

## Type 2 diabetes in adults: management (medicines update)

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

*NICE guideline GID-NG10336*

*Evidence reviews underpinning recommendations 1.8.6-1.8.32, 1.8.34, 1.8.38-1.8.60 and recommendations for research in the NICE guideline*

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*Draft for Consultation*

*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.

## 291. Marso S, 2020

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

### 291.1. Study details

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

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

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



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

## 291.2. Study arms

### 291.2.1. Liraglutide (N = 4668)

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

### 291.2.2. Placebo (N = 4672)

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

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

## 292. Marso Steven, 2016

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

### 292.1. Study details

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

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

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

<b>type 2 diabetes mellitus and chronic kidney disease</b>	Overall 28.5% participants with eGFR below 60 ml/min/1.73 m <sup>2</sup> .  353 (10.7%) had CKD only, 442 (13.4%) had both CVD and CKD (therefore 795 (24.1%) had CKD in total).
<b>Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk</b>	People at higher risk of developing cardiovascular disease  Participants were aged 50 + with history of CV disease, or 60+ with one or more CV risk factors (see inclusion criteria).  Overall 92.8% with hypertension.
<b>Subgroup 1: People with moderate or severe frailty</b>	Not stated/unclear
<b>Subgroup 2: Onset of type 2 diabetes mellitus</b>	Not stated/unclear
<b>Subgroup 3: People with non-alcoholic fatty liver disease</b>	Not stated/unclear  People with end-stage liver disease were excluded (see appendix)
<b>Subgroup 4: People with obesity</b>	Not stated/unclear
<b>Subgroup 5: eGFR category at baseline</b>	eGFR ≥30mL/min/1.73m <sup>2</sup>  baseline characteristics show that only 3.3% were <30ml/min/1.73m <sup>2</sup>
<b>Subgroup 6: Albuminuria category at baseline</b>	Not stated/unclear
<b>Population subgroups</b>	For primary composite outcome only (3 item MACE - death from cardiovascular causes, nonfatal MI or nonfatal stroke) for the following baseline characteristics:  sex, age (<65 years/≥ 65 years), BMI (≤ 30kg/m <sup>2</sup> />30kg/m <sup>2</sup> ), HbA1c (≤8.5%/>8.5%), duration of diabetes (≤10 years/>10 years), region (USA/EU/rest of world), race (Asian, Black/African-American/White/Other), ethnicity (Hispanic or Latino/ not Hispanic or Latino), chronic heart failure NY Heart Association class II-III), prior MI/stroke, CV disease status (established CV disease/CV risk factors), insulin treatment (pre-mixed

	/basal/none), eGFR <30 ml/min/1.73 <sup>2</sup> (MDRD), eGFR <60 ml/min/1.73 <sup>2</sup> (MDRD)
	MDRD=modification of diet in renal disease
<b>Comparator</b>	<p>Placebo 0.5 mg N=824</p> <p>Volume-matched placebo. 0.5 mg subcutaneous injection once weekly. Starting dose of 0.25 mg for 4 weeks, then escalated to 0.5 mg for 4 weeks. Treatment period = 104 weeks.</p> <p>Placebo 1.0 mg N=825</p> <p>Volume-matched placebo. 1.0 mg subcutaneous injection once per week. Starting dose of 0.25 mg for 4 weeks. Escalated to 0.5 mg for 4 weeks, then escalated to 1.0 mg. Treatment period = 104 weeks.</p> <p>Placebo 0.5mg and 1.0mg combined N=1649</p>
<b>Number of participants</b>	3297
<b>Duration of follow-up</b>	<p>104 week treatment period with 5 week follow up.</p> <p>Median observation time was 2.1 years.</p>
<b>Indirectness</b>	No additional information.
<b>Method of analysis</b>	ITT
<b>Additional comments</b>	All results analysed using ITT, except for adverse events leading to premature treatment discontinuation, which were included in the as-treated safety analysis.

## 292.2. Study arms

### 292.2.1. Semaglutide 0.5 mg (N = 826)

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

**292.2.2. Semaglutide 1.0 mg (N = 822)**

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

**292.2.3. Placebo 0.5 mg (N = 824)**

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

**292.2.4. Placebo 1.0 mg (N = 825)**

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

**292.2.5. Semaglutide 0.5mg and 1.0mg combined (N = 1648)****292.2.6. Placebo 0.5mg and 1.0mg combined (N = 1649)****292.3. Characteristics****292.3.1. Arm-level characteristics**

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



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

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

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

Characteristic	Semaglutide 0.5 mg (N = 826)	Semaglutide 1.0 mg (N = 822)	Placebo 0.5 mg (N = 824)	Placebo 1.0 mg (N = 825)	Semaglutide 0.5mg and 1.0mg combined (N = 1648)	Placebo 0.5mg and 1.0mg combined (N = 1649)
<b>Cholesterol and lipid levels</b> (mg/dL)	NA (NA)	NA (NA)	NA (NA)	NA (empty data)	NA (NA)	NA (NA)
Mean (SD)						
<b>LDL cholesterol</b> Geometric mean and coefficient of variation	81.6 (47.1)	83.3 (41.2)	80.9 (48.1)	83.6 (48.1)	NA (NA)	NA (NA)
Mean (SD)						
<b>HDL cholesterol</b> Geometric mean and coefficient of variation	44.2 (27.76)	43.4 (26.9)	44.2 (27.3)	43.1 (26.3)	NA (NA)	NA (NA)
Mean (SD)						
<b>Albumin creatinine ratio</b>	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)
Mean (SD)						
<b>eGFR</b> <b>mL/min/1.73m<sup>2</sup></b>	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Sample size						
<b>Normal</b> <b>eGFR ≥90</b>	n = 247 ; % = 29.9	n = 246 ; % = 29.9	n = 245 ; % = 29.7	n = 252 ; % = 30.5	n = NA ; % = NA	n = NA ; % = NA
Sample size						
<b>Mild renal impairment</b> <b>eGFR 60 - &lt;90</b>	n = 329 ; % = 39.8	n = 357 ; % = 43.4	n = 336 ; % = 40.8	n = 346 ; % = 41.9	n = NA ; % = NA	n = NA ; % = NA
Sample size						
<b>Moderate renal impairment</b> <b>eGFR 30 - &lt;60</b>	n = 229 ; % = 27.7	n = 194 ; % = 23.6	n = 215 ; % = 26.1	n = 194 ; % = 23.5	n = NA ; % = NA	n = NA ; % = NA
Sample size						

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

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

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

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



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

## 293. Marso Steven, 2016

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

### 293.1. Study details

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

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

<b>atherosclerotic cardiovascular disease</b>	Inclusion was history of CVD or CV risk factors. Majority had established cardiovascular disease (7598/9340 = 81.3%) - however, established CVD definition could include HF and CKD too, proportion with CVD alone likely to be <80% (2307 of these had CKD stage 3, with 1473 of these having both CKD and CVD, therefore 2307-1473=834 had CKD alone; therefore 7598-834=6764 had CVD (not including those with CKD alone); 6764/9340=72.4% likely to have CVD when definition doesn't include those with CKD alone).
<b>Strata 3: People with type 2 diabetes mellitus and chronic kidney disease</b>	Not stated/unclear  Baseline characteristics state 25% had chronic kidney disease but based on eGFR not CKD diagnosis.
<b>Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk</b>	People at higher risk of developing cardiovascular disease
<b>Subgroup 1: People with moderate or severe frailty</b>	Not stated/unclear
<b>Subgroup 2: Onset of type 2 diabetes mellitus</b>	People with type 2 diabetes first diagnosed above 40 years of age  Most likely based on mean age and mean diabetes duration
<b>Subgroup 3: People with non-alcoholic fatty liver disease</b>	Not stated/unclear
<b>Subgroup 4: People with obesity</b>	People with obesity  Mean BMI 32.5
<b>Subgroup 5: eGFR category at baseline</b>	eGFR $\geq 30$ mL/min/1.73m <sup>2</sup>  baseline characteristics show that only 2.4% were <30 mL/min/1.73m <sup>2</sup>
<b>Subgroup 6: Albuminuria</b>	Not stated/unclear

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

## 293.2. Study arms

### 293.2.1. Liraglutide (N = 4668)

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

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

### 293.2.2. Placebo (N = 4672)

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

## 293.3. Characteristics

### 293.3.1. Arm-level characteristics

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

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

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



<b>Characteristic</b>	<b>Liraglutide (N = 4668)</b>	<b>Placebo (N = 4672)</b>
<b>Alcohol consumption</b>		
Sample size	n = NA ; % = NA	n = NA ; % = NA
<b>Presence of severe mental illness</b>		
Sample size	n = NA ; % = NA	n = NA ; % = NA
<b>People with significant cognitive impairment</b>		
Sample size	n = NR ; % = NR	n = NR ; % = NR
<b>People with a learning disability</b>		
Sample size	n = NR ; % = NR	n = NR ; % = NR
<b>Weight</b>		
Mean (SD)	NR (NR)	NR (NR)
<b>BMI ( kg/m<sup>2</sup>)</b>		
Mean (SD)	32.5 (6.3)	32.5 (6.3)
<b>Number of people with obesity</b>		
Sample size	n = NR ; % = NR	n = NR ; % = NR
<b>Albumin creatinine ratio</b>		
Mean (SD)	NR (NR)	NR (NR)
<b>eGFR mL/min/1.73m<sup>2</sup></b>		
Sample size	n = NR ; % = NR	n = NR ; % = NR
<b>Normal (eGFR &gt;90)</b>		
Sample size	n = 1620 ; % = 34.7	n = 1655 ; % = 35.4
<b>Mild impairment (eGFR 60-89)</b>		
Sample size	n = 1932 ; % = 41.4	n = 1975 ; % = 42.3
<b>Moderate impairment (eGFR 30-59)</b>		
Sample size	n = 999 ; % = 21.4	n = 935 ; % = 20
<b>Severe impairment (eGFR &lt;30)</b>		
Sample size	n = 117 ; % = 2.5	n = 107 ; % = 2.3
<b>Other antidiabetic medication used</b>		
Sample size	n = 4113 ; % = 88.1	n = 4129 ; % = 88.4

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

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

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

## 294. Marso, 2013

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

### 294.1. Study details

<b>Secondary publication of another included study- see primary study for details</b>	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
<b>Other publications associated with this study included in review</b>	<p>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</p> <p>Mann et al (2017) Liraglutide and Renal Outcomes in Type 2 Diabetes. The New England journal of medicine; 2017; vol. 377 (no. 9); 839-848</p>
<b>Trial name / registration number</b>	LEADER trial. ClinicalTrials.gov number, NCT01179048

## 295. Marx, 2015

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

### 295.1. Study details

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

## 296. Mathieu, 2016

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

### 296.1. Study details

<b>Secondary publication of another included study- see primary study for details</b>	Mathieu 2015  Mathieu C, Ranetti AE, Li D, Ekholm E, Cook W, Hirshberg B, Chen H, Hansen L, Iqbal N. Randomized, Double-Blind, Phase 3 Trial of Triple Therapy With Dapagliflozin Add-on to Saxagliptin Plus Metformin in Type 2 Diabetes. Diabetes Care. 2015 Nov;38(11):2009-17. doi: 10.2337/dc15-0779. Epub 2015 Aug 5. PMID: 26246458.
<b>Strata 1: People with type 2 diabetes mellitus and heart failure</b>	Not stated/unclear
<b>Strata 2: People with atherosclerotic cardiovascular disease</b>	Not stated/unclear
<b>Strata 3: People with type 2 diabetes mellitus and chronic kidney disease</b>	Not stated/unclear
<b>Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk</b>	Not stated/unclear

## 297. Mathieu, 2014

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

### 297.1. Study details

<b>Secondary publication of another included study- see primary study for details</b>	No additional information.
<b>Other publications associated with this study included in review</b>	No additional information.
<b>Trial name / registration number</b>	No additional information.
<b>Study type</b>	Randomised controlled trial (RCT)
<b>Study location</b>	Multicenter trial.
<b>Study setting</b>	Outpatient follow-up.
<b>Study dates</b>	September 2011-July 2012.
<b>Sources of funding</b>	Sponsored by Novo Nordisk A/S.
<b>Inclusion criteria</b>	Informed consent; completed the end-of-treatment visit of trial NN1250-3643 with insulin degludec once daily and metformin; ability and willingness to adhere to the protocol including self-measurement of plasma glucose according to the protocol.
<b>Exclusion criteria</b>	Known or suspected hypersensitivity to trial product(s) or related products; previous participation in the trial; participated in NN1250-3643 and was treated with insulin glargine + metformin +/- DPP-4 inhibitor or insulin degludec + metformin + DPP-4 inhibitor; previous treatment with GLP-1 receptor agonist; impaired liver function (ALT at least 2.5 times the upper limit of normal at the end of treatment in NN1250-3643); impaired renal



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

<b>type 2 diabetes mellitus and high cardiovascular risk</b>	
<b>Subgroup 1: People with moderate or severe frailty</b>	Not stated/unclear
<b>Subgroup 2: Onset of type 2 diabetes mellitus</b>	Not stated/unclear
<b>Subgroup 3: People with non-alcoholic fatty liver disease</b>	People without non-alcoholic fatty liver disease Based on exclusion criteria
<b>Subgroup 4: People with obesity</b>	Not stated/unclear
<b>Subgroup 5: eGFR category at baseline</b>	Not stated/unclear
<b>Subgroup 6: Albuminuria category at baseline</b>	Not stated/unclear
<b>Population subgroups</b>	No additional information.
<b>Comparator</b>	<p>Insulin degludec/insulin aspart N=89</p> <p>Insulin aspart was started at 4 U once a day before the largest daily meal. Insulin aspart was titrated once weekly based on the mean of three pre-meal or bedtime SMBG values. Everyone continued insulin degludec as per the previous trial with the dose being titrated according to pre-breakfast plasma glucose levels. Treatments were received for 24 weeks.</p> <p>A third arm (n=236) received insulin degludec only. This arm was not included in this data extraction and analysis as the arm was a non-randomised treatment arm.</p>

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

## 297.2. Study arms

### 297.2.1. Insulin degludec/liraglutide (N = 88)

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

### 297.2.2. Insulin degludec/insulin aspart (N = 89)

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

## 297.3. Characteristics

### 297.3.1. Arm-level characteristics

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

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

Characteristic	Insulin degludec/liraglutide (N = 88)	Insulin degludec/insulin aspart (N = 89)
Sample size		
<b>Blood pressure-lowering medication used</b>	n = NR ; % = NR	n = NR ; % = NR
Sample size		
<b>Statins/lipid-lowering medication used</b>	n = NR ; % = NR	n = NR ; % = NR
Sample size		
<b>Other treatment being received</b>	n = NR ; % = NR	n = NR ; % = NR
Sample size		

## 298. Mathieu, 2015

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

### 298.1. Study details

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

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



	<p>Patients with systolic blood pressure <math>\geq 160</math> mm Hg or a diastolic blood pressure <math>\geq 90</math> mm Hg. Patient may have blood pressure medication adjusted and may be enrolled if the patient's blood pressure no longer meets exclusion criteria.</p> <p>Patients with human immunodeficiency virus</p> <p>Patients with severe peripheral vascular disease</p> <p>Patients with clinically important hematological disorder (such as aplastic anemia, myeloproliferative or myelodysplastic syndromes, thrombocytopenia).</p> <p>Patients with a history of malignancy <math>\leq 5</math> years prior to signing informed consent, except for adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer.</p> <p>Laboratory exclusion criteria included serum creatinine <math>\geq 1.4</math> mg/dL (males) or <math>\geq 1.3</math> mg/dL (females), an estimated glomerular filtration rate <math>&lt; 60</math> mL/min/1.73 m<sup>2</sup> (calculated by modification of diet in renal disease equation), alanine aminotransferase or aspartate aminotransferase <math>&gt; 2</math> times the upper limit of normal, hemoglobin <math>&lt; 12</math> g/dL (male) or <math>&lt; 11</math> g/dL (female), triglycerides <math>&gt; 600</math> mg/dL or thyroid-stimulating hormone outside the normal range</p>
<b>Recruitment / selection of participants</b>	No additional information
<b>Intervention(s)</b>	<p>Sitagliptin (n=329)</p> <p>Patients received 100 mg once daily sitagliptin as an oral tablet for 24 weeks</p>
<b>Cointervention</b>	<p>Insulin +/- metformin</p> <p>Open-label insulin glargine will be titrated in a treat-to target algorithm outlined in the protocol</p> <p>The dose of metformin will remain stable throughout the study period if patient was receiving metformin at Visit 1.</p>
<b>Strata 1: People with type 2 diabetes mellitus and heart failure</b>	People without heart failure

<b>Strata 2: People with atherosclerotic cardiovascular disease</b>	People without atherosclerotic cardiovascular diseases
<b>Strata 3: People with type 2 diabetes mellitus and chronic kidney disease</b>	Not stated/unclear  Exclusion criteria based on eGFR but no specific mention of CKD
<b>Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk</b>	Not stated/unclear
<b>Subgroup 1: People with moderate or severe frailty</b>	Not stated/unclear
<b>Subgroup 2: Onset of type 2 diabetes mellitus</b>	Not stated/unclear
<b>Subgroup 3: People with non-alcoholic fatty liver disease</b>	Not stated/unclear
<b>Subgroup 4: People with obesity</b>	Not stated/unclear
<b>Subgroup 5: eGFR category at baseline</b>	Not stated/unclear
<b>Subgroup 6: Albuminuria category at baseline</b>	Not stated/unclear

<b>Population subgroups</b>	NA
<b>Comparator</b>	<p>Placebo (n=329)</p> <p>Patients received the placebo as a single oral tablet for 24 weeks.</p> <p>Open-label insulin glargine will be titrated in a treat-to target algorithm outlined in the protocol</p> <p>The dose of metformin will remain stable throughout the study period if patient was receiving metformin at Visit 1.</p>
<b>Number of participants</b>	660
<b>Duration of follow-up</b>	24 weeks
<b>Indirectness</b>	NA
<b>Method of analysis</b>	ITT
<b>Additional comments</b>	<p>The population for all efficacy analyses consisted of all randomized patients who received at least one dose of study medication and had at least one measurement of the analysis endpoint at or after baseline.</p> <p>The primary efficacy endpoint, mean change from baseline in daily insulin dose at Week 24, was compared between the sitagliptin group and the placebo group using a longitudinal data analysis model with a constraint that both groups came from a single population with a common baseline mean. The model adjusted for the patients' use of metformin at the screening visit.</p> <p>Missing outcome data were handled implicitly by the model without the need for imputation. In the analysis model, the daily insulin dose for any given week was defined as the average dose from the three most recent days preceding the index date for that week. The continuous secondary endpoints of mean change from baseline in HbA1c at week 24 were analysed using a model analogous to that for the primary endpoint, including the time points of Weeks 0, 6, 12, 18, and 24.</p>

## 298.2. Study arms

### 298.2.1. Sitagliptin (N = 330)

Patients received 100 mg sitagliptin once daily for 24 weeks

**298.2.2. Placebo (N = 330)**

Patients received once daily placebo

**298.3. Characteristics****298.3.1. Arm-level characteristics**

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

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



## 299. Mathieu, 2015

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

### 299.1. Study details

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

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



<b>type 2 diabetes mellitus and chronic kidney disease</b>	Exclusion criteria based on eGFR and serum creatinine but no explicit mention on CKD
<b>Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk</b>	Not stated/unclear
<b>Subgroup 1: People with moderate or severe frailty</b>	Not stated/unclear
<b>Subgroup 2: Onset of type 2 diabetes mellitus</b>	Not stated/unclear
<b>Subgroup 3: People with non-alcoholic fatty liver disease</b>	Not stated/unclear
<b>Subgroup 4: People with obesity</b>	Not stated/unclear
<b>Subgroup 5: eGFR category at baseline</b>	Not stated/unclear
<b>Subgroup 6: Albuminuria category at baseline</b>	Not stated/unclear
<b>Population subgroups</b>	NA
<b>Comparator</b>	<p>Placebo (n=160)</p> <p>Patients receive daily placebo as an add-on to 5 mg sitagliptin daily and ≥1500 mg metformin daily for 52 weeks</p>

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

## 299.2. Study arms

### 299.2.1. Dapagliflozin (N = 160)

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

### 299.2.2. Placebo (N = 160)

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

## 299.3. Characteristics

### 299.3.1. Arm-level characteristics

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

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



## 300. Matthaei, 2015

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

### 300.1. Study details

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

<b>Exclusion criteria</b>	Patients were excluded from the study if they had a diagnosis of type 1 diabetes, BMI $\geq 45.0$ kg/m <sup>2</sup> , measured serum creatinine value of $\geq 1.5$ mg/dL (133 mmol/L) for men or $\geq 1.4$ mg/dL (124 mmol/L) for women, unstable or rapidly progressing renal disease, cardiovascular events within 2 months prior to enrolment, congestive heart failure (New York Heart Association Class IV), systolic BP (SBP) $\geq 160$ mmHg, or diastolic BP (DBP) $\geq 100$ mmHg at randomisation.
<b>Recruitment / selection of participants</b>	Participants were
<b>Intervention(s)</b>	Dapagliflozin 10 mg daily Administered orally.
<b>Strata 1: People with type 2 diabetes mellitus and heart failure</b>	Not stated/unclear  Excluded "congestive heart failure (New York Heart Association Class IV)", otherwise unclear. No information in baseline characteristics.
<b>Strata 2: People with atherosclerotic cardiovascular disease</b>	Not stated/unclear  Baseline characteristics show around 86% had a prior history of CV disease (not further defined), however, a subsequent paper Grandy 2016 states that this included hypertension.
<b>Strata 3: People with type 2 diabetes mellitus and chronic kidney disease</b>	Not stated/unclear  Excluded "unstable or rapidly progressing renal disease", otherwise unclear. No information in baseline characteristics.
<b>Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk</b>	Not stated/unclear
<b>Subgroup 1: People with moderate or severe frailty</b>	Not stated/unclear
<b>Subgroup 2: Onset of type</b>	Not stated/unclear

<b>2 diabetes mellitus</b>	
<b>Subgroup 3: People with non-alcoholic fatty liver disease</b>	Not stated/unclear
<b>Subgroup 4: People with obesity</b>	Not stated/unclear
<b>Subgroup 5: eGFR category at baseline</b>	Not stated/unclear
<b>Subgroup 6: Albuminuria category at baseline</b>	Not stated/unclear
<b>Population subgroups</b>	
<b>Comparator</b>	Placebo daily Administered orally.
<b>Number of participants</b>	N=219
<b>Duration of follow-up</b>	24-week + 28-week extension with results reported in the subsidiary paper.
<b>Indirectness</b>	
<b>Method of analysis</b>	ITT

## 300.2. Study arms

### 300.2.1. Dapagliflozin 10 mg daily (N = 109)

Administered orally

### 300.2.2. Placebo (N = 109)

Administered orally

### 300.3. Characteristics

#### 300.3.1. Arm-level characteristics

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



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

## 301. Matthaei, 2015

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

### 301.1. Study details

<b>Secondary publication of another included study- see primary study for details</b>	No additional information.
<b>Other publications associated with this study included in review</b>	Matthaei, S; Aggarwal, N; Garcia-Hernandez, P; Iqbal, N; Chen, H; Johnsson, E; Chin, A; Hansen, L. One-year efficacy and safety of saxagliptin add-on in patients receiving dapagliflozin and metformin. Diabetes, obesity & metabolism; 2016; vol. 18 (no. 11); 1128-1133.
<b>Trial name / registration number</b>	NCT01619059
<b>Study type</b>	Randomised controlled trial (RCT)
<b>Study location</b>	US Puerto Rico Canada Romania Russia Poland Czech Republic Mexico Hungary
<b>Study setting</b>	No additional information.

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

<b>chronic kidney disease</b>	
<b>Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk</b>	Not stated/unclear
<b>Subgroup 1: People with moderate or severe frailty</b>	Not stated/unclear
<b>Subgroup 2: Onset of type 2 diabetes mellitus</b>	Not stated/unclear
<b>Subgroup 3: People with non-alcoholic fatty liver disease</b>	Not stated/unclear
<b>Subgroup 4: People with obesity</b>	Not stated/unclear
<b>Subgroup 5: eGFR category at baseline</b>	eGFR $\geq 30$ mL/min/1.73m <sup>2</sup>
<b>Subgroup 6: Albuminuria category at baseline</b>	Not stated/unclear
<b>Population subgroups</b>	
<b>Comparator</b>	Placebo administered daily.
<b>Number of participants</b>	N=315
<b>Duration of follow-up</b>	24-week
<b>Indirectness</b>	

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

## 301.2. Study arms

### 301.2.1. Saxagliptin 5 mg daily (N = 153)

Administered orally

### 301.2.2. Placebo daily (N = 162)

Administered orally

## 301.3. Characteristics

### 301.3.1. Arm-level characteristics

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

<b>Characteristic</b>	<b>Saxagliptin 5 mg daily (N = 153)</b>	<b>Placebo daily (N = 162)</b>
<b>Time since type 2 diabetes diagnosed (years)</b>		
Mean (SD)	8.1 (7)	7.4 (5.8)
<b>HbA1c (%)</b>		
Mean (SD)	7.97 (0.83)	7.86 (0.93)
<b>Smoking status</b>		
Nominal	NR	NR
<b>Alcohol consumption</b>		
Nominal	NR	NR
<b>Presence of severe mental illness</b>		
Nominal	NR	NR
<b>People with significant cognitive impairment</b>		
Nominal	NR	NR
<b>People with a learning disability</b>		
Nominal	NR	NR
<b>Weight (kg)</b>		
Mean (SD)	88.1 (20)	87.9 (17.1)
<b>BMI ( kg/m<sup>2</sup>)</b>		
Mean (SD)	31.4 (5.2)	31.4 (5.3)
<b>Number of people with obesity</b>		
Nominal	NR	NR
<b>eGFR mL/min/1.73m<sup>2</sup></b>		
Mean (SD)	92.8 (21.6)	93.9 (20.6)
<b>Metformin + dapagliflozin</b>		
No of events	n = 153 ; % = 100	n = 162 ; % = 100

## 302. Matthaei, 2016

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

### 302.1. Study details

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

### 302.2. Study arms

#### 302.2.1. Saxagliptin 5 mg daily (N = 153)

Administered orally

**302.2.2. Placebo (N = 162)**

Administered orally



## 303. Matthaei, 2015

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

### 303.1. Study details

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

## 304. Matthews, 2005

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

### 304.1. Study details

<b>Secondary publication of another included study- see primary study for details</b>	NA
<b>Other publications associated with this study included in review</b>	<p>2-year efficacy results reported in:</p> <ul style="list-style-type: none"> <li>Charbonnel, B., Schernthaner, G., Brunetti, P., Matthews, D. R., Urquhart, R., Tan, M. H., &amp; Hanefeld, M. (2005). Long-term efficacy and tolerability of add-on pioglitazone therapy to failing monotherapy compared with addition of gliclazide or metformin in patients with type 2 diabetes. <i>Diabetologia</i>, 48, 1093-1104.</li> </ul> <p>2-year lipid/cholesterol results reported in:</p> <ul style="list-style-type: none"> <li>Betteridge, D. J., &amp; Verges, B. (2005). Long-term effects on lipids and lipoproteins of pioglitazone versus gliclazide addition to metformin and pioglitazone versus metformin addition to sulphonylurea in the treatment of type 2 diabetes. <i>Diabetologia</i>, 48, 2477-2481.</li> </ul>
<b>Trial name / registration number</b>	Not reported
<b>Study type</b>	<p>Randomised controlled trial (RCT)</p> <p>Double-blind parallel-group RCTs</p>
<b>Study location</b>	International (75 centres in Australia, Bulgaria, Czech Republic, France, Germany, Greece, Latvia, Poland, Romania, Turkey)
<b>Study setting</b>	Outpatient
<b>Study dates</b>	Dates not reported

<b>Sources of funding</b>	Takeda Europe R&D Centre and Eli Lilly and Company, USA
<b>Inclusion criteria</b>	<ul style="list-style-type: none"> <li>• Aged 35-75 years</li> <li>• Diagnosis of type 2 diabetes</li> <li>• Diabetes inadequately managed with sulphonylurea monotherapy (<math>\geq 50\%</math> maximal recommended dose or at maximal tolerated dose <math>\geq 3</math>-mo)</li> <li>• Stable or worsening glycaemic control <math>\geq 3</math>-mo</li> <li>• HbA1c level 7.5-11% inclusive at screening</li> <li>• Fasting C-peptide <math>\geq 1.5</math> ng/ml at screening</li> <li>• If female, postmenopausal or sterilized or using adequate contraception</li> </ul>
<b>Exclusion criteria</b>	<ul style="list-style-type: none"> <li>• Type 1 diabetes or ketoacidosis</li> <li>• History of myocardial infarction, transient ischemic attacks, or stroke in previous 6-mo</li> <li>• Symptomatic heart failure</li> <li>• Malabsorption or pancreatitis</li> <li>• Familial polyposis coli</li> <li>• Malignant disease in previous 10 years</li> <li>• History of, or states associated with, lactic acidosis or hypoxemia</li> <li>• Substance abuse</li> <li>• Pregnant or breast-feeding women</li> <li>• Previous treatment with insulin, gliclazide, pioglitazone or other sulphonylureas or thiazolidinediones</li> </ul>
<b>Recruitment / selection of participants</b>	Participants block randomised using central telephone system to pioglitazone or gliclazide. Dietary advice given at baseline and instructed to adhere to disease- and body-weight-oriented diet for trial duration; participants provided with individually appropriate calories and nutrients. If weight increased $>5\%$ during treatment or HbA1c level increased $>9\%$ after dose titration completion, participants given further intensive dietary advice.
<b>Intervention(s)</b>	<ul style="list-style-type: none"> <li>• Pioglitazone 15-45 mg daily</li> </ul> <p>Oral pioglitazone 15-45 mg daily for 104 months, in addition to concurrent metformin therapy. Initial 16-week forced dose-titration period (pioglitazone titrated to 30 mg and 45 mg; gliclazide titrated to 160 mg, 240 mg, and 360 (160 mg twice daily)) followed by 90-week maintenance period. No change in metformin dose from pre-study level was permitted. Cessation of titration or down titration permitted only if tolerability issues (e.g. actual hypoglycaemia or increased risk of it). Participants continued to next dose unless: (i) risk of hypoglycaemia (increase postponed for 1 visit from week 4 to week 8, or week 8 dose maintained for rest of study); (ii) reported symptomatic hypoglycaemia (one-step reduction followed by increase at next visit if possible); or (iii) adverse events requiring dose reduction (one-step reduction at weeks 8 or 12 (or week 16 for Pioglitazone v Gliclazide trial) with no further down titration).</p>
<b>Cointervention</b>	<ul style="list-style-type: none"> <li>• Metformin + Placebo (Gliclazide placebo for pioglitazone arm arm; Pioglitazone placebo for gliclazide arm)</li> </ul>

	Pre-study metformin dose maintained for duration of trial with no change in dose permitted.
<b>Strata 1: People with type 2 diabetes mellitus and heart failure</b>	<p>People without heart failure</p> <p>Excluded "symptomatic heart failure".</p>
<b>Strata 2: People with atherosclerotic cardiovascular disease</b>	<p>Not stated/unclear</p> <p>Excluded "myocardial infarction, transient ischaemic attacks or stroke in the previous 6 months", prior to this unclear. No information in baseline characteristics.</p>
<b>Strata 3: People with type 2 diabetes mellitus and chronic kidney disease</b>	<p>Not stated/unclear</p> <p>Not an inclusion/exclusion criteria. No information in baseline characteristics.</p>
<b>Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk</b>	Not stated/unclear
<b>Subgroup 1: People with moderate or severe frailty</b>	Not stated/unclear
<b>Subgroup 2: Onset of type 2 diabetes mellitus</b>	Not stated/unclear
<b>Subgroup 3: People with non-alcoholic fatty liver disease</b>	Not stated/unclear
<b>Subgroup 4: People with obesity</b>	Not stated/unclear

<b>Subgroup 5: eGFR category at baseline</b>	Not stated/unclear
<b>Subgroup 6: Albuminuria category at baseline</b>	Not stated/unclear
<b>Comparator</b>	<ul style="list-style-type: none"> <li>Metformin + Placebo (Gliclazide placebo for pioglitazone arm; Pioglitazone placebo for gliclazide arm)</li> </ul> <p>Pre-study metformin dose maintained for duration of trial with no change in dose permitted.</p>
<b>Number of participants</b>	N=630
<b>Duration of follow-up</b>	88 weeks
<b>Indirectness</b>	None
<b>Method of analysis</b>	<p>Per protocol</p> <p>PP analysis (all randomised participants who received at least one dose of study drug after randomisation and who has at least one HbA1c assessment at week 72 or later) also conducted for all outcomes</p> <p>Modified ITT</p> <p>mITT LOCF analysis (all randomised participants who received at least one dose of study drug after randomisation and who has at least one post-baseline HbA1c assessment) for all outcomes</p>
<b>Additional comments</b>	

## 304.2. Study arms

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

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

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

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

### 304.3. Characteristics

#### 304.3.1. Arm-level characteristics

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

<b>Characteristic</b>	<b>Pioglitazone 15-45 mg daily (N = 319)</b>	<b>Gliclazide 80-320 mg daily (N = 313)</b>
<b>Presence of severe mental illness</b>	NR	NR
Nominal		
<b>People with significant cognitive impairment</b>	NR	NR
Nominal		
<b>People with a learning disability</b>	NR	NR
Nominal		
<b>Number of people with obesity</b>	NR	NR
Nominal		
<b>Blood pressure-lowering medication used</b>	NR	NR
Nominal		
<b>Statins/lipid-lowering medication used</b>	NR	NR
Nominal		
<b>Other treatment being received</b>	NR	NR
Nominal		

Baseline characteristics are for n=317 in Pioglitazone arm.

