = 2 ; % = 0	n = 0 ; % = 0
Native Hawaiian or other Pacific Islander Sample size	n = 3 ; % = 0	n = 1 ; % = 0
White Sample size	n = 978 ; % = 91	n = 329 ; % = 91
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed (years)	8.5 (6.3)	8.1 (6)

Characteristic	Tirzepatide (N = 1079)	Insulin degludec (N = 365)
Mean (SD)		
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR
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 alone Sample size	n = 735 ; % = 68	n = 244 ; % = 68
Metformin plus SGLT-2 inhibitor Sample size	n = 342 ; % = 32	n = 116 ; % = 32
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

284. Lukashevich, 2011

Bibliographic Reference	Lukashevich, V.; Schweizer, A.; Shao, Q.; Groop, P. H.; Kothny, W.; Safety and efficacy of vildagliptin versus placebo in patients with type 2 diabetes and moderate or severe renal impairment: a prospective 24-week randomized placebo-controlled trial; Diabetes Obes Metab; 2011; vol. 13 (no. 10); 947-54

284.1. Study details

Other publications associated with this study included in review	Kothny W, Shao Q, Groop PH, Lukashevich V. One-year safety, tolerability and efficacy of vildagliptin in patients with type 2 diabetes and moderate or severe renal impairment. Diabetes Obes Metab. 2012 Nov;14(11):1032-9. doi: 10.1111/j.1463-1326.2012.01634.x. Epub 2012 Jul 8. PMID: 22690943.
Trial name / registration number	NR
Study type	Randomised controlled trial (RCT)
Study location	108 centres worldwide
Study setting	No additional information
Study dates	NR
Sources of funding	Four of the five authors are employees of Novartis. The remaining authors declares honoraria and funding from multiple pharmaceutical companies
Inclusion criteria	Adult patients (age 18–85 years) with T2DM and moderate or severe renal impairment (RI) (estimated Glomerular Filtration Rate [eGFR] by the Modification of Diet in Renal Disease formula ≥30 to <50 ml/min/1.73 m2 and <30 ml/min/1.73 m2, respectively). Patients were either untreated (no therapy in previous 8 weeks) or treated with an SU, AGI, TZD, insulin, meglitinide or a combination of agents were eligible, provided that their dosages were stable for the previous 4 weeks, A1C was between 6.5 and 10% and BMI was between 18 and 42 kg/m2.
Exclusion criteria	Patients were excluded if their fasting plasma glucose (FPG) was ≥15 mmol/l, they had a history of renal transplant, significant cardiovascular history within 6 months, active liver disease or abnormal liver tests (ALT, AST or bilirubin 2× upper limit of normal [ULN]). The initial protocol excluded patients undergoing any dialysis, but this was subsequently amended to remove that restriction.
Recruitment / selection of participants	No additional information

Intervention(s)	Moderate renal impairment (RI); Vildagliptin (n=165) Sever RI; Vildagliptin (n=124); Patients received 50 mg vildagliptin once daily for 52 weeks
Cointervention	Patients received background therapy (untreated, insulin, oral antidiabetic drugs (OADs) or any combination) for 52 weeks
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Exclusion criteria for significant cardiovascular history within 6 months but not clear as to what this means.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Exclusion criteria for significant cardiovascular history within 6 months but not clear as to what this means.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Exclusion criteria for renal transplant but no mention specifically of CKD
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear

Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Mixed population
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	Please note; for the purposes of extraction, patients with severe RI (eGFR >30 ml/min) will be listed as patients with CKD whilst patients with moderate RI (eGFR <30 ml/min - <50 mol/min) will be listed as not stated /unclear for CKD
Comparator	Moderate renal impairment (RI); Placebo (n=129) Severe RI; Placebo (n=97); Patients received Placebo for 52 weeks in addition to background therapy (untreated, insulin, oral antidiabetic drugs (OADs) or any combination)
Number of participants	525
Duration of follow-up	52 weeks
Indirectness	NA
Method of analysis	Modified ITT
Additional comments	The adjusted mean changes in A1C and FPG from baseline to rescue-censored endpoint (with final post-week 24 observation carried forward for data censored at initiation of rescue medication) were compared between treatments for patients stratified by severity of RI, using an analysis of covariance (ANCOVA) model with baseline value as covariate and background therapy, pooled centre and treatment as factors. Safety analysis was performed on all collected data regardless of rescue medication use.

284.2. Study arms

284.2.1. Moderate RI: Vildagliptin (N = 165)

Patients received 50 mg vildagliptin once daily added to a stable background therapy for 52 weeks

284.2.2. Moderate RI: Placebo (N = 129)

Patients received Placebo added to a stable background therapy for 52 weeks

284.2.3. Severe RI: Vildagliptin (N = 124)

Patients received 50 mg vildagliptin once daily added to a stable background therapy for 52 weeks

284.2.4. Severe RI: Placebo (N = 97)

Patients received Placebo added to a stable background therapy for 52 weeks

284.3. Characteristics

284.3.1. Arm-level characteristics

Characteristic	Moderate RI: Vildagliptin (N = 165)	Moderate RI: Placebo (N = 129)	Severe RI: Vildagliptin (N = 124)	Severe RI: Placebo (N = 97)
% Male Sample size	n = 96 ; % = 58.2	n = 80 ; % = 62	n = 65 ; % = 52.4	n = 53 ; % = 54.6
Mean age (SD) (Years (mean, SD)) Mean (SD)	67.7 (8.8)	69.7 (7.3)	64.1 (9.2)	64.5 (10.8)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Europid Sample size	n = 116 ; % = 70.3	n = 94 ; % = 72.9	n = 61 ; % = 49.2	n = 49 ; % = 50.4
Asian (Indian subcontinent) Sample size	n = 24 ; % = 14.5	n = 15 ; % = 11.6	n = 22 ; % = 17.7	n = 21 ; % = 21.6
Asian (non-Indian subcontinent) Sample size	n = 0 ; % = 0	n = 0 ; % = 0	n = 2 ; % = 1.6	n = 0 ; % = 0
Hispanic or Latino	n = 21 ; % = 12.7	n = 16 ; % = 12.4	n = 36 ; % = 29	n = 26 ; % = 26.8

