National Institute for Health and Care Excellence

Type 2 diabetes in adults: management

Evidence reviews for SGLT-2 inhibitors and GLP-1 mimetics

NICE guideline NG28

Evidence reviews

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Final

These evidence reviews were developed by the NICE Guideline Updates Team

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SGLT-2 inhibitors

Review question

In adults with Type 2 diabetes, what is the clinical effectiveness of SGLT-2 inhibitors on cardiovascular outcomes?

Introduction

The aim of this question was to provide recommendations to supplement NICE technology appraisals 288, 315, 336 and 418 on canagliflozin, dapagliflozin and empagliflozin, which are reproduced in the NICE guideline on type 2 diabetes management in adults (NG28). This work will not update any of the NICE technology appraisals, and any recommendations that result from this update are not intended to affect the interpretation of the NICE technology appraisal guidance.

PICO table

Population	Adults (aged 18 years and older) with Type 2 diabetes mellitus.
Intervention	Sodium-glucose cotransporter-2 inhibitors (SGLT-2), including: • Canaglifozin • Dapaglifozin • Empaglifozin In mono, dual or triple therapy or as an add-on to insulin therapy.
Comparison	There will be a stepwise approach to comparators: 1. Studies that compare SGLT2 inhibitors to each other (active comparators within class) 2. If no studies that identify SGLT2 inhibitor v another SGLT2 inhibitor, then comparators of usual care, no treatment or placebo will be used.
Outcomes	Cardiovascular outcomes: • Cardiovascular mortality • Fatal MI • Non-fatal MI • Fatal stroke • Non-fatal stroke • Heart failure • Lower limb amputation Microvascular patient oriented outcomes: • Retinopathy • Nephropathy • End-stage renal disease • Neuropathy

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A.

Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy.

Meta-analyses of the evidence were conducted with reference to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011). A pooled relative risk was calculated for dichotomous outcomes (using the Mantel–Haenszel method). Forest plots are presented in Appendix E – Forest plots. Minimal important differences for clinical significance were discussed and the committee agreed that a difference of 25% (which is the GRADE default when no other dichotomous MID is specified) was too high. The committee decided that it was appropriate to use the line of no effect for mortality outcomes, and an MID of a 10% increase or decrease for other outcomes.

Clinical evidence

Included studies

A systematic literature search was carried out to identify randomised controlled trials (RCTs) or systematic reviews of RCTs (see Appendix B for literature search strategy). The search identified 1,742 articles, which were screened at the title and abstract level. Of these, 193 articles were screened in full. Two additional articles were also identified (only the German version was found by the search for 1 of the additional articles and the other additional article was published after the search). Of these, 96 articles were included based on their relevance to the review protocol (Appendix A – Review protocols). The clinical evidence study selection is available in Appendix C – Clinical evidence study selection.

In total, 81 reported in 96 articles which met the inclusion criteria defined in the review protocol were included in the clinical evidence review. None of these trials compared SGLT-2 inhibitors to each other (active comparators within class). Included trials compared SGLT-2 inhibitors to other active treatments or placebo. Of these, 57 trials reported in 61 articles did not report outcomes of interest other than that there were no cardiovascular deaths. These trials were agreed to not provide useful data as they were all small studies reporting deaths as adverse events and provided no information on relative mortality risks between the 2 groups, and therefore they were not incorporated into the statistical analysis. A summary of all included trials is presented in Appendix D – Clinical evidence tables. The table below is a summary of the 24 trials which reported at least 1 event per outcome.

Excluded studies

The excluded studies table is available in Appendix J – Excluded studies.