## 305. Matthews, 2010

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

### 305.1. Study details

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



	glucose control in the 4 weeks prior to visit 1, serious cardiac conditions (history of torsades de pointes or ventricular tachycardia; percutaneous coronary intervention in the past 3 months; myocardial infarction, coronary artery bypass surgery, unstable angina or stroke in the past 6 months; congestive heart failure requiring pharmacological treatment; second- or third-degree atrioventricular block or prolonged QTc) or clinically significant liver or renal disease. Any of the following laboratory abnormalities at screening also precluded participation: alanine aminotransferase or aspartate aminotransferase >3 times the upper limit of normal, direct bilirubin >1.3 times upper limit of normal, serum creatinine levels $\geq 132$ $\mu\text{mol/l}$ in men or $\geq 123$ $\mu\text{mol/l}$ in women, clinically significant thyroid-stimulating hormone outside of normal range at screening; or fasting triglycerides >7.9 mmol/l.
<b>Recruitment / selection of participants</b>	Patients were randomized to receive either vildagliptin or glimepiride in addition to metformin.
<b>Intervention(s)</b>	Glimepiride up to 6 mg daily
<b>Cointervention</b>	All participants also received metformin.
<b>Strata 1: People with type 2 diabetes mellitus and heart failure</b>	<p>People without heart failure</p> <p>Exclusion criteria for congestive heart failure requiring pharmacological treatment</p>
<b>Strata 2: People with atherosclerotic cardiovascular disease</b>	<p>People without atherosclerotic cardiovascular diseases</p> <p>Exclusion criteria for people with percutaneous coronary intervention in the past 3 months, myocardial infarction, coronary artery bypass surgery, unstable angina or stroke in the past 6 months.</p>
<b>Strata 3: People with type 2 diabetes mellitus and chronic kidney disease</b>	<p>Mixed population</p> <p>Around 50% of people had a mild-moderate renal insufficiency</p>
<b>Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk</b>	Not stated/unclear

<b>Subgroup 1: People with moderate or severe frailty</b>	Not stated/unclear
<b>Subgroup 2: Onset of type 2 diabetes mellitus</b>	Not stated/unclear
<b>Subgroup 3: People with non-alcoholic fatty liver disease</b>	Not stated/unclear
<b>Subgroup 4: People with obesity</b>	Not stated/unclear
<b>Subgroup 5: eGFR category at baseline</b>	Not stated/unclear
<b>Subgroup 6: Albuminuria category at baseline</b>	Not stated/unclear
<b>Population subgroups</b>	
<b>Comparator</b>	Vildagliptin 50 mg twice daily, administered orally.
<b>Number of participants</b>	N=3118
<b>Duration of follow-up</b>	2-year
<b>Indirectness</b>	
<b>Method of analysis</b>	Modified ITT
<b>Additional comments</b>	All patients who received at least one dose of study drug and had at least one postbaseline efficacy assessment (primary or secondary).

## 305.2. Study arms

### 305.2.1. Glimepiride 2-6 mg (N = 1556)

Administered daily, orally

### 305.2.2. Vildagliptin 50 mg (N = 1562)

Administered twice daily, orally

## 305.3. Characteristics

### 305.3.1. Study-level characteristics

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

### 305.3.2. Arm-level characteristics

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

<b>Characteristic</b>	<b>Glimepiride 2-6 mg (N = 1556)</b>	<b>Vildagliptin 50 mg (N = 1562)</b>
<b>Hispanic or Latino</b>	n = 133 ; % = 8.5	n = 129 ; % = 8.3
No of events		
<b>Other</b>	n = 15 ; % = 1	n = 7 ; % = 0.4
No of events		
<b>Presence of frailty</b>	NR	NR
Nominal		
<b>Time since type 2 diabetes diagnosed (years)</b>	5.7 (5)	5.7 (5.2)
Mean (SD)		
<b>Current smoker</b>	n = 255 ; % = 16.4	n = 263 ; % = 16.8
No of events		
<b>Alcohol consumption</b>	NR	NR
Nominal		
<b>Presence of severe mental illness</b>	NR	NR
Nominal		
<b>People with significant cognitive impairment</b>	NR	NR
Nominal		
<b>People with a learning disability</b>	NR	NR
Nominal		
<b>Number of people with obesity</b>	NR	NR
Nominal		
<b>Albumin creatinine ratio</b>	NR	NR
Nominal		
<b>Metformin</b>	n = 1556 ; % = 100	n = 1562 ; % = 100
No of events		

## 306. Mattoo, 2005

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

### 306.1. Study details

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

<b>Cointervention</b>	Insulin
<b>Strata 1: People with type 2 diabetes mellitus and heart failure</b>	Not stated/unclear  Exclusion criteria on diminished cardiac function but no information on what this means
<b>Strata 2: People with atherosclerotic cardiovascular disease</b>	Not stated/unclear  Exclusion criteria on diminished cardiac function but no information on what this means
<b>Strata 3: People with type 2 diabetes mellitus and chronic kidney disease</b>	Not stated/unclear  Exclusion criteria on renal impairment but no information on what this means
<b>Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk</b>	Not stated/unclear
<b>Subgroup 1: People with moderate or severe frailty</b>	Not stated/unclear
<b>Subgroup 2: Onset of type 2 diabetes mellitus</b>	Not stated/unclear
<b>Subgroup 3: People with non-alcoholic fatty liver disease</b>	People without non-alcoholic fatty liver disease
<b>Subgroup 4: People with obesity</b>	Not stated/unclear

<b>Subgroup 5: eGFR category at baseline</b>	Not stated/unclear
<b>Subgroup 6: Albuminuria category at baseline</b>	A2 (ACR 30-300 mg/g or 3-30mg/mmol)
<b>Comparator</b>	Placebo (oral) + insulin (subcutaneous) daily
<b>Number of participants</b>	N=289
<b>Duration of follow-up</b>	6 months
<b>Method of analysis</b>	Modified ITT
<b>Additional comments</b>	The ITT sample was defined as all randomized patients who received at least 1 dose of study medication and had both a baseline measurement and at least 1 efficacy measurement during the treatment period.

## 306.2. Study arms

### 306.2.1. Pioglitazone 30 mg daily (N = 142)

Administered orally

### 306.2.2. Placebo (N = 147)

Administered orally

## 306.3. Characteristics

### 306.3.1. Arm-level characteristics

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

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





## 307. Mazzone, 2006

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

### 307.1. Study details

<b>Secondary publication of another included study- see primary study for details</b>	No additional information.
<b>Other publications associated with this study included in review</b>	Sam, S et al. Pioglitazone-Mediated Changes in Lipoprotein Particle Composition Are Predicted by Changes in Adiponectin Level in Type 2 Diabete. J Clin Endocrinol Metab. 2012 Jan; 97(1): E110–E114.
<b>Trial name / registration number</b>	CHICAGO/NCT00225264
<b>Study type</b>	Randomised controlled trial (RCT)
<b>Study location</b>	US, Chicago at 28 clinical sites.
<b>Study setting</b>	Hospital
<b>Study dates</b>	10/2003 - 05/2006
<b>Sources of funding</b>	Takeda Pharmaceuticals North America Inc, Lincolnshire, Ill, sponsored and funded this study and provided the study drugs.
<b>Inclusion criteria</b>	Individuals eligible for participation were men and women between the ages of 45 and 85 years with type 2 diabetes mellitus by American Diabetes Association criteria who were newly diagnosed with type 2 diabetes mellitus that was diet-controlled or treated with sulfonylurea or metformin monotherapy, sulfonylurea/ metformin combination therapy, or any of these plus insulin. Individuals taking medication for glycemia were included if they had HbA1c values of 6.5% or greater and less than 9%; those not taking medication for glycemia were included if they had HbA1c values of greater than 6.5% and less than 10%.

<b>Exclusion criteria</b>	Exclusion criteria included symptomatic coronary artery disease, cerebrovascular disease, or peripheral artery disease; functional New York Heart Association class III or IV heart failure; left ventricular dysfunction measured as left ventricular ejection fraction less than 40%; current use of diuretics or angiotensin-converting enzyme inhibitors for the treatment of heart failure; or significant cardiac valvular disease. Individuals also were excluded if they had been treated with a thiazolidinedione within 12 weeks of treatment randomization; did not respond to or were intolerant of sulfonylurea or thiazolidinedione treatment; required more than 2 oral agents for glycemic control; had unexplained microscopic hematuria, a triglycerides level greater than 500 mg/dL (5.7 mmol/L), elevated serum creatinine level, decreased hemoglobin level, an alanine transaminase level of 2.5 or more times the upper limit of normal; had active liver disease or jaundice; or weighed more than 135 kg or had a body mass index (calculated as weight in kilograms divided by height in meters squared) greater than 45.
<b>Recruitment / selection of participants</b>	Patients were recruited from a large US city. Patients who were newly diagnosed with type 2 diabetes that was diet-controlled or treated with sulfonylurea or metformin monotherapy, sulfonylurea/ metformin combination therapy, or any of these plus insulin were randomly assigned 1:1 to pioglitazone (15-45 mg daily) or glimepiride (1-4 mg daily).
<b>Intervention(s)</b>	Pioglitazone 15-45 mg/d  The initial dose was based on sulfonylurea use and dose at study entry.
<b>Cointervention</b>	Metformin ± sulfonylurea ± insulin
<b>Strata 1: People with type 2 diabetes mellitus and heart failure</b>	People without heart failure  Excluded "functional New York Heart Association class III or IV heart failure" but other HF unclear. Less than 2 % had congestive heart failure.
<b>Strata 2: People with atherosclerotic cardiovascular disease</b>	Not stated/unclear  Excluded "symptomatic coronary artery disease, cerebrovascular disease, or peripheral artery disease". However, baseline characteristics show history of CVD, breakdown by type of CVD only and unclear if any overlap to calculate overall proportion.
<b>Strata 3: People with type 2 diabetes mellitus and chronic kidney disease</b>	Not stated/unclear  Not an inclusion/exclusion criteria. No information in baseline characteristics.
<b>Strata 4: People with</b>	Not stated/unclear

<b>type 2 diabetes mellitus and high cardiovascular risk</b>	
<b>Subgroup 1: People with moderate or severe frailty</b>	Not stated/unclear
<b>Subgroup 2: Onset of type 2 diabetes mellitus</b>	Not stated/unclear
<b>Subgroup 3: People with non-alcoholic fatty liver disease</b>	Not stated/unclear
<b>Subgroup 4: People with obesity</b>	Not stated/unclear
<b>Subgroup 5: eGFR category at baseline</b>	Not stated/unclear
<b>Subgroup 6: Albuminuria category at baseline</b>	Not stated/unclear
<b>Population subgroups</b>	
<b>Comparator</b>	Glimepiride 1-4mg /d  The initial dose was based on sulfonylurea use and dose at study entry.
<b>Number of participants</b>	N=462
<b>Duration of follow-up</b>	73 weeks
<b>Indirectness</b>	In total around 10% of patients in this study were oral antidiabetic treatment naïve.

<b>Method of analysis</b>	ITT
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## 307.2. Study arms

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

Administered orally

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

Administered orally

## 307.3. Characteristics

### 307.3.1. Arm-level characteristics

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

<b>Characteristic</b>	<b>Pioglitazone 15 - 45 mg daily (N = 232)</b>	<b>Glimepiride 1-4 mg daily (N = 230)</b>
<b>Stroke/transient ischemic attack</b>	n = 9 ; % = 3.9	n = 8 ; % = 3.5
No of events		
<b>Angina</b>	n = 14 ; % = 6.1	n = 20 ; % = 8.8
No of events		
<b>Cardiac arrhythmia</b>	n = 15 ; % = 6.5	n = 13 ; % = 5.7
No of events		
<b>Congestive heart failure</b>	n = 2 ; % = 0.9	n = 4 ; % = 1.8
No of events		
<b>Peripheral arterial disease</b>	n = 3 ; % = 1.3	n = 4 ; % = 1.8
No of events		
<b>Presence of frailty</b>	NR	NR
Nominal		
<b>Time since type 2 diabetes diagnosed (years)</b>	8 (7.6)	7.5 (6.8)
Mean (SD)		
<b>Smoking status</b>	NR	NR
Nominal		
<b>Alcohol consumption</b>	NR	NR
Nominal		
<b>Presence of severe mental illness</b>	NR	NR
Nominal		
<b>People with significant cognitive impairment</b>	NR	NR
Nominal		
<b>People with a learning disability</b>	NR	NR
Nominal		
<b>Number of people with obesity</b>	NR	NR
Nominal		
<b>Sulfonylurea monotherapy</b>	n = 39 ; % = 17	n = 32 ; % = 14
No of events		

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

## 308. McCluskey, 2004

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

### 308.1. Study details

<b>Secondary publication of another included study- see primary study for details</b>	No additional information.
<b>Other publications associated with this study included in review</b>	No additional information.
<b>Trial name / registration number</b>	No additional information.
<b>Study type</b>	Randomised controlled trial (RCT)
<b>Study location</b>	US (17 sites)
<b>Study setting</b>	No additional information.
<b>Study dates</b>	No additional information.
<b>Sources of funding</b>	No additional information.
<b>Inclusion criteria</b>	Men and women aged 18 to 80 years who had type 2 diabetes mellitus for >1 year were eligible for inclusion if their disease was managed with rosiglitazone 4 or 8 mg for >2 months before study entry. None of the subjects had received insulin. Patients were required to have a screening HbA1c value between 7.5% and 9.5% and a baseline BMI between 26 and 42 kg/m <sup>2</sup> . All enrollees had to demonstrate evidence of insulin secretory capacity (fasting C-peptide >0.27 nmol/L during the stabilization period) and to have FPG levels between 126 and 235 mg/dL at randomization. All patients signed informed consent forms prior to the conduct of any study-related procedures.



<b>Exclusion criteria</b>	Individuals who required insulin therapy, were receiving other sulfonylureas, or had a history of sulfonylurea hypersensitivity were excluded.
<b>Recruitment / selection of participants</b>	Patients with uncontrolled type 2 diabetes mellitus on rosiglitazone were recruited and randomly assigned to glimepiride or placebo.
<b>Intervention(s)</b>	Glimepiride 2-8 mg daily, administered orally.  Glimepiride was titrated over a maximum of 2 sequential biweekly steps to 4 and 8 mg.
<b>Cointervention</b>	Rosiglitazone 4 or 8 mg daily at study entry.
<b>Strata 1: People with type 2 diabetes mellitus and heart failure</b>	Not stated/unclear
<b>Strata 2: People with atherosclerotic cardiovascular disease</b>	Not stated/unclear
<b>Strata 3: People with type 2 diabetes mellitus and chronic kidney disease</b>	Not stated/unclear
<b>Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk</b>	Not stated/unclear
<b>Subgroup 1: People with moderate or severe frailty</b>	Not stated/unclear
<b>Subgroup 2: Onset of type</b>	Not stated/unclear

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

## 308.2. Study arms

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

Administered orally

### 308.2.2. Placebo daily (N = 15)

Administered orally

### 308.3. Characteristics

#### 308.3.1. Arm-level characteristics

Characteristic	Glimepiride 2-8 mg daily (N = 25)	Placebo daily (N = 15)
<b>% Male</b>	n = 11 ; % = 44	n = 6 ; % = 4
No of events		
<b>Mean age (SD) (years)</b>	60.2 (7.8)	50.8 (9.7)
Mean (SD)		
<b>White</b>	n = 24 ; % = 96	n = 12 ; % = 80
No of events		
<b>Other</b>	n = 1 ; % = 4	n = 3 ; % = 20
No of events		
<b>Presence of frailty</b>	NR	NR
Nominal		
<b>Time since type 2 diabetes diagnosed</b>	7.2 (8.8)	4.6 (4)
Mean (SD)		
<b>Smoking status</b>	NR	NR
Nominal		
<b>Alcohol consumption</b>	NR	NR
Nominal		
<b>Presence of severe mental illness</b>	NR	NR
Nominal		
<b>People with significant cognitive impairment</b>	NR	NR
Nominal		
<b>People with a learning disability</b>	NR	NR
Nominal		
<b>Number of people with obesity</b>	NR	NR
Nominal		
<b>Rosiglitazone</b>	n = 25 ; % = 100	n = 15 ; % = 100
No of events		

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

## 309. McGill, 2013

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

### 309.1. Study details

<b>Secondary publication of another included study- see primary study for details</b>	NA
<b>Other publications associated with this study included in review</b>	NA
<b>Trial name / registration number</b>	NR
<b>Study type</b>	Randomised controlled trial (RCT)
<b>Study location</b>	53 sites in six countries (Australia, Hong Kong, Israel, New Zealand, Ukraine, and U.S.)
<b>Study setting</b>	NR
<b>Study dates</b>	11 December 2008 to 5 January 2011
<b>Sources of funding</b>	Boehringer Ingelheim
<b>Inclusion criteria</b>	<ul style="list-style-type: none"> <li>• Women (non-fertile or using a medically approved birth control method) and men aged 18–80 years, previously diagnosed with type 2 diabetes</li> <li>• Treated with glucose-lowering agents, including insulin, sulfonylurea, glinides, pioglitazone, and <math>\alpha</math>-glucosidase inhibitors. Existing glucose-lowering therapy must have remained unchanged for 8 weeks before study entry.</li> <li>• Participants fulfilled the criteria for severe RI (CKD stage 4/5) at screening, having an estimated glomerular filtration rate (eGFR) calculated by the Modification of Diet in Renal Disease study</li> </ul>

	<p>equation of <math>&lt;30 \text{ mL/min/1.73 m}^2</math> (while not receiving chronic dialysis).</p> <ul style="list-style-type: none"> <li>Participants had an HbA1c <math>&gt;7</math> and <math>\leq 10\%</math> (<math>&gt;53</math> and <math>\leq 86 \text{ mmol/mol}</math>)</li> <li>BMI <math>\leq 45 \text{ kg/m}^2</math></li> </ul>
<b>Exclusion criteria</b>	<ul style="list-style-type: none"> <li>Myocardial infarction (MI), stroke, or transient ischemic attack within the previous 6 months</li> <li>Any requirement for acute dialysis within the previous 3 months</li> <li>Renal transplantation</li> <li>Impaired hepatic function</li> <li>Use of any other DPP-4 inhibitor or anti-obesity drug within the previous 3 months</li> </ul>
<b>Recruitment / selection of participants</b>	Study participants who met the eligibility criteria at screening and at the end of the 2-week placebo run-in period were randomized (1:1) to receive double-blind treatment.
<b>Intervention(s)</b>	Linagliptin 5 mg/day
<b>Cointervention</b>	Glucose-lowering background therapy
<b>Strata 1: People with type 2 diabetes mellitus and heart failure</b>	Not stated/unclear
<b>Strata 2: People with atherosclerotic cardiovascular disease</b>	Not stated/unclear
<b>Strata 3: People with type 2 diabetes mellitus and chronic kidney disease</b>	<p>People with chronic kidney disease</p> <p>Inclusion of people with severe renal impairment (eGFR <math>&lt;30</math>)</p>
<b>Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk</b>	Not stated/unclear

<b>Subgroup 1: People with moderate or severe frailty</b>	Not stated/unclear
<b>Subgroup 2: Onset of type 2 diabetes mellitus</b>	Not stated/unclear
<b>Subgroup 3: People with non-alcoholic fatty liver disease</b>	Not stated/unclear
<b>Subgroup 4: People with obesity</b>	Not stated/unclear
<b>Subgroup 5: eGFR category at baseline</b>	Mixed population Participants fulfilled the criteria for severe RI (CKD stage 4/5) at screening, having an estimated glomerular filtration rate (eGFR) calculated by the Modification of Diet in Renal Disease study equation of $<30 \text{ mL/min/1.73 m}^2$ (while not receiving chronic dialysis).
<b>Subgroup 6: Albuminuria category at baseline</b>	Not stated/unclear
<b>Population subgroups</b>	NA
<b>Comparator</b>	Placebo
<b>Number of participants</b>	133 participants randomised. Out of 68 participants randomised to Linagliptin, 19 discontinued, 49 completed, and 66 were in the full-analysis set. Out of 65 participants randomised to placebo, 17 discontinued, 48 completed, and 62 were in the full analysis set.
<b>Duration of follow-up</b>	12 weeks and 52 months
<b>Indirectness</b>	Directly applicable
<b>Method of analysis</b>	ITT Although not explicitly stated, it appears that ITT analysis was conducted. Change from baseline scores in HbA1c were calculated using ANCOVA with treatment and glucose-lowering background drugs as fixed-classification effects and continuous HbA1c and renal function at baseline as linear covariates. Analysis was performed on the full analysis set (FAS)

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

## 309.2. Study arms

### 309.2.1. Linagliptin (N = 68)

### 309.2.2. Placebo (N = 65)

## 309.3. Characteristics

### 309.3.1. Arm-level characteristics

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



<b>Characteristic</b>	<b>Linagliptin (N = 68)</b>	<b>Placebo (N = 65)</b>
Sample size		
<b>Comorbidities</b>	n = NA	n = NA
Sample size		
<b>Hypertension</b>	n = 64 ; % = 94.1	n = 65 ; % = 100
Sample size		
<b>Diabetic nephropathy</b>	n = 60 ; % = 88.2	n = 62 ; % = 95.4
Sample size		
<b>Diabetic retinopathy</b>	n = 43 ; % = 63.2	n = 35 ; % = 53.8
Sample size		
<b>Metabolic syndrome</b>	n = 37 ; % = 54.4	n = 40 ; % = 61.5
Sample size		
<b>Presence of frailty</b>	NR	NR
Nominal		
<b>Time since type 2 diabetes diagnosed</b>	n = 64 ; % = 97	n = 59 ; % = 95.2
Duration >5 years		
Sample size		
<b>Smoking status</b>	NR	NR
Nominal		
<b>Alcohol consumption</b>	NR	NR
Nominal		
<b>Presence of severe mental illness</b>	NR	NR
Nominal		
<b>People with significant cognitive impairment</b>	NR	NR
Nominal		
<b>People with a learning disability</b>	NR	NR
Nominal		
<b>Number of people with obesity</b>	n = 50 ; % = 73.5	n = 38 ; % = 58.5
BMI $\geq 30$ kg/m <sup>2</sup>		
Sample size		
<b>eGFR mL/min/1.73m<sup>2</sup></b>	n = NA	n = NA

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



## 310. McGuire Darren, 2019

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

### 310.1. Study details

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

### 310.2. Study arms

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

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

**310.2.2. Linagliptin - Heart failure, Ejection fraction  $\geq 50\%$  (N = 312)**

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

**310.2.3. Placebo - Heart failure, Ejection fraction  $< 50\%$  (N = 142)**

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

**310.2.4. Placebo - Heart failure, Ejection fraction  $\geq 50\%$  (N = 345)**

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

## 311. McGuire, 2016

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

### 311.1. Study details

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

## 312. McMurray, 2018

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

### 312.1. Study details

<b>Secondary publication of another included study- see primary study for details</b>	Not applicable
<b>Other publications associated with this study included in review</b>	Not applicable
<b>Trial name / registration number</b>	VIVID (Vildagliptin in Ventricular Dysfunction Diabetes)
<b>Study type</b>	Randomised controlled trial (RCT)
<b>Study location</b>	Czechia, Denmark, Estonia, Germany, Greece, Guatemala, India, Italy, Latvia, Lithuania, Poland, Romania, Russian Federation, Singapore, Slovakia [Taken from Clinicaltrials.gov]
<b>Study setting</b>	Novartis Investigative Site [Taken from Clinicaltrials.gov]
<b>Study dates</b>	May 2009 to August 2012
<b>Sources of funding</b>	Novartis
<b>Inclusion criteria</b>	<ul style="list-style-type: none"> <li>Men and women between 18 and 85 years of age with type 2 diabetes</li> <li>Hemoglobin A1c: 6.5% to 10.0% [48.0 to 86.0 mmol/mol]</li> <li>Body mass index ranging from 22 to 42 kg/m<sup>2</sup></li> <li>With heart failure with a reduced ejection fraction (&lt;40%), and in New York Heart Association (NYHA) functional class I to III</li> </ul>

<b>Exclusion criteria</b>	<ul style="list-style-type: none"> <li>• NYHA functional class IV</li> <li>• A fasting plasma glucose concentration of <math>\geq 15</math> mmol/l</li> <li>• Receiving thiazolidinedione or incretin therapy</li> <li>• A recent cardiovascular event or procedure</li> <li>• Creatinine clearance of <math>&lt; 30</math> ml/min</li> <li>• Liver disease or elevated transaminases or bilirubin.</li> </ul>
<b>Recruitment / selection of participants</b>	Not reported
<b>Intervention(s)</b>	Vildagliptin 50 mg twice daily, oral (50 mg once daily if treated with a sulfonylurea)
<b>Cointervention</b>	Individuals continued their usual diet, exercise regimen, and drug therapy for diabetes (if taking drug therapy)
<b>Strata 1: People with type 2 diabetes mellitus and heart failure</b>	<p>People with heart failure</p> <p>People with heart failure NYHA class I-III were included. People with class IV were excluded.</p> <p>Baseline table reports 89.8% in vildagliptin group and 90% in placebo group had class II or III.</p>
<b>Strata 2: People with atherosclerotic cardiovascular disease</b>	<p>Not stated/unclear</p> <p>People with recent cardiovascular event or procedure were excluded. Baseline characteristics table report MI, angina, CABG, PCI, and stroke, but it is not possible to determine the number of participants who had more than one event.</p>
<b>Strata 3: People with type 2 diabetes mellitus and chronic kidney disease</b>	<p>Not stated/unclear</p> <p>CKD not an inclusion/exclusion criteria. CKD not reported in baseline characteristics table.</p>
<b>Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk</b>	Not stated/unclear
<b>Subgroup 1: People with moderate or severe frailty</b>	Not stated/unclear



<b>Subgroup 2: Onset of type 2 diabetes mellitus</b>	Not stated/unclear
<b>Subgroup 3: People with non-alcoholic fatty liver disease</b>	Not stated/unclear
<b>Subgroup 4: People with obesity</b>	Mixed population  Baseline characteristics table shows that 42.2 and 39.7% of participants in the intervention and control group respectively had obesity.
<b>Subgroup 5: eGFR category at baseline</b>	Not stated/unclear
<b>Subgroup 6: Albuminuria category at baseline</b>	Not stated/unclear
<b>Population subgroups</b>	Patients with heart failure and reduced ejection fraction
<b>Comparator</b>	Placebo, oral
<b>Number of participants</b>	254 participants were randomized
<b>Duration of follow-up</b>	16 and 52 weeks
<b>Indirectness</b>	Directly applicable - 12.5% intervention and 7.1% participants were on diet alone
<b>Method of analysis</b>	Not stated/unclear  Although the report presented per-protocol, intent-to-treat, and full-set analyses for the LVEF outcome, the type of analyses used to present the other outcomes was unclear.
<b>Additional comments</b>	Study sample size was calculated based upon 90% power and a 1-sided significance level of 0.025 to declare noninferiority of vildagliptin compared with placebo for the effect of treatment of LVEF, using a margin of -3.5% and an expected difference between the 2 treatments of 0%. It was calculated that a total of 172 patients with at least 1 LVEF measurement after randomization were required.