Characteristic	Moderate RI: Vildagliptin (N = 165)	Moderate RI: Placebo (N = 129)	Severe RI: Vildagliptin (N = 124)	Severe RI: Placebo (N = 97)
Sample size				
Black Sample size	n = 2 ; % = 1.2	n = 0 ; % = 0	n = 2 ; % = 1.6	n = 0 ; % = 0
Other Sample size	n = 2 ; % = 1.2	n = 4 ; % = 3.1	n = 1 ; % = 0.8	n = 1 ; % = 1
Time since type 2 diabetes diagnosed (Years (mean, SD)) Mean (SD)	15 (9.1)	15.2 (10)	17.3 (8.6)	19 (9.6)
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Any Sample size	n = 159 ; % = 96.4	n = 124 ; % = 96.1	n = 119 ; % = 96	n = 96 ; % = 99
Insulin monotherapy Sample size	n = 95 ; % = 57.6	n = 68 ; % = 52.7	n = 87 ; % = 70.2	n = 66 ; % = 68
Insulin and OAD Sample size	n = 18 ; % = 10.9	n = 20 ; % = 15.5	n = 13 ; % = 10.5	n = 12 ; % = 12.4

Characteristic	Moderate RI: Vildagliptin (N = 165)	Moderate RI: Placebo (N = 129)	Severe RI: Vildagliptin (N = 124)	Severe RI: Placebo (N = 97)
OAD monotherapy Sample size	n = 39 ; % = 23.6	n = 33 ; % = 25.6	n = 18 ; % = 14.5	n = 14 ; % = 14.4
OAD combination therapy Sample size	n = 7 ; % = 4.2	n = 3 ; % = 2.3	n = 1 ; % = 0.8	n = 4 ; % = 4.1
Statins/lipid-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR

285. Lukashevich, 2014

Bibliographic Reference	Lukashevich, V; Del Prato, S; Araga, M; Kothny, W; Efficacy and safety of vildagliptin in patients with type 2 diabetes mellitus inadequately controlled with dual combination of metformin and sulphonylurea.; Diabetes, obesity & metabolism; 2014; vol. 16 (no. 5); 403-9

285.1. Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.
Trial name / registration number	No additional information.
Study type	Randomised controlled trial (RCT)
Study location	Australia Germany Hungary India Italy Mexico Philippines Romania
Study setting	No additional information.
Study dates	No additional information.

Sources of funding	Novartis Pharmaceuticals Corporation
Inclusion criteria	• 18–80 years of age, • BMI ≥22 to ≤45 kg/m2 • Inadequately controlled on a stable dose of oral antidiabetic drugs for at least 12 weeks prior to the screening visit. • Acceptable background therapy prior to enrolment included metformin ≥1500 mg as monotherapy [haemoglobin A1c (HbA1c) ≥8.5 and ≤11%] or dual combination of metformin ≥1500 mg with SU, thiazolidinedione or glinide (HbA1c ≥7.5 and ≤11%). • Eligible patients continued their current metformin treatment ≥1500 mg throughout the study
Exclusion criteria	• Fasting plasma glucose (FPG) ≥15.0 mmol/l • Significant hepatic, renal or cardiovascular medical conditions • Significant laboratory abnormalities • Pregnant or lactating females
Recruitment / selection of participants	In total 564 participants with type 2 diabetes were screened and randomised 1:1 to receive treatment with vildagliptin 50 mg twice daily (n=158) or placebo (n=160).
Intervention(s)	Vildagliptin 50 mg twice daily
Cointervention	Metformin (≥ 1500 mg) + glimepiride (≥ 4 mg) Rescue medication (insulin or pioglitazone, per investigator discretion) was prescribed if the patient had FPG >13.3 mmol/l between week 6 and 12, FPG >11.1 mmol/l between week 12 and 24 or symptoms of worsening of hyperglycaemia at any visit.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Exclusion criteria for cardiovascular medical conditions but no clear statement as to what this means
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Exclusion criteria for cardiovascular medical conditions but no clear statement as to what this means

Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Mixed population Based off of GFR categories there are a mixture of people of the mild and moderate group and the normal group (around 35% of people are in the mild and moderate groups).
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Mixed population
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	No additional information.
Comparator	Placebo, administered twice daily, orally.

Number of participants	N=246
Duration of follow-up	24 weeks
Method of analysis	Modified ITT
Additional comments	Full analysis set consisting of all randomised patients who received at least one dose of the study drug and had at least one post-randomisation efficacy parameter measurement.

285.2. Study arms

285.2.1. Vildagliptin 50 mg (N = 158)

Administered twice daily, orally.

285.2.2. Placebo (N = 160)

Administered twice daily, orally.

285.3. Characteristics

285.3.1. Arm-level characteristics

Characteristic	Vildagliptin 50 mg (N = 158)	Placebo (N = 160)
% Male No of events	n = 80 ; % = 51	n = 72 ; % = 45
Mean age (SD) (years) Mean (SD)	55.3 (10.2)	55 (11.1)
Asian No of events	n = 116 ; % = 73.4	n = 116 ; % = 72.5
Indian No of events	n = 81 ; % = 51.3	n = 77 ; % = 48.1
Chinese No of events	n = 12 ; % = 7.6	n = 21 ; % = 13.1

Characteristic	Vildagliptin 50 mg (N = 158)	Placebo (N = 160)
Caucasian No of events	n = 34 ; % = 21.5	n = 38 ; % = 23.8
Other No of events	n = 8 ; % = 5.1	n = 6 ; % = 3.8
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	7.1 (6.2)	7.5 (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 Nominal	NR	NR
Metformin + glimepiride No of events	n = 158 ; % = 100	n = 160 ; % = 100

286. Lundby Christensen, 2009

Bibliographic Reference	Lundby Christensen, L; Almdal, T; Boesgaard, T; Breum, L; Dunn, E; Gade-Rasmussen, B; Gluud, C; Hedetoft, C; Jarloev, A; Jensen, T; Krarup, T; Johansen, L B; Lund, S S; Madsbad, S; Mathiesen, E; Moelvig, J; Nielsen, F; Perrild, H; Pedersen, O; Roeder, M; Sneppen, S B; Snorgaard, O; Tarnow, L; Thorsteinsson, B; Vaag, A; Vestergaard, H; Wetterslev, J; Wiinberg, N; Study rationale and design of the CIMT trial: the Copenhagen Insulin and Metformin Therapy trial.; Diabetes, obesity & metabolism; 2009; vol. 11 (no. 4); 315-22