Summary of clinical studies included in the evidence review, and reporting at least 1 event

Study ID	Population	Intervention	Comparison	Outcomes
Amin 2015	Men and women aged 18 to 70 years Type 2 diabetes Background therapy: metformin up to 3,000mg/d N=328 Follow-up/treatment duration: 12 weeks	Ertugliflozin up to 25mg/d	Sitagliptin 100mg/d Placebo	• Non-fatal acute myocardial infarction
AstraZeneca & Bristol-Myers Squibb 2010	Men and women aged 18 to 89 years Type 2 diabetes Background therapy: oral antidiabetic drug with or without insulin N=944 Follow-up/treatment duration: 12 weeks	Dapagliflozin 2.5mg/d 5mg/d 10mg/d	Placebo	• Non-fatal ischaemic stroke
Bailey 2010 Bailey 2013	Men and women aged 18 to 77 years Type 2 diabetes Background therapy: metformin ≥1,500mg/d N=546 Follow-up/treatment duration: 24 and 102 weeks	Dapagliflozin 2.5mg/d 5mg/d 10mg/d	Placebo	• Fatal myocardial infarction
Bode 2013 Bode 2015	Men and women aged 55 to 80 years Type 2 diabetes Background therapy: N=714 Follow-up/treatment duration: 104 weeks	Canagliflozin 100mg/d 300mg/d	Placebo	• Fatal stroke

Study ID	Population	Intervention	Comparison	Outcomes
Cefalu 2015	Adults Type 2 diabetes Background therapy: pre-existing stable background treatment, excluding rosiglitazone N=922 Follow-up/treatment duration: 52 weeks	Dapagliflozin 10mg/d	Placebo	• Fatal myocardial infarction • Non-fatal myocardial infarction • Non-fatal acute myocardial infarction
Ferrannini 2013b	Men and women aged 18 to 79 years Type 2 diabetes Background therapy: none N=408 Follow-up/treatment duration: 12 weeks	Empagliflozin 5mg/d 10mg/d 25mg/d	Placebo Open-label metformin	• Non-fatal myocardial infarction • Non-fatal acute myocardial infarction • Diabetic nephropathy
Frias 2017	Men and women aged ≥18 years Type 2 diabetes Background therapy: metformin N=695 Follow-up/treatment duration: 28 weeks	Dapagliflozin 10mg/d plus exenatide 2mg once weekly Dapagliflozin 10mg/d plus placebo injections once weekly	Exenatide 2mg once weekly plus placebo	• Cardiovascular events
Haring 2013 EMPA-REG-METSU Haering 2015 EMPA-REG EXTENDTM METSU	Men and women aged ≥18 years Type 2 diabetes Background therapy: add-on to metformin and sulfonylurea N=666 Follow-up/treatment duration: 24 and 76 weeks	Empagliflozin 10mg/d 25mg/d	Placebo	• Fatal acute myocardial infarction
Henry 2012	Men and women aged 18 to 77 years Type 2 diabetes	Study 2 Dapagliflozin 10mg plus metformin XR	Study 2 Metformin XR plus placebo	Study 2 • Fatal myocardial infarction

Study ID	Population	Intervention	Comparison	Outcomes
	Background therapy: add-on to metformin N=638 (study 2) Follow-up/treatment duration: 24 weeks	Dapagliflozin 5mg plus placebo		
Kadowaki 2017	Men and women aged 20 to 75 years Type 2 diabetes Background therapy: add-on to teneligliptin N=138 Follow-up/treatment duration: 24 weeks	Canagliflozin 100mg/d	Placebo	• Cardiovascular-related events
Kashiwagi 2015a EMIT	Men and women aged ≥20 years Type 2 diabetes Background therapy: add-on to sulfonylurea N=245 Follow-up/treatment duration: 24 weeks	Ipragliflozin 50mg/d	Placebo	• Proliferative retinopathy
Kohan 2014	Adults Type 2 diabetes Background therapy: add-on to original pre-enrolment antidiabetic regimen. N=252 Follow-up/treatment duration:104 weeks	Dapagliflozin 5mg/d 10mg/d b	Placebo	• Fatal acute myocardial infarction • Fatal myocardial infarction
Kovacs 2014 EMPA-REG PIOTM Kovacs 2015	Men and women aged ≥18 years Type 2 diabetes	Empagliflozin 10mg/d 25mg/d	Placebo	• Fatal myocardial infarction • Fatal stroke