## 312.2. Study arms

### 312.2.1. Vildagliptin (N = 128)

### 312.2.2. Placebo (N = 126)

## 312.3. Characteristics

### 312.3.1. Arm-level characteristics

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

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

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

## 313. Meneghini, 2010

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

### 313.1. Study details

<b>Secondary publication of another included study- see primary study for details</b>	No additional information.
<b>Other publications associated with this study included in review</b>	No additional information.
<b>Trial name / registration number</b>	No additional information.
<b>Study type</b>	Randomised controlled trial (RCT)
<b>Study location</b>	US
<b>Study setting</b>	Medical centres (60 in total)
<b>Study dates</b>	11/2001 - 02/2005
<b>Sources of funding</b>	One of the authors is employed by Sanofi Aventis group and editorial support was also provided by the Sanofi Aventis U.S. group which suggests that they provided at least some funding towards the study.
<b>Inclusion criteria</b>	Included men and women 18 to 79 years old who had had type 2 diabetes for at least 6 months, with A1C levels $\geq 8.0\%$ to $\leq 12.0\%$ despite $\geq 3$ months of treatment with a stable dose of either a sulfonylurea (at least half of the maximally labelled dose) or metformin (1 to 2.5 g/d). Patients were also required to have a demonstrated ability and willingness to inject insulin and to perform self-monitoring of blood glucose at least twice daily with use of a plasma-referenced glucose meter.
<b>Exclusion criteria</b>	<ul style="list-style-type: none"> <li>Stroke, myocardial infarction, angina, and/or cardiovascular surgical procedure within the previous 12 months</li> </ul>

	<p>and/or:</p> <ul style="list-style-type: none"> <li>• Congestive heart failure</li> <li>• Impaired renal function or liver disease</li> <li>• Treatment with nonselective b-adrenergic blocking agents</li> <li>• Acute infection</li> <li>• History or current signs of severe peripheral edema</li> <li>• Current or history of acute or chronic metabolic acidosis</li> <li>• History of hypoglycemia unawareness</li> <li>• Planned radiologic studies necessitating administration of contrast agents</li> <li>• Women who were pregnant, breastfeeding, or failing to use adequate contraception, if applicable</li> <li>• Body mass index &lt;25 kg/m<sup>2</sup></li> <li>• Treatment with systemic corticosteroids or large doses of inhaled corticosteroids</li> <li>• Treatment with any diabetes medication other than those required in this study</li> <li>• History of cancer within the previous 5 years (except adequately treated basal cell carcinoma and adequately treated cervical carcinoma in situ)</li> <li>• Current or history of addiction or alcohol abuse within the past 2 years</li> <li>• Diagnosis of dementia</li> <li>• Presence of any condition that may interfere with study completion or the inability to comply with study procedures</li> </ul>
<b>Recruitment / selection of participants</b>	<p>This study included men and women 18 to 79 years old who had had type 2 diabetes for at least 6 months, with A1C levels <math>\geq 8.0\%</math> to <math>\leq 12.0\%</math> despite <math>\geq 3</math> months of treatment with a stable dose of either a sulfonylurea (at least half of the maximally labelled dose) or metformin (1 to 2.5 g/d). Patients were randomized in a parallel-group, 2-arm, noninferiority, open-label study consisting of a 2-week screening period and a 48-week treatment phase, conducted at 60 medical centres.</p>
<b>Intervention(s)</b>	<p>Pioglitazone 15 mg - 45 mg daily.</p> <p>The starting dosage of pioglitazone was a single dose of 15 mg/daily titrated upward in 15-mg increments at weeks 6, 12, and 18 up to a maximum of 45 mg/daily.</p>
<b>Cointervention</b>	<ul style="list-style-type: none"> <li>• Sulfonylurea (glyburide/glipizide/glimepiride)</li> <li>• Metformin</li> </ul>
<b>Strata 1: People with type 2 diabetes mellitus and heart failure</b>	<p>People without heart failure</p> <p>Exclusion criteria for congestive heart failure</p>
<b>Strata 2: People with atherosclerotic</b>	<p>People without atherosclerotic cardiovascular diseases</p> <p>Exclusion criteria for stroke, myocardial infarction, angina and/or cardiovascular surgical procedure within the previous 12 months</p>

<b>cardiovascular disease</b>	
<b>Strata 3: People with type 2 diabetes mellitus and chronic kidney disease</b>	Not stated/unclear  Exclusion criteria for impaired renal function but not clear as to what this means
<b>Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk</b>	Not stated/unclear
<b>Subgroup 1: People with moderate or severe frailty</b>	Not stated/unclear
<b>Subgroup 2: Onset of type 2 diabetes mellitus</b>	Not stated/unclear
<b>Subgroup 3: People with non-alcoholic fatty liver disease</b>	Not stated/unclear
<b>Subgroup 4: People with obesity</b>	Not stated/unclear
<b>Subgroup 5: eGFR category at baseline</b>	Not stated/unclear
<b>Subgroup 6: Albuminuria category at baseline</b>	Not stated/unclear
<b>Comparator</b>	Insulin glargine (n=121)
<b>Number of participants</b>	N=247

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

## 313.2. Study arms

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

Administered orally

### 313.2.2. Insulin glargine titrated (N = 121)

Administered subcutaneously at bedtime

## 313.3. Characteristics

### 313.3.1. Arm-level characteristics

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



<b>Characteristic</b>	<b>Pioglitazone 15 mg - 45 mg daily (N = 126)</b>	<b>Insulin glargine titrated (N = 121)</b>
<b>Other</b>	n = 2 ; % = 1.6	n = 2 ; % = 1.6
No of events		
<b>Presence of frailty</b>	NR	NR
Nominal		
<b>Time since type 2 diabetes diagnosed</b>	NR	NR
Nominal		
<b>Smoking status</b>	NR	NR
Nominal		
<b>Alcohol consumption</b>	NR	NR
Nominal		
<b>Presence of severe mental illness</b>	NR	NR
Nominal		
<b>People with significant cognitive impairment</b>	NR	NR
Nominal		
<b>People with a learning disability</b>	NR	NR
Nominal		
<b>Number of people with obesity</b>	NR	NR
Nominal		
<b>Glyburide</b>	n = 11 ; % = 8.7	n = 11 ; % = 9.1
No of events		
<b>Glipizide</b>	n = 27 ; % = 21.4	n = 25 ; % = 20.7
No of events		
<b>Glimepiride</b>	n = 13 ; % = 10.3	n = 13 ; % = 10.7
No of events		

## 314. Meneilly, 2017

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

### 314.1. Study details

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

<b>Intervention(s)</b>	<p>Lixisenatide (n=176)</p> <p>Lixisenatide was self administered once daily by subcutaneous injection 30–60 min before breakfast. Lixisenatide treatment was initiated at the starting dose of 10 mg once daily for 2 weeks and then increased to the maintenance dose of 20 mg, which was continued until the end of the treatment period. If the target maintenance dose was not tolerated, the lixisenatide dose could be reduced to 10 mg during the first 8 weeks of treatment. Thereafter, the maintenance dose was kept stable</p>
<b>Cointervention</b>	<p>Oral antidiabetic drug therapy:</p> <p>In patients who were receiving basal insulin at the start of the study and whose HbA1c was 7.0–8.0% (53–64 mmol/mol) inclusive, the basal insulin dose was reduced by 20% when lixisenatide was initiated to avoid hypoglycemia. Between study weeks 4 and 12, the insulin dose was titrated according to self-monitored plasma glucose values, and the dose was permitted to be increased to the baseline value in the absence of hypoglycemia. Patients with HbA1c between 7.0% (53 mmol/mol) and 8.5% (69 mmol/mol) who were receiving a sulfonylurea at baseline were required to reduce the sulfonylurea dose by 25% for the first 4 weeks of lixisenatide therapy. Similarly, the sulfonylurea dose could be titrated back to the baseline dose by week 12, provided that no hypoglycemia occurred. Patients whose HbA1c was greater than the upper limits of the ranges described above did not have a mandated dose reduction of insulin or sulfonylurea at the time of lixisenatide initiation, but doses could be reduced in the case of two or more symptomatic or one severe symptomatic hypoglycemic episode.</p>
<b>Strata 1: People with type 2 diabetes mellitus and heart failure</b>	Not stated/unclear
<b>Strata 2: People with atherosclerotic cardiovascular disease</b>	Not stated/unclear
<b>Strata 3: People with type 2 diabetes mellitus and chronic kidney disease</b>	<p>Not stated/unclear</p> <p>Exclusion criteria for severe renal impairment (eGFR &lt;30 mL/min/1.73m<sup>2</sup>) but not explicitly for CKD and not for all stages of CKD</p>
<b>Strata 4: People with type 2 diabetes</b>	Not stated/unclear

<b>mellitus and high cardiovascular risk</b>	
<b>Subgroup 1: People with moderate or severe frailty</b>	People without frailty
<b>Subgroup 2: Onset of type 2 diabetes mellitus</b>	Not stated/unclear
<b>Subgroup 3: People with non-alcoholic fatty liver disease</b>	Not stated/unclear
<b>Subgroup 4: People with obesity</b>	Not stated/unclear
<b>Subgroup 5: eGFR category at baseline</b>	eGFR $\geq 30$ mL/min/1.73m <sup>2</sup>
<b>Subgroup 6: Albuminuria category at baseline</b>	Not stated/unclear
<b>Population subgroups</b>	NA
<b>Comparator</b>	<p>Placebo (n=173)</p> <p>Placebo was self administered once daily by subcutaneous injection 30–60 min before breakfast for 24 weeks</p> <p>Background oral antidiabetic drug therapy:</p> <p>In patients who were receiving basal insulin at the start of the study and whose HbA1c was 7.0–8.0% (53–64 mmol/mol) inclusive, the basal insulin dose was reduced by 20% when lixisenatide was initiated to avoid hypoglycemia. Between study weeks 4 and 12, the insulin dose was titrated according to self-monitored plasma glucose values, and the dose was permitted to be increased to the baseline value in the absence of hypoglycemia. Patients with HbA1c between 7.0% (53 mmol/mol) and 8.5% (69 mmol/mol) who were receiving a sulfonylurea at baseline were required to reduce the sulfonylurea dose by 25% for the first 4 weeks of lixisenatide therapy. Similarly, the sulfonylurea dose could be titrated back</p>

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

## 314.2. Study arms

### 314.2.1. Lixisenatide (N = 176)

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

### 314.2.2. Placebo (N = 174)

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

### 314.3. Characteristics

#### 314.3.1. Arm-level characteristics

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

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

## 315. Mentz, 2017

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

### 315.1. Study details

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



# 316. Merker, 2015

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

<b>Secondary publication of another included study- see primary study for details</b>	Parent study Haring 2014
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## 317. Miller, 2019

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

### 317.1. Study details

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

## 318. Miras, 2019

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

### 318.1. Study details

<b>Trial name / registration number</b>	GRAVITAS / ISRCTN 13643081
<b>Study type</b>	Randomised controlled trial (RCT)
<b>Study location</b>	London, UK
<b>Study setting</b>	All assessments and interventions took place at the NIHR Imperial Clinical Research Facility at Hammersmith Hospital, UK
<b>Study dates</b>	February 2016 to November 2018
<b>Sources of funding</b>	JP Moulton Charitable Foundation. Liraglutide and Placebo pens provided by Novo Nordisk. Multiple authors declare funding and honoraria from numerous pharmaceutical companies
<b>Inclusion criteria</b>	Obese patients with persistent or recurrent T2DM that had undergone Roux-en-Y gastric bypass or vertical sleeve gastrectomy aged 18-70 and HbA1c >48mmol/l (>6.5%).
<b>Exclusion criteria</b>	Key exclusion criteria included current treatment with GLP-1 RA or dipeptidyl peptidase 4 (DPP-4) inhibitors, the presence of anatomical or endocrinological pathology causing suboptimal weight loss or weight regain (e.g. gastro-gastric fistula, hypothyroidism or Cushing's syndrome), specific contraindication to the use of GLP-1 RA, pregnancy and breastfeeding.
<b>Recruitment / selection of participants</b>	Patients were recruited from the Imperial College Healthcare NHS Trust, Guy's and St Thomas's NHS Foundation Trust, University College London Hospitals NHS Foundation Trust, St George's University Hospitals NHS Trust and Chelsea and Westminster Hospital NHS Foundation Trust.
<b>Intervention(s)</b>	Liraglutide (n=53)  The starting dose was 0.6 mg/day . The dose was increased by 0.6 mg/day each week as tolerated, such that between trial week 6 and 26 all patients administered 1.8 mg/day or their maximum tolerated dose. Doses were self administered subcutaneous injections using a pen device
<b>Cointervention</b>	Glucose lowering agents ± Insulin

	The management of glucose-lowering agents (GLAs) was based on the NICE guideline NG28.
<b>Strata 1: People with type 2 diabetes mellitus and heart failure</b>	Not stated/unclear
<b>Strata 2: People with atherosclerotic cardiovascular disease</b>	Not stated/unclear
<b>Strata 3: People with type 2 diabetes mellitus and chronic kidney disease</b>	Not stated/unclear
<b>Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk</b>	Not stated/unclear
<b>Subgroup 1: People with moderate or severe frailty</b>	Not stated/unclear
<b>Subgroup 2: Onset of type 2 diabetes mellitus</b>	Not stated/unclear
<b>Subgroup 3: People with non-alcoholic fatty liver disease</b>	Not stated/unclear
<b>Subgroup 4: People with obesity</b>	People with obesity

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

## 318.2. Study arms

### 318.2.1. Liraglutide (N = 53)

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

**318.2.2. Placebo (N = 27)**

Patients received placebo subcutaneously for 24 weeks

**318.3. Characteristics****318.3.1. Arm-level characteristics**

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

Characteristic	Liraglutide (N = 53)	Placebo (N = 27)
Sample size		
<b>3 GLAs</b>	n = 2 ; % = 4	n = 1 ; % = 4
Sample size		
<b>Insulin</b>	n = 15 ; % = 28	n = 6 ; % = 22
Sample size		
<b>Blood pressure-lowering medication used</b>	n = NR ; % = NR	n = NR ; % = NR
Sample size		
<b>Statins/lipid-lowering medication used</b>	n = NR ; % = NR	n = NR ; % = NR
Sample size		
<b>Other treatment being received</b>	n = NR ; % = NR	n = NR ; % = NR
Sample size		

## 319. Moeinzadeh, 2021

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

### 319.1. Study details

<b>Secondary publication of another included study- see primary study for details</b>	NR
<b>Other publications associated with this study included in review</b>	NR
<b>Trial name / registration number</b>	Study protocol approved by ethics committee IRCT20090905002417N23
<b>Study type</b>	Randomised controlled trial (RCT)
<b>Study location</b>	Iran
<b>Study setting</b>	Nephrology clinic, Alzahra Hospital
<b>Study dates</b>	NR
<b>Sources of funding</b>	NR
<b>Inclusion criteria</b>	<ul style="list-style-type: none"> <li>• Adult (<math>\geq 18</math> years) with type 2 diabetic</li> <li>• a eGFR of 30 to 60 mL/min/ 1.73m<sup>2</sup> or urinary albumin excretion of more than 300 mg/24h</li> </ul>
<b>Exclusion criteria</b>	Unstable doses of anti-hypertensive medications, poor compliance, impaired hepatic function, pancreatitis, use of any other DPP-4 inhibitor, using weight control, and immunosuppressive medications during last 3 months.



<b>Recruitment / selection of participants</b>	140 patients were screened and 136 patient were randomised. All patients were completely informed about study objectives and signed an informed consent form before the enrolment. Patients who met the inclusion criteria were subjected to a 6-month treatment period.
<b>Intervention(s)</b>	5 mg/d Linagliptin
<b>Cointervention</b>	Doses of other glucose-lowering medication were reduced in patients who experienced hypoglycaemia during the study period.
<b>Strata 1: People with type 2 diabetes mellitus and heart failure</b>	Not stated/unclear
<b>Strata 2: People with atherosclerotic cardiovascular disease</b>	Not stated/unclear
<b>Strata 3: People with type 2 diabetes mellitus and chronic kidney disease</b>	People with chronic kidney disease  Inclusion criteria of people with severely increased albuminuria (>300mg/24hr) and reduced eGFR (eGFR 30-60 mL/min/1.73m <sup>2</sup> ). People referred to nephrology clinic.
<b>Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk</b>	Not stated/unclear
<b>Subgroup 1: People with moderate or severe frailty</b>	Not stated/unclear
<b>Subgroup 2: Onset of type 2 diabetes mellitus</b>	Not stated/unclear
<b>Subgroup 3: People with non-alcoholic</b>	Not stated/unclear

<b>fatty liver disease</b>	
<b>Subgroup 4: People with obesity</b>	Not stated/unclear
<b>Subgroup 5: eGFR category at baseline</b>	eGFR $\geq 30$ mL/min/1.73m <sup>2</sup> eGFR 30-60 mL/min/1.73 m <sup>2</sup>
<b>Subgroup 6: Albuminuria category at baseline</b>	A3 (ACR >300mg/g or >30mgmmol)
<b>Population subgroups</b>	Subgroup analysis was conducted based on Statin and angiotensin II receptor blocker (ARB) use.
<b>Comparator</b>	Placebo
<b>Number of participants</b>	136 participants were randomised. Out of 68 participants in the intervention arm, 6-month follow-up was completed for 68 participants, and data were analysed for 62 participants. Out of 68 participants in the control arm, 2 participants were excluded due to gastrointestinal symptoms, and 3 were excluded due to poor compliance. Therefore, in the control arm, 63 participants completed 6-month follow-up, and 59 participants were analysed.
<b>Duration of follow-up</b>	6 months
<b>Indirectness</b>	Indirectly applicable - the study did not specifically recruit participants that were currently receiving treatment for T2D. However, a high proportion of participants were receiving insulin and/or oral anti-hypoglycaemic agents.
<b>Method of analysis</b>	Not stated/unclear  The method of analysis was unclear. The participant flow diagram states that 62 participants out of 68 participants randomised to the intervention group, and 59 out of 68 participants randomised to the control group were included in the analysis. However, the participant flow diagram also states that 68 out of 68 participants randomised to the intervention group and 68 out of 68 participants randomised to the control group completed the 6-month follow-up, and it is unclear why all these participants were not included in the analysis.
<b>Additional comments</b>	None

## 319.2. Study arms

### 319.2.1. Linagliptin (N = 68)

### 319.2.2. Placebo (N = 68)

## 319.3. Characteristics

### 319.3.1. Arm-level characteristics

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

<b>Characteristic</b>	<b>Linagliptin (N = 68)</b>	<b>Placebo (N = 68)</b>
<b>People with significant cognitive impairment</b>	NR	NR
Nominal		
<b>People with a learning disability</b>	NR	NR
Nominal		
<b>Number of people with obesity</b>	NR	NR
Nominal		
<b>eGFR mL/min/1.73m<sup>2</sup></b>	NR	NR
Nominal		
<b>Other antidiabetic medication used</b> Reported characteristics were for analysed patients only. Linagliptin n=62, placebo n=59.	n = NA	n = NA
Sample size		
<b>Insulin</b>	n = 13 ; % = 20.9	n = 11 ; % = 18.8
Sample size		
<b>Oral hypoglycaemic agents</b>	n = 29 ; % = 46.3	n = 41 ; % = 68.8
Sample size		
<b>Both</b>	n = 20 ; % = 32.8	n = 7 ; % = 12.4
Sample size		
<b>Blood pressure-lowering medication used</b> Reported characteristics were for analysed patients only. Linagliptin n=62, placebo n=59.	n = NA	n = NA
Sample size		
<b>Angiotensin-converting-enzyme (ACE) inhibitor</b>	n = 40 ; % = 65	n = 21 ; % = 35
Sample size		
<b>Angiotensin II receptor blocker (ARB)</b>	n = 48 ; % = 78.2	n = 13 ; % = 21.8
Sample size		
<b>Statins</b>	n = 40 ; % = 64.6	n = 21 ; % = 35.4
Sample size		
<b>Statins/lipid-lowering medication used</b>	NR	NR
Nominal		

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

## 320. Moon, 2014

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

### 320.1. Study details

<b>Secondary publication of another included study- see primary study for details</b>	No additional information.
<b>Other publications associated with this study included in review</b>	No additional information.
<b>Trial name / registration number</b>	NCT00562172
<b>Study type</b>	Randomised controlled trial (RCT)
<b>Study location</b>	Korea
<b>Study setting</b>	Hospital
<b>Study dates</b>	09/2007 to 10/2009
<b>Sources of funding</b>	
<b>Inclusion criteria</b>	Patients with type 2 diabetes, aged 18–75 years, with HbA1c 7.5–12.0 % (58–108 mmol/ mol), BMI 35 kg/m <sup>2</sup> , and who received metformin treatment at a dose of >1,000 mg/day for [3 months, prior to enrolment, were eligible.
<b>Exclusion criteria</b>	Patient with type 1 diabetes, gestational diabetes or diabetes with identifiable secondary causes, significant renal impairment (serum creatinine C 1.5 mg/ dL [133 μmol/L] in men, and 1.4 mg/dl [124 μmol/L] in women), or alanine aminotransferase/aspartate aminotransferase (ALT/AST) [3 times the upper limit of its normal range at study entry.

	Patients taking medications (other than antidiabetic medications) known to affect glycemic control, such as glucocorticoids, were also excluded.
<b>Recruitment / selection of participants</b>	Participants with type 2 diabetes uncontrolled on metformin monotherapy were screened and recruited from 10 hospitals to the multi-centre trial conducted in Korea. Participants were randomised to glimepiride or insulin glargine in a 1:1 ratio.
<b>Intervention(s)</b>	Glimepiride 1-8 mg daily
<b>Cointervention</b>	Metformin dose >1,000 mg daily
<b>Strata 1: People with type 2 diabetes mellitus and heart failure</b>	Not stated/unclear
<b>Strata 2: People with atherosclerotic cardiovascular disease</b>	Not stated/unclear
<b>Strata 3: People with type 2 diabetes mellitus and chronic kidney disease</b>	Not stated/unclear Exclusion criteria for significant renal impairment based on creatinine but not explicitly CKD
<b>Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk</b>	Not stated/unclear
<b>Subgroup 1: People with moderate or severe frailty</b>	Not stated/unclear
<b>Subgroup 2: Onset of type 2 diabetes mellitus</b>	Not stated/unclear
<b>Subgroup 3: People with</b>	Not stated/unclear

<b>non-alcoholic fatty liver disease</b>	
<b>Subgroup 4: People with obesity</b>	Not stated/unclear
<b>Subgroup 5: eGFR category at baseline</b>	Not stated/unclear
<b>Subgroup 6: Albuminuria category at baseline</b>	Not stated/unclear
<b>Population subgroups</b>	No additional information.
<b>Comparator</b>	Insulin glargine; titrated every three days by 2 IU after starting at 0.2 U/kg of body weight to target a fasting blood glucose (FBG) level of 90–130 mg/dL.  Administered subcutaneously.
<b>Number of participants</b>	N= 75
<b>Duration of follow-up</b>	52-week study
<b>Indirectness</b>	None
<b>Method of analysis</b>	Modified ITT
<b>Additional comments</b>	Analysis was performed on all randomised patients who received at least one dose of study medication and who had both baseline and follow-up measurements.

## 320.2. Study arms

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

Administered orally

### 320.2.2. Insulin glargine daily (N = 39)



Administered subcutaneously

### 320.3. Characteristics

#### 320.3.1. Arm-level characteristics

Characteristic	Glimepiride 1-8 mg daily (N = 36)	Insulin glargine daily (N = 39)
<b>% Male</b>	n = 17 ; % = 47.1	n = 12 ; % = 31.6
No of events		
<b>Mean age (SD)</b>	54.9 (8.6)	51.3 (8.1)
Mean (SD)		
<b>Korean</b>	n = 36 ; % = 100	n = 39 ; % = 100
No of events		
<b>Presence of frailty</b>	NR	NR
Nominal		
<b>Time since type 2 diabetes diagnosed (Months)</b>	95.6 (72.2)	79 (59.9)
Mean (SD)		
<b>Smoking status</b>	NR	NR
Nominal		
<b>Alcohol consumption</b>	NR	NR
Nominal		
<b>Presence of severe mental illness</b>	NR	NR
Nominal		
<b>People with significant cognitive impairment</b>	NR	NR
Nominal		
<b>People with a learning disability</b>	NR	NR
Nominal		
<b>Number of people with obesity</b>	NR	NR
Nominal		
<b>Albumin creatinine ratio</b>	NR	NR

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

## 321. Morikawa, 2011

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

### 321.1. Study details

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

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

<b>mellitus and high cardiovascular risk</b>	
<b>Subgroup 1: People with moderate or severe frailty</b>	Not stated/unclear
<b>Subgroup 2: Onset of type 2 diabetes mellitus</b>	Not stated/unclear
<b>Subgroup 3: People with non-alcoholic fatty liver disease</b>	Not stated/unclear
<b>Subgroup 4: People with obesity</b>	Not stated/unclear
<b>Subgroup 5: eGFR category at baseline</b>	eGFR $\geq 30$ mL/min/1.73 m <sup>2</sup> Baseline eGFR (mL/min/1.73 m <sup>2</sup> ) $79 \pm 3.4$ and $75 \pm 3.3$ indicates these values are comfortably above 30.
<b>Subgroup 6: Albuminuria category at baseline</b>	A2 (ACR 30-300 mg/g or 3-30 mg/mmol) microalbuminuria (defined by twice measured UACR $\geq 30$ mg/g Cr and $\geq 300$ mg/g Cr in first-morning urine samples in the screening period)
<b>Population subgroups</b>	NA
<b>Comparator</b>	After treatment of hypertension at least 12 weeks with angiotensin receptor blockers (ARBs) or angiotensin converting enzyme inhibitors (ACE-Is) in usual dose, patients receive metformin 500 or 750 mg/day. Metformin dose is titrated up to 750 mg/day to achieve HbA1c less than 6.9%, and maintained to 52 weeks of treatment.
<b>Number of participants</b>	70 randomised. Because two of the randomized patients were withdrawn before the start of therapy, the actual number of patients was 36 in the pioglitazone group and 32 in the metformin group. Five patients (n = 4 with pioglitazone; n = 1 with metformin) were not eligible for ITT analysis due to missing post-baseline data
<b>Duration of follow-up</b>	52 weeks
<b>Indirectness</b>	None

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

## 321.2. Study arms

### 321.2.1. Pioglitazone (N = 32)

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

### 321.2.2. Metformin (N = 31)

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

## 321.3. Characteristics

### 321.3.1. Arm-level characteristics

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

<b>Characteristic</b>	<b>Pioglitazone (N = 32)</b>	<b>Metformin (N = 31)</b>
Mean (SD)		
<b>Cardiovascular risk factors</b>	NR	NR
Nominal		
<b>Smoking status</b>	NR	NR
Nominal		
<b>Alcohol consumption</b>	NR (NR)	NR (NR)
Mean (SD)		
<b>Presence of severe mental illness</b>	NR	NR
Nominal		
<b>People with significant cognitive impairment</b>	NR	NR
Nominal		
<b>People with a learning disability</b>	NR	NR
Nominal		
<b>Number of people with obesity</b>	NR	NR
Nominal		
<b>Albumin creatinine ratio</b>	143 (84 to 202)	111 (85 to 139)
Mean (95% CI)		
<b>eGFR mL/min/1.73m<sup>2</sup></b>	79 (3.4)	75 (3.3)
Mean (SD)		
<b>Diet only</b>	21.9	16.1
Nominal		
<b>Sulfonylurea</b>	59.4	64.5
Nominal		
<b>Alpha glucosidase inhibitors</b>	21.9	16.1
Nominal		
<b>Glinide</b>	9.4	3.2
Nominal		
<b>insulin or analog</b>	15.6	16.1
Nominal		

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



## 322. Mosenzon, 2019

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

### 322.1. Study details

<b>Secondary publication of another included study- see primary study for details</b>	Not applicable
<b>Other publications associated with this study included in review</b>	Not applicable
<b>Trial name / registration number</b>	PIONEER 5 European Clinical Trials Database, EudraCT 2015-005326-19 ClinicalTrials.gov, number NCT02827708.
<b>Study type</b>	Randomised controlled trial (RCT)
<b>Study location</b>	88 sites in Denmark, Finland, Israel, Poland, Russia, Sweden, the UK, and the USA
<b>Study setting</b>	Not reported
<b>Study dates</b>	Screening was conducted between Sept 20, 2016, and Sept 29, 2017
<b>Sources of funding</b>	Novo Nordisk
<b>Inclusion criteria</b>	<ul style="list-style-type: none"> <li>• Aged 18 years or older with type 2 diabetes (diagnosed <math>\geq 90</math> days before screening)</li> <li>• HbA1c of 7.0 to 95% (53–80 mmol/mol)</li> <li>• Moderate renal impairment (Chronic Kidney Disease-Epidemiology Collaboration [CKD-EPI] stage 3), defined as an eGFR of 30–59 mL/min per 1.73 m<sup>2</sup>, calculated by use of the CKD-EPI formula</li> <li>• Required to be able to provide informed consent</li> </ul>

	<ul style="list-style-type: none"> <li>Required to be treated with stable doses of one of the following regimens for 90 days before screening: metformin (<math>\geq 1500</math> mg or maximum tolerated dose), a sulfonylurea (at least half of the maximum approved dose or maximum tolerated dose), or both; or basal insulin with or without metformin.</li> </ul>
<b>Exclusion criteria</b>	<ul style="list-style-type: none"> <li>Rapidly progressing renal disease or known nephrotic albuminuria (<math>&gt;2200</math> mg per 24 h or <math>&gt;2200</math> mg/g)</li> <li>Family or personal history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma</li> <li>History of malignant neoplasms within the past 5 years</li> <li>History of pancreatitis; myocardial infarction, stroke, or admission to hospital for unstable angina or transient ischaemic attack within the past 180 days,</li> <li>New York Heart Association Class IV heart failure</li> <li>Proliferative retinopathy or maculopathy (determined by fundus photography or dilated fundoscopy 90 days or fewer before randomisation and requiring acute treatment).</li> </ul>
<b>Recruitment / selection of participants</b>	Not reported
<b>Intervention(s)</b>	<p>Once-daily oral semaglutide escalated to 14 mg. Oral semaglutide was initiated at a 3 mg dose, then escalated to 7 mg at 4 weeks, and 14 mg at 8 weeks. No dose adjustment of study drug were permitted during the trial.</p> <p>[Both groups were instructed to take the medication in the morning in a fasted state with up to half a glass of water (approximately 120 mL), 30 min before any other food, beverage, or other oral medication.]</p>
<b>Cointervention</b>	<ul style="list-style-type: none"> <li>Background glucose-lowering medication throughout the trial. Patients receiving metformin and sulfonylureas were required to maintain the same dose level and frequency as at trial entry. Patients receiving basal insulin were recommended to have the dose decreased by 20% after random assignment to treatment group to minimise the risk of hypoglycaemic episodes.</li> <li>Up-titration of basal insulin (to a dose not exceeding that at randomisation) was permitted in weeks 10–16, after the maximum dose of oral semaglutide was reached.</li> <li>Patients with persistent and unacceptable hyperglycaemia were offered treatment intensification with rescue medication, as an add-on to assigned treatment.</li> </ul>
<b>Strata 1: People with type 2 diabetes mellitus and heart failure</b>	<p>Not stated/unclear</p> <p>Exclusion criteria for NYHA class IV heart failure but unclear about other stages</p>

<b>Strata 2: People with atherosclerotic cardiovascular disease</b>	People without atherosclerotic cardiovascular diseases  Exclusion criteria for admission with myocardial infarction, stroke, unstable angina or TIA within the past 180 days
<b>Strata 3: People with type 2 diabetes mellitus and chronic kidney disease</b>	People with chronic kidney disease  CKD stage 3
<b>Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk</b>	Not stated/unclear
<b>Subgroup 1: People with moderate or severe frailty</b>	Not stated/unclear
<b>Subgroup 2: Onset of type 2 diabetes mellitus</b>	Not stated/unclear
<b>Subgroup 3: People with non-alcoholic fatty liver disease</b>	Not stated/unclear
<b>Subgroup 4: People with obesity</b>	Not stated/unclear
<b>Subgroup 5: eGFR category at baseline</b>	eGFR $\geq 30$ mL/min/1.73m <sup>2</sup>
<b>Subgroup 6: Albuminuria category at baseline</b>	Mixed population

<b>Population subgroups</b>	Moderate renal impairment
<b>Comparator</b>	Placebo
<b>Number of participants</b>	<p>Intervention: 163 participants assigned, 163 received treatment, 30 discontinued treatment, 5 withdrew from trial, 133 completed treatment, 127 completed treatment without rescue medication, 158 completed trial</p> <p>Comparator: 161 participants assigned, 161 received treatment, 20 discontinued treatment, 5 withdrew from trial, 141 completed treatment, 127 completed treatment without rescue medication, 156 completed trial</p>
<b>Duration of follow-up</b>	26 weeks
<b>Indirectness</b>	Directly applicable
<b>Method of analysis</b>	<p>ITT</p> <p>HbA1c and bodyweight outcomes were analysed by analysis of covariance using data irrespective of discontinuation of trial product or initiation of rescue medication using a pattern mixture model with multiple imputation to handle missing data at week 26 for both confirmatory endpoints. Binary endpoints were analysed using a logistic regression model, and for the treatment policy estimand, missing data were imputed similarly as for the continuous endpoints. Safety endpoints during the on-treatment and in-trial periods using data from all participants exposed to a study drug (the safety analysis set). Sensitivity analyses were performed on the primary and confirmatory secondary endpoints, primarily to assess the effect of missing data.</p>
<b>Additional comments</b>	<ul style="list-style-type: none"> <li>• The primary estimand was treatment policy, which was defined as effect regardless of treatment discontinuation or rescue medication.</li> <li>• The secondary estimand was trial product policy, which was defined as effect on treatment without rescue medication.</li> <li>• Patients who prematurely discontinued their allocated treatment (eg, due to adverse events) were switched to an appropriate locally approved treatment selected at the investigator's discretion, excluding GLP-1 receptor agonists. All participants were asked to complete the protocol-specified visit schedule, regardless of premature discontinuation of allocated treatment or use of rescue medication, unless consent was withdrawn.</li> <li>• Sample size was calculated to ensure a power of 90% or more for testing superiority of oral semaglutide versus placebo in change of HbA1c for the treatment policy estimand.</li> </ul>