286.1. Study details

Secondary publication of another included study- see primary study for details	Parent study Lundby 2016 Lundby-Christensen L, Tarnow L, Boesgaard TW, Lund SS, Wiinberg N, Perrild H, Krarup T, Snorgaard O, Gade-Rasmussen B, Thorsteinsson B, Røder M, Mathiesen ER, Jensen T, Vestergaard H, Hedetoft C, Breum L, Duun E, Sneppen SB, Pedersen O, Hemmingsen B, Carstensen B, Madsbad S, Gluud C, Wetterslev J, Vaag A, Almdal TP. Metformin versus placebo in combination with insulin analogues in patients with type 2 diabetes mellitus-the randomised, blinded Copenhagen Insulin and Metformin Therapy (CIMT) trial. BMJ Open. 2016 Feb 25;6(2):e008376. doi: 10.1136/bmjopen-2015-008376.
Other publications associated with this study included in review	Hansen CS, Lundby-Christiansen L, Tarnow L, Gluud C, Hedetoft C, Thorsteinsson B, Hemmingsen B, Wiinberg N, Sneppen SB, Lund SS, Krarup T, Madsbad S, Almdal T, Carstensen B, Jørgensen ME; CIMT study group. Metformin may adversely affect orthostatic blood pressure recovery in patients with type 2 diabetes: substudy from the placebo-controlled Copenhagen Insulin and Metformin Therapy (CIMT) trial. Cardiovasc Diabetol. 2020 Sep 26;19(1):150. doi: 10.1186/s12933-020-01131-3. PMID: 32979921; PMCID: PMC7520024. Nordklint AK, Almdal TP, Vestergaard P, Lundby-Christensen L, Boesgaard TW, Breum L, Gade-Rasmussen B, Sneppen SB, Gluud C, Hemmingsen B, Perrild H, Madsbad S, Mathiesen ER, Tarnow L, Thorsteinsson B, Vestergaard H, Lund SS, Eiken P. Effect of metformin and insulin vs. placebo and insulin on whole body composition in overweight patients with type 2 diabetes: a randomized placebo-controlled trial. Osteoporos Int. 2021 Sep;32(9):1837-1848. doi: 10.1007/s00198-021-05870-1. Epub 2021 Feb 16. PMID: 33594488.

287. Lundby-Christensen, 2016

Bibliographic Reference	Lundby-Christensen, L.; Tarnow, L.; Boesgaard, T. W.; Lund, S. S.; Wiinberg, N.; Perrild, H.; Krarup, T.; Snorgaard, O.; Gade-Rasmussen, B.; Thorsteinsson, B.; Roder, M.; Mathiesen, E. R.; Jensen, T.; Vestergaard, H.; Hedetoft, C.; Breum, L.; Duun, E.; Sneppen, S. B.; Pedersen, O.; Hemmingsen, B.; Carstensen, B.; Madsbad, S.; Gluud, C.; Wetterslev, J.; Vaag, A.; Almdal, T. P.; Metformin versus placebo in combination with insulin analogues in patients with type 2 diabetes mellitus-the randomised, blinded Copenhagen Insulin and Metformin Therapy (CIMT) trial; BMJ Open; 2016; vol. 6 (no. 2); e008376

287.1. Study details

Secondary publication of another included study- see primary study for details	
Other publications associated with this study included in review	Lundby Christensen L, Almdal T, Boesgaard T, Breum L, Dunn E, Gade-Rasmussen B, Gluud C, Hedetoft C, Jarloev A, Jensen T, Krarup T, Johansen LB, Lund SS, Madsbad S, Mathiesen E, Moelvig J, Nielsen F, Perrild H, Pedersen O, Roeder M, Sneppen SB, Snorgaard O, Tarnow L, Thorsteinsson B, Vaag A, Vestergaard H, Wetterslev J, Wiinberg N; CIMT Trial Group. Study rationale and design of the CIMT trial: the Copenhagen Insulin and Metformin Therapy trial. Diabetes Obes Metab. 2009 Apr;11(4):315-22. doi: 10.1111/j.1463-1326.2008.00959.x. PMID: 19267709.
Trial name / registration number	NCT00657943
Study type	Randomised controlled trial (RCT)
Study location	Eight hospitals in the greater Copenhagen region
Study setting	No additional information
Study dates	May 2008 to December 2012
Sources of funding	Novo Nordisk A/S. Numerous authors declare multiple funding and honoraria from numerous pharmaceutical companies

Inclusion criteria	• T2DM (World Health Organization criteria) • Body mass index: 25–40 kg/m2 (both limits included) • HbA1c ≥ 7.5% • Antidiabetic tablet treatment during 1 year minimum and/or • Insulin treatment during a minimum period of 3 months, where investigator deems the patient capable of insulin therapy once daily • Negative pregnancy test
Exclusion criteria	Major cardiovascular disease within the past 3 months, carotid artery stenosis >70%, heart failure, recent cancer, renal or liver disease, alcohol or drug abuse, unstable retinopathy, pregnant or breastfeeding women, fertile women not using anticonception or allergy towards trial medication.
Recruitment / selection of participants	No additional information
Intervention(s)	Metformin (n=206) Patients received 2000 mg per day (1000 mg twice daily) for 18 months
Cointervention	Insulin Patients were randomly assigned to one of the following insulin regimens • Insulin detemir once daily before bedtime. • Biphasic insulin aspart 30 before dinner with possible increase to two or three daily injections. • Insulin aspart before the main meals (three times daily) and detemir before bedtime Insulin dose will be adjusted according to predefined algorithms. Adjustment of insulin dose during the first 12 weeks will be carried out by at least weekly telephonic contact with a diabetic nurse. After the 12th week, telephone contacts will be every 2 or 3 weeks
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Excluded ">70%, heart failure", otherwise unclear. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Excluded "major cardiovascular disease within the past 3 months", prior unclear. Baseline characteristics given for CVD around 25%, but this includes 'heart insufficiency', taken to mean HF.
Strata 3: People with type 2 diabetes	Not stated/unclear Excluded "renal disease", otherwise unclear. No information in baseline characteristics.