Study ID	Population	Intervention	Comparison	Outcomes
EMPA-REG EXTENDTM PIO	Background therapy: add-on to pioglitazone with or without metformin N=499 Follow-up/treatment duration: 24 and 52 weeks			• Non-fatal heart failure
Leiter 2014	Adults Type 2 diabetes Background therapy: add-on to pre-existing stable antidiabetic therapy including insulin. N=964 Follow-up/treatment duration: 52 weeks	Dapagliflozin 10mg/d	Placebo	• Fatal myocardial infarction • Fatal heart failure
Leiter 2015 Patel 2016 (post-hoc analysis) CANTATA-SU	Men and women aged 18 to 80 years Type 2 diabetes Background therapy: metformin N=1,450 Follow-up/treatment duration: 104 weeks	Canagliflozin 100mg 300mg	Glimepiride up to 8mg	• Cardiovascular mortality • Non-fatal myocardial infarction • Non-fatal stroke
Lewin 2015	Men and women aged ≥18 years Type 2 diabetes Background therapy: none N=677 Follow-up/treatment duration: 52 weeks	Empagliflozin 25mg and linagliptin 5mg Empagliflozin 10mg and linagliptin 5mg Empagliflozin 25mg Empagliflozin 10mg	Linagliptin 5mg	• Fatal haemorrhagic stroke
Ljunggren 2012	Women aged 55 to 75 years Men aged 30 to 75 years Type 2 diabetes Background therapy: add-on to metformin	Dapagliflozin 10mg/d	Placebo	• Non-fatal acute myocardial infarction

Study ID	Population	Intervention	Comparison	Outcomes
	N=180 Follow-up/treatment duration: 50 weeks			
Mathieu 2015 Mathieu 2016	Men and women aged ≥18 years Type 2 diabetes Background therapy: add-on to saxagliptin plus metformin N=320 Follow-up/treatment duration: 24 and 52 weeks	Dapagliflozin 10mg/d	Placebo	• Non-fatal heart failure
Nauck 2011 Nauck 2014	Men and women aged ≥18 years Type 2 diabetes Background therapy: add-on to metformin N=814 Follow-up/treatment duration: 52 and 104 weeks	Dapagliflozin up to 10mg/d	Glipizide up to 20mg/d	• Fatal acute myocardial infarction
Neal 2017 CANVAS and CANVAS-R	Men and women aged ≥30 years Type 2 diabetes Background therapy: not specified N=10,142 Follow-up/treatment duration: median 126.1 weeks	Canagliflozin 100mg/d or 300mg/d	Placebo	• Cardiovascular mortality • Non-fatal myocardial infarction • Non-fatal stroke • Hospitalisation for heart failure • Lower limb amputation • All-cause mortality
Rosenstock 2012b	Men and women aged ≥18 years Type 2 diabetes Background therapy: add-on to pioglitazone	Dapagliflozin 5mg/d 10mg/d	Placebo	• Non-fatal heart failure

Study ID	Population	Intervention	Comparison	Outcomes
	N=420 Follow-up/treatment duration: 48 weeks			
Strojek 2011 Strojek 2014	Men and women aged ≥18 years Type 2 diabetes Background therapy: add-on to glimepiride N=596 Follow-up/treatment duration: 24 and 48 weeks	Dapagliflozin 2.5mg/d 5mg/d 10mg/d	Placebo	• Non-fatal stroke
Wilding 2012 Wilding 2014	Men and women aged 18 to 80 years Type 2 diabetes Background therapy: add-on to daily insulin, existing oral antidiabetic drugs, and a stable diet and exercise regimen N=808 Follow-up/treatment duration: 48 and 104 weeks	Dapagliflozin 2.5mg/d 5mg/d 10mg/d	Placebo	• Fatal acute myocardial infarction
Zinman 2015 Fitchett 2016 Wanner 2016 Kaku 2017 (Asian population, n=1,517 participants) EMPA-REG OUTCOME®	Men and women aged ≥18 years Type 2 diabetes Background therapy: add-on to background glucose-lowering therapy N=7,020 Follow-up/treatment duration: median observation time 3.1 years	Empagliflozin 5mg/d 25mg/d	Placebo	• Cardiovascular mortality • Fatal acute myocardial infarction • Non-fatal myocardial infarction • Non-fatal silent myocardial infarction • Fatal stroke • Non-fatal stroke • Fatal heart failure • Non-fatal heart failure

Study ID	Population	Intervention	Comparison	Outcomes
				• Hospitalisation for heart failure • Incident or worsening nephropathy • Initiation of laser therapy for retinopathy • Coronary revascularisation procedure • All-cause mortality

See appendix D for full evidence tables.