## 322.2. Study arms

### 322.2.1. Semaglutide (N = 163)

**322.2.2. Placebo (N = 161)****322.3. Characteristics****322.3.1. Arm-level characteristics**

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

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

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

## 323. Mosenzon, 2017

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

### 323.1. Study details

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



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

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

## 323.2. Study arms

### 323.2.1. Saxagliptin (N = 8280)

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

### 323.2.2. Placebo (N = 8212)

Matching placebo

## 324. Mosenzon, 2019

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

### 324.1. Study details

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

## **324.2. Study arms**

### **324.2.1. Dapagliflozin (N = 8582)**

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

### **324.2.2. Placebo (N = 8578)**

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

## 325. Moses, 2014

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

### 325.1. Study details

<b>Secondary publication of another included study- see primary study for details</b>	No additional information.
<b>Other publications associated with this study included in review</b>	No additional information.
<b>Trial name / registration number</b>	EudraCT Number: 2010-019428-30  Protocol number: D1680L00006
<b>Study type</b>	Randomised controlled trial (RCT)
<b>Study location</b>	Conducted in 35 outpatient centres in the following countries: <ul style="list-style-type: none"> <li>• Australia</li> <li>• Canada</li> <li>• India</li> <li>• Korea</li> <li>• Thailand</li> <li>• UK</li> </ul>
<b>Study setting</b>	Outpatient centre
<b>Study dates</b>	06/2010 - 06/2011
<b>Sources of funding</b>	Bristol-Myers Squibb and Astra Zeneca

<b>Inclusion criteria</b>	<ul style="list-style-type: none"> <li>• ≥18 years old with type 2 diabetes</li> <li>• BMI ≤40 kg/m<sup>2</sup></li> <li>• Inadequate glycaemic control [HbA1c, 7.0–10.0% (53–86 mmol/mol)] on combination therapy with a stable maximum tolerated dose of metformin immediate release (IR) or extended release (XR) (≥1500 mg, either formulation) plus a sulphonylurea (≥50% of the maximum recommended dose) daily for ≥8 weeks before screening.</li> <li>• Women of childbearing potential were required to be using an adequate method of contraception and have a negative urine pregnancy test at visit 2 and each visit thereafter.</li> </ul>
<b>Exclusion criteria</b>	<ul style="list-style-type: none"> <li>• Symptoms of poorly controlled diabetes;</li> <li>• Estimated creatinine clearance (CrCl) &lt;1.0 ml/s or creatinine kinase ≥10 times upper limit of normal (ULN) at visit 2</li> <li>• Congestive heart failure (New York Heart Association class III or IV and/or left ventricular ejection fraction &lt;40%); active liver disease and/or significant abnormal liver function (aspartate aminotransferase &gt;3 times ULN and/or alanine aminotransferase &gt;3 times ULN and/or bilirubin &gt;34.2 µmol/l at visit 2); history of haemoglobinopathies; history of alcohol abuse or drug abuse ≤12 months before screening; use of insulin, DPP-4 inhibitors, GLP-1 analogues or oral antidiabetic agents other than metformin and sulphonylureas currently or within 3 months of screening; treatment with systemic glucocorticoids other than replacement therapy; treatment with cytochrome P450 3A4 inducers or potent 3A4 or 3A5 inhibitors; and pregnancy or breast-feeding.</li> </ul>
<b>Recruitment / selection of participants</b>	Patients with type 2 diabetes from 35 outpatient centres in Australia, Canada, India, Korea, Thailand and the UK were recruited and randomised to saxagliptin or placebo.
<b>Intervention(s)</b>	Saxagliptin 5 mg daily, administered orally
<b>Cointervention</b>	Metformin and sulphonylurea
<b>Strata 1: People with type 2 diabetes mellitus and heart failure</b>	<p>People without heart failure</p> <p>Congestive heart failure (NYHA class III-IV and/or LVEF &lt;40%)</p>
<b>Strata 2: People with atherosclerotic cardiovascular disease</b>	Not stated/unclear
<b>Strata 3: People with type 2</b>	Not stated/unclear

<b>diabetes mellitus and chronic kidney disease</b>	
<b>Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk</b>	Not stated/unclear
<b>Subgroup 1: People with moderate or severe frailty</b>	Not stated/unclear
<b>Subgroup 2: Onset of type 2 diabetes mellitus</b>	Not stated/unclear
<b>Subgroup 3: People with non-alcoholic fatty liver disease</b>	Not stated/unclear
<b>Subgroup 4: People with obesity</b>	Not stated/unclear
<b>Subgroup 5: eGFR category at baseline</b>	Not stated/unclear
<b>Subgroup 6: Albuminuria category at baseline</b>	Not stated/unclear
<b>Population subgroups</b>	
<b>Comparator</b>	Placebo administered orally
<b>Number of participants</b>	N=257
<b>Duration of follow-up</b>	24 weeks

<b>Method of analysis</b>	ITT
<b>Additional comments</b>	

## 325.2. Study arms

### 325.2.1. Saxagliptin 5 mg daily (N = 129)

Administered orally

### 325.2.2. Placebo daily (N = 128)

Administered orally

## 325.3. Characteristics

### 325.3.1. Arm-level characteristics

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



<b>Characteristic</b>	<b>Saxagliptin 5 mg daily (N = 129)</b>	<b>Placebo daily (N = 128)</b>
Nominal		
<b>Alcohol consumption</b>	NR	NR
Nominal		
<b>Presence of severe mental illness</b>	NR	NR
Nominal		
<b>People with significant cognitive impairment</b>	NR	NR
Nominal		
<b>People with a learning disability</b>	NR	NR
Nominal		
<b>Number of people with obesity</b>	NR	NR
Nominal		
<b>Metformin</b>	n = 129 ; % = 100	n = 128 ; % = 100
No of events		
<b>Sulfonylurea</b>	n = 129 ; % = 100	n = 128 ; % = 100
No of events		
<b>Blood pressure-lowering medication used</b>	NR	NR
Nominal		
<b>Statins/lipid-lowering medication used</b>	NR	NR
Nominal		
<b>Other treatment being received</b>	NR	NR
Nominal		

## 326. Moses, 2017

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

### 326.1. Study details

<b>Secondary publication of another included study- see primary study for details</b>	No additional information.
<b>Other publications associated with this study included in review</b>	No additional information.
<b>Trial name / registration number</b>	NCT01076075
<b>Study type</b>	Randomised controlled trial (RCT)
<b>Study location</b>	USA
<b>Study setting</b>	Not reported.
<b>Study dates</b>	06/2010 - 01/2012
<b>Sources of funding</b>	Merck & Co., Inc. (Kenilworth, NJ, USA).
<b>Inclusion criteria</b>	<ul style="list-style-type: none"> <li>• Type 2 diabetes mellitus</li> <li>• Hemoglobin A1C of <math>\geq 7.5\%</math> and <math>\leq 10.5\%</math></li> <li>• Currently taking a stable dose of metformin (at least 1500 mg/day) and either glimepiride (at least 2 mg/day) or gliclazide (at least 50% of maximum registered dose) for at least 10 weeks prior to study start</li> <li>• Male, or a female who is highly unlikely to conceive</li> </ul>

<b>Exclusion criteria</b>	<p>Patients were excluded for the following reasons:</p> <ul style="list-style-type: none"> <li>• if they had type 1 diabetes mellitus,</li> <li>• a history of ketoacidosis,</li> <li>• previous treatment with either a DPP-4 inhibitor or a GLP-1 receptor agonist</li> <li>• required insulin therapy within 12 weeks prior to signing informed consent</li> <li>• they had a significant cardiovascular disorder within the prior 3months</li> <li>• renal impairment (estimated creatinine clearance &lt;60mL/min)</li> <li>• elevated (&gt;2-fold the upper limit of normal) alanine aminotransferase or aspartate aminotransferase, or fasting fingerstick glucose &lt;7.2 mmol/L or &gt;14.4mmol/L at randomisation.</li> </ul>
<b>Recruitment / selection of participants</b>	Patients with uncontrolled type 2 diabetes mellitus from 48 sites in 9 countries and on a stable dose of either glimepiride or gliclazide and metformin for 10 weeks prior to screening for the study were randomised 1:1 to either sitagliptin 100 mg/day or matching placebo.
<b>Intervention(s)</b>	Sitagliptin 100 mg once daily; administered orally.
<b>Cointervention</b>	Metformin and sulfonylurea (glimepiride/gliclazide). Patients continued on their pre-study stable doses of sulfonylurea and metformin, which were to remain stable unless down-titration of sulfonylurea was required to manage hypoglycemia.
<b>Strata 1: People with type 2 diabetes mellitus and heart failure</b>	Not stated/unclear
<b>Strata 2: People with atherosclerotic cardiovascular disease</b>	<p>People without atherosclerotic cardiovascular diseases</p> <p>Exclusion criteria for significant cardiovascular disorder</p>
<b>Strata 3: People with type 2 diabetes mellitus and chronic kidney disease</b>	<p>Not stated/unclear</p> <p>Exclusion criteria for people with renal impairment (estimated creatinine clearance &lt;60mL/min)</p>

<b>Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk</b>	Not stated/unclear
<b>Subgroup 1: People with moderate or severe frailty</b>	Not stated/unclear
<b>Subgroup 2: Onset of type 2 diabetes mellitus</b>	Not stated/unclear
<b>Subgroup 3: People with non-alcoholic fatty liver disease</b>	Not stated/unclear
<b>Subgroup 4: People with obesity</b>	Not stated/unclear
<b>Subgroup 5: eGFR category at baseline</b>	Not stated/unclear
<b>Subgroup 6: Albuminuria category at baseline</b>	Not stated/unclear
<b>Comparator</b>	Placebo daily; administered orally.
<b>Number of participants</b>	N=427
<b>Duration of follow-up</b>	24 weeks
<b>Indirectness</b>	No additional information.
<b>Method of analysis</b>	Modified ITT

## 326.2. Study arms

### 326.2.1. Sitagliptin 100 mg daily (N = 213)

Administered orally

### 326.2.2. Placebo once daily (N = 214)

Administered orally

## 326.3. Characteristics

### 326.3.1. Arm-level characteristics

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

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

## 327. Muller-Wieland, 2018

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

### 327.1. Study details

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

	Dapagliflozin + Saxagliptin (n = 312)
	Dapagliflozin 10 mg and saxagliptin 5 mg were taken orally, once daily as add-on therapy to metformin for 52 weeks
<b>Cointervention</b>	Metformin;
	All patients received background therapy with Metformin ( $\geq 1500$ mg/day)
<b>Strata 1: People with type 2 diabetes mellitus and heart failure</b>	People without heart failure  Exclusion criteria for NYHA III-IV heart failure, decompensated or acute heart failure and LVEF less than or equal to 40%
<b>Strata 2: People with atherosclerotic cardiovascular disease</b>	People without atherosclerotic cardiovascular diseases  Exclusion criteria for a cardiovascular event in the last 3 months
<b>Strata 3: People with type 2 diabetes mellitus and chronic kidney disease</b>	Not stated/unclear  Exclusion criteria for creatinine clearance of $<60$ mL/min but not explicitly CKD
<b>Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk</b>	Not stated/unclear
<b>Subgroup 1: People with moderate or severe frailty</b>	Not stated/unclear
<b>Subgroup 2: Onset of type 2 diabetes mellitus</b>	Not stated/unclear
<b>Subgroup 3: People with non-alcoholic fatty liver disease</b>	Not stated/unclear



<b>Subgroup 4: People with obesity</b>	Not stated/unclear
<b>Subgroup 5: eGFR category at baseline</b>	Not stated/unclear
<b>Subgroup 6: Albuminuria category at baseline</b>	Not stated/unclear
<b>Population subgroups</b>	NA
<b>Comparator</b>	<p>Glimepiride (n=313)</p> <p>Glimepiride treatment (1-6 mg) was initiated at 1 mg/day and was titrated upwards or downwards in 1 mg increments at subsequent visits, in accordance with prescribing information. The glimepiride/placebo dose was titrated to achieve an individualized FPG target, agreed by the patient and investigator at the start of treatment; a general target of approximately 110 mg/dL (6.1 mmol/L) was proposed in the study protocol. In order to reflect real-life clinical practice as closely as possible, glimepiride titration was allowed for the duration of the study (52 weeks).</p> <p>Patients received matching placebo plus background therapy with Metformin <math>\geq 1500</math> mg/ day</p>
<b>Number of participants</b>	939
<b>Duration of follow-up</b>	52 weeks
<b>Indirectness</b>	NA
<b>Method of analysis</b>	ITT
<b>Additional comments</b>	<p>All efficacy analyses were conducted on the full analysis set (FAS), which comprised randomized patients who received at least 1 dose of study medication and for whom there were a baseline value and at least 1 post-baseline efficacy value. Analyses were performed using values prior to rescue treatment or discontinuation. The primary efficacy variable was analysed using a mixed-model repeated measures model with fixed effects for treatment group and covariates.</p> <p>Safety analyses were performed on the safety analysis set, which comprised patients who received at least 1 dose of study medication, regardless of rescue treatment; safety data were summarized using descriptive statistics</p>

## 327.2. Study arms

### 327.2.1. Dapagliflozin (N = 314)

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

### 327.2.2. Dapagliflozin + Saxagliptin (N = 312)

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

### 327.2.3. Glimepiride (N = 313)

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

## 327.3. Characteristics

### 327.3.1. Arm-level characteristics

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

<b>Characteristic</b>	<b>Dapagliflozin (N = 314)</b>	<b>Dapagliflozin + Saxagliptin (N = 312)</b>	<b>Glimepiride (N = 313)</b>
<b>Alcohol consumption</b>	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Sample size			
<b>Presence of severe mental illness</b>	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Sample size			
<b>People with significant cognitive impairment</b>	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Sample size			
<b>People with a learning disability</b>	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Sample size			
<b>Other antidiabetic medication used</b>	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Sample size			
<b>Metformin</b>	n = 314 ; % = 100	n = 312 ; % = 100	n = 313 ; % = 100
Sample size			
<b>Blood pressure-lowering medication used</b>	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Sample size			
<b>ACE inhibitors</b>	n = 143 ; % = 45.7	n = 163 ; % = 52.2	n = 164 ; % = 52.6
Sample size			
<b>Angiotensin II antagonists</b>	n = 96 ; % = 30.7	n = 70 ; % = 22.4	n = 74 ; % = 23.7
Sample size			
<b>Beta blockers</b>	n = 114 ; % = 36.4	n = 110 ; % = 35.3	n = 104 ; % = 33.3
Sample size			
<b>Thiazides (plain)</b>	n = 39 ; % = 12.5	n = 41 ; % = 13.1	n = 48 ; % = 15.4
Sample size			
<b>Statins/lipid-lowering medication used</b>	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Sample size			
<b>Other treatment being received</b>	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR

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

## 328. Nahra, 2021

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

### 328.1. Study details

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

<b>Strata 1: People with type 2 diabetes mellitus and heart failure</b>	Not stated/unclear
<b>Strata 2: People with atherosclerotic cardiovascular disease</b>	Not stated/unclear
<b>Strata 3: People with type 2 diabetes mellitus and chronic kidney disease</b>	Not stated/unclear
<b>Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk</b>	Not stated/unclear
<b>Subgroup 1: People with moderate or severe frailty</b>	Not stated/unclear
<b>Subgroup 2: Onset of type 2 diabetes mellitus</b>	Not stated/unclear
<b>Subgroup 3: People with non-alcoholic fatty liver disease</b>	People with non-alcoholic fatty liver disease
<b>Subgroup 4: People with obesity</b>	Not stated/unclear

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

## 328.2. Study arms

### 328.2.1. Liraglutide (N = 110)

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

### 328.2.2. Placebo (N = 112)

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

## 328.3. Characteristics

### 328.3.1. Arm-level characteristics

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



<b>Characteristic</b>	<b>Liraglutide (N = 110)</b>	<b>Placebo (N = 112)</b>
<b>Smoking status</b>	n = NR ; % = NR	n = NR ; % = NR
Sample size		
<b>Alcohol consumption</b>	n = NR ; % = NR	n = NR ; % = NR
Sample size		
<b>Presence of severe mental illness</b>	n = NR ; % = NR	n = NR ; % = NR
Sample size		
<b>People with significant cognitive impairment</b>	n = NR ; % = NR	n = NR ; % = NR
Sample size		
<b>People with a learning disability</b>	n = NR ; % = NR	n = NR ; % = NR
Sample size		
<b>Other antidiabetic medication used</b>	n = NA ; % = NA	n = NA ; % = NA
Sample size		
<b>Metformin</b>	n = 110 ; % = 100	n = 112 ; % = 100
Sample size		
<b>Blood pressure-lowering medication used</b>	n = NR ; % = NR	n = NR ; % = NR
Sample size		
<b>Statins/lipid-lowering medication used</b>	n = NR ; % = NR	n = NR ; % = NR
Sample size		
<b>Other treatment being received</b>	n = NR ; % = NR	n = NR ; % = NR
Sample size		

## 329. Nakaguchi, 2020

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

### 329.1. Study details

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

	<p>(iii) renal dysfunction (eGFR&lt;30 mL/min/1.73 m<sup>2</sup> );</p> <p>(iv) steroid medication;</p> <p>(v) hepatic dysfunction (aspartate transaminase and/or alanine aminotransferase &gt;3 times the upper limit of normal);</p> <p>(vi) active malignant neoplasm;</p> <p>(vii) severe infection or injury;</p> <p>(viii) hypersensitivity to liraglutide or empagliflozin;</p> <p>(ix) pregnant or intending to become pregnant during this study;</p> <p>(x) unable to obtain informed consent for this study; and</p> <p>(xi) inadequate use of this therapy</p>
<b>Recruitment / selection of participants</b>	The participants included patients who visited Yokohama City University Hospital and Yokohama Chuo Hospital from June 2017 to May 2019
<b>Intervention(s)</b>	<p>Liraglutide (n=30)</p> <p>Patients received a starting dose of Liraglutide 0.3 mg/day, followed by 0.6 mg/day after 1 week and 0.9 mg/day after another week in addition to any prior treatment. If no side-effects appeared, a final maintenance dose of 0.9 mg/day was continued for up to 24 weeks. If side-effects occurred during the dose increase, the dose was decreased by 0.3 mg and treatment was continued, if possible. Patients subcutaneously injected themselves with liraglutide at approximately the same time each day.</p>
<b>Cointervention</b>	<p>Insulin</p> <p>Insulin dose was maintained for 24 weeks of the trial; with dose increases when marked hyperglycaemia was sustained.</p>
<b>Strata 1: People with type 2 diabetes mellitus and heart failure</b>	Not stated/unclear
<b>Strata 2: People with atherosclerotic cardiovascular disease</b>	Not stated/unclear
<b>Strata 3: People with type 2</b>	Not stated/unclear

<b>diabetes mellitus and chronic kidney disease</b>	Exclusion criteria for renal dysfunction (eGFR <30mL/min/1.73m <sup>2</sup> ) but no other information
<b>Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk</b>	Not stated/unclear
<b>Subgroup 1: People with moderate or severe frailty</b>	Not stated/unclear
<b>Subgroup 2: Onset of type 2 diabetes mellitus</b>	Not stated/unclear
<b>Subgroup 3: People with non-alcoholic fatty liver disease</b>	Not stated/unclear
<b>Subgroup 4: People with obesity</b>	Not stated/unclear
<b>Subgroup 5: eGFR category at baseline</b>	Not stated/unclear
<b>Subgroup 6: Albuminuria category at baseline</b>	Not stated/unclear
<b>Population subgroups</b>	NA
<b>Comparator</b>	<p>Empagliflozin (n=30)</p> <p>Patients received 10 mg/day empagliflozin treatment for 24 weeks in addition to any prior treatment. If glycemic control was inadequate (FBG ≥180 mg/dL or HbA1c ≥8.5%) at 12 weeks after the initiation of the intervention, the dosage was increased to 25 mg/ day empagliflozin.</p>

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

## 329.2. Study arms

### 329.2.1. Liraglutide (N = 30)

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

### 329.2.2. Empagliflozin (N = 31)

Patients received 10 - 25 mg Empagliflozin for 24 weeks.

## 329.3. Characteristics

### 329.3.1. Arm-level characteristics

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

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

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

## 330. Natali, 2017

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

### 330.1. Study details

**Secondary publication of another included study- see primary study for details**

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



## 331. Nathan, 2022

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

### 331.1. Study details

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

## 332. Nauck Michael, 2019

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

### 332.1. Study details

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

## 333. Nauck, 2007

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

### 333.1. Study details

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

<b>Cointervention</b>	Metformin + Sulfonylurea  Patients received optimally effective pre-study metformin and sulfonylurea dosages; if hypoglycaemia events occurred, investigators reduced the sulfonylurea dose by approximately 50% for patients on exenatide or adapted the insulin dose for patients on insulin.
<b>Strata 1: People with type 2 diabetes mellitus and heart failure</b>	Not stated/unclear
<b>Strata 2: People with atherosclerotic cardiovascular disease</b>	Not stated/unclear
<b>Strata 3: People with type 2 diabetes mellitus and chronic kidney disease</b>	Not stated/unclear
<b>Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk</b>	Not stated/unclear
<b>Subgroup 1: People with moderate or severe frailty</b>	Not stated/unclear
<b>Subgroup 2: Onset of type 2 diabetes mellitus</b>	Not stated/unclear
<b>Subgroup 3: People with non-alcoholic fatty liver disease</b>	Not stated/unclear

<b>Subgroup 4: People with obesity</b>	Not stated/unclear
<b>Subgroup 5: eGFR category at baseline</b>	Not stated/unclear
<b>Subgroup 6: Albuminuria category at baseline</b>	Not stated/unclear
<b>Population subgroups</b>	NA
<b>Comparator</b>	<p>Insulin (n=248)</p> <p>Patients subcutaneously injected premixed insulin before the morning and evening meals. Investigators chose the starting insulin dose for patients, and contacted patients at regular intervals to discuss glycaemic control. A forced titration schedule was not used in this trial. Investigators were instructed to adjust insulin doses to achieve an optimal balance between glycaemic control and risk of hypoglycaemia as dictated by best clinical practice.</p> <p>Patients entering this study maintained optimally effective pre-study metformin and sulfonylurea dosages if hypoglycaemia events occurred, investigators reduced the sulfonylurea dose by approximately 50% for patients on exenatide or adapted the insulin dose for patients on insulin</p>
<b>Number of participants</b>	501
<b>Duration of follow-up</b>	52 weeks
<b>Indirectness</b>	NA
<b>Method of analysis</b>	ITT
<b>Additional comments</b>	Two analysis sets were predefined for the analysis of HbA1c: (1) an intention-to-treat (ITT) sample, defined as patients who received at least one dose of study medication and had at least one post-baseline measurement of HbA1c; and (2) a per-protocol sample, defined as patients who had at least 12 weeks of exposure to study medication and no violations of screening criteria or discontinuation criteria. In non-inferiority trials, non-ITT analyses provide protection from type 1 error risk, and greater confidence is evoked when conclusions from ITT and per-protocol datasets are consistent

## 333.2. Study arms

### 333.2.1. Exenatide (N = 253)

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

### 333.2.2. Insulin (N = 248)

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

## 333.3. Characteristics

### 333.3.1. Arm-level characteristics

Characteristic	Exenatide (N = 253)	Insulin (N = 248)
<b>% Male</b>		
Sample size	n = 134 ; % = 53	n = 122 ; % = 49
<b>Mean age (SD) (Years (mean, SD))</b>		
Mean (SD)	59 (9)	58 (9)
<b>Ethnicity</b>		
Sample size	n = NR ; % = NR	n = NR ; % = NR
<b>Time since type 2 diabetes diagnosed (Years (mean, SD))</b>		
Mean (SD)	9.8 (6.3)	10 (6.2)
<b>Smoking status</b>		
Sample size	n = NR ; % = NR	n = NR ; % = NR
<b>Alcohol consumption</b>		
Sample size	n = NR ; % = NR	n = NR ; % = NR
<b>Presence of severe mental illness</b>		
Sample size	n = NR ; % = NR	n = NR ; % = NR
<b>People with significant cognitive impairment</b>		
Sample size	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Exenatide (N = 253)	Insulin (N = 248)
<b>People with a learning disability</b>		
Sample size	n = NR ; % = NR	n = NR ; % = NR
<b>Other antidiabetic medication used</b>		
Sample size	n = NA ; % = NA	n = NA ; % = NA
<b>Metformin + a sulphonylurea</b>		
Sample size	n = 253 ; % = 100	n = 248 ; % = 100
<b>Blood pressure-lowering medication used</b>		
Sample size	n = NR ; % = NR	n = NR ; % = NR
<b>Statins/lipid-lowering medication used</b>		
Sample size	n = NR ; % = NR	n = NR ; % = NR
<b>Other treatment being received</b>		
Sample size	n = NR ; % = NR	n = NR ; % = NR

## 334. Nauck, 2009

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

### 334.1. Study details

<b>Trial name / registration number</b>	NCT00286442
<b>Study type</b>	Randomised controlled trial (RCT)
<b>Study location</b>	115 sites in 15 countries
<b>Study setting</b>	No additional information
<b>Study dates</b>	NR
<b>Sources of funding</b>	Takeda Global Research and Development Center, Inc. A number of authors are employees of Takeda Global Research and Development Center, Inc. The primary authors declares honoraria from numerous pharmaceutical companies
<b>Inclusion criteria</b>	Men and women (aged 18-80 years) with an historical diagnosis of T2DM and inadequate glycaemic control (HbA1c between 7.0% and 10.0%) despite $\geq 3$ months stable metformin monotherapy regimen ( $\geq 1500$ mg per day for at least 8 weeks). BMI of 23 - 45 kg/m <sup>2</sup> ; a C-peptide concentration $\geq 0.26$ nmol/l (0.8 ng/ml) and serum creatinine $< 1.5$ mg/dl (men) or $< 1.4$ mg/dl (women). FPG $< 275$ mg/dl ( $< 15.3$ mmol/l) and $\geq 75\%$ compliance with the single-blind placebo regimen
<b>Exclusion criteria</b>	Patients who had used antidiabetic agents other than metformin within the 3 months prior to screening. Patients with a urine albumin/creatinine ratio $\geq 113$ mg/mol ( $\geq 1000$ mg/g); a history of cancer (other than squamous cell or basal cell carcinoma of the skin that had not been in full remission for at least 5 years); laser treatment for proliferative diabetic retinopathy within 6 months; a history of treated diabetic gastroparesis; New York Heart Association Class III or IV heart failure; or history of coronary angioplasty, coronary stent placement, coronary bypass surgery or myocardial infarction within 6 months were also excluded. The use of oral or systemically injected glucocorticoids or the use of weight-loss drugs within the 3 months prior to randomisation was prohibited
<b>Recruitment / selection of participants</b>	No additional information



<b>Intervention(s)</b>	<p>Alogliptin 12.5 mg (n=213)</p> <p>Alogliptin 25 mg (n=210)</p> <p>Patients received once daily doses of 12.5mg or 25mg alogliptin for 26 weeks</p>
<b>Cointervention</b>	<p>Metformin</p> <p>Patients were switched from their own metformin medication to open-label treatment with an equivalent dose of a generic immediate release metformin formulation (<math>\geq 1500</math> mg daily, except those with intolerance to this dose whereupon the patients maximum tolerated dose was used)</p>
<b>Strata 1: People with type 2 diabetes mellitus and heart failure</b>	<p>People without heart failure</p> <p>Exclusion criteria for NYHA class III or IV heart failure</p>
<b>Strata 2: People with atherosclerotic cardiovascular disease</b>	Not stated/unclear
<b>Strata 3: People with type 2 diabetes mellitus and chronic kidney disease</b>	<p>Not stated/unclear</p> <p>Exclusion criteria for people with a urine albumin/creatinine ratio above or equal to 113mg/mol but no other information and no explicit mention of CKD</p>
<b>Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk</b>	Not stated/unclear
<b>Subgroup 1: People with moderate or severe frailty</b>	Not stated/unclear
<b>Subgroup 2: Onset of type</b>	Not stated/unclear

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

## 334.2. Study arms

### 334.2.1. Alogliptin 12.5 mg (N = 213)

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

**334.2.2. Alogliptin 25 mg (N = 210)**

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

**334.2.3. Placebo (N = 104)**

Patients received placebo in combination with metformin for 26 weeks

**334.3. Characteristics****334.3.1. Arm-level characteristics**

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

<b>Characteristic</b>	<b>Alogliptin 12.5 mg (N = 213)</b>	<b>Alogliptin 25 mg (N = 210)</b>	<b>Placebo (N = 104)</b>
<b>Time since type 2 diabetes diagnosed</b> (Years (mean, SD))	6 (5)	6 (4)	6 (5)
Mean (SD)			
<b>Smoking status</b>	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Sample size			NR
<b>Alcohol consumption</b>	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Sample size			NR
<b>Presence of severe mental illness</b>	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Sample size			NR
<b>People with significant cognitive impairment</b>	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Sample size			NR
<b>People with a learning disability</b>	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Sample size			NR
<b>Other antidiabetic medication used</b>	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Sample size			NA
<b>Metformin</b>	n = 213 ; % = 100	n = 210 ; % = 100	n = 104 ; % = 100
Sample size			100
<b>Blood pressure-lowering medication used</b>	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Sample size			NR
<b>Statins/lipid-lowering medication used</b>	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Sample size			NR
<b>Other treatment being received</b>	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Sample size			NR

## 335. Nauck, 2007

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

### 335.1. Study details

<b>Secondary publication of another included study- see primary study for details</b>	NA
<b>Other publications associated with this study included in review</b>	<p>Krobot, Karl J, Ferrante, Shannon Allen, Davies, Michael J et al. (2012) Lower risk of hypoglycemia with sitagliptin compared to glipizide when either is added to metformin therapy: a pre-specified analysis adjusting for the most recently measured HbA(1c) value. Current medical research and opinion 28(8): 1281-7</p> <p>Seck, T., Nauck, M., Sheng, D. et al. (2010) Safety and efficacy of treatment with sitagliptin or glipizide in patients with type 2 diabetes inadequately controlled on metformin: a 2-year study. Int J Clin Pract 64(5): 562-76</p>
<b>Trial name / registration number</b>	Sitagliptin Protocol 024 [NCT00094770]
<b>Study type</b>	Randomised controlled trial (RCT)
<b>Study location</b>	Multinational study
<b>Study setting</b>	NR
<b>Study dates</b>	NR
<b>Sources of funding</b>	Merck & Co.
<b>Inclusion criteria</b>	<ul style="list-style-type: none"> <li>• Men and women aged 18 to 78 years with type 2 diabetes</li> <li>• Eligible patients were those who were not currently on an OHA, were taking any OHA in monotherapy or were taking metformin in combination with another OHA</li> </ul>