mellitus and chronic kidney disease	
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	NA
Comparator	Placebo (n=206) Patients receive placebo twice daily for 18 months Insulin

	Patients were randomly assigned to one of the following insulin regimens • Insulin detemir once daily before bedtime. • Biphasic insulin aspart 30 before dinner with possible increase to two or three daily injections. • Insulin aspart before the main meals (three times daily) and detemir before bedtime Insulin dose will be adjusted according to predefined algorithms. Adjustment of insulin dose during the first 12 weeks will be carried out by at least weekly telephonic contact with a diabetic nurse. After the 12th week, telephone contacts will be every 2 or 3 weeks
Number of participants	412
Duration of follow-up	18 months
Indirectness	NA
Method of analysis	ITT
Additional comments	The primary analysis was intention-to-treat of the mean carotid IMT at 18 months adjusted for stratification variables and baseline value of carotid IMT. Secondary analyses were adjusted only for baseline value. Further, a per protocol analysis was performed (exclusion of participants not fulfilling the criteria for participation, never receiving the allocated trial medication or having major deviations to the protocol (not meeting to at least four visits).

287.2. Study arms

287.2.1. Metformin (N = 206)

Patients received 1000 mg metformin twice daily for 18 months

287.2.2. Placebo (N = 206)

Patients received placebo twice daily for 18 months

287.3. Characteristics

287.3.1. Arm-level characteristics

Characteristic	Metformin (N = 206)	Placebo (N = 206)
% Male Sample size	n = 140 ; % = 68	n = 141 ; % = 68
Mean age (SD) (Years (mean, SD)) Mean (SD)	61 (8.7)	60.3 (9.1)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Caucasian Sample size	n = 201 ; % = 98	n = 201 ; % = 98
Time since type 2 diabetes diagnosed (Years (mean, SD)) Mean (SD)	13.5 (6.2)	12.2 (6.5)
Smoking status Sample size	n = 36 ; % = 18	n = 27 ; % = 13
Alcohol consumption (units/week) Median (IQR)	2 (0 to 6)	1 (0 to 5)
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
Sulfonlyurea Sample size	n = 61 ; % = 30	n = 55 ; % = 27
Other antihyperglycaemic drug Sample size	n = 32 ; % = 16	n = 27 ; % = 13

Characteristic	Metformin (N = 206)	Placebo (N = 206)
Blood pressure-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
RAS blockade Sample size	n = 159 ; % = 77	n = 149 ; % = 72
Statins/lipid-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Statin Sample size	n = 170 ; % = 83	n = 181 ; % = 88
Other treatment being received Sample size	n = NA ; % = NA	n = NA ; % = NA
Aspirin Sample size	n = 112 ; % = 54	n = 119 ; % = 58

288. Macauley, 2015

Bibliographic Reference	Macauley, M.; Hollingsworth, K. G.; Smith, F. E.; Thelwall, P. E.; Al-Mrabeh, A.; Schweizer, A.; Foley, J. E.; Taylor, R.; Effect of vildagliptin on hepatic steatosis; J Clin Endocrinol Metabol; 2015; vol. 100 (no. 4); 1578-85

288.1. 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	NCT01356381
Study type	Randomised controlled trial (RCT)
Study location	UK
Study setting	Not additional information.
Study dates	04/2011 - 08/2013
Sources of funding	Novartis Pharma AG
Inclusion criteria	• Age in the range of 18-70 years. • Patients with type 2 diabetes mellitus, diagnosed at least 6 months prior to Visit 1, who have received metformin for at least 3 months and have been on a stable dose of at least 1000mg daily for a minimum of 4 weeks prior to Visit 1. • HbA1c ≤ 7.6% at Visit 1. • BMI in the range of 22-38kg/m2 inclusive at Visit
Exclusion criteria	• Pregnant or nursing (lactating) women. • Patients with cardiac pacemakers or with metallic implants incompatible with magnetic resonance methodology.

	• Congestive heart failure requiring pharmacologic treatment. Other protocol-defined inclusion/exclusion criteria may apply
Recruitment / selection of participants	Patients were recruited and screened for inclusion from a single centre. In total 42 patients were included and randomised 1:1 vildagliptin 50 mg twice daily and placebo.
Intervention(s)	Vildagliptin 50 mg twice daily
Cointervention	Metformin
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	Placebo taken orally twice daily.
Number of participants	N=44
Duration of follow-up	6 months
Indirectness	
Method of analysis	Not stated/unclear
Additional comments	

288.2. Study arms

288.2.1. Vildagliptin 50 mg twice daily (N = 22)

Administered orally.

288.2.2. Placebo twice daily (N = 22)

Administered orally.

288.3. Characteristics

288.3.1. Study-level characteristics

Characteristic	Study (N = 44)
% Male No of events	n = 28 ; % = 64
Time since type 2 diabetes diagnosed (years) Mean (SD)	5.7 (0.7)

288.3.2. Arm-level characteristics

Characteristic	Vildagliptin 50 mg twice daily (N = 22)	Placebo twice daily (N = 22)
Mean age (SD) (years) Mean (SD)	65.2 (0.7)	58.9 (1.6)
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Alcohol consumption Nominal	NR	NR
Presence of severe mental illness Nominal	NR	NR
People with significant cognitive impairment Nominal	NR	NR
People with a learning disability Nominal	NR	NR
Number of people with obesity Nominal	NR	NR
Metformin No of events	n = 22 ; % = 100	n = 22 ; % = 100

Characteristic	Vildagliptin 50 mg twice daily (N = 22)	Placebo twice daily (N = 22)
Other treatment being received Nominal	NR	NR

289. Mahaffey Kenneth, 2018

Bibliographic Reference	Mahaffey Kenneth, W; Neal, Bruce; Perkovic, Vlado; de Zeeuw, Dick; Fulcher, Greg; Erondu, Ngozi; Shaw, Wayne; Fabbrini, Elisa; Sun, Tao; Li, Qiang; Desai, Mehul; Matthews David, R; CANVAS Program, Collaborative; Group; Canagliflozin for Primary and Secondary Prevention of Cardiovascular Events: Results From the CANVAS Program (Canagliflozin Cardiovascular Assessment Study).; Circulation; 2018; vol. 137 (no. 4); 323-334