Quality assessment of clinical studies included in the evidence review

See appendix F for full GRADE tables. Both hazard ratios and relative risks are reported where available, with imprecision calculated based on relative risks if both measures were presented. Because a significant proportion of the included studies did not contain sufficient events to produce meaningful results, GRADE tables are only presented for studies where at least 5 events occurred for cardiovascular or microvascular outcomes regarded as primary or secondary outcomes by 2 trials (CANVAS trial reported by Neal 2017 and EMPA-REG trial reported by Zinman 2015). Adverse events were not considered for GRADE tables which were reported by 22 trials.

Economic evidence

Included studies

A literature search was conducted to identify cost–utility analyses that included at least one SGLT-2 inhibitor therapy. The MEDLINE, Embase, EconLit and PubMed databases were searched, along with the Health Technology Assessment database and the NHS Economic Evaluation Database (EED). A total of 1,208 articles were identified. After review of titles and abstracts, 18 articles were ordered for full-text review.

Excluded studies

Studies excluded from the review of economic evaluations are listed in Appendix J, including reasons for exclusion.

Summary of studies included in the economic evidence review

This topic is concerned with the clinical effectiveness of SGLT-2 inhibitors on cardiovascular outcomes. We therefore sought to include any cost–utility analyses that modelled using relative effects on cardiovascular outcomes directly. After review of the 18 full text articles, no articles were included for this part of the topic.

Economic model

Economic modelling was not conducted for this topic. However, an exploratory modelling analysis was conducted, to establish how accurately the UKPDS Outcomes Model 1 – a series of risk equations developed to predict CV event rates using intermediate outcomes – predicts the number of CV events reported in the 2 recent SGLT-2 inhibitor trials (CANVAS, EMPA-REG). The health economic model for the original guideline (NG28) was driven by the UKPDS prediction model, therefore this analysis explores the extent to which the CV outcomes in the high-risk CANVAS and EMPA-REG populations would be captured by the original model. The UKPDS prediction equations also underpin most previous modelling studies in diabetes.

The NG28 model was used to create a cohort of 5,000 patients, whose population-level characteristics matched the CANVAS and EMPA-REG study participants as closely as possible. Where such information was not reported, the original NG28 model characteristics from the THIN database were applied. Results suggest that when applying treatment effects on either HbA1c alone or HbA1c and systolic blood pressure (SBP) simultaneously, the UKPDS model may be inaccurate at predicting

the incidence of CV events in people receiving canagliflozin and empagliflozin, particularly MI and all-cause mortality. It may be that SGLT-2 inhibitors affect the risk of CV events via a mechanism that is not captured by changes in HbA1c or SBP reduction. Similarly, the model has difficulty predicting the relative effects of those interventions compared with placebo. It may therefore also be poorly suited for modelling populations with high baseline CV risk, such as those included in the CANVAS and EMPA-REG studies.

Details of these exploratory analyses are provided in Appendix I.

Evidence statements

When results other than mortality are reported below, these are based on defined minimal important differences of a 10% change, so the result needs to be statistically significant, and the point estimate needs to correspond to an increase or decrease of greater than 10%. For mortality outcomes, it was only needed that the outcome be statistically significant.

Canagliflozin versus placebo (CANVAS study)

- Low- to high-quality evidence from 1 RCT containing 10,142 people diagnosed with type 2 diabetes and with a history of symptomatic atherosclerotic cardiovascular disease, or with 2 or more risk factors for cardiovascular disease, found that fewer people randomised to canagliflozin were hospitalised for heart failure at a median follow-up of 126.1 weeks compared to people randomised to placebo. However, it could not detect a