<b>Exclusion criteria</b>	<ul style="list-style-type: none"> <li>History of type 1 diabetes</li> <li>Insulin use within 8 weeks of screening</li> <li>Renal function impairment inconsistent with the use of metformin or a fasting plasma glucose (FPG) (or a fasting fingerstick glucose) at or just prior to randomization &gt;15.0 mmol/l (270 mg/dl)</li> </ul>
<b>Recruitment / selection of participants</b>	<ul style="list-style-type: none"> <li>Patients who were already on metformin <math>\geq 1500</math> mg/day and had an HbA1c <math>\geq 6.5</math> and <math>\leq 10\%</math> directly entered a 2-week placebo run-in period and were eligible to be randomized.</li> <li>Patients not currently on an OHA, patients on an OHA other than metformin monotherapy at a dose <math>\geq 1500</math> mg/day or patients on metformin in combination with another OHA entered a metformin monotherapy treatment titration and dose-stable period of at least 8 weeks.</li> <li>Patients with an HbA1c <math>\geq 6.5</math> and <math>\leq 10\%</math> after the metformin dose-stable period entered a 2-week single-blind placebo run-in period. Following this 2-week period, eligible patients had baseline measurements and then were randomized in a 1 : 1 ratio to the addition of sitagliptin 100 mg once daily or glipizide (at an initial dose of 5 mg/day).</li> </ul>
<b>Intervention(s)</b>	<ul style="list-style-type: none"> <li>Sitagliptin 100 mg once daily</li> <li>Glipizide - starting dose of 5 mg/day and up-titrated according to protocol-specified criteria to a potential maximum dose of 20 mg/day. During the first 18 weeks of treatment, glipizide was up-titrated, in 3-week intervals, if premeal fingerstick glucose values were &gt;6.1 mmol/l (110 mg/dl). Up-titration of glipizide could be withheld if the investigator considered that it would place the patient at risk of hypoglycaemia. Glipizide could also be down-titrated at any point in the study to prevent recurrent hypoglycaemic events.</li> </ul>
<b>Cointervention</b>	<ul style="list-style-type: none"> <li>Other treatments for hyperglycaemia were prohibited during the study.</li> <li>Concurrent lipid lowering and antihypertensive medications, thyroid medications, hormone replacement therapy and birth control medications were allowed but were expected to remain at stable doses.</li> <li>Patients received counselling on exercise and a diet consistent with American Diabetes Association recommendations</li> </ul>
<b>Strata 1: People with type 2 diabetes mellitus and heart failure</b>	<p>Not stated/unclear</p> <p>Not an inclusion/exclusion criteria. No information in baseline characteristics.</p>
<b>Strata 2: People with atherosclerotic</b>	<p>Not stated/unclear</p> <p>Not an inclusion/exclusion criteria. No information in baseline characteristics.</p>

<b>cardiovascular disease</b>	
<b>Strata 3: People with type 2 diabetes mellitus and chronic kidney disease</b>	Not stated/unclear  CKD not an inclusion/exclusion criteria. No information in baseline characteristics.
<b>Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk</b>	Not stated/unclear
<b>Subgroup 1: People with moderate or severe frailty</b>	Not stated/unclear
<b>Subgroup 2: Onset of type 2 diabetes mellitus</b>	Not stated/unclear
<b>Subgroup 3: People with non-alcoholic fatty liver disease</b>	Not stated/unclear
<b>Subgroup 4: People with obesity</b>	Not stated/unclear
<b>Subgroup 5: eGFR category at baseline</b>	Not stated/unclear
<b>Subgroup 6: Albuminuria category at baseline</b>	Not stated/unclear
<b>Population subgroups</b>	NA
<b>Comparator</b>	NA

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

## 335.2. Study arms

**335.2.1. Sitagliptin (N = 588)**

**335.2.2. Glipizide (N = 584)**



### 335.3. Characteristics

#### 335.3.1. Arm-level characteristics

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

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

## 336. Nauck, 2011

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

### 336.1. Study details

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

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

<b>Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk</b>	Not stated/unclear
<b>Subgroup 1: People with moderate or severe frailty</b>	Not stated/unclear
<b>Subgroup 2: Onset of type 2 diabetes mellitus</b>	Not stated/unclear
<b>Subgroup 3: People with non-alcoholic fatty liver disease</b>	Not stated/unclear
<b>Subgroup 4: People with obesity</b>	Mixed population  Around 56% had a BMI $\geq 30$
<b>Subgroup 5: eGFR category at baseline</b>	eGFR $\geq 30$ mL/min/1.73m <sup>2</sup>
<b>Subgroup 6: Albuminuria category at baseline</b>	Not stated/unclear
<b>Population subgroups</b>	NA
<b>Comparator</b>	Glipizide
<b>Number of participants</b>	814
<b>Duration of follow-up</b>	52 week (then 156 week extension)
<b>Indirectness</b>	None

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

## 336.2. Study arms

### 336.2.1. Dapagliflozin (N = 406)

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

### 336.2.2. Glipizide (N = 408)

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

### 336.3. Characteristics

#### 336.3.1. Arm-level characteristics

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

Characteristic	Dapagliflozin (N = 406)	Glipizide (N = 408)
<b>Cardiovascular risk factors</b>	n = NA ; % = NA	n = NA ; % = NA
Sample size		
<b>Hypertension</b>	n = 282 ; % = 70.5	n = 282 ; % = 70.3
Sample size		
<b>Smoking status</b>	n = NR ; % = NR	n = NR ; % = NR
Sample size		
<b>Alcohol consumption</b>	NR (NR)	NR (NR)
Mean (SD)		
<b>Presence of severe mental illness</b>	n = NR ; % = NR	n = NR ; % = NR
Sample size		
<b>People with significant cognitive impairment</b>	n = NR ; % = NR	n = NR ; % = NR
Sample size		
<b>People with a learning disability</b>	n = NR ; % = NR	n = NR ; % = NR
Sample size		
<b>BMI</b>	n = NA ; % = NA	n = NA ; % = NA
Sample size		
<b>≥25 kg/m<sup>2</sup></b>	n = 380 ; % = 95	n = 364 ; % = 90.8
Sample size		
<b>≥30 kg/m<sup>2</sup></b>	n = 228 ; % = 57	n = 222 ; % = 55.4
Sample size		
<b>Number of people with obesity</b>	n = NR ; % = NR	n = NR ; % = NR
Sample size		
<b>Other antidiabetic medication used</b>	n = NA ; % = NA	n = NA ; % = NA
Sample size		
<b>Metformin monotherapy</b>	n = 265 ; % = 65.3	n = 275 ; % = 67.6
Sample size		
<b>Metformin + 1 OAD</b>	n = 141 ; % = 34.7	n = 132 ; % = 32.4
Sample size		
<b>Blood pressure-lowering medication used</b>	n = NR ; % = NR	n = NR ; % = NR



Characteristic	Dapagliflozin (N = 406)	Glipizide (N = 408)
Sample size		
<b>Statins/lipid-lowering medication used</b>	n = NR ; % = NR	n = NR ; % = NR
Sample size		
<b>Other treatment being received</b>	n = NR ; % = NR	n = NR ; % = NR
Sample size		

## 337. Nauck, 2009

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

### 337.1. Study details

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

	<p>Glimepiride (n=242)</p> <p>Patients received up to 4 mg Glimepiride (with 1-, 2-, and 4-mg doses at weeks 1, 2, and 3) orally once daily with the first meal of the day</p>
<b>Cointervention</b>	<p>Metformin.</p> <p>Patients received Metformin at a maintenance dose titrated prior to study therapy commencement however , metformin could be decreased to a minimum of 1,500 mg/day in the case of unacceptable hypoglycemia or other adverse events but had to be maintained between 1,500 and 2000 mg/day during the maintenance period.</p>
<b>Strata 1: People with type 2 diabetes mellitus and heart failure</b>	Not stated/unclear
<b>Strata 2: People with atherosclerotic cardiovascular disease</b>	Not stated/unclear
<b>Strata 3: People with type 2 diabetes mellitus and chronic kidney disease</b>	Not stated/unclear
<b>Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk</b>	Not stated/unclear
<b>Subgroup 1: People with moderate or severe frailty</b>	Not stated/unclear
<b>Subgroup 2: Onset of type 2 diabetes mellitus</b>	Not stated/unclear

<b>Subgroup 3: People with non-alcoholic fatty liver disease</b>	Not stated/unclear
<b>Subgroup 4: People with obesity</b>	Not stated/unclear
<b>Subgroup 5: eGFR category at baseline</b>	Not stated/unclear
<b>Subgroup 6: Albuminuria category at baseline</b>	Not stated/unclear
<b>Population subgroups</b>	NA
<b>Comparator</b>	Placebo (n=122)  Patients received glimepiride oral placebo plus a liraglutide placebo injection for the duration of the trial
<b>Number of participants</b>	1087
<b>Duration of follow-up</b>	2 years;  An initial 26 weeks followed by an 18 months extension period
<b>Indirectness</b>	NA
<b>Method of analysis</b>	ITT
<b>Additional comments</b>	The analyses of efficacy end points were based on the intent-to-treat population defined as subjects who were exposed to at least one dose of trial product and had one postbaseline measurement of the parameter. Each end point was analysed using an ANCOVA model with treatment, country, and previous antidiabetic treatment as fixed effects and baseline as the covariate. Missing data were imputed as the last observation carried forward.

## 337.2. Study arms

### 337.2.1. Liraglutide 0.6 mg (N = 242)

Patients received 0.6 mg Liraglutide once daily for 2 years

### 337.2.2. Liraglutide 1.2 mg (N = 241)

Patients received 1.2 mg Liraglutide once daily for 2 years

### 337.2.3. Liraglutide 1.8 mg (N = 242)

Patients received 1.8 mg Liraglutide once daily for 2 years

### 337.2.4. Glimepiride (N = 244)

Patients received 4.0 mg Glimepiride once daily for 2 years

### 337.2.5. Placebo (N = 122)

Patients received oral placebo daily for 2 years

## 337.3. Characteristics

### 337.3.1. Arm-level characteristics

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

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

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

## 338. Nauck, 2014

**Bibliographic Reference** Nauck, M.; Weinstock, R. S.; Umpierrez, G. E.; Guerci, B.; Skrivanek, Z.; Milicevic, Z.; Efficacy and safety of dulaglutide versus sitagliptin after 52 weeks in type 2 diabetes in a randomized controlled trial (AWARD-5); Diabetes Care; 2014; vol. 37 (no. 8); 2149-2158

### 338.1. Study details

<b>Secondary publication of another included study- see primary study for details</b>	No additional information.
<b>Other publications associated with this study included in review</b>	<p>Weinstock, R S; Guerci, B; Umpierrez, G; Nauck, M A; Skrivanek, Z; Milicevic, Z. Safety and efficacy of once-weekly dulaglutide versus sitagliptin after 2 years in metformin-treated patients with type 2 diabetes (AWARD-5): a randomized, phase III study. Diabetes, obesity &amp; metabolism; 2015; vol. 17 (no. 9); 849-58.</p> <p>Skrivanek, Z; Gaydos, B L; Chien, J Y; Geiger, M J; Heathman, M A; Berry, S; Anderson, J H; Forst, T; Milicevic, Z; Berry, D. Dose-finding results in an adaptive, seamless, randomized trial of once-weekly dulaglutide combined with metformin in type 2 diabetes patients (AWARD-5). Diabetes, obesity &amp; metabolism; 2014; vol. 16 (no. 8); 748-56</p> <p><b>(N.B. this study was a dose finding study, where patients randomised to 7 different doses of dulaglutide, this study has been included but as a separate study altogether because it included only a small subset of the total number of patients included in the AWARD-5 trial; after the dose selection occurred, patients from the non-selected arms were discontinued and additional patients were assigned to the remaining arms: dulaglutide 1.5 mg, dulaglutide 0.75 mg, sitagliptin 100 mg, or placebo in a 2:2:2:1 ratio.)</b></p>
<b>Trial name / registration number</b>	AWARD-5/NCT00734474
<b>Study type</b>	Randomised controlled trial (RCT)
<b>Study location</b>	US, Canada, France, Germany, India, Korea, Mexico, Poland, Puerto Rico, Romania, Russian, Spain and Taiwan.
<b>Study setting</b>	Hospital



<b>Study dates</b>	08/2008 - 07/2012
<b>Sources of funding</b>	Eli Lilly and company
<b>Inclusion criteria</b>	Eligible patients were those 18–75 years old, had type 2 diabetes ( $\geq 6$ months) with an HbA1c value of $> 8\%$ (64 mmol/mol) and $\leq 9.5\%$ (80 mmol/mol) on diet and exercise alone or $\geq 7\%$ (53 mmol/mol) and $\leq 9.5\%$ (80 mmol/mol) on oral antihyperglycaemic medication monotherapy or combination therapy (metformin plus another oral antihyperglycaemic), a BMI between 25 and 40 kg/m <sup>2</sup> , and a stable weight during the 3-month period before entering the study.
<b>Exclusion criteria</b>	Taking GLP-1 receptor agonists during the 6 months prior to screening or were on chronic insulin therapy. The protocol was approved by local ethics review boards, and all patients provided written informed consent. The study was conducted in compliance with the Declaration of Helsinki and the International Conference on Harmonization guideline on good clinical practices.
<b>Recruitment / selection of participants</b>	Patients aged 18 - 75 years old with uncontrolled type 2 diabetes were randomised in a 2:2:2:1 ratio to dulaglutide 1.5 mg, dulaglutide 0.75 mg, sitagliptin 100 mg or placebo (replaced with sitagliptin after 26-weeks).
<b>Intervention(s)</b>	Dulaglutide 0.75 mg - 1.5 mg weekly Administered subcutaneously.
<b>Cointervention</b>	
<b>Strata 1: People with type 2 diabetes mellitus and heart failure</b>	Not stated/unclear  Not an inclusion/exclusion criteria. No information in baseline characteristics.
<b>Strata 2: People with atherosclerotic cardiovascular disease</b>	Not stated/unclear  Not an inclusion/exclusion criteria. No information in baseline characteristics.
<b>Strata 3: People with type 2 diabetes mellitus and chronic kidney disease</b>	Not stated/unclear  Not an inclusion/exclusion criteria. No information in baseline characteristics.
<b>Strata 4: People with type 2</b>	Not stated/unclear

<b>diabetes mellitus and high cardiovascular risk</b>	
<b>Subgroup 1: People with moderate or severe frailty</b>	Not stated/unclear
<b>Subgroup 2: Onset of type 2 diabetes mellitus</b>	Mixed population
<b>Subgroup 3: People with non-alcoholic fatty liver disease</b>	Not stated/unclear
<b>Subgroup 4: People with obesity</b>	Not stated/unclear
<b>Subgroup 5: eGFR category at baseline</b>	Not stated/unclear
<b>Subgroup 6: Albuminuria category at baseline</b>	Not stated/unclear
<b>Population subgroups</b>	
<b>Comparator</b>	Sitagliptin 100 mg daily or placebo daily
	Both administered orally.
<b>Number of participants</b>	N=1098
<b>Duration of follow-up</b>	104 weeks
<b>Indirectness</b>	

<b>Method of analysis</b>	ITT
<b>Additional comments</b>	All randomised patients were included in the analysis.

## 338.2. Study arms

### 338.2.1. Dulaglutide 1.5 mg weekly (N = 304)

Administered subcutaneously

### 338.2.2. Dulaglutide 0.75 mg weekly (N = 302)

Administered subcutaneously

### 338.2.3. Sitagliptin 100 mg daily (N = 315)

Administered orally

### 338.2.4. Placebo daily (N = 177)

Administered orally

## 338.3. Characteristics

### 338.3.1. Arm-level characteristics

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

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

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

# 339. Nauck, 2013

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

## 339.1. Study details

<b>Secondary publication of another included study- see primary study for details</b>	<p>Nauck 2009B</p> <p>Nauck M, Frid A, Hermansen K, Shah NS, Tankova T, Mitha IH, Zdravkovic M, Düring M, Matthews DR; LEAD-2 Study Group. Efficacy and safety comparison of liraglutide, glimepiride, and placebo, all in combination with metformin, in type 2 diabetes: the LEAD (liraglutide effect and action in diabetes)-2 study. Diabetes Care. 2009 Jan;32(1):84-90. doi: 10.2337/dc08-1355. Epub 2008 Oct 17. PMID: 18931095; PMCID: PMC2606836.</p>
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## 340. Nauck, 2016

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

### 340.1. Study details

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

	personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2, impaired liver function (alanine aminotransferase $\geq 2.5$ times the upper normal limit [UNL]), impaired renal function (estimated glomerular filtration rate $< 60$ mL/min/1.73 m <sup>2</sup> per MDRD formula), or any chronic disorder or severe disease that in the opinion of the investigator might jeopardize the patient's safety or compliance with the protocol.
<b>Recruitment / selection of participants</b>	NR
<b>Intervention(s)</b>	liraglutide, lixisenatide
<b>Cointervention</b>	Metformin treatment at the maximum tolerated dose (1,000 to 3,000 mg/day) for at least 90 days prior to screening
<b>Strata 1: People with type 2 diabetes mellitus and heart failure</b>	Not stated/unclear
<b>Strata 2: People with atherosclerotic cardiovascular disease</b>	Not stated/unclear
<b>Strata 3: People with type 2 diabetes mellitus and chronic kidney disease</b>	Not stated/unclear Exclusion criteria for impaired renal function (eGFR $< 60$ mL/min/1.73 m <sup>2</sup> ) but not explicitly CKD
<b>Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk</b>	Not stated/unclear
<b>Subgroup 1: People with moderate or severe frailty</b>	Not stated/unclear
<b>Subgroup 2: Onset of type</b>	Not stated/unclear



<b>2 diabetes mellitus</b>	
<b>Subgroup 3: People with non-alcoholic fatty liver disease</b>	Not stated/unclear
<b>Subgroup 4: People with obesity</b>	Not stated/unclear
<b>Subgroup 6: Albuminuria category at baseline</b>	Not stated/unclear
<b>Population subgroups</b>	NA
<b>Comparator</b>	NA
<b>Number of participants</b>	404
<b>Duration of follow-up</b>	26-week
<b>Indirectness</b>	None
<b>Method of analysis</b>	ITT Modified ITT
<b>Additional comments</b>	The full analysis set (FAS) included all randomized patients. The safety analysis set (SAS) included all patients receiving at least one dose of any of the trial products. All efficacy end points were summarized and analysed using the FAS, and all safety end points were summarized and analysed using the SAS.

## 340.2. Study arms

### 340.2.1. Liraglutide (N = 202)

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

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

### 340.2.2. Lixisenatide (N = 202)

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

## 340.3. Characteristics

### 340.3.1. Arm-level characteristics

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

<b>Characteristic</b>	<b>Liraglutide (N = 202)</b>	<b>Lixisenatide (N = 202)</b>
<b>Alcohol consumption</b>		
Mean (SD)	NR (NR)	NR (NR)
<b>Presence of severe mental illness</b>		
Sample size	n = NR ; % = NR	n = NR ; % = NR
<b>People with significant cognitive impairment</b>		
Sample size	n = NR ; % = NR	n = NR ; % = NR
<b>People with a learning disability</b>		
Sample size	n = NR ; % = NR	n = NR ; % = NR
<b>Number of people with obesity</b>		
Sample size	n = NR ; % = NR	n = NR ; % = NR
<b>Other antidiabetic medication used</b>		
Sample size	n = NA ; % = NA	n = NA ; % = NA
<b>Metformin</b>		
Sample size	n = 202 ; % = 100	n = 202 ; % = 100
<b>Blood pressure-lowering medication used</b>		
Sample size	n = NR ; % = NR	n = NR ; % = NR
<b>Statins/lipid-lowering medication used</b>		
Sample size	n = NR ; % = NR	n = NR ; % = NR
<b>Other treatment being received</b>		
Sample size	n = NR ; % = NR	n = NR ; % = NR

## 341. Neal, 2013

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

### 341.1. Study details

<b>Secondary publication of another included study- see primary study for details</b>	Mahaffey Kenneth, W, Neal, Bruce, Perkovic, Vlado et al. (2018) Canagliflozin for Primary and Secondary Prevention of Cardiovascular Events: Results From the CANVAS Program (Canagliflozin Cardiovascular Assessment Study). Circulation 137(4): 323-334
<b>Other publications associated with this study included in review</b>	<p>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 &amp; metabolism 19(3): 387-393</p> <p>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</p> <p>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</p>
<b>Trial name / registration number</b>	CANVAS Program combines the CANVAS trial (NCT01032629) and the CANVAS-R trial (NCT01989754)

## 342. Neal, 2017

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

### 342.1. Study details

<b>Secondary publication of another included study- see primary study for details</b>	Mahaffey Kenneth, W, Neal, Bruce, Perkovic, Vlado et al. (2018) Canagliflozin for Primary and Secondary Prevention of Cardiovascular Events: Results From the CANVAS Program (Canagliflozin Cardiovascular Assessment Study). Circulation 137(4): 323-334
<b>Other publications associated with this study included in review</b>	<p>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</p> <p>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</p> <p>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</p>
<b>Trial name / registration number</b>	CANVAS Program combines the CANVAS trial (NCT01032629) and the CANVAS-R trial (NCT01989754)

## 343. Nesti, 2022

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

### 343.1. Study details

<b>Other publications associated with this study included in review</b>	Natali A, Nesti L, Fabiani I, Calogero E, Di Bello V. Impact of empagliflozin on subclinical left ventricular dysfunctions and on the mechanisms involved in myocardial disease progression in type 2 diabetes: rationale and design of the EMPA-HEART trial. Cardiovasc Diabetol. 2017 Oct 12;16(1):130. doi: 10.1186/s12933-017-0615-6. PMID: 29025406; PMCID: PMC5639750.
<b>Trial name / registration number</b>	EMPA-HEART / EUDRACT Code 2016-002225-10
<b>Study type</b>	Randomised controlled trial (RCT)
<b>Study location</b>	Single centre in Pisa, Italy.
<b>Study setting</b>	Outpatients
<b>Study dates</b>	July 2017 to July 2019
<b>Sources of funding</b>	Supported at 49% by an unrestricted grant from Boehringer Ingelheim
<b>Inclusion criteria</b>	<ul style="list-style-type: none"> <li>• Male or female affected by type 2 diabetes mellitus (T2D).</li> <li>• Age <math>\geq 40</math> and <math>\leq 80</math> years.</li> <li>• HbA1c levels <math>\geq 53</math> (7%) and <math>\leq 69</math> mmol/mol (8.5%).</li> <li>• On stable (since 3 months) antidiabetic therapy with either Metformin alone or Metformin + basal insulin (this constraint is determined by the present Italian prescription rules).</li> <li>• On stable (since 3 months) cardio-active therapies (e.g. anti-hypertensive drugs, diuretics, drugs for asthma or migraine prophylaxis).</li> <li>• Preserved kidney function as defined by <math>\text{eGFR} \geq 45 \text{ ml min}^{-1} 1.73 \text{ m}^2</math>.</li> <li>• Preserved left ventricular function as defined by <math>\text{EF} \geq 50\%</math>.</li> </ul>

<b>Exclusion criteria</b>	<p>(a) impaired kidney function (CK-EPI eGFR&lt;50 mL/ min/1.76m<sup>2</sup> )</p> <p>(b) any heart disease defined as presence of clinically relevant cardiovascular symptom, cardiac or vascular disease or valvular defects, history of coronary artery disease or evidence of stress-induced ischemia, reduced (<math>\leq 50\%</math>) 2D LV ejection fraction (LVEF), cardiac autonomic neuropathy</p> <p>(c) any pulmonary, muscular, or orthopaedic diseases potentially limiting exercise capacity.</p> <ul style="list-style-type: none"> <li>•• Patients with type 1 diabetes mellitus.</li> <li>•• Pregnancy or active breast feeding.</li> <li>•• History of hospitalization for acute coronary syndrome or heart failure.</li> <li>•• Respiratory insufficiency or history of clinically significant respiratory diseases (chronic obstructive pulmonary disease).</li> <li>•• NYHA class III and IV or other symptoms of heart failure (breathlessness, orthopnoea, paroxysmal nocturnal dyspnoea, fatigue, increased time to recover after exercise, ankle swelling) unrelated to most common non-cardiac causes</li> </ul>
<b>Recruitment / selection of participants</b>	No additional information
<b>Intervention(s)</b>	<p>Empagliflozin (n=22)</p> <p>Patients will receive 26 weeks of treatment with empagliflozin 10 mg daily as add on to the background therapy</p>
<b>Cointervention</b>	<p>Metformin and or basal insulin:</p> <p>Patients were on stable metformin and / or basal insulin</p>
<b>Strata 1: People with type 2 diabetes mellitus and heart failure</b>	<p>People without heart failure</p> <p>Excluded "any heart disease defined as presence of clinically relevant cardiovascular symptom, cardiac or vascular disease or valvular defects, history of coronary artery disease or evidence of stress-induced ischemia, reduced (<math>\leq 50\%</math>) 2D LV ejection fraction (LVEF), cardiac autonomic neuropathy"</p>
<b>Strata 2: People with atherosclerotic</b>	<p>People without atherosclerotic cardiovascular diseases</p> <p>Excluded "any heart disease defined as presence of clinically relevant cardiovascular symptom, cardiac or vascular disease or valvular defects, history of coronary artery disease or evidence of stress-induced ischemia,</p>

<b>cardiovascular disease</b>	reduced ( $\leq 50\%$ ) 2D LV ejection fraction (LVEF), cardiac autonomic neuropathy". No person had peripheral artery disease (as assessed by ankle-brachial index)
<b>Strata 3: People with type 2 diabetes mellitus and chronic kidney disease</b>	Not stated/unclear  Excluded "impaired kidney function (CK-EPI eGFR $<50$ mL/ min/1.76m <sup>2</sup> ) $>50$ mL/ min/1.76m <sup>2</sup> )", otherwise unclear. No information in baseline characteristics.
<b>Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk</b>	Not stated/unclear
<b>Subgroup 1: People with moderate or severe frailty</b>	Not stated/unclear
<b>Subgroup 2: Onset of type 2 diabetes mellitus</b>	Not stated/unclear
<b>Subgroup 3: People with non-alcoholic fatty liver disease</b>	Not stated/unclear
<b>Subgroup 4: People with obesity</b>	Not stated/unclear
<b>Subgroup 5: eGFR category at baseline</b>	Not stated/unclear
<b>Subgroup 6: Albuminuria category at baseline</b>	Not stated/unclear
<b>Population subgroups</b>	NA



<b>Comparator</b>	Sitagliptin (n=22)  Patients received 26 weeks of treatment with 100 mg sitagliptin in addition to background therapy or metformin and / or basal insulin
<b>Number of participants</b>	56
<b>Duration of follow-up</b>	26 weeks
<b>Indirectness</b>	NA
<b>Method of analysis</b>	Not stated/unclear
<b>Additional comments</b>	Analysis not clearly stated however the exclusion of patients from analysis owing to abandoning trial and unreliable data suggests per protocol analysis

## 343.2. Study arms

### 343.2.1. Empagliflozin (N = 27)

Patients received 10 mg empagliflozin per day for 6 months

### 343.2.2. Sitagliptin (N = 29)

Patients received 100 mg Sitagliptin per day for 6 months

## 343.3. Characteristics

### 343.3.1. Arm-level characteristics

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

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

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

## 344. Ning, 2016

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

### 344.1. Study details

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

<b>Recruitment / selection of participants</b>	No additional information
<b>Intervention(s)</b>	Vildagliptin (n=146) Patients received 50 mg vildagliptin twice daily for 24 weeks
<b>Cointervention</b>	Insulin ± Metformin Patients remained on a stable dose (maximum ≤1 unit/kg per day) of basal long-acting, intermediate-acting, or premixed insulin with or without concomitant metformin therapy (≥1500 mg daily or a maximally tolerated dose) throughout the trial
<b>Strata 1: People with type 2 diabetes mellitus and heart failure</b>	People without heart failure Exclusion criteria for congestive heart failure (NYHA class III-IV)
<b>Strata 2: People with atherosclerotic cardiovascular disease</b>	Not stated/unclear
<b>Strata 3: People with type 2 diabetes mellitus and chronic kidney disease</b>	Not stated/unclear Exclusion criteria for significant renal impairment (eGFR <30mL/min/1.73m <sup>2</sup> ) but not explicitly CKD
<b>Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk</b>	Not stated/unclear
<b>Subgroup 1: People with moderate or severe frailty</b>	Not stated/unclear
<b>Subgroup 2: Onset of type 2 diabetes mellitus</b>	Not stated/unclear

<b>Subgroup 3: People with non-alcoholic fatty liver disease</b>	Not stated/unclear
<b>Subgroup 4: People with obesity</b>	Not stated/unclear
<b>Subgroup 5: eGFR category at baseline</b>	Not stated/unclear
<b>Subgroup 6: Albuminuria category at baseline</b>	Not stated/unclear
<b>Population subgroups</b>	NA
<b>Comparator</b>	<p>Placebo (n=147)</p> <p>Patients received placebo for 24 weeks</p> <p>Insulin ± Metformin</p> <p>Patients remained on a stable dose (maximum ≤1 unit/kg per day) of basal long-acting, intermediate-acting, or premixed insulin with or without concomitant metformin therapy (≥1500 mg daily or a maximally tolerated dose) throughout the trial</p>
<b>Number of participants</b>	293
<b>Duration of follow-up</b>	24 weeks
<b>Indirectness</b>	NA
<b>Method of analysis</b>	ITT
<b>Additional comments</b>	Efficacy analyses were performed on the full analysis set (FAS), which consisted of all randomized patients who received at least one dose of the study medication and had at least one post-randomization efficacy parameter measurement. Analysis of covariance (ANCOVA) was performed for the primary endpoint with treatment, population, metformin use, and insulin type (long- or intermediate-acting vs premixed) as the classification factors and baseline HbA1c as the covariate. The change in FPG from baseline to Week 24 (secondary endpoint) was analysed using the same model as for the primary endpoint (ANCOVA)

## 344.2. Study arms

### 344.2.1. Vildagliptin (N = 146)

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

### 344.2.2. Placebo (N = 147)

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

## 344.3. Characteristics

### 344.3.1. Arm-level characteristics

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

<b>Characteristic</b>	<b>Vildagliptin (N = 146)</b>	<b>Placebo (N = 147)</b>
<b>Alcohol consumption</b>	n = NR ; % = NR	n = NR ; % = NR
Sample size		
<b>Presence of severe mental illness</b>	n = NR ; % = NR	n = NR ; % = NR
Sample size		
<b>People with significant cognitive impairment</b>	n = NR ; % = NR	n = NR ; % = NR
Sample size		
<b>People with a learning disability</b>	n = NR ; % = NR	n = NR ; % = NR
Sample size		
<b>Other antidiabetic medication used</b>	n = NA ; % = NA	n = NA ; % = NA
Sample size		
<b>Long acting insulin</b>	n = 46 ; % = 31.5	n = 46 ; % = 31.3
Sample size		
<b>Intermediate acting insulin</b>	n = 11 ; % = 7.5	n = 12 ; % = 8.2
Sample size		
<b>Premixed insulin</b>	n = 89 ; % = 61	n = 89 ; % = 60.5
Sample size		
<b>Concomitant Metformin</b>	n = 104 ; % = 71.2	n = 104 ; % = 70.7
Sample size		
<b>Blood pressure-lowering medication used</b>	n = NR ; % = NR	n = NR ; % = NR
Sample size		
<b>Statins/lipid-lowering medication used</b>	n = NR ; % = NR	n = NR ; % = NR
Sample size		
<b>Other treatment being received</b>	n = NR ; % = NR	n = NR ; % = NR
Sample size		



## 345. Nissen, 2008

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

### 345.1. Study details

<b>Secondary publication of another included study- see primary study for details</b>	No additional information.
<b>Other publications associated with this study included in review</b>	No additional information.
<b>Trial name / registration number</b>	NCT00225277. PERISCOPE.
<b>Study type</b>	Randomised controlled trial (RCT)
<b>Study location</b>	Multicentre trial.
<b>Study setting</b>	Outpatient follow-up.
<b>Study dates</b>	August 2003-March 2006.
<b>Sources of funding</b>	Financially supported by Takeda Pharmaceuticals North America Inc.
<b>Inclusion criteria</b>	People aged 35 to 85 years; baseline HbA1c of 6.0-9.0% (if taking a glucose-lowering medication) or 6.5-10% (if not currently receiving drug therapy); required to have coronary angiography performed for clinical indications that demonstrated at least 1 angiographic stenosis with at least 20% narrowing; a "target vessel" for IVUS examination was required to have less than 50% obstruction throughout a 40-mm or longer segment.
<b>Exclusion criteria</b>	Type 1 diabetes; taking 3 or more antidiabetic medications; received any thiazolidinedione within the past 12 weeks; serum creatinine level of >2.0 mg/dL; triglyceride level of more than 500mg/dL; uncontrolled hypertension