289.1. Study details

Secondary publication of another included study- see primary study for details	This record is used as the parent study for the CANVAS and CANVAS-R trials (The CANVAS Program). Any outcomes relating to the whole cohort for the trial are included in this record.
Other publications associated with this study included in review	Neal, Bruce; Perkovic, Vlado; de Zeeuw, Dick et al. (2013) Rationale, design, and baseline characteristics of the Canagliflozin Cardiovascular Assessment Study (CANVAS)--a randomized placebo-controlled trial. American heart journal; 2013; vol. 166 (no. 2); 217-223e11 Neal, Bruce, Perkovic, Vlado, Matthews David, R et al. (2017) Rationale, design and baseline characteristics of the CANagliflozin cardioVascular Assessment Study-Renal (CANVAS-R): A randomized, placebo-controlled trial. Diabetes, obesity & metabolism 19(3): 387-393 Radholm, Karin, Figtree, Gemma, Perkovic, Vlado et al. (2018) Canagliflozin and Heart Failure in Type 2 Diabetes Mellitus: Results From the CANVAS Program. Circulation 138(5): 458-468 Zhou, Z, Lindley R, I, Radholm, K et al. (2019) Canagliflozin and Stroke in Type 2 Diabetes Mellitus: Results from the Randomized CANVAS Program Trials. Stroke 50(2): 396-404
Trial name / registration number	CANVAS Program combines the CANVAS trial (NCT01032629) and the CANVAS-R trial (NCT01989754)
Study type	Randomised controlled trial (RCT)
Study location	667 centres in 30 countries - Not further specified
Study setting	Likely outpatient.
Study dates	Recruitment commencing December 2009, completing in March 2011.

Sources of funding	Supported by Janssen Research & Development, LLC. Medical writing support was funded by Janssen Global Services, LLC. Canagliflozin has been developed by Janssen Research & Development, LLC, in collaboration with Mitsubishi Tanabe Pharma Corp.
Inclusion criteria	Men or women with a diagnosis of type 2 diabetes mellitus with HbA1c level at least 7.0% to no more than 10.5% at screening and be either 1) not currently on antihyperglycaemic agent therapy, 2) on antihyperglycaemic monotherapy or combination therapy with any approved agent: e.g., sulfonylurea, metformin, pioglitazone, alpha-glucosidase inhibitor, glucagon-like peptide-1 analogue, dipeptidyl peptidase-4 inhibitor or insulin; history or high risk of cardiovascular disease defined on the basis of either: age 30 years with documented symptomatic atherosclerotic cardiovascular disease: including stroke; MI; hospital admission for unstable angina; coronary artery bypass graft; percutaneous coronary intervention (with or without stenting); peripheral revascularisation (angioplasty or surgery); symptomatic with documented hemodynamically-significant carotid or peripheral vascular disease; or amputation secondary to vascular disease; or age 50 years with 2 or more of the following risk factors determined at the screening visit: duration of T2DM of 10 years or more, systolic blood pressure >140 mmHg while the subject is on at least one blood pressure-lowering treatment, current daily cigarette smoker, documented micro- or macro-albuminuria or documented HDL-C of <1mmol/L (<39 mg/dL); women were required to be postmenopausal, defined as >45 years of age with amenorrhea for at least 18 months or >45 years of age with amenorrhea for at least 6 months and less than 18 months and a serum follicle stimulating hormone level >40 IU/L, or surgically sterile (have had a hysterectomy or bilateral oophorectomy, tubal ligation) or otherwise incapable of pregnancy, or heterosexually active and practicing a highly effective method of birth control, including hormonal prescription oral contraceptives, contraceptive injections, contraceptive patch, intrauterine device, double-barrier method (e.g., condoms, diaphragm or cervical cap with spermicidal foam, cream or gel) or male partner sterilisation, consistent with local regulations regarding use of birth control methods for subjects participating in clinical trials, for the duration of their participation in the study, or not heterosexually active, women of childbearing potential were required to have a negative urine beta-human chorionic gonadotrophin pregnancy test at screening and baseline (not people who were not heterosexually active at screening were required to agree to utilize a highly effective method of birth control if they became heterosexually active during their participation in the study); willing and able to adhere to the prohibitions and restrictions specified in the protocol; all were required to have signed an informed consent document indicating that they understood the purpose of and procedures required for the study and were willing to participate in the study; to participate in the optional pharmacogenomic component of the study, subjects were required to have signed the informed consent form for pharmacogenomic research indicating willingness to participate in the pharmacogenomic component of the study (where local regulations permit). Refusal to give consent for this component did not exclude a subject from participation in the clinical study; subject must have taken at least 80% of their single-blind placebo capsules during the 2-week run-in period at Day 1 to have been eligible for randomisation.

Exclusion criteria	History of diabetic ketoacidosis, type 1 diabetes mellitus, pancreas or beta-cell transplantation, or diabetes secondary to pancreatitis or pancreatectomy; on an antihyperglycaemic agent and not on a stable regimen (ie agents and doses) for at least 8 weeks before the screening visit and through the screening/run-in period (note: a stable dose of insulin was defined as no change in the insulin regimen and no more than 15% change in the total daily dose of insulin averaged over 1 week); fasting fingerstick glucose at home or at investigational site >270 mg/dL (>15 mmol/L) at baseline/day 1; for people on a sulfonylurea agent or on insulin: fingerstick glucose at home or at investigational site <110mg/dL (<6 mmol/L) at baseline/day 1 (note: at the investigator's discretion, based upon an assessment of recent self-monitored blood glucose values, subjects meeting either of these fingerstick glucose exclusion criteria could continue the single-blind placebo and return to the investigational site within 14 days and were eligible to be randomised if the repeat fasting fingerstick value no longer met the exclusion criterion. People with fingerstick glucose >270mg/dL (>15 mmol/L) were able to have their antihyperglycaemic regimen adjusted, and be rescreened once on e a stable regimen for at least 8 weeks); history of one or more severe hypoglycaemic episode within 6 months before screening (note: a severe hypoglycaemic episode was defined as an event that required the help of another person); history of hereditary glucose-galactose malabsorption or primary renal glucosuria; ongoing, inadequately controlled thyroid disorder (note: subjects on thyroid hormone replacement therapy were required to be on a stable dose for at least 6 weeks before day 1); renal disease that required treatment with immunosuppressive therapy or a history of chronic dialysis or renal transplant (note: people with a history of treated childhood renal disease, without sequelae, were eligible to participate); myocardial infarction, unstable angina, revascularisation procedure or cerebrovascular accident within 3 months before screening, or a planned revascularisation procedure, or history of New York Heart Association class IV cardiac disease; findings on a 12-lead electrocardiogram that would require urgent diagnostic evaluation or intervention (e.g., new clinically important arrhythmia or conduction disturbance); myocardial infarction, unstable angina, revascularisation procedure, or cerebrovascular accident within 3 months before screening, or a planned revascularisation procedure, or history of New York Heart Association Class IV cardiac disease; findings on a 12-lead electrocardiovascular that would require urgent diagnostic evaluation or intervention (e.g., new clinically important arrhythmia or conduction disturbance); history of hepatitis B surface antigen or hepatitis C antibody positive (unless associated with documented persistently stable/normal range aspartate aminotransferase and alanine aminotransferase levels), or other clinically active liver disease; any history of or planned bariatric surgery; estimated glomerular filtration rate <30mL/min per 1.73m2 at screening (provided by the central laboratory); for people taking metformin: at screening, serum creatinine at least 1.4mg/dL (124 micromol/L) for men or at least 1.3mg/dL (115 micromol/L) for women; no contraindication to the use of metformin (including eGFR) based on the label of the country of investigational site; alanine aminotransferase levels >2.0 times the upper limit of normal or total bilirubin >1.5 times the upper limit of normal at screening, unless in the opinion of the investigator and as agreed upon by the sponsor's medical officer, the findings are consistent with Gilbert's disease; history of malignancy within 5 years before screening (exceptions: squamous and

	basal cell carcinomas of the skin and carcinoma of the cervix in situ, or a malignancy that in the opinion of the investigator, with concurrence with the sponsor's medical monitor, is considered cured with minimal risk of recurrence); history of HIV antibody positive; a current clinically important hematological disorder (e.g., symptomatic anaemia, proliferative bone marrow disorder, thrombocytopenia); investigator's assessment that the subject's life expectance is less than 1 year, or any condition that in the opinion of the investigator would make participation not in the best interest of the subject, or could prevent, limit or confound the protocol-specified safety or efficacy assessments; major surgery (ie, requiring general anaesthesia) within 3 months of the screening visit or any surgery planned during the subject's expected participation in the study (except minor surgery, ie, outpatient surgery under local anaesthesia); any condition that, in the opinion of the investigator, would compromise the wellbeing of the subject or prevent the subject from meeting or performing study requirements; current use of other SGLT2 inhibitor; use of rosiglitazone within 8 weeks of screening (note: subjects identified as taking rosiglitazone who were already in screening were not eligible for randomisation); known allergies, hypersensitivity or intolerance to canagliflozin or its excipients; current use of a corticosteroid medication or immunosuppresive agent, or likely to require treatment with a corticosteroid medication (for longer than 2 weeks in duration) or an immunosuppressive agent (note: subjects using inhaled, intranasal, intra-articular or topical corticosteroids, or corticosteroids in therapeutic replacement doses may participate); received an active investigational drug (including vaccines) or used an investigational medical device within 3 months before day 1/baseline or received at least one dose of canagliflozin in a prior study; history of drug or alcohol abuse within 3 years before screening; pregnant or breast-feeding or planning to become pregnant or breast-feed during the study; employees of the investigator or study centre, with direct involvement in the proposed study or other studies under the direction of that investigator or study centre, as well as family members of the employees or the investigator (note: investigators were required at randomisation to assure that all study enrolment criteria had been met and determined that the subject has not had any interval change in clinical status since screening. Before randomisation, subjects whose status changed after screening, such that they now met an exclusion criteria, were excluded from participation).
Recruitment / selection of participants	Recruitment at 386 centres in 24 countries. A primary prevention and secondary prevent cohort was recruited.
Intervention(s)	Canagliflozin N=5795 Oral canagliflozin 100mg once a day or 300mg once a day (groups combined in the study analysis). Mean duration of follow up was 188 weeks.
Cointervention	Concomitant therapy: Use of other background therapy for glycaemic management and other risk factor control was according to best practice instituted in line with local guidelines.
Strata 1: People with	People without heart failure 11% of people had heart failure

type 2 diabetes mellitus and heart failure	
Strata 2: People with atherosclerotic cardiovascular disease	Mixed population Two thirds of the population were receiving secondary prevention for cardiovascular disease, one third were receiving primary prevention
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Excluded "Estimated glomerular filtration rate (eGFR) <30 mL/min per 1.73m2 at screening" otherwise unclear.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	People at higher risk of developing cardiovascular disease
Subgroup 1: People with 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 the mean eGFR, it would be very unlikely that the majority of the population did not have an eGFR >30.

Subgroup 6: Albuminuria category at baseline	Mixed population Based on the interquartile range between A1 and A2 - therefore at least 25% of the population are in A2.
Population subgroups	Primary and secondary prevention - Mahaffey 2018 History of heart failure - Radholm 2018 eGFR categories - Neuen 2018 KDIGO risk categories - Neuen 2020 Canagliflozin and sulfonylureas - Fulcher 2015, Yale 2017 Canagliflozin and DPP4 inhibitors, Canagliflozin and GLP-1 receptor agonists - Fulcher 2016 Canagliflozin and insulin - Neal 2015
Comparator	Placebo N=4347 Oral matching placebo once a day. Mean duration of follow up was 188 weeks. Concomitant therapy: Use of other background therapy for glycaemic management and other risk factor control was according to best practice instituted in line with local guidelines.
Number of participants	4327
Duration of follow-up	Mean: 188 weeks.
Indirectness	No additional information.
Method of analysis	Per protocol For safety outcomes only ITT
Additional comments	Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated for participants; Cardiovascular, death, and safety outcomes were analysed using a stratified Cox proportional hazards regression model; Renal outcomes were analysed using a stratified Cox proportional hazards model with treatment and the stage of baseline chronic kidney disease measured by estimated glomerular filtration rate (<60 or ≥60 mL/min/1.73 m2) as the exploratory variables and study as the stratification factor. Homogeneity of treatment effects across the primary and secondary prevention groups was examined via a test for the treatment-by-prevention interaction by adding

	this term and the prevention cohort as covariates to the respective Cox proportional hazards model. The risk differences were calculated by subtracting the incidence rate (per 1000 patient-years) with placebo from the incidence rate with canagliflozin and multiplying by 5 years. Similarly, the CI was estimated by multiplying the lower and upper CI values by 5 years.