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

<b>Subgroup 1: People with moderate or severe frailty</b>	Not stated/unclear
<b>Subgroup 2: Onset of type 2 diabetes mellitus</b>	Not stated/unclear
<b>Subgroup 3: People with non-alcoholic fatty liver disease</b>	Not stated/unclear
<b>Subgroup 4: People with obesity</b>	Not stated/unclear
<b>Subgroup 5: eGFR category at baseline</b>	Not stated/unclear
<b>Subgroup 6: Albuminuria category at baseline</b>	Not stated/unclear
<b>Population subgroups</b>	No additional information.
<b>Comparator</b>	<p>Pioglitazone N=270</p> <p>Pioglitazone 15mg if people were naive to glucose lowering therapy at screening or taking less than glimepiride 2mg/day (or an equivalent dosage of another sulfonylurea) at baseline. Pioglitazone at a starting dosage of 30mg for those taking 2mg/day or more of glimepiride (or the equivalent) or metformin monotherapy. At the subsequent visits the study drug was increased to the next level (30mg or 45mg of glimepiride). The study drug was titrated to the maximum dose by 16 weeks, if tolerated. Total duration of 18 months.</p>
<b>Number of participants</b>	543
<b>Duration of follow-up</b>	18 months.
<b>Indirectness</b>	No additional information.
<b>Method of analysis</b>	Modified ITT

<b>Additional comments</b>	No additional information.
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## 345.2. Study arms

### 345.2.1. Glimepiride (N = 273)

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

### 345.2.2. Pioglitazone (N = 270)

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

## 345.3. Characteristics

### 345.3.1. Arm-level characteristics

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

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

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

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

## 346. Nogueira, 2014

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

### 346.1. Study details

<b>Secondary publication of another included study- see primary study for details</b>	NA
<b>Other publications associated with this study included in review</b>	NA
<b>Trial name / registration number</b>	NR
<b>Study type</b>	Randomised controlled trial (RCT)
<b>Study location</b>	Unclear- appears to be Brazil
<b>Study setting</b>	NR
<b>Study dates</b>	NR
<b>Sources of funding</b>	grants from Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP)
<b>Inclusion criteria</b>	Outpatients with type 2 diabetes inadequately controlled with metformin plus glyburide
<b>Exclusion criteria</b>	<ul style="list-style-type: none"> <li>• Severe heart failure</li> <li>• Respiratory failure</li> <li>• Uncontrolled hypertension</li> <li>• Coronary heart disease</li> <li>• Arrhythmias</li> <li>• Hepatic and renal dysfunctions</li> <li>• Endocrine and gastrointestinal disorders</li> <li>• Malignancy</li> </ul>



	<ul style="list-style-type: none"> <li>• Alcohol abuse</li> <li>• Use of insulin</li> <li>• Beta blockers or calcium channel antagonists</li> <li>• Type 1 DM</li> </ul>
<b>Recruitment / selection of participants</b>	NR
<b>Intervention(s)</b>	Sitagliptin 100 mg daily
<b>Cointervention</b>	All medications were kept constant during the study
<b>Strata 1: People with type 2 diabetes mellitus and heart failure</b>	<p>Not stated/unclear</p> <p>Exclusion criteria for severe heart failure but unclear about other forms</p>
<b>Strata 2: People with atherosclerotic cardiovascular disease</b>	<p>Not stated/unclear</p> <p>Note that there is exclusion criteria for coronary heart disease</p>
<b>Strata 3: People with type 2 diabetes mellitus and chronic kidney disease</b>	<p>Not stated/unclear</p> <p>Exclusion criteria for renal dysfunction but not explicitly CKD</p>
<b>Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk</b>	Not stated/unclear
<b>Subgroup 1: People with moderate or severe frailty</b>	Not stated/unclear
<b>Subgroup 2: Onset of type 2 diabetes mellitus</b>	Not stated/unclear

<b>Subgroup 3: People with non-alcoholic fatty liver disease</b>	Not stated/unclear
<b>Subgroup 4: People with obesity</b>	Not stated/unclear
<b>Subgroup 5: eGFR category at baseline</b>	Not stated/unclear
<b>Subgroup 6: Albuminuria category at baseline</b>	Not stated/unclear
<b>Population subgroups</b>	NA
<b>Comparator</b>	Bedtime NPH-insulin (final dose $11.0 \pm 6.7$ IU)
<b>Number of participants</b>	35 participants: 18 allocated to sitagliptin and 17 allocated to NHP insulin. No information around attrition
<b>Duration of follow-up</b>	24 weeks
<b>Indirectness</b>	Directly applicable
<b>Method of analysis</b>	Not stated/unclear  Methods state that differences were assessed with two-way ANOVA models
<b>Additional comments</b>	

## 346.2. Study arms

### 346.2.1. Sitagliptin (N = 18)

### 346.2.2. Insulin NPH (N = 17)

### 346.3. Characteristics

#### 346.3.1. Arm-level characteristics

Characteristic	Sitagliptin (N = 18)	Insulin NPH (N = 17)
<b>% Male</b>	n = 9 ; % = 50	n = 6 ; % = 35.3
Sample size		
<b>Mean age (SD)</b>	55.1 (6.7)	58.4 (6.9)
Mean (SD)		
<b>Ethnicity</b>	NR	NR
Nominal		
<b>Comorbidities</b>	NR	NR
Nominal		
<b>Presence of frailty</b>	NR	NR
Nominal		
<b>Time since type 2 diabetes diagnosed</b>	10.9 (5.8)	10.9 (7.5)
Mean (SD)		
<b>Cardiovascular risk factors</b>	NR	NR
Nominal		
<b>Smoking status</b>	NR	NR
Nominal		
<b>Alcohol consumption</b>	NR	NR
Nominal		
<b>Presence of severe mental illness</b>	NR	NR
Nominal		
<b>People with significant cognitive impairment</b>	NR	NR
Nominal		
<b>People with a learning disability</b>	NR	NR
Nominal		
<b>Number of people with obesity</b>	NR	NR
Nominal		
<b>Other antidiabetic medication used (mg/day)</b>	NA (NA)	NA (NA)

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

## 347. Nowicki, 2011

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

### 347.1. Study details

<b>Secondary publication of another included study- see primary study for details</b>	Not applicable
<b>Other publications associated with this study included in review</b>	Nowicki M, Rychlik I, Haller H, Warren ML, Suchower L, Gause-Nilsson I; D1680C00007 Investigators. Saxagliptin improves glycaemic control and is well tolerated in patients with type 2 diabetes mellitus and renal impairment. Diabetes Obes Metab. 2011 Jun;13(6):523-32. doi: 10.1111/j.1463-1326.2011.01382.x. PMID: 21332627.
<b>Trial name / registration number</b>	NCT00614939
<b>Study type</b>	Randomised controlled trial (RCT)
<b>Study location</b>	Multi-centre - Belarus, Croatia, Czech Republic, Estonia, Germany, Hungary, Latvia, Lithuania, Poland, Romania, Russia, Ukraine, USA
<b>Study setting</b>	Not reported
<b>Study dates</b>	January 2008 to March 2010
<b>Sources of funding</b>	Bristol-Myers Squibb and AstraZeneca
<b>Inclusion criteria</b>	<ul style="list-style-type: none"> <li>• Adult patients with type 2 diabetes and CrCl &lt;50 ml/min within the past 3 months</li> <li>• C-peptide ≥ 0.33 nmol/l</li> <li>• HbA1c ≥7.0% and ≤11.0%</li> </ul>
<b>Exclusion criteria</b>	<ul style="list-style-type: none"> <li>• Current or anticipated need for peritoneal dialysis or expected kidney transplant within 3 months after enrolment</li> <li>• Aspartate aminotransferase, alanine aminotransferase and/or total bilirubin &gt; 1.5 times the upper limit of normal</li> </ul>

	<ul style="list-style-type: none"> <li>• Creatine kinase <math>\geq 3</math> times the upper limit of normal</li> <li>• Treatment with metformin within 4 weeks before enrolment</li> <li>• Previous or current treatment with any DPP-4 inhibitor or GLP-1 agonist</li> </ul>
<b>Recruitment / selection of participants</b>	Not reported
<b>Intervention(s)</b>	Saxagliptin 2.5 mg once daily
<b>Cointervention</b>	<ul style="list-style-type: none"> <li>• Other antidiabetic drugs in use at enrolment were continued, subject to adjustment as needed to prevent hypoglycaemia throughout the 52-week study or to improve glycaemic control during the 40-week extension</li> <li>• Addition of new drugs except thiazolidinediones, glucagon-like peptide-1 (GLP-1) agonists, metformin and other DPP-4 inhibitors was allowed</li> </ul>
<b>Strata 1: People with type 2 diabetes mellitus and heart failure</b>	Not stated/unclear
<b>Strata 2: People with atherosclerotic cardiovascular disease</b>	Not stated/unclear
<b>Strata 3: People with type 2 diabetes mellitus and chronic kidney disease</b>	<p>People with chronic kidney disease</p> <p>People with renal impairment entering the study (creatinine clearance <math>&lt;50\text{mL/min}</math> within the past 3 months)</p>
<b>Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk</b>	Not stated/unclear
<b>Subgroup 1: People with</b>	Not stated/unclear

<b>moderate or severe frailty</b>	
<b>Subgroup 2: Onset of type 2 diabetes mellitus</b>	Not stated/unclear
<b>Subgroup 3: People with non-alcoholic fatty liver disease</b>	Not stated/unclear
<b>Subgroup 4: People with obesity</b>	Not stated/unclear
<b>Subgroup 5: eGFR category at baseline</b>	Not stated/unclear
<b>Subgroup 6: Albuminuria category at baseline</b>	Not stated/unclear
<b>Population subgroups</b>	<ul style="list-style-type: none"> <li>• Moderate baseline renal impairment (<math>\text{CrCl} \geq 30</math> and <math>&lt; 50</math> nml/min)</li> <li>• Severe baseline renal impairment (<math>\text{CrCl} &lt; 30</math> ml/min and not receiving dialysis)</li> <li>• End-stage renal disease on haemodialysis at baseline</li> </ul>
<b>Comparator</b>	Placebo
<b>Number of participants</b>	170 participants
<b>Duration of follow-up</b>	<ul style="list-style-type: none"> <li>• 12 weeks</li> <li>• 52 weeks</li> </ul>
<b>Indirectness</b>	Directly applicable
<b>Method of analysis</b>	<p>ACA</p> <p>Extracted data - absolute changes in HbA1c from baseline to week 52 were assessed using observed data only.</p> <p>Per protocol</p> <p>Sensitivity analysis was reported with per-protocol analysis set (i.e. those without significant protocol deviations) using LOCF methodology</p>

	ITT
	Absolute changes in HbA1c were compared using an ANCOVA model with treatment group and baseline renal impairment as fixed effects and baseline value as covariate. Data were included up to completion, discontinuation, or change in insulin or OAD dose. Missing efficacy data were imputed using last observed data carried forward.
<b>Additional comments</b>	<ul style="list-style-type: none"> <li>Patients were stratified based on degree of renal impairment were and randomized (1 : 1) via an interactive voice response system in balanced blocks within each renal impairment category.</li> <li>Study-specific discontinuation criteria were FPG &gt; 15.0 mmol/l at weeks 2 or 4, &gt; 13.3 mmol/l at weeks 6 or 9, &gt; 12.2 mmol/l at week 12 or &gt; 11.1 mmol/l at week 20; and HbA1c &gt; 8% (&gt; 7.5% at sites in Germany) at weeks 28, 36 or 44.</li> </ul>

## 347.2. Study arms

### 347.2.1. Saxagliptin (N = 85)

### 347.2.2. Placebo (N = 85)

## 347.3. Characteristics

### 347.3.1. Arm-level characteristics

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



<b>Characteristic</b>	<b>Saxagliptin (N = 85)</b>	<b>Placebo (N = 85)</b>
<b>Time since type 2 diabetes diagnosed</b>		
Mean (SD)	15.1 (7.5)	18.2 (8.5)
<b>HbA1c (%)</b>		
Sample size	n = 85 ; % = 100	n = 84 ; % = 98.8
<b>HbA1c (%)</b>		
Mean (SD)	8.5 (1.2)	8.1 (1.1)
<b>Smoking status</b>		
Nominal	NR	NR
<b>Alcohol consumption</b>		
Nominal	NR	NR
<b>Presence of severe mental illness</b>		
Nominal	NR	NR
<b>People with significant cognitive impairment</b>		
Nominal	NR	NR
<b>People with a learning disability</b>		
Nominal	NR	NR
<b>Weight (kg)</b>		
Mean (SD)	83.6 (15.7)	82.2 (14.4)
<b>BMI (kg/m<sup>2</sup>)</b>		
Mean (SD)	31.2 (6.1)	30.2 (6.8)
<b>Number of people with obesity</b>		
Nominal	NR	NR
<b>Other antidiabetic medication used</b>		
Sample size	n = 83 ; % = 97.6	n = 84 ; % = 98.8
<b>Insulin</b>		
Sample size	n = 71 ; % = 83.5	n = 57 ; % = 67.1
<b>Oral blood glucose-lowering drug</b>		
Sample size	n = 23 ; % = 27.1	n = 30 ; % = 35.3

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

## 348. Nowicki, 2011

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

### 348.1. Study details

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

### 348.2. Study arms

**348.2.1. Saxagliptin (N = 85)**

**348.2.2. Placebo (N = 85)**

## 349. Oh, 2021

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

### 349.1. Study details

<b>Secondary publication of another included study- see primary study for details</b>	No information available.
<b>Other publications associated with this study included in review</b>	No information available.
<b>Trial name / registration number</b>	ELITE trial NCT03208465
<b>Study type</b>	Randomised controlled trial (RCT)
<b>Study location</b>	South Korea
<b>Study setting</b>	University, medical centre
<b>Study dates</b>	August 2017 - August 2019
<b>Sources of funding</b>	No information available.
<b>Inclusion criteria</b>	Adults ( $\geq 18$ years of age) with type 2 diabetes with stable coronary artery disease, global myocardial perfusion reserve (MPR) $< 2.5$ and a glycated hemoglobin level $< 10.0\%$ .
<b>Exclusion criteria</b>	Patients were excluded if they had <ul style="list-style-type: none"> <li>Contraindications to empagliflozin or sitagliptin; had received SGLT2 inhibitors or dipeptidyl peptidase-4 inhibitors within the previous 4 weeks;</li> </ul>

	<ul style="list-style-type: none"> <li>• Had insulin-requiring diabetes; acute coronary syndrome; stent placement or coronary artery bypass graft surgery within the previous 6 months; planned revascularisation within 6 months;</li> <li>• Heart failure requiring loop diuretics; chronic kidney disease; hepatic disease or biliary tract obstruction;</li> <li>• Were pregnant, breast-feeding, or had child-bearing potential or if they had an expected life expectancy &lt;1 year.</li> </ul>
<b>Recruitment / selection of participants</b>	Eligible patients who met all the inclusion criteria and none of the exclusion criteria were included and randomly assigned to empagliflozin group or sitagliptin group using a computer generated randomisation program.
<b>Intervention(s)</b>	Empagliflozin 10 mg, administered orally once daily
<b>Cointervention</b>	Other conventional oral antidiabetic drugs, including metformin, sulfonylurea and pioglitazone were used to control the glucose levels in both groups.
<b>Strata 1: People with type 2 diabetes mellitus and heart failure</b>	<p>People without heart failure</p> <p>Heart failure requiring loop diuretics as an exclusion criteria - likely a large proportion of people with heart failure</p>
<b>Strata 2: People with atherosclerotic cardiovascular disease</b>	<p>People with atherosclerotic cardiovascular diseases</p> <p>People with coronary artery disease</p>
<b>Strata 3: People with type 2 diabetes mellitus and chronic kidney disease</b>	<p>People without chronic kidney disease</p> <p>Exclusion criteria</p>
<b>Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk</b>	Not stated/unclear
<b>Subgroup 1: People with moderate or severe frailty</b>	Not stated/unclear

<b>Subgroup 2: Onset of type 2 diabetes mellitus</b>	Not stated/unclear
<b>Subgroup 3: People with non-alcoholic fatty liver disease</b>	Not stated/unclear
<b>Subgroup 4: People with obesity</b>	Not stated/unclear
<b>Subgroup 5: eGFR category at baseline</b>	eGFR $\geq 30$ mL/min/1.73m <sup>2</sup>
<b>Subgroup 6: Albuminuria category at baseline</b>	Not stated/unclear
<b>Population subgroups</b>	
<b>Comparator</b>	Sitagliptin 100 mg, administered orally once daily.
<b>Number of participants</b>	N=100
<b>Duration of follow-up</b>	6 months
<b>Indirectness</b>	
<b>Method of analysis</b>	ITT
<b>Additional comments</b>	

## 349.2. Study arms

### 349.2.1. Empagliflozin 10 mg (N = 48)

Administered orally, once daily

**349.2.2. Sitagliptin 100 mg (N = 49)**

Administered orally, once daily

**349.3. Characteristics****349.3.1. Arm-level characteristics**

<b>Characteristic</b>	<b>Empagliflozin 10 mg (N = 48)</b>	<b>Sitagliptin 100 mg (N = 49)</b>
<b>% Male</b>	n = 41 ; % = 85.4	n = 44 ; % = 89.8
No of events		
<b>Mean age (SD) (years)</b>	63.6 (9.2)	66.3 (7.6)
Mean (SD)		
<b>Ethnicity</b>	NR	NR
Nominal		
<b>Presence of frailty</b>	NR	NR
Nominal		
<b>Time since type 2 diabetes diagnosed (Months)</b>	75.2 (75)	73.2 (64.7)
Mean (SD)		
<b>Smokers</b>	n = 11 ; % = 23.4	n = 8 ; % = 17
No of events		
<b>Alcohol consumption</b>	NR	NR
Nominal		
<b>Presence of severe mental illness</b>	NR	NR
Nominal		
<b>People with significant cognitive impairment</b>	NR	NR
Nominal		
<b>People with a learning disability</b>	NR	NR
Nominal		
<b>Number of people with obesity</b>	NR	NR
Nominal		

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



## 350. Ohira, 2014

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

### 350.1. Study details

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

<b>Intervention(s)</b>	Sitagliptin 50 mg/day
<b>Cointervention</b>	Participants continued to take metformin 500 mg/day. All participants maintained their same diet and exercise therapies and did not change medications including statins. Participants received nutritional guidance from a dietitian every month.
<b>Strata 1: People with type 2 diabetes mellitus and heart failure</b>	Not stated/unclear
<b>Strata 2: People with atherosclerotic cardiovascular disease</b>	Not stated/unclear
<b>Strata 3: People with type 2 diabetes mellitus and chronic kidney disease</b>	Not stated/unclear
<b>Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk</b>	Not stated/unclear
<b>Subgroup 1: People with moderate or severe frailty</b>	Not stated/unclear
<b>Subgroup 2: Onset of type 2 diabetes mellitus</b>	Not stated/unclear
<b>Subgroup 3: People with non-alcoholic fatty liver disease</b>	Not stated/unclear

<b>Subgroup 4: People with obesity</b>	Not stated/unclear
<b>Subgroup 5: eGFR category at baseline</b>	Not stated/unclear
<b>Subgroup 6: Albuminuria category at baseline</b>	Not stated/unclear
<b>Population subgroups</b>	NA
<b>Comparator</b>	Additional 500 mg/day metformin (total metformin dose 1000 mg/day)
<b>Number of participants</b>	70 participants were randomised, 35 participants were allocated to the sitagliptin arm, and 35 participants were allocated to the additional metformin arm. No information was provided about treatment or study completion.
<b>Duration of follow-up</b>	6 months
<b>Indirectness</b>	Directly applicable
<b>Method of analysis</b>	Not stated/unclear
<b>Additional comments</b>	NA

## 350.2. Study arms

### 350.2.1. Sitagliptin + metformin (N = 35)

### 350.2.2. Metformin (N = 35)

### 350.3. Characteristics

#### 350.3.1. Arm-level characteristics

Characteristic	Sitagliptin + metformin (N = 35)	Metformin (N = 35)
<b>% Male</b>	n = 21 ; % = 60	n = 15 ; % = 42.9
Sample size		
<b>Mean age (SD) (years)</b>	60.03 (12.35)	60.71 (11.01)
Mean (SD)		
<b>Ethnicity</b>	NR	NR
Nominal		
<b>Comorbidities</b>	NR	NR
Nominal		
<b>Presence of frailty</b>	NR	NR
Nominal		
<b>Time since type 2 diabetes diagnosed</b>	NR	NR
Nominal		
<b>Cardiovascular risk factors</b>	NR	NR
Nominal		
<b>Blood pressure</b>	NR	NR
Nominal		
<b>Smoking status</b>	NR	NR
Nominal		
<b>Alcohol consumption</b>	NR	NR
Nominal		
<b>Presence of severe mental illness</b>	NR	NR
Nominal		
<b>People with significant cognitive impairment</b>	NR	NR
Nominal		
<b>People with a learning disability</b>	NR	NR
Nominal		

<b>Characteristic</b>	<b>Sitagliptin + metformin (N = 35)</b>	<b>Metformin (N = 35)</b>
<b>Number of people with obesity</b> Nominal	NR	NR
<b>Other antidiabetic medication used</b> Nominal	NR	NR
<b>Blood pressure-lowering medication used</b> Nominal	NR	NR
<b>Statins/lipid-lowering medication used</b> Sample size	n = 7 ; % = 20	n = 12 ; % = 34.2
<b>Other treatment being received</b> Nominal	NR	NR

## 351. Ohira, 2014

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

### 351.1. Study details

<b>Secondary publication of another included study- see primary study for details</b>	NR
<b>Other publications associated with this study included in review</b>	NA
<b>Trial name / registration number</b>	NR
<b>Study type</b>	Randomised controlled trial (RCT)
<b>Study setting</b>	NR
<b>Study dates</b>	NR
<b>Sources of funding</b>	NR
<b>Inclusion criteria</b>	<ul style="list-style-type: none"> <li>• Participants with type 2 diabetes (HbA1c &gt; 7.0%)</li> <li>• All participants treated solely with 500 mg/day of metformin</li> </ul>
<b>Exclusion criteria</b>	NR
<b>Recruitment / selection of participants</b>	Before participation, the purpose of the study was explained to each subject, and consent was obtained for both participation in this study and for release of the study data.
<b>Intervention(s)</b>	<ul style="list-style-type: none"> <li>• Pioglitazone 15 mg/day</li> </ul>

	<ul style="list-style-type: none"> <li>• Glimepiride 1 mg/day</li> </ul>
<b>Cointervention</b>	<ul style="list-style-type: none"> <li>• 500 mg/day metformin</li> <li>• All patients maintained the same diet and exercise therapies and did not change medications during this study</li> <li>• A dietician provided nutritional guidance to all subjects on a monthly basis</li> </ul>
<b>Strata 1: People with type 2 diabetes mellitus and heart failure</b>	Not stated/unclear
<b>Strata 2: People with atherosclerotic cardiovascular disease</b>	Not stated/unclear
<b>Strata 3: People with type 2 diabetes mellitus and chronic kidney disease</b>	Not stated/unclear
<b>Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk</b>	Not stated/unclear
<b>Subgroup 1: People with moderate or severe frailty</b>	Not stated/unclear
<b>Subgroup 2: Onset of type 2 diabetes mellitus</b>	Not stated/unclear
<b>Subgroup 3: People with non-alcoholic</b>	Not stated/unclear

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

## 351.2. Study arms

### 351.2.1. Pioglitazone (N = 30)

### 351.2.2. Glimepiride (N = 30)



### 351.3. Characteristics

#### 351.3.1. Arm-level characteristics

Characteristic	Pioglitazone (N = 30)	Glimepiride (N = 30)
<b>% Male</b>	n = 19 ; % = 63.3	n = 15 ; % = 50
Sample size		
<b>Mean age (SD)</b>	63.7 (7.94)	62.23 (12.26)
Mean (SD)		
<b>Ethnicity</b>	NR	NR
Nominal		
<b>Comorbidities</b>	NR	NR
Nominal		
<b>Presence of frailty</b>	NR	NR
Nominal		
<b>Time since type 2 diabetes diagnosed</b>	NR	NR
Nominal		
<b>Cardiovascular risk factors</b>	NR	NR
Nominal		
<b>Smoking status</b>	NR	NR
Nominal		
<b>Alcohol consumption</b>	NR	NR
Nominal		
<b>Presence of severe mental illness</b>	NR	NR
Nominal		
<b>People with significant cognitive impairment</b>	NR	NR
Nominal		
<b>People with a learning disability</b>	NR	NR
Nominal		
<b>Number of people with obesity</b>	NR	NR
Nominal		

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

## 352. Owens, 2011

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

### 352.1. Study details

<b>Secondary publication of another included study- see primary study for details</b>	NA
<b>Other publications associated with this study included in review</b>	NA
<b>Trial name / registration number</b>	NCT00602472
<b>Study type</b>	Randomised controlled trial (RCT)
<b>Study location</b>	100 trial centres in 11 countries: Argentina, Belgium, Canada, China, Germany, Korea, the Philippines, Russia, Taiwan, Turkey and the UK
<b>Study setting</b>	NR
<b>Study dates</b>	NR
<b>Sources of funding</b>	Boehringer Ingelheim
<b>Inclusion criteria</b>	<ul style="list-style-type: none"> <li>• Type 2 diabetes aged <math>\geq 18</math> and <math>\leq 80</math> years</li> <li>• BMI <math>\leq 40</math> kg/m<sup>2</sup></li> <li>• HbA1c <math>\geq 7.0\%</math> and <math>\leq 10\%</math> despite receiving a total daily dose of <math>\geq 1500</math> mg metformin (or the maximum tolerated dose, if lower) and the maximum tolerated dose of sulphonylurea. The dose and regimen of metformin and the sulphonylurea were unchanged for <math>\geq 10</math> weeks before enrolment</li> </ul>

<b>Exclusion criteria</b>	<ul style="list-style-type: none"> <li>• Clinical conditions that would, in the investigator's opinion, interfere with participation and safety.</li> <li>• Myocardial infarction, stroke or transient ischaemic attack within 6 months before enrolment</li> <li>• Impaired hepatic function</li> <li>• Renal failure or renal impairment</li> <li>• Current acute or chronic metabolic acidosis</li> <li>• Hereditary galactose intolerance</li> <li>• Being unable or unwilling to avoid nursing or pregnancy</li> <li>• Patients treated with rosiglitazone, pioglitazone, GLP-1 analogues, insulin or anti-obesity drugs (e.g. sibutramine, rimonabant, orlistat) within 3 months</li> </ul>
<b>Recruitment / selection of participants</b>	NR
<b>Intervention(s)</b>	Linagliptin 5 mg once daily
<b>Cointervention</b>	Participants received established background therapy of metformin in combination with a sulfonylurea
<b>Strata 1: People with type 2 diabetes mellitus and heart failure</b>	Not stated/unclear
<b>Strata 2: People with atherosclerotic cardiovascular disease</b>	<p>Not stated/unclear</p> <p>Exclusion criteria for myocardial infarction, stroke or TIA within 6 months of enrolment</p>
<b>Strata 3: People with type 2 diabetes mellitus and chronic kidney disease</b>	Not stated/unclear
<b>Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk</b>	Not stated/unclear

<b>Subgroup 1: People with moderate or severe frailty</b>	Not stated/unclear
<b>Subgroup 2: Onset of type 2 diabetes mellitus</b>	Not stated/unclear
<b>Subgroup 3: People with non-alcoholic fatty liver disease</b>	Not stated/unclear
<b>Subgroup 4: People with obesity</b>	Mixed population
<b>Subgroup 5: eGFR category at baseline</b>	Not stated/unclear
<b>Subgroup 6: Albuminuria category at baseline</b>	Not stated/unclear
<b>Population subgroups</b>	NA
<b>Comparator</b>	Placebo
<b>Number of participants</b>	1,058 participants were randomised. Of 793 participants allocated to linagliptin, 792 received the intervention, and of these 58 participants discontinued. Of 265 participants allocated to placebo, 263 received the intervention, of these 21 discontinued.
<b>Duration of follow-up</b>	24 weeks
<b>Indirectness</b>	Directly applicable
<b>Method of analysis</b>	Per protocol  For HbA1c change, sensitivity analyses were performed to assess the impact of important protocol violations and premature discontinuation, and to assess missing data assumptions i.e. mixed-model repeated measures  Not stated/unclear

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

## 352.2. Study arms

### 352.2.1. Linagliptin (N = 793)

### 352.2.2. Placebo (N = 265)

## 352.3. Characteristics

### 352.3.1. Arm-level characteristics

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

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

<b>Characteristic</b>	<b>Linagliptin (N = 793)</b>	<b>Placebo (N = 265)</b>
<b>Cardiovascular risk factors</b>	NR	NR
Nominal		
<b>Smoking status</b>	NR	NR
Nominal		
<b>Alcohol consumption</b>	NR	NR
Nominal		
<b>Presence of severe mental illness</b>	NR	NR
Nominal		
<b>People with significant cognitive impairment</b>	NR	NR
Nominal		
<b>People with a learning disability</b>	NR	NR
Nominal		
<b>BMI ( kg/m<sup>2</sup>)</b>	28.4 (4.8)	28.2 (4.5)
Mean (SD)		
<b>Number of people with obesity BMI ≥30</b>	n = 260 ; % = 32.8	n = 78 ; % = 29.7
Sample size		
<b>Other antidiabetic medication used</b>	NR	NR
Nominal		
<b>Blood pressure-lowering medication used</b>	NR	NR
Nominal		
<b>Statins/lipid-lowering medication used</b>	NR	NR
Nominal		
<b>Other treatment being received</b>	NR	NR
Nominal		



## 353. Pan, 2012

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

### 353.1. Study details

<b>Secondary publication of another included study- see primary study for details</b>	NR
<b>Other publications associated with this study included in review</b>	NA
<b>Trial name / registration number</b>	NR
<b>Study type</b>	Randomised controlled trial (RCT)
<b>Study location</b>	Multicentre trial in China
<b>Study setting</b>	NR
<b>Study dates</b>	NR
<b>Sources of funding</b>	Novartis Beijing
<b>Inclusion criteria</b>	<ul style="list-style-type: none"> <li>• Patients with T2DM (aged 18–78) who were inadequately controlled by metformin monotherapy with HbA1c of 7.0–10.0% at week -2.</li> <li>• Patients were required to have been treated with metformin for at least 8 weeks and be on a stable dose of at least 1500 mg daily for a minimum of 4 weeks prior to the screening visit 1 (week -2).</li> <li>• Men, non-fertile women or women of childbearing potential using a medically approved contraceptive method, whose body mass index (BMI) of 20–40 kg/m<sup>2</sup> and fasting plasma glucose (FPG) level was &lt;270 mg/dl (15 mmol/l) were included.</li> </ul>