289.2. Study arms

289.2.1. Canagliflozin (N = 5795)

Oral canagliflozin 100mg once a day or 300mg once a day (groups combined in the study analysis). Mean duration of follow up was 188 weeks. Concomitant therapy: Use of other background therapy for glycaemic management and other risk factor control was according to best practice instituted in line with local guidelines.

289.2.2. Placebo (N = 4347)

Oral matching placebo once a day. Mean duration of follow up was 188 weeks. Concomitant therapy: Use of other background therapy for glycaemic management and other risk factor control was according to best practice instituted in line with local guidelines.

289.3. Characteristics

289.3.1. Arm-level characteristics

Characteristic	Canagliflozin (N = 5795)	Placebo (N = 4347)
% Male Sample size	n = 3759 ; % = 65	n = 2750 ; % = 63
Mean age (SD) (years) Mean (SD)	63.2 (8.3)	63.5 (8.2)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 4508 ; % = 78	n = 3436 ; % = 79
Asian Sample size	n = 777 ; % = 13	n = 507 ; % = 12

Characteristic	Canagliflozin (N = 5795)	Placebo (N = 4347)
Black or African American Sample size	n = 176 ; % = 3	n = 160 ; % = 4
Other Sample size	n = 334 ; % = 6	n = 244 ; % = 6
Comorbidities Sample size	n = NA ; % = NA	n = NA ; % = NA
History of hypertension Sample size	n = 5188 ; % = 90	n = 3937 ; % = 91
History of heart failure Sample size	n = 803 ; % = 14	n = 658 ; % = 15
Retinopathy Sample size	n = 1203 ; % = 21	n = 926 ; % = 21
Nephropathy Sample size	n = 994 ; % = 17	n = 780 ; % = 18
Neuropathy Sample size	n = 1787 ; % = 31	n = 1323 ; % = 30
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	13.5 (7.7)	13.7 (7.8)
HbA1c Mean (SD)	NR (NR)	NR (NR)
Cardiovascular risk factors Sample size	n = NA ; % = NA	n = NA ; % = NA
History of myocardial infarction Sample size	n = 1660 ; % = 29	n = 1296 ; % = 30
History of hospitalisation for unstable angina Sample size	n = 402 ; % = 7	n = 325 ; % = 8

Characteristic	Canagliflozin (N = 5795)	Placebo (N = 4347)
History of coronary revascularisation Sample size	n = 1999 ; % = 35	n = 1565 ; % = 36
History of stroke Sample size	n = 739 ; % = 13	n = 552 ; % = 13
History of carotid revascularisation Sample size	n = 47 ; % = 0.8	n = 32 ; % = 0.7
History of peripheral revascularisation Sample size	n = 274 ; % = 5	n = 251 ; % = 6
History of amputation Sample size	n = 136 ; % = 2	n = 102 ; % = 2
Current smoker Sample size	n = 1020 ; % = 18	n = 786 ; % = 18
Blood pressure (mmHg) Mean (SD)	NA (NA)	NA (NA)
Systolic blood pressure Mean (SD)	136.5 (15.8)	136.9 (15.8)
Diastolic blood pressure Mean (SD)	77.7 (9.7)	77.8 (9.7)
Heart rate Mean (SD)	NR (NR)	NR (NR)
Smoking status Sample size	n = 1020 ; % = 18	n = 786 ; % = 18
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Canagliflozin (N = 5795)	Placebo (N = 4347)
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR
Weight Mean (SD)	NR (NR)	NR (NR)
BMI (kg/m2) Sample size	n = NR ; % = NR	n = NR ; % = NR
BMI (kg/m2) Mean (SD)	31.9 (6)	32 (6)
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR
Cholesterol and lipid levels Mean (SD)	NA (NA)	NA (NA)
Total cholesterol mmol/L Mean (SD)	4.7 (1.2)	4.4 (1.2)
Triglycerides mmol/L Mean (SD)	2 (1.3)	2 (1.6)
HDL cholesterol mmol/L Mean (SD)	1.2 (0.3)	1.2 (0.3)
LDL cholesterol mmol/L Mean (SD)	2.3 (0.9)	2.3 (0.9)
Albumin creatinine ratio Median (IQR)	NR (NR to NR)	NR (NR to NR)
Secondary prevention Canagliflozin n=3756. Placebo n=2900. Median (IQR)	12.4 (6.6 to 42.3)	12.1 (6.6 to 43.4)
Primary prevention Canagliflozin n=2039. Placebo n=1447. Median (IQR)	12.3 (6.8 to 40)	12.4 (6.6 to 45.2)

Characteristic	Canagliflozin (N = 5795)	Placebo (N = 4347)
eGFR mL/min/1.73m2 (ml/min/1.73 m2) Mean (SD)	76.7 (20.3)	76.2 (20.9)
Other antidiabetic medication used See drug therapy received during trial Sample size	n = NA ; % = NA	n = NA ; % = NA
Blood pressure-lowering medication used See drug therapy received during trial Sample size	n = NA ; % = NA	n = NA ; % = NA
Statins/lipid-lowering medication used See drug therapy received during trial Sample size	n = NA ; % = NA	n = NA ; % = NA
Other treatment being received See drug therapy received during trial Sample size	n = NA ; % = NA	n = NA ; % = NA
Drug therapy received during trial Sample size	n = NA ; % = NA	n = NA ; % = NA
Insulin Sample size	n = 2890 ; % = 50	n = 2205 ; % = 51
Sulfonylurea Sample size	n = 2528 ; % = 44	n = 1833 ; % = 42
Metformin Sample size	n = 4447 ; % = 77	n = 3378 ; % = 78
GLP-1 receptor agonist Sample size	n = 222 ; % = 4	n = 185 ; % = 4
DPP-4 inhibitor Sample size	n = 697 ; % = 12	n = 564 ; % = 13
Statin Sample size	n = 4330 ; % = 75	n = 3270 ; % = 75
Antithrombotic Sample size	n = 4236 ; % = 73	n = 3235 ; % = 74