<b>Exclusion criteria</b>	<ul style="list-style-type: none"> <li>History of type 1 diabetes mellitus or diabetes due to pancreatic injury or secondary forms of diabetes</li> <li>Any acute metabolic diabetic complications such as ketoacidosis or hyperosmolar state (coma) within past 6 months</li> <li>Myocardial infarction, unstable angina or coronary artery bypass surgery within past 6 months.</li> <li>Patients with congestive heart failure, liver disease such as cirrhosis or chronic active hepatitis</li> <li>Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) &gt;2 times the upper limit of normal (ULN), total bilirubin &gt;2 times ULN, serum creatinine levels [men: <math>\geq 1.5</math> mg/dl (132 <math>\mu</math>mol/l); women: <math>\geq 1.4</math> mg/dl (123 <math>\mu</math>mol/l)] or thyroid-stimulating hormone beyond the normal range, fasting triglycerides <math>\geq 500</math> mg/dl (5.64 mmol/l) at Visit 1</li> </ul>
<b>Recruitment / selection of participants</b>	Patients were screened for eligibility at Visit 1 and were randomised at Visit 2
<b>Intervention(s)</b>	<ul style="list-style-type: none"> <li>Vildagliptin 50 mg BID</li> <li>Vildagliptin 50 mg QD</li> </ul>
<b>Cointervention</b>	Metformin
<b>Strata 1: People with type 2 diabetes mellitus and heart failure</b>	<p>People without heart failure</p> <p>Congestive heart failure was an exclusion criterion.</p>
<b>Strata 2: People with atherosclerotic cardiovascular disease</b>	<p>Not stated/unclear</p> <p>Not an inclusion/exclusion criteria. No information in baseline characteristics.</p>
<b>Strata 3: People with type 2 diabetes mellitus and chronic kidney disease</b>	<p>Not stated/unclear</p> <p>CKD not an inclusion/exclusion criteria. People with the following serum creatinine results based on lab test at visit 1 were excluded: men: <math>\geq 1.5</math>mg/dl; women: 132<math>\mu</math>mol/l. No information in baseline characteristics.</p>
<b>Strata 4: People with type 2 diabetes</b>	Not stated/unclear

<b>mellitus and high cardiovascular risk</b>	
<b>Subgroup 4: People with obesity</b>	Mixed population
<b>Subgroup 5: eGFR category at baseline</b>	Not stated/unclear
<b>Subgroup 6: Albuminuria category at baseline</b>	Not stated/unclear
<b>Population subgroups</b>	Pre-specified subgroup analysis of <30 kg/m <sup>2</sup> (without obesity) and ≥30 kg/m <sup>2</sup> (with obesity)
<b>Comparator</b>	Placebo
<b>Number of participants</b>	774 participants were assessed for eligibility and 438 were randomised. 148 participants were allocated to vildagliptin 50 mg qd, and of these 13 discontinued and 135 completed (91.2%). 146 participants were allocated to Vildagliptin 50 mg bid, of these 9 discontinued and 137 completed (93.8%). 144 participants were allocated to placebo, of these 13 discontinued and 131 completed (91%).
<b>Duration of follow-up</b>	24 weeks
<b>Indirectness</b>	Directly applicable
<b>Method of analysis</b>	<p>Per protocol</p> <p>Methods describe that robustness of data were assessed in the per-protocol set, however, the results of this analysis were not reported</p> <p>Other</p> <p>'Full analysis set' used for efficacy analysis - no definition provided</p> <p>Safety population - All patients who received at least one dose of the study drug</p>
<b>Additional comments</b>	NA

## 353.2. Study arms

### 353.2.1. Vildagliptin 50 mg qd (N = 148)

### 353.2.2. Vildagliptin 50 mg bid (N = 146)

### 353.2.3. Placebo (N = 144)

## 353.3. Characteristics

### 353.3.1. Arm-level characteristics

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

<b>Characteristic</b>	<b>Vildagliptin 50 mg qd (N = 148)</b>	<b>Vildagliptin 50 mg bid (N = 146)</b>	<b>Placebo (N = 144)</b>
<b>Presence of severe mental illness</b>	NR	NR	NR
Nominal			
<b>People with significant cognitive impairment</b>	NR	NR	NR
Nominal			
<b>People with a learning disability</b>	NR	NR	NR
Nominal			
<b>Weight</b>	68.36 (11.1)	71.58 (11.93)	69.83 (11.18)
Mean (SD)			
<b>BMI</b>	25.03 (3.09)	26.01 (3.26)	25.46 (3.09)
Mean (SD)			
<b>Number of people with obesity</b>	n = 10 ; % = 6.8	n = 16 ; % = 11	n = 13 ; % = 9
Sample size			
<b>Other antidiabetic medication used</b>	NR	NR	NR
Nominal			
<b>Blood pressure-lowering medication used</b>	NR	NR	NR
Nominal			
<b>Statins/lipid-lowering medication used</b>	NR	NR	NR
Nominal			
<b>Other treatment being received</b>	NR	NR	NR
Nominal			
<b>% Female</b>	n = 82 ; % = 55.4	n = 73 ; % = 50	n = 78 ; % = 54.2
Sample size			

## 354. Pan, 2014

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

### 354.1. Study details

<b>Secondary publication of another included study- see primary study for details</b>	No
<b>Other publications associated with this study included in review</b>	None
<b>Trial name / registration number</b>	GetGoal-M-Asia/NCT01169779
<b>Study type</b>	Randomised controlled trial (RCT) Double-blind placebo-controlled randomised trial
<b>Study location</b>	International (37 centres in 3 countries: China, Hong Kong, Malaysia, Thailand)
<b>Study setting</b>	Outpatient
<b>Study dates</b>	07/2010 to 12/2011
<b>Sources of funding</b>	Funded by Sanofi, France.
<b>Inclusion criteria</b>	<ul style="list-style-type: none"> <li>• Diagnosis of type 2 diabetes for at least 1 year</li> <li>• Inadequately controlled on metformin with or without sulphonylurea <ul style="list-style-type: none"> <li>◦ HbA1c 7-10% inclusive</li> <li>◦ FPG <math>\leq</math>13.9 mmol/L</li> </ul> </li> <li>• Stable metformin dose 1000-1500 mg daily for 3 months before screening</li> </ul>

	<ul style="list-style-type: none"> <li>Maximum effective sulphonylurea dose and stable for 3 months before screening</li> </ul>
<b>Exclusion criteria</b>	<ul style="list-style-type: none"> <li>Treatment with oral antidiabetic drug other than metformin and sulphonylurea for 3 months or more prior to screening</li> <li>History of: <ul style="list-style-type: none"> <li>Hypoglycaemia unawareness</li> <li>Unexplained pancreatitis</li> <li>Chronic pancreatitis</li> <li>Pancreatectomy</li> <li>Stomach/gastric surgery</li> <li>Inflammatory bowel disease or patients considered by investigator to be at high risk for acute pancreatitis</li> </ul> </li> <li>Personal or family history of medullary thyroid cancer</li> <li>History of metabolic acidosis, including diabetic ketoacidosis within 1 year prior to screening</li> <li>Renal impairment</li> <li>History of gastrointestinal disease associated with prolonged nausea and vomiting within 6 months prior to screening</li> </ul>
<b>Recruitment / selection of participants</b>	Three-week screening period (screening phase of 2 weeks, 1 week blinded placebo run-in period), followed by randomisation 1:1 using interactive voice response system/interactive web-based system, stratified by HbA1c level (<8%, ≥8%) and sulphonylurea use, to 24-week treatment period.
<b>Intervention(s)</b>	<ul style="list-style-type: none"> <li>Lixisenatide 20 mcg daily</li> </ul> <p>Subcutaneous injection of lixisenatide 20 mcg daily 1 hour before breakfast for 24 weeks, in addition to metformin with or without sulphonylurea. Starting dose of 10 mcg for 2 weeks, then maintenance dose of 20 mcg for remainder of trial. Study drug (but not study drug dose) blinded</p>
<b>Cointervention</b>	<ul style="list-style-type: none"> <li>Metformin</li> </ul> <p>All participants received background metformin 1000-1500 mg daily. In participants receiving sulphonylurea, dose was reduced 25-50% at randomisation in those with screening HbA1c&lt;8%; in participants with HbA1c ≥8%, dose was kept stable at baseline dose of at least maximal effective dose (equating to half maximum recommended dose acc. to local labelling). For participants whose sulphonylurea dose was reduced at screening, sulphonylurea dose was increased to baseline dose between weeks 4 and 12 acc. to FPG values. Treatment period followed by 3 day follow up safety period.</p>
<b>Strata 1: People with type 2 diabetes mellitus and heart failure</b>	<p>Not stated/unclear</p> <p>Not an inclusion/exclusion criteria. No information in baseline characteristics.</p>

<b>Strata 2: People with atherosclerotic cardiovascular disease</b>	Not stated/unclear  Not an inclusion/exclusion criteria. No information in baseline characteristics.
<b>Strata 3: People with type 2 diabetes mellitus and chronic kidney disease</b>	People without chronic kidney disease  Exclusion criteria included renal impairment.
<b>Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk</b>	Not stated/unclear
<b>Subgroup 1: People with moderate or severe frailty</b>	Not stated/unclear
<b>Subgroup 2: Onset of type 2 diabetes mellitus</b>	Not stated/unclear
<b>Subgroup 3: People with non-alcoholic fatty liver disease</b>	Not stated/unclear
<b>Subgroup 4: People with obesity</b>	Not stated/unclear
<b>Subgroup 5: eGFR category at baseline</b>	Not stated/unclear
<b>Subgroup 6: Albuminuria category at baseline</b>	Not stated/unclear



<b>Population subgroups</b>	
<b>Comparator</b>	<ul style="list-style-type: none"> <li>• Placebo</li> </ul> <p>Volume-matched subcutaneous placebo injection for 24 weeks, in addition to metformin with or without sulphonylurea.</p>
<b>Number of participants</b>	N=390 randomised
<b>Duration of follow-up</b>	24 weeks
<b>Indirectness</b>	None
<b>Method of analysis</b>	<p>Modified ITT</p> <p>mITT LOCF analysis (all randomised participants who received at least one double-blind study dose and had both baseline and post-baseline efficacy assessment) for all efficacy outcomes. Safety population was all randomised participants who received at least one dose of double-blind treatment.</p>

## 354.2. Study arms

### 354.2.1. Lixisenatide 20 mcg daily (N = 196)

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

### 354.2.2. Placebo (N = 195)

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

## 354.3. Characteristics

### 354.3.1. Arm-level characteristics

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

<b>Characteristic</b>	<b>Lixisenatide 20 mcg daily (N = 196)</b>	<b>Placebo (N = 195)</b>
<b>Mean age (SD) (years)</b>	54.5 (10.3)	55.1 (10.5)
Mean (SD)		
<b>Ethnicity</b>	n = NA ; % = NA	n = NA ; % = NA
Sample size		
<b>Asian/Oriental</b>	n = 196 ; % = 100	n = 194 ; % = 100
Sample size		
<b>Comorbidities</b>	NR	NR
Nominal		
<b>Presence of frailty</b>	n = NR ; % = NR	n = NR ; % = NR
Sample size		
<b>Time since type 2 diabetes diagnosed</b>	6.5 (4.6)	6.8 (4.8)
Mean (SD)		
<b>Cardiovascular risk factors</b>	NR	NR
Nominal		
<b>Smoking status</b>	NR	NR
Nominal		
<b>Alcohol consumption</b>	NR	NR
Nominal		
<b>Presence of severe mental illness</b>	NR	NR
Nominal		
<b>People with significant cognitive impairment</b>	NR	NR
Nominal		
<b>People with a learning disability</b>	NR	NR
Nominal		
<b>Number of people with obesity</b>	NR	NR
Nominal		
<b>Other antidiabetic medication used (years)</b>	NA (NA)	NA (NA)
Mean (SD)		

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

Data for placebo arm is for N=194.

## 355. Papathanassiou, 2009

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

### 355.1. Study details

<b>Secondary publication of another included study- see primary study for details</b>	No
<b>Other publications associated with this study included in review</b>	None
<b>Trial name / registration number</b>	Not reported
<b>Study type</b>	Randomised controlled trial (RCT) Open-label, parallel-group RCT
<b>Study location</b>	Ioannina, Greece
<b>Study setting</b>	Outpatient
<b>Study dates</b>	Not reported
<b>Sources of funding</b>	Funded in part by Michaelidion Cardiac Center, University of Ioannina, Ioannina, Greece
<b>Inclusion criteria</b>	<ul style="list-style-type: none"> <li>• Type 2 diabetes diagnosis</li> <li>• Treated with metformin only for 6-mo prior to screening</li> <li>• HbA1c&gt;6.5%</li> <li>• Normal liver enzymes and renal function</li> </ul>
<b>Exclusion criteria</b>	<ul style="list-style-type: none"> <li>• History of coronary artery, cerebrovascular, or peripheral vascular disease, chronic heart failure, liver or renal disease, anemia,</li> </ul>

	thyroid dysfunction, and new onset of any medications within previous 8 weeks
<b>Recruitment / selection of participants</b>	Recruited at endocrinology outpatient clinic of University and Hatzikosta General Hospital of Ioannina, Greece. Eligible participants randomly assigned 1:1, using block randomisation, on basis of order of presentation to outpatient clinic. Participants maintained same diet and physical activity level, as well as other antihypertensive/hypolipidaemic/antiplatelet medications, for duration of trial.
<b>Intervention(s)</b>	<ul style="list-style-type: none"> <li>• Pioglitazone 30 mg daily</li> </ul> <p>Oral pioglitazone 30 mg daily for 26 weeks, in addition to metformin.</p>
<b>Cointervention</b>	<ul style="list-style-type: none"> <li>• Metformin</li> </ul> <p>All participants continued with metformin for duration of trial.</p>
<b>Strata 1: People with type 2 diabetes mellitus and heart failure</b>	<p>People without heart failure</p> <p>Heart failure an exclusion criterion.</p>
<b>Strata 2: People with atherosclerotic cardiovascular disease</b>	<p>People without atherosclerotic cardiovascular diseases</p> <p>Coronary artery, cerebrovascular, or peripheral vascular disease were exclusion criteria.</p>
<b>Strata 3: People with type 2 diabetes mellitus and chronic kidney disease</b>	<p>People without chronic kidney disease</p> <p>Normal renal function stated in the inclusion criteria.</p> <p>Renal disease stated in the exclusion criteria.</p>
<b>Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk</b>	Not stated/unclear
<b>Subgroup 1: People with moderate or severe frailty</b>	Not stated/unclear

<b>Subgroup 2: Onset of type 2 diabetes mellitus</b>	Not stated/unclear
<b>Subgroup 3: People with non-alcoholic fatty liver disease</b>	Not stated/unclear
<b>Subgroup 4: People with obesity</b>	Not stated/unclear
<b>Subgroup 5: eGFR category at baseline</b>	Not stated/unclear
<b>Subgroup 6: Albuminuria category at baseline</b>	Not stated/unclear
<b>Population subgroups</b>	
<b>Comparator</b>	<ul style="list-style-type: none"> <li>• Glimepiride 4 mg daily</li> </ul> <p>Oral glimepiride 4 mg daily for 26 weeks, in addition to metformin.</p>
<b>Number of participants</b>	N=28 randomised
<b>Duration of follow-up</b>	26 weeks
<b>Indirectness</b>	None
<b>Method of analysis</b>	<p>ITT</p> <p>Appears to be ITT completer population</p> <p>Not stated/unclear</p>
<b>Additional comments</b>	Method of analysis not explicitly reported but reports all randomised participants completed study and data reported for this number

## 355.2. Study arms

### 355.2.1. Pioglitazone 30 mg daily (N = 14)

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

### 355.2.2. Glimepiride 4 mg daily (N = 14)

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

## 355.3. Characteristics

### 355.3.1. Arm-level characteristics

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

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



## 356. Park, 2014

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

### 356.1. Study details

<b>Secondary publication of another included study- see primary study for details</b>	NA
<b>Other publications associated with this study included in review</b>	NA
<b>Trial name / registration number</b>	NCT00708578
<b>Study type</b>	Randomised controlled trial (RCT)
<b>Study location</b>	Multicentre trial in Korea
<b>Study setting</b>	Participants were enrolled from outpatient clinics of 5 centres
<b>Study dates</b>	20 June 2008 to 18 December 2009
<b>Sources of funding</b>	Sanofi-Korea
<b>Inclusion criteria</b>	<ul style="list-style-type: none"> <li>• Men and women 18 to 80 years old who had had type 2 diabetes for at least 6 months</li> <li>• BMI of &lt;30 kg/m<sup>2</sup></li> <li>• HbA1c levels ≥7.0% to ≤11.0% despite ≥3 months of treatment with a stable dose of both a sulfonylurea (more than daily 4 mg glimepiride or equivalent to dose of other sulfonylureas) and metformin (at least 1000 mg/day) up to the maximum tolerated dose)</li> <li>• Fasting serum C-peptide &gt;0.99 ng/mL</li> </ul>

	<ul style="list-style-type: none"> <li>Patients were also required to have a demonstrated ability and willingness to inject insulin and to perform self-monitoring of blood glucose (SMBG) with use of a plasma-referenced glucose meter</li> </ul>
<b>Exclusion criteria</b>	<ul style="list-style-type: none"> <li>Type 1 diabetes</li> <li>Insulin treated type 2 diabetes or having previously received long-term insulin</li> <li>History of hypersensitivity to the investigational product or to drugs with similar chemical structures</li> <li>Levels of alanine aminotransferase or aspartate aminotransferase greater than twice the upper limit of the normal range</li> <li>A creatinine level greater than 1.5 mg/dL in men and 1.4 mg/dL in women</li> <li>Pregnancy or lactation</li> <li>Systemic treatment with corticosteroids within 3 months</li> <li>Patients unable to perform SMBG or inject insulin on their own</li> </ul>
<b>Recruitment / selection of participants</b>	There was a 4-week screening/titration phase, and patients who did not achieve good metabolic control while receiving nearly maximal dose of oral anti-diabetic drugs, were subsequently randomised to assigned treatment.
<b>Intervention(s)</b>	<ul style="list-style-type: none"> <li>Glimepiride 4 mg/day</li> <li>Metformin 1500 mg/day</li> <li>Glimepiride 4 mg/day plus metformin 1500 mg/day</li> </ul>
<b>Cointervention</b>	Insulin glargine administered as a single daily subcutaneous injection in the morning at a starting dose of 0.2 U/kg, sometimes 10 IU for 3 days, which was titrated every third day to achieve a target FPG value of 5.0 to 7.2 mmol/l. Study medication accountability logs for insulin glargine, glimepiride and metformin were collected and evaluated for compliance.
<b>Strata 1: People with type 2 diabetes mellitus and heart failure</b>	<p>Not stated/unclear</p> <p>Not an inclusion/exclusion criteria. No information in baseline characteristics.</p>
<b>Strata 2: People with atherosclerotic cardiovascular disease</b>	<p>Not stated/unclear</p> <p>Not an occlusion/exclusion criteria. No information in baseline characteristics.</p>
<b>Strata 3: People with type 2 diabetes mellitus and chronic kidney disease</b>	<p>Not stated/unclear</p> <p>CKD not an inclusion/exclusion criteria. Exclusion criteria state: "a creatinine level greater than 1.5mg/dL in man and 1.4mg/dL in woman."</p>

<b>Subgroup 1: People with moderate or severe frailty</b>	Not stated/unclear
<b>Subgroup 2: Onset of type 2 diabetes mellitus</b>	Not stated/unclear
<b>Subgroup 3: People with non-alcoholic fatty liver disease</b>	Not stated/unclear
<b>Subgroup 4: People with obesity</b>	Not stated/unclear
<b>Subgroup 5: eGFR category at baseline</b>	Not stated/unclear
<b>Subgroup 6: Albuminuria category at baseline</b>	Not stated/unclear
<b>Population subgroups</b>	NA
<b>Comparator</b>	NA
<b>Number of participants</b>	122 patients were screened and 99 were randomised. Of 33 participants allocated to metformin, 33 were included in the safety analysis, 32 were included in the ITT analysis and 26 were included in the PP analysis. Of 34 participants allocated to glimepiride, 34 were included in the safety analysis, 32 were included in the ITT analysis, and 27 were included in the PP analysis. Of 32 participants allocated to metformin + glimepiride, 32 were included in the safety analysis, 32 were included in the ITT analysis, and 24 were included in the PP analysis.
<b>Duration of follow-up</b>	24 weeks
<b>Indirectness</b>	Directly applicable
<b>Method of analysis</b>	Per protocol Described in the methods, but results were not reported

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

## 356.2. Study arms

### 356.2.1. Metformin (N = 33)

### 356.2.2. Glimepiride (N = 34)

### 356.2.3. Metformin + Glimepiride (N = 32)

## 356.3. Characteristics

### 356.3.1. Arm-level characteristics

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

<b>Characteristic</b>	<b>Metformin (N = 33)</b>	<b>Glimepiride (N = 34)</b>	<b>Metformin + Glimepiride (N = 32)</b>
Nominal			
<b>Time since type 2 diabetes diagnosed</b> (years)	11.3 (6.4)	13 (8)	11.7 (5)
Mean (SD)			
<b>Cardiovascular risk factors</b>	NR	NR	NR
Nominal			
<b>Smoking status</b>	NR	NR	NR
Nominal			
<b>Alcohol consumption</b>	NR	NR	NR
Nominal			
<b>Presence of severe mental illness</b>	NR	NR	NR
Nominal			
<b>People with significant cognitive impairment</b>	NR	NR	NR
Nominal			
<b>People with a learning disability</b>	NR	NR	NR
Nominal			
<b>Weight</b>	NR	NR	NR
Nominal			
<b>BMI</b> ( kg/m <sup>2</sup> )	25.1 (3.6)	25.6 (2.7)	25.2 (2.7)
Mean (SD)			
<b>Number of people with obesity</b>	NR	NR	NR
Nominal			
<b>Other antidiabetic medication used</b>	NR	NR	NR
Nominal			
<b>Blood pressure-lowering medication used</b>	NR	NR	NR
Nominal			

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

## 357. Park, 2023

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

### 357.1. Study details

<b>Secondary publication of another included study- see primary study for details</b>	NA
<b>Other publications associated with this study included in review</b>	NA
<b>Trial name / registration number</b>	BEYOND study [(NCT02564926)]
<b>Study type</b>	Randomised controlled trial (RCT)
<b>Study location</b>	14 centres in Korea
<b>Study setting</b>	NR
<b>Study dates</b>	Between January 2016 and January 2018
<b>Sources of funding</b>	AstraZeneca
<b>Inclusion criteria</b>	Adults aged 19-75 years with T2D and inadequately controlled glycated haemoglobin (HbA1c) of 7.0 to <10.0% on stable metformin monotherapy (≥1000 mg/day) for at least 8 weeks before randomization
<b>Exclusion criteria</b>	NR

<b>Recruitment / selection of participants</b>	NR
<b>Intervention(s)</b>	<ul style="list-style-type: none"> <li>• Dapagliflozin 10 mg orally once daily</li> <li>• Glimepiride 1 mg orally, 1 or 2 tablets at a dose of 1 to 2 mg/day</li> </ul>
<b>Cointervention</b>	<ul style="list-style-type: none"> <li>• <math>\geq 100</math> mg metformin</li> <li>• Rescue therapy was prescribed for participants who met the following criteria: weeks 4-8, fasting blood glucose (FBG) <math>&gt;240</math> mg/dl; weeks 8-24, FBG <math>&gt;200</math> mg/dl; and weeks 24-56, HbA1c <math>&gt;8\%</math>. Sitagliptin was provided as rescue therapy.</li> </ul>
<b>Strata 1: People with type 2 diabetes mellitus and heart failure</b>	Not stated/unclear
<b>Strata 2: People with atherosclerotic cardiovascular disease</b>	Not stated/unclear
<b>Strata 3: People with type 2 diabetes mellitus and chronic kidney disease</b>	Not stated/unclear
<b>Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk</b>	Not stated/unclear
<b>Subgroup 1: People with moderate or severe frailty</b>	Not stated/unclear
<b>Subgroup 2: Onset of type 2 diabetes mellitus</b>	Not stated/unclear



<b>Subgroup 3: People with non-alcoholic fatty liver disease</b>	Not stated/unclear
<b>Subgroup 4: People with obesity</b>	Not stated/unclear
<b>Subgroup 5: eGFR category at baseline</b>	Not stated/unclear
<b>Subgroup 6: Albuminuria category at baseline</b>	Not stated/unclear
<b>Population subgroups</b>	NA
<b>Comparator</b>	NA
<b>Number of participants</b>	178 participants were enrolled and 124 were randomised. Of 62 participants allocated to dapagliflozin, 2 participants were not treated, 56 participants were analysed at week 52, and 52 completed. Of 62 participants allocated to glimepiride, 1 participant was not treated, 56 participants were analysed at week 52. and 54 completed.
<b>Duration of follow-up</b>	52 weeks
<b>Indirectness</b>	Directly applicable
<b>Method of analysis</b>	<p>Not stated/unclear</p> <p>Efficacy analyses were performed on the full analysis set, which was defined as all randomised participants who received at least one dose of study medication during the treatment period with no missing baseline values and at least one post-baseline value for primary efficacy variables. Analysis were performed using a mixed model repeated measures or analysis of covariance for continuous variables.</p> <p>Safety analysis set included participant who received at least one dose of study medication.</p>
<b>Additional comments</b>	NA

## 357.2. Study arms

### 357.2.1. Dapagliflozin (N = 62)

### 357.2.2. Glimepiride (N = 62)

## 357.3. Characteristics

### 357.3.1. Arm-level characteristics

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

<b>Characteristic</b>	<b>Dapagliflozin (N = 62)</b>	<b>Glimepiride (N = 62)</b>
<b>Patients with cardiac disorders</b>	n = 2 ; % = 3.3	n = 5 ; % = 8.2
Sample size		
<b>Renal and urinary disorders</b>	n = 7 ; % = 11.7	n = 6 ; % = 9.8
Sample size		
<b>Presence of frailty</b>	NR	NR
Nominal		
<b>Time since type 2 diabetes diagnosed (years)</b>	6 (4.8)	6.5 (4.9)
Mean (SD)		
<b>Cardiovascular risk factors</b>	NR	NR
Nominal		
<b>Smoking status</b>	NR	NR
Nominal		
<b>Alcohol consumption</b>	NR	NR
Nominal		
<b>Presence of severe mental illness</b>	NR	NR
Nominal		
<b>People with significant cognitive impairment</b>	NR	NR
Nominal		
<b>People with a learning disability</b>	NR	NR
Nominal		
<b>Number of people with obesity</b>	NR	NR
Nominal		
<b>Blood pressure-lowering medication used</b>	n = NA ; % = NA	n = NA ; % = NA
Sample size		
<b>Amlodipine + valsartan</b>	n = 4 ; % = 6.7	n = 2 ; % = 3.3
Sample size		
<b>Losartan potassium</b>	n = 3 ; % = 5	n = 2 ; % = 3.3
Sample size		

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



## 358. Park, 2011

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

### 358.1. Study details

<b>Secondary publication of another included study- see primary study for details</b>	No
<b>Other publications associated with this study included in review</b>	None
<b>Trial name / registration number</b>	Not reported
<b>Study type</b>	Randomised controlled trial (RCT) Open-label, parallel-group, RCT
<b>Study location</b>	Seoul, South Korea
<b>Study setting</b>	Outpatient
<b>Study dates</b>	Not reported
<b>Sources of funding</b>	Supported by Faculty research grant of Yonsei University College of Medicine for 2007 and Yonsei University College of Medicine, Internal Medicine Research Grant 2007.
<b>Inclusion criteria</b>	<ul style="list-style-type: none"> <li>• Type 2 diabetes diagnosis with stable or worsening glycaemic control on glimepiride <math>\geq 2</math> mg or equivalent dose of other sulphonylurea (e.g. gliclazide MR 30 mg) for <math>\geq 3</math> months before screening</li> <li>• Aged 40-70 years</li> <li>• HbA1c 7-10% inclusive at screening</li> <li>• Fasting C-peptide <math>\geq 1.5</math> ng/ml at screening</li> </ul>

<b>Exclusion criteria</b>	<ul style="list-style-type: none"> <li>• Type 1 diabetes</li> <li>• Diabetic ketoacidosis</li> <li>• Symptomatic heart failure</li> <li>• Malignant disease in the previous 10 years</li> <li>• Renal failure</li> </ul>
<b>Recruitment / selection of participants</b>	Eligible participants recruited from Diabetes Clinic, Kangnam Severance Hospital, South Korea and randomised to pioglitazone or metformin.
<b>Intervention(s)</b>	<ul style="list-style-type: none"> <li>• Pioglitazone 15 mg daily</li> </ul> <p>Oral pioglitazone 15 mg daily for 24 weeks, in addition to glimepiride or equivalent dose of other sulphonylurea.</p>
<b>Cointervention</b>	<ul style="list-style-type: none"> <li>• Glimepiride <math>\geq 2</math> mg daily or equivalent dose of other sulphonylurea</li> </ul> <p>It is not explicit in article whether participants continued with existing blood-glucose lowering drugs but likely that they did.</p>
<b>Strata 1: People with type 2 diabetes mellitus and heart failure</b>	<p>People without heart failure</p> <p>People with symptomatic heart failure were excluded.</p>
<b>Strata 2: People with atherosclerotic cardiovascular disease</b>	<p>Not stated/unclear</p> <p>Not an inclusion/exclusion criteria. No information in baseline characteristics.</p>
<b>Strata 3: People with type 2 diabetes mellitus and chronic kidney disease</b>	<p>Not stated/unclear</p> <p>CKD not an inclusion/exclusion criteria. Renal failure is an exclusion criteria. No information in baseline characteristics.</p>
<b>Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk</b>	Not stated/unclear
<b>Subgroup 1: People with</b>	Not stated/unclear

<b>moderate or severe frailty</b>	
<b>Subgroup 2: Onset of type 2 diabetes mellitus</b>	Not stated/unclear
<b>Subgroup 3: People with non-alcoholic fatty liver disease</b>	Not stated/unclear
<b>Subgroup 4: People with obesity</b>	Not stated/unclear
<b>Subgroup 5: eGFR category at baseline</b>	Not stated/unclear
<b>Subgroup 6: Albuminuria category at baseline</b>	Not stated/unclear
<b>Comparator</b>	<ul style="list-style-type: none"> <li>Metformin 1000 mg daily</li> </ul> <p>Oral metformin 1000 mg daily for 24 weeks, (probably) in addition to glimepiride or equivalent dose of other sulphonylurea.</p>
<b>Number of participants</b>	N=67 randomised
<b>Duration of follow-up</b>	24 weeks
<b>Indirectness</b>	Not explicitly stated whether study is an add-on trial or switching trial.
<b>Method of analysis</b>	<p>ITT</p> <p>Appears to be ITT analysis for all outcomes</p> <p>Other</p> <p>Not explicitly reported, appears to be for all randomised participants</p>

## 358.2. Study arms

### 358.2.1. Pioglitazone 15 mg daily (N = 34)



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

### 358.2.2. Metformin 1000 mg daily (N = 33)

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

## 358.3. Characteristics

### 358.3.1. Arm-level characteristics

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

<b>Characteristic</b>	<b>Pioglitazone 15 mg daily (N = 34)</b>	<b>Metformin 1000 mg daily (N = 33)</b>
<b>People with significant cognitive impairment</b>	NR	NR
Nominal		
<b>People with a learning disability</b>	NR	NR
Nominal		
<b>Number of people with obesity</b>	NR	NR
Nominal		
<b>Other antidiabetic medication used</b>	NR	NR
Nominal		
<b>Blood pressure-lowering medication used</b>	NR	NR
Nominal		
<b>Statins/lipid-lowering medication used</b>	NR	NR
Nominal		
<b>Other treatment being received</b>	NR	NR
Nominal		

## 359. Pasquel, 2021

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

### 359.1. Study details

<b>Secondary publication of another included study- see primary study for details</b>	NA
<b>Other publications associated with this study included in review</b>	NA
<b>Trial name / registration number</b>	NCT01919489
<b>Study type</b>	Randomised controlled trial (RCT)
<b>Study location</b>	United States
<b>Study setting</b>	Multicentre trial carried out at four academic institutions
<b>Study dates</b>	NR
<b>Sources of funding</b>	Novo Nordisk
<b>Inclusion criteria</b>	<ul style="list-style-type: none"> <li>• Glucose levels between 7.8 and 22.2 mmol/L and HbA1c levels &gt;7% to 10%</li> <li>• Aged 18 to 80 years</li> <li>• Home diabetes regimen included diet and/or OADs including sulfonylureas, repaglinide, nateglinide, or metformin, either as</li> </ul>

	monotherapy or in combination therapy, or taking a low total daily dose of insulin ( $\leq 0.4$ unit/kg/d)
<b>Exclusion criteria</b>	<ul style="list-style-type: none"> <li>History of diabetic ketoacidosis or hyperosmolar hyperglycaemic state or with laboratory evidence of ketoacidosis</li> <li>Patients with history of type 1 diabetes, medullary thyroid cancer or multiple endocrine neoplasia, acute or chronic pancreatitis, pancreatic cancer or gallbladder disease</li> <li>Previous treatment with GLP-1RAs during the past 3 months prior to admission</li> <li>Patients admitted to or expected to require admission to an intensive care unit</li> <li>Corticosteroid therapy <math>&gt;5</math> mg/d of prednisone equivalent</li> <li>Clinically relevant hepatic disease or impaired renal function (estimated glomerular filtration rate <math>&lt;30</math> mL/min per <math>1.73</math> m<math>^2</math>)</li> <li>Body mass index (BMI) <math>&lt;25</math> and <math>&gt; 45</math> kg/m<math>^2</math></li> <li>Pregnancy</li> <li>Parenteral nutrition</li> <li>Immunosuppressive treatment</li> <li>Mental condition rendering the participant unable to understand the nature, scope and possible consequences of the study.</li> </ul>
<b>Recruitment / selection of participants</b>	Patients with T2D were screened during their hospital admission from medical or general surgical services. During the hospital stay, patients were managed with a standard basal or basal-bolus regimen according to hospital protocol.
<b>Intervention(s)</b>	Liraglutide beginning at 0.6 mg once daily by subcutaneous injections, with dose escalation every 2 weeks by increments of 0.6 mg until the maintenance dose of 1.8 mg was reached. Injections were given at any time of the day and irrespective of meals; however, it was recommended that the time of injection be consistent throughout the trial. Dose escalation was extended over 4 weeks at the discretion of the investigator in case of adverse events. Treatment-naïve patients with HbA1c $< 8\%$ ( $<64$ mmol/mol) received liraglutide as monotherapy or in combination with metformin if HbA1c was $> 8\%$ ( $> 64$ mmol/mol). Dipeptidyl peptidase-4 inhibitors were not used in combination with liraglutide during the study period.
<b>Cointervention</b>	Treatment was given as add-on to the participant's preadmission OAD regimen. The dose of insulin secretagogues (sulfonylureas, nateglinide and repaglinide) was reduced by 50% or stopped at the discretion of the investigator, otherwise, the dose of OAD remained unchanged throughout the trial.
<b>Strata 1: People with type 2 diabetes mellitus and heart failure</b>	<p>Not stated/unclear</p> <p>Not an inclusion/exclusion criteria. No information in baseline characteristics.</p>
<b>Strata 2: People with</b>	Not stated/unclear

<b>atherosclerotic cardiovascular disease</b>	Not an inclusion/exclusion criteria. No information in baseline characteristics.
<b>Strata 3: People with type 2 diabetes mellitus and chronic kidney disease</b>	Not stated/unclear  People with "impaired renal function (estimated glomerular filtration rate <30 mL/min per 1.73 m <sup>2</sup> )" were excluded. No information in baseline characteristics.
<b>Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk</b>	Not stated/unclear
<b>Subgroup 1: People with moderate or severe frailty</b>	Not stated/unclear
<b>Subgroup 2: Onset of type 2 diabetes mellitus</b>	Not stated/unclear
<b>Subgroup 3: People with non-alcoholic fatty liver disease</b>	Not stated/unclear
<b>Subgroup 4: People with obesity</b>	Not stated/unclear
<b>Subgroup 5: eGFR category at baseline</b>	eGFR ≥30mL/min/1.73m <sup>2</sup>
<b>Subgroup 6: Albuminuria category at baseline</b>	Not stated/unclear
<b>Population subgroups</b>	NA

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

## 359.2. Study arms

### 359.2.1. Liraglutide (N = 140)

### 359.2.2. Insulin glargine (N = 147)

### 359.3. Characteristics

#### 359.3.1. Arm-level characteristics

Characteristic	Liraglutide (N = 140)	Insulin glargine (N = 147)
<b>% Male</b> Based on ITT population	n = 89 ; % = 65	n = 76 ; % = 55
Sample size		
<b>Mean age (SD)</b> Mean (SD)	56.1 (9.5)	55.9 (11.2)
<b>Ethnicity</b> Sample size	n = NA ; % = NA	n = NA ; % = NA
<b>Black</b> Sample size	n = 97	<i>empty data</i>
<b>White</b> Sample size	n = 23 ; % = 17	n = 27 ; % = 20
<b>Other</b> Sample size	n = 16 ; % = 12	n = 15 ; % = 11
<b>Comorbidities</b> Nominal	NR	NR
<b>Presence of frailty</b> Nominal	NR	NR
<b>Time since type 2 diabetes diagnosed (years)</b> Mean (SD)	9.5 (7.8)	9.8 (9.1)
<b>Cardiovascular risk factors</b> Nominal	NR	NR
<b>Smoking status</b> Nominal	NR	NR
<b>Alcohol consumption</b> Nominal	NR	NR
<b>Presence of severe mental illness</b> Nominal	NR	NR

<b>Characteristic</b>	<b>Liraglutide (N = 140)</b>	<b>Insulin glargine (N = 147)</b>
<b>People with significant cognitive impairment</b>	NR	NR
Nominal		
<b>People with a learning disability</b>	NR	NR
Nominal		
<b>BMI (years)</b>	33.5 (5.3)	33.3 (5.3)
Mean (SD)		
<b>Number of people with obesity</b>	NR	NR
Nominal		
<b>Other antidiabetic medication used</b>	n = NA ; % = NA	n = NA ; % = NA
Sample size		
<b>No diabetes medication</b>	n = 22 ; % = 16	n = 24 ; % = 18
Sample size		
<b>Oral agents</b>	n = 61 ; % = 45	n = 69 ; % = 51
Sample size		
<b>Insulin</b>	n = 22 ; % = 16	n = 19 ; % = 14
Sample size		
<b>Oral agents + insulin</b>	n = 30 ; % = 22	n = 23 ; % = 17
Sample size		
<b>Blood pressure-lowering medication used</b>	NR	NR
Nominal		
<b>Statins/lipid-lowering medication used</b>	NR	NR
Nominal		
<b>Other treatment being received</b>	NR	NR
Nominal		



# 360. Patel, 2019

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

<b>Secondary publication of another included study- see primary study for details</b>	Abreu 2019
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## 361. Pei, 2021

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

### 361.1. Study details

<b>Secondary publication of another included study- see primary study for details</b>	NA
<b>Other publications associated with this study included in review</b>	NA
<b>Trial name / registration number</b>	DUAL II China [NCT03175120]
<b>Study type</b>	Randomised controlled trial (RCT)
<b>Study location</b>	40 sites across mainland China and Hong Kong
<b>Study setting</b>	
<b>Study dates</b>	May 2017 to July 2019
<b>Sources of funding</b>	Novo Nordisk
<b>Inclusion criteria</b>	<ul style="list-style-type: none"> <li>• Participants aged 18 years or older with clinically diagnosed T2D</li> <li>• BMI of 24 kg/m<sup>2</sup> or higher</li> <li>• HbA1c of 7.5% or more</li> <li>• Treated for 90 days or longer prior to screening with basal insulin and metformin, with or without one other of the following OADs: AGIs, sulphonylureas, glinides, or thiazolidinediones. Additionally, participants had received stable doses for 60 days or longer of</li> </ul>

	1500 mg or more of metformin (or maximum tolerated dose), and 20 to 50 U/day of a basal insulin.
<b>Exclusion criteria</b>	<ul style="list-style-type: none"> <li>• Known or suspected hypersensitivity to trial product(s) or related products.</li> <li>• Previous participation in this trial. Participation is defined as informed consent.</li> <li>• Female who is pregnant, breast-feeding or intends to become pregnant or is of child-bearing potential and not using adequate contraceptive methods (sterilization, intrauterine device, oral contraceptives or barrier methods).</li> <li>• Receipt of any investigational medicinal product within 30 calendar days before Visit 1.</li> <li>• Current use of any antidiabetic drug (except for basal insulin, AGI, SU, glinides and TZD) or anticipated change in concomitant medication that, in the investigator's opinion, could interfere with glucose level (e.g. systemic corticosteroids).</li> <li>• Use of non-herbal Chinese medicine or other non-herbal local medicine with unknown/unspecified content within 90 calendar days prior to screening. Herbal traditional Chinese medicine or other local herbal medicines may, at the investigator's discretion, be continued throughout the trial.</li> <li>• Treatment with GLP-1 RAs or DPP-4is or insulin (except for basal insulin) within 90 days prior to Visit 1.</li> <li>• Impaired liver function defined as alanine aminotransferase <math>\geq 2.5</math> times the upper normal range.</li> <li>• Impaired renal function defined as serum-creatinine <math>\geq 133</math> <math>\mu\text{mol/L}</math> for males and <math>\geq 125</math> <math>\mu\text{mol/L}</math> for females, or as defined according to local contraindications for metformin.</li> <li>• Screening calcitonin <math>\geq 50</math> ng/L.</li> <li>• Personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2.</li> <li>• Cardiac disorder defined as: congestive heart failure (New York Heart Association class III-IV), diagnosis of unstable angina pectoris, cerebral stroke and/or myocardial infarction within the last 12 months period to screening and/or planned coronary, carotid or peripheral artery revascularization procedures.</li> <li>• Severe uncontrolled treated or untreated hypertension (systolic blood pressure <math>\geq 180</math> mmHg or diastolic blood pressure <math>\geq 100</math> mmHg).</li> <li>• Proliferative retinopathy or maculopathy (macular oedema) requiring acute treatment.</li> <li>• Subject with a clinically significant, active (during the past 12 months) disease of the gastrointestinal, pulmonary, neurological, genito-urinary or haematological system (except for conditions associated with T2D) that, in the opinion of the investigator, may confound compliance and the results of the trial or pose additional risk in administering trial drug.</li> <li>• Mental incapacity, unwillingness or language barrier precluding adequate understanding of the trial procedure or cooperation with the trial site personnel.</li> <li>• Known or suspected abuse of alcohol or narcotics.</li> <li>• History of pancreatitis (acute or chronic).</li> </ul>

	<ul style="list-style-type: none"> <li>Suffer from a life-threatening disease, including malignant neoplasms, and medical history of malignant neoplasms and medical history of malignant neoplasms within the last 5 years (except basal and squamous cell skin cancer).</li> </ul>
<b>Recruitment / selection of participants</b>	555 participants were screened for eligibility over a 2-week period. 102 participants were excluded at screening and 453 participants were randomised.
<b>Intervention(s)</b>	Subcutaneous IDegLira received once daily. The recommended starting doses were 16 dose steps for IDegLira (16 units degludec/0.6 mg liraglutide).
<b>Cointervention</b>	Treatment received in combination with metformin. Other OADs were discontinued at randomisation. Doses were titrated twice weekly for both treatments to a target fasting plasma glucose (FPG) of 4 to 5 mmol/L.
<b>Strata 1: People with type 2 diabetes mellitus and heart failure</b>	Not stated/unclear  Exclusion criteria: "Cardiac disorder defined as: congestive heart failure (New York Heart Association class III-IV), diagnosis of unstable angina pectoris, cerebral stroke and/or myocardial infarction within the last 12 months period to screening and/or planned coronary, carotid or peripheral artery revascularization procedures."
<b>Strata 2: People with atherosclerotic cardiovascular disease</b>	Not stated/unclear
<b>Strata 3: People with type 2 diabetes mellitus and chronic kidney disease</b>	Not stated/unclear  Exclusion criteria: "Impaired renal function defined as serum-creatinine $\geq 133 \mu\text{mol/L}$ for males and $\geq 125 \mu\text{mol/L}$ for females, or as defined according to local contraindications for metformin."
<b>Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk</b>	Not stated/unclear
<b>Subgroup 1: People with moderate or severe frailty</b>	Not stated/unclear

<b>Subgroup 2: Onset of type 2 diabetes mellitus</b>	Not stated/unclear
<b>Subgroup 3: People with non-alcoholic fatty liver disease</b>	Not stated/unclear
<b>Subgroup 4: People with obesity</b>	Not stated/unclear
<b>Subgroup 5: eGFR category at baseline</b>	Not stated/unclear
<b>Subgroup 6: Albuminuria category at baseline</b>	Not stated/unclear
<b>Population subgroups</b>	NA
<b>Comparator</b>	Subcutaneous insulin degludec once daily. The recommended starting dose was 16 units.
<b>Number of participants</b>	Of 302 participants allocated to IDegLira, 301 received treatment, and 290 (96%) completed treatment. Of 151 participants allocated to insulin degludec, 151 received treatment, and 92.1% completed treatment.
<b>Duration of follow-up</b>	26 weeks at end of treatment with follow-up at 27 and 30 weeks.
<b>Indirectness</b>	Directly applicable
<b>Method of analysis</b>	Per protocol  Per-protocol and completer analysis were assessed for HbA1c outcome.  Other  Full analysis set with missing values after 26 weeks of treatment imputed by last observation carried forward with ANCOVA analysis.
<b>Additional comments</b>	Double-blind study

## 361.2. Study arms

361.2.1. IDegLira (N = 302)

361.2.2. Insulin degludec (N = 151)

## 361.3. Characteristics

361.3.1. Arm-level characteristics

Characteristic	IDegLira (N = 302)	Insulin degludec (N = 151)
<b>% Male</b>		
Sample size	n = 183 ; % = 60.6	n = 91 ; % = 60.3
<b>Mean age (SD)</b>		
Mean (SD)	54.5 (9.8)	55.3 (10)
<b>Ethnicity</b>		
Nominal	NR	NR
<b>Comorbidities</b>		
Nominal	NR	NR
<b>Presence of frailty</b>		
Nominal	NR	NR
<b>Time since type 2 diabetes diagnosed (years)</b>		
Mean (SD)	11.52 (5.9)	11.33 (6.3)
<b>Cardiovascular risk factors</b>		
Nominal	NR	NR
<b>Smoking status</b>		
Nominal	NR	NR
<b>Alcohol consumption</b>		
Nominal	NR	NR
<b>Presence of severe mental illness</b>		
Nominal	NR	NR

<b>Characteristic</b>	<b>IDegLira (N = 302)</b>	<b>Insulin degludec (N = 151)</b>
<b>People with significant cognitive impairment</b>	NR	NR
Nominal		
<b>People with a learning disability</b>	NR	NR
Nominal		
<b>Number of people with obesity</b>	NR	NR
Nominal		
<b>Other antidiabetic medication used</b>	n = NR ; % = NR	n = NR ; % = NR
Sample size		
<b>Metformin only</b>	n = 141 ; % = 46.7	n = 74 ; % = 49
Sample size		
<b>Metformin + sulphonylurea</b>	n = 44 ; % = 14.6	n = 22 ; % = 14.6
Sample size		
<b>Metformin + glinide</b>	n = 20 ; % = 6.6	n = 10 ; % = 6.6
Sample size		
<b>Metformin + alpha-glucosidase inhibitors</b>	n = 89 ; % = 29.5	n = 44 ; % = 29.1
Sample size		
<b>metformin + TZD</b>	n = 8 ; % = 2.6	n = 1 ; % = 0.7
Sample size		
<b>Statins/lipid-lowering medication used</b>	NR	NR
Nominal		
<b>Basal insulin use during screening period</b>	n = NR ; % = NR	n = NR ; % = NR
Sample size		
<b>Insulin detemir</b>	n = 33 ; % = 10.9	n = 17 ; % = 11.3
Sample size		
<b>Insulin glargine</b>	n = 218 ; % = 72.2	n = 111 ; % = 73.5
Sample size		
<b>Insulin isophane</b>	n = 46 ; % = 15.2	n = 23 ; % = 15.2
Sample size		

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



## 362. Perkovic, 2019

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

### 362.1. Study details

<b>Secondary publication of another included study- see primary study for details</b>	Parent study CREDENCE trial
<b>Other publications associated with this study included in review</b>	<p>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</p> <p>Jardine, Meg J, Mahaffey, Kenneth W, Neal, Bruce et al. (2017) The Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) Study Rationale, Design, and Baseline Characteristics. American journal of nephrology 46(6): 462-472</p>
<b>Trial name / registration number</b>	CREDENCE trial. NCT02065791
<b>Study type</b>	Randomised controlled trial (RCT)
<b>Study location</b>	690 sites in 34 countries
<b>Study setting</b>	Unspecified clinical setting
<b>Study dates</b>	February 17, 2014 - October 30, 2018
<b>Sources of funding</b>	Janssen Research & Development, LLC

<b>Inclusion criteria</b>	<ul style="list-style-type: none"> <li>• Type 2 diabetes mellitus with a hemoglobin A1c (HbA1c) greater than or equal to (<math>\geq</math>) 6.5 percent (%) and less than or equal to (<math>\leq</math>) 12.0%, with an estimated glomerular filtration rate (eGFR) of <math>\geq</math> 30 millilitre (mL)/minute (min)/1.73meter (m)<sup>2</sup> and less than (<math>&lt;</math>) 90 mL/min/1.73 m<sup>2</sup></li> <li>• Participants need to be on a stable maximum tolerated labelled daily dose of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) for at least 4 weeks prior to randomization</li> <li>• Must have a urine albumin to creatinine ratio (UACR) of greater than (<math>&gt;</math>) 300 milligram (mg)/gram (g) and <math>\leq</math> 5000 mg/g</li> <li>• 30 years or older</li> </ul>
<b>Exclusion criteria</b>	<ul style="list-style-type: none"> <li>• History of diabetic ketoacidosis or type 1 diabetes mellitus</li> <li>• History of hereditary glucose-galactose malabsorption or primary renal glucosuria</li> <li>• Renal disease that required treatment with immunosuppressive therapy</li> <li>• Known significant liver disease</li> <li>• Current or history of New York Heart Association (NYHA) Class IV heart failure</li> <li>• Blood potassium level <math>&gt;5.5</math> millimole (mmol)/litre (L) during Screening</li> </ul>
<b>Recruitment / selection of participants</b>	No information
<b>Intervention(s)</b>	Drug: Canagliflozin. One 100 mg over-encapsulated tablet orally once daily
<b>Cointervention</b>	angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker
<b>Strata 1: People with type 2 diabetes mellitus and heart failure</b>	<p>People without heart failure</p> <p>14.8% had HF</p>
<b>Strata 2: People with atherosclerotic cardiovascular disease</b>	<p>Mixed population</p> <p>50.4% had CVD</p>
<b>Strata 3: People with type 2 diabetes mellitus and</b>	<p>People with chronic kidney disease</p> <p>Included "chronic kidney disease, defined as an estimated glomerular filtration rate (GFR, as calculated by the Chronic Kidney Disease Epidemiology Collaboration formula) of 30 to <math>&lt;90</math> ml per minute per 1.73 m<sup>2</sup> of body-surface area and albuminuria (urinary albumin-to-creatinine</p>

<b>chronic kidney disease</b>	ratio, >300 to 5000, with albumin measured in milligrams and creatinine in grams), as measured in a central laboratory. "
<b>Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk</b>	Not stated/unclear
<b>Subgroup 1: People with moderate or severe frailty</b>	Not stated/unclear
<b>Subgroup 2: Onset of type 2 diabetes mellitus</b>	Not stated/unclear
<b>Subgroup 3: People with non-alcoholic fatty liver disease</b>	Not stated/unclear
<b>Subgroup 4: People with obesity</b>	Not stated/unclear
<b>Subgroup 5: eGFR category at baseline</b>	eGFR $\geq 30$ mL/min/1.73m <sup>2</sup>
<b>Subgroup 6: Albuminuria category at baseline</b>	A3 (ACR >300mg/g or >30mgmmol)
<b>Population subgroups</b>	None
<b>Comparator</b>	Placebo
<b>Number of participants</b>	A total of 4401 participants were randomized, with 2199 and 2202 participants assigned to placebo and canagliflozin 100 milligrams (mg), respectively.
<b>Duration of follow-up</b>	Median 31.44 months

<b>Indirectness</b>	None
<b>Method of analysis</b>	ITT
<b>Additional comments</b>	Post-hoc analysis by

## 362.2. Study arms

### 362.2.1. Canagliflozin (N = 2202)

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

### 362.2.2. Placebo (N = 2199)

Participants received matching placebo orally once daily

## 362.3. Characteristics

### 362.3.1. Arm-level characteristics

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

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

## 363. Perkovic, 2020

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

### 363.1. Study details

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

### 363.2. Study arms

#### 363.2.1. Linagliptin - eGFR $\geq 60$ (N = 1294)

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

**363.2.2. Linagliptin - eGFR  $\geq 45$ -<60 (N = 690)**

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

**363.2.3. Linagliptin - eGFR  $\geq 30$  to <45 (N = 994)**

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

**363.2.4. Linagliptin - eGFR <30 (N = 516)**

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

**363.2.5. Placebo - eGFR  $\geq 60$  (N = 1337)**

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

**363.2.6. Placebo - eGFR  $\geq 45$ -<60 (N = 658)**

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

**363.2.7. Placebo - eGFR  $\geq 30$  to <45 (N = 944)**

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

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

#### **363.2.8. Placebo - eGFR <30 (N = 546)**

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



# 364. Perkovic, 2024

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

## 364.1. Study details

<b>Secondary publication of another included study- see primary study for details</b>	NA
<b>Other publications associated with this study included in review</b>	NA
<b>Trial name / registration number</b>	FLOW [NCT03819153]
<b>Study type</b>	Randomised controlled trial (RCT)
<b>Study location</b>	International multicentre trial: Argentina, Australia, Belgium, Bulgaria, Brazil, Canada, China, France, Germany, Greece, Hungary, India, Israel, Italy, Japan, Mexico, Malaysia, Netherlands, Poland, Russia, Slovakia, Spain, Thailand, Turkey, Ukraine, United Kingdom, United States, South Africa
<b>Study setting</b>	Not reported
<b>Study dates</b>	Participants were recruited between June 2019 and May 2021. The prespecified single interim analysis was triggered on October 2023, and the final trial visit was in January 2024.
<b>Sources of funding</b>	Novo Nordisk
<b>Inclusion criteria</b>	<ul style="list-style-type: none"> <li>Adults with T2DM and HbA1c ≤10%</li> <li>With high-risk chronic kidney disease (renal impairment defined either by serum creatinine-based eGFR ≥ 50 and ≤ 75 mL/min/1.73 m<sup>2</sup> (CKD-EPI), and UACR &gt; 300 and &lt; 5000 mg/g or serum creatinine-based eGFR ≥ 25 and &lt; 50 mL/min/1.73 m<sup>2</sup> (CKD-EPI) and UACR &gt; 100 and &lt; 5000 mg/g)</li> <li>Receiving stable maximal labelled dose (or the maximal dose without unacceptable side effects) of RAS inhibitors</li> </ul>

<b>Exclusion criteria</b>	<ul style="list-style-type: none"> <li>• Known or suspected hypersensitivity to trial product(s) or related products.</li> <li>• Female who is pregnant, breast-feeding or intends to become pregnant or is of child-bearing potential and not using a highly effective contraceptive method.</li> <li>• Any disorder, which in the investigator's opinion might have jeopardized the subject's safety or compliance with the protocol.</li> <li>• Congenital or hereditary kidney diseases including polycystic kidney disease, autoimmune kidney diseases including glomerulonephritis or congenital urinary tract malformations.</li> <li>• Use of any GLP-1 receptor agonist within 30 days prior to screening.</li> <li>• Personal or first-degree relative(s) history of multiple endocrine neoplasia type 2 (MEN2) or medullary thyroid carcinoma (MTC).</li> <li>• Myocardial infarction, stroke, hospitalisation for unstable angina pectoris or transient ischemic attack within 60 days prior to the day of screening.</li> <li>• Presently classified as being in New York Heart Association (NYHA) Class IV heart failure.</li> <li>• Planned coronary, carotid or peripheral artery revascularization.</li> <li>• Current (or within 90 days) chronic or intermittent haemodialysis or peritoneal dialysis.</li> <li>• Uncontrolled and potentially unstable diabetic retinopathy or maculopathy. Verified by a fundus examination performed within the past 90 days prior to screening or in the period between screening and randomization. Pharmacological pupil-dilation is a requirement unless using a digital fundus photography camera specified for non-dilated examination.</li> <li>• Presence or history of malignant neoplasm within 5 years prior to the day of screening. Basal and squamous cell skin cancer and any carcinoma in-situ are allowed.</li> <li>• prior solid organ transplant or awaiting solid organ transplant.</li> <li>• Combination use of an angiotensin converting enzyme (ACE) inhibitor and an angiotensin II receptor blocker (ARB).</li> </ul>
<b>Recruitment / selection of participants</b>	Not reported
<b>Intervention(s)</b>	Subcutaneous semaglutide with 8-week dose escalation regimen from 0.25 mg per week for 4 weeks and and 0.5 mg per week for another 4 weeks followed by a maintenance dose of 1.0 mg per week for the remainder of the treatment period. If unacceptable adverse events occurred, the dose-escalation intervals could be extended, treatment could be paused, or lower maintenance doses could be used.
<b>Cointervention</b>	The use of SGLT2 inhibitors was permitted
<b>Strata 1: People with type 2 diabetes mellitus and heart failure</b>	<p>Not stated/unclear</p> <p>Exclusion criteria state people with NYHA class IV were excluded</p>

<b>Strata 2: People with atherosclerotic cardiovascular disease</b>	Not stated/unclear
<b>Strata 3: People with type 2 diabetes mellitus and chronic kidney disease</b>	People with chronic kidney disease
<b>Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk</b>	Not stated/unclear
<b>Subgroup 1: People with moderate or severe frailty</b>	Not stated/unclear
<b>Subgroup 2: Onset of type 2 diabetes mellitus</b>	Not stated/unclear
<b>Subgroup 3: People with non-alcoholic fatty liver disease</b>	Not stated/unclear
<b>Subgroup 4: People with obesity</b>	Not stated/unclear
<b>Subgroup 5: eGFR category at baseline</b>	Mixed population
<b>Subgroup 6: Albuminuria category at baseline</b>	Mixed population
<b>Population subgroups</b>	Not applicable - subgroup analyses were reported, however, these were only for a composite renal outcome that wasn't eligible for extraction
<b>Comparator</b>	Matching placebo
<b>Number of participants</b>	5581 participants were screened and 3533 were randomised. Of 1767 participants randomised to semaglutide, 43 (2.4%) did not complete the trial and 439 (24.8%) did not complete treatment. Of 1766 participant

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

## 364.2. Study arms

**364.2.1. Semaglutide. s.c. (N = 1767)**

**364.2.2. Placebo (N = 1766)**

## 365. Characteristics

### 365.1. Arm-level characteristics

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

<b>Characteristic</b>	<b>Semaglutide. s.c. (N = 1767)</b>	<b>Placebo (N = 1766)</b>
<b>Less than 15 years</b>	n = 774 ; % = 43.8	n = 753 ; % = 42.6
Sample size		
<b>15 years and greater</b>	n = 992 ; % = 56.1	n = 1013 ; % = 57.4
Sample size		
<b>HbA1c</b>	7.8 (1.3)	7.8 (1.3)
Mean (SD)		
<b>Cardiovascular risk factors</b>	NR	NR
Nominal		
<b>Blood pressure (mmHg)</b>	138.9 (16.1)	138.4 (15.4)
Systolic blood pressure		
Mean (SD)		
<b>Heart rate</b>	NA	NA
Nominal		
<b>Smoking status</b>	n = NA ; % = NA	n = NA ; % = NA
Sample size		
<b>Current smoker</b>	n = 223 ; % = 12.6	n = 206 ; % = 11.7
Sample size		
<b>Previous smoker</b>	n = 661 ; % = 37.4	n = 696 ; % = 39.4
Sample size		
<b>Never smoked</b>	n = 883 ; % = 50	n = 864 ; % = 48.9
Sample size		
<b>Alcohol consumption</b>	NR	NR
Nominal		
<b>Presence of severe mental illness</b>	NR	NR
Nominal		
<b>People with significant cognitive impairment</b>	NR	NR
Nominal		
<b>People with a learning disability</b>	NR	NR
Nominal		

<b>Characteristic</b>	<b>Semaglutide. s.c. (N = 1767)</b>	<b>Placebo (N = 1766)</b>
<b>Weight (kg)</b>	89.5 (19.8)	89.8 (21.2)
Mean (SD)		
<b>BMI ( kg/m<sup>2</sup>)</b>	31.9 (6.1)	32 (6.5)
Mean (SD)		
<b>Number of people with obesity BMI&gt;30 kg/m<sup>2</sup></b>	n = 1031 ; % = 58.5	n = 1029 ; % = 58.3
Sample size		
<b>Cholesterol and lipid levels</b>	NR	NR
Nominal		
<b>Albumin creatinine ratio (ratio)</b>	582.3	557.8
Nominal		
<b>eGFR mL/min/1.73m<sup>2</sup> ( ml/min/1.73 m<sup>2</sup>)</b>	46.9 (15.6)	47.1 (14.7)
Mean (SD)		
<b>Other antidiabetic medication used</b>	n = NA ; % = NA	n = NA ; % = NA
Sample size		
<b>SGLT2 inhibitor</b>	n = 277 ; % = 15.7	n = 273 ; % = 15.5
Sample size		
<b>Metformin</b>	n = 908 ; % = 51.4	n = 924 ; % = 52.3
Sample size		
<b>Insulin</b>	n = 1083 ; % = 61.3	n = 1085 ; % = 61.4
Sample size		
<b>Blood pressure-lowering medication used</b>	n = NA ; % = NA	n = NA ; % = NA
Sample size		
<b>ACE-inhibitor</b>	n = 625 ; % = 35.4	n = 615 ; % = 34.8
Sample size		
<b>ARB</b>	n = 1066 ; % = 60.3	n = 1061 ; % = 60.1
Sample size		
<b>Diuretic agent</b>	n = 870 ; % = 49.2	n = 910 ; % = 51.5
Sample size		

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



## 366. Petrica, 2011

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

### 366.1. Study details

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

<b>diabetes mellitus and heart failure</b>	
<b>Strata 2: People with atherosclerotic cardiovascular disease</b>	Not stated/unclear  Exclusion criteria were symptoms and/or history of cerebrovascular disease (transient ischaemic attack, stroke). No information about other types of CVD. No information in baseline characteristics.
<b>Strata 3: People with type 2 diabetes mellitus and chronic kidney disease</b>	People without chronic kidney disease  CKD not an inclusion/exclusion criteria. Inclusion criteria state: normoalbuminuria at time of enrolment, absence of microangiopathic complications, no chronic kidney disease of non-diabetic origin.
<b>Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk</b>	Not stated/unclear
<b>Subgroup 1: People with moderate or severe frailty</b>	Not stated/unclear
<b>Subgroup 2: Onset of type 2 diabetes mellitus</b>	Not stated/unclear
<b>Subgroup 3: People with non-alcoholic fatty liver disease</b>	Not stated/unclear
<b>Subgroup 4: People with obesity</b>	Not stated/unclear
<b>Subgroup 5: eGFR category at baseline</b>	Not stated/unclear
<b>Subgroup 6: Albuminuria</b>	Not stated/unclear

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

## 366.2. Study arms

### 366.2.1. Pioglitazone (N = 39)

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

### 366.2.2. Glimepiride (N = 39)

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

## 366.3. Characteristics

### 366.3.1. Arm-level characteristics

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

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

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