Characteristic	Canagliflozin (N = 5795)	Placebo (N = 4347)
RAAS inhibitor Sample size	n = 4645 ; % = 80	n = 3471 ; % = 80
Beta-blocker Sample size	n = 3039 ; % = 52	n = 2382 ; % = 55
Diuretics Sample size	n = 2536 ; % = 44	n = 1954 ; % = 45
Calcium channel blocker Sample size	n = 1930 ; % = 33	n = 1513 ; % = 35

290. Mann, 2017

Bibliographic Reference	Mann, Johannes F E; Orsted, David D; Brown-Frandsen, Kirstine; Marso, Steven P; Poulter, Neil R; Rasmussen, Soren; Tornoe, Karen; Zinman, Bernard; Buse, John B; Liraglutide and Renal Outcomes in Type 2 Diabetes.; The New England journal of medicine; 2017; vol. 377 (no. 9); 839-848

290.1. Study details

Secondary publication of another included study- see primary study for details	Parent study: Marso et al (2016) Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. The New England journal of medicine; 2016; vol. 375 (no. 4); 311-22
Other publications associated with this study included in review	Marso et al (2013). Design of the liraglutide effect and action in diabetes: evaluation of cardiovascular outcome results (LEADER) trial. American heart journal; 2013; vol. 166 (no. 5); 823-30e5 Marso et al (2020) Effects of Liraglutide on Cardiovascular Outcomes in Patients With Diabetes With or Without Heart Failure. Journal of the American College of Cardiology; 2020; vol. 75 (no. 10); 1128-1141
Trial name / registration number	LEADER trial. ClinicalTrials.gov number, NCT01179048

291. Marre, 2009

Bibliographic Reference	Marre, M.; Shaw, J.; Brändle, M.; Bebakar, W. M.; Kamaruddin, N. A.; Strand, J.; Zdravkovic, M.; Thi, T. D.; Colagiuri, S.; Liraglutide, a once-daily human GLP-1 analogue, added to a sulphonylurea over 26 weeks produces greater improvements in glycaemic and weight control compared with adding rosiglitazone or placebo in subjects with Type 2 diabetes (LEAD-1 SU); Diabet Med; 2009; vol. 26 (no. 3); 268-78

291.1. 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	LEAD-1
Study type	Randomised controlled trial (RCT)
Study location	The study was conducted at 116 sites in 21 countries which were primarily in Europe and Asia.
Study setting	Hospital
Study dates	No additional information.
Sources of funding	Novo Nordisk
Inclusion criteria	• Type 2 diabetes treated with oral glucose-lowering agents for ≥ 3 months; • 18–80 years of age; • HbA1c 7.0–11.0% (previous oral glucose lowering monotherapy) or 7.0–10.0% (previous oral glucose-lowering agent combination therapy); BMI ≤ 45.0 kg/m2 .

Exclusion criteria	• Used insulin within 3 months, impaired liver or renal function • Uncontrolled hypertension (≥ 180/100 mmHg), cancer or used any drugs apart from oral glucose lowering agents likely to affect glucose concentrations. Subjects provided written informed consent. The study was conducted in accordance with good clinical practice guidelines and approved by independent ethics committees.
Recruitment / selection of participants	Adult patients with type 2 diabetes were enrolled from 116 sites in 21 countries
Intervention(s)	Liraglutide 0.6 - 1.8 mg daily administered subcutaneously.
Cointervention	Monotherapy or combination antidiabetic therapy prior to beginning the trial. All patients were receiving glimepiride during the trial.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with	Not stated/unclear

moderate or severe frailty	
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Comparator	Placebo administered daily, orally. N.B. rosiglitazone was also assessed in this study as a comparator to liraglutide however it does not meet the scope of this review so has not been included.
Number of participants	N=809
Duration of follow-up	26-week
Indirectness	
Method of analysis	Modified ITT

291.2. Study arms

291.2.1. Liraglutide 0.6 mg daily (N = 233)

Administered subcutaneously

291.2.2. Liraglutide 1.2 mg daily (N = 228)

Administered subcutaneously

291.2.3. Liraglutide 1.8 mg daily (N = 234)

Administered subcutaneously

291.2.4. Placebo daily (N = 114)

Administered orally

291.3. Characteristics

291.3.1. Arm-level characteristics

Characteristic	Liraglutide 0.6 mg daily (N = 233)	Liraglutide 1.2 mg daily (N = 228)	Liraglutide 1.8 mg daily (N = 234)	Placebo daily (N = 114)
% Male No of events	n = 126 ; % = 54	n = 103 ; % = 45	n = 124 ; % = 53	n = 54 ; % = 47
Mean age (SD) Mean (SD)	55.7 (9.9)	57.7 (9)	55.6 (10)	54.7 (10)
Ethnicity Nominal	NR	NR	NR	NR
Presence of frailty Nominal	NR	NR	NR	NR
Time since type 2 diabetes diagnosed (years) Median (IQR)	6.5 (4 to 100.2)	6.7 (4 to 10.7)	6.5 (3.7 to 10.5)	6.5 (4.5 to 10.6)
Smoking status Nominal	NR	NR	NR	NR
Alcohol consumption Nominal	NR	NR	NR	NR

Characteristic	Liraglutide 0.6 mg daily (N = 233)	Liraglutide 1.2 mg daily (N = 228)	Liraglutide 1.8 mg daily (N = 234)	Placebo daily (N = 114)
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
Albumin creatinine ratio Nominal	NR	NR	NR	NR
Glimepiride No of events	n = 233 ; % = 100	n = 228 ; % = 100	n = 234 ; % = 100	n = 114 ; % = 100
Statins/lipid-lowering medication used Nominal	NR	NR	NR	NR
Other treatment being received Nominal	NR	NR	NR	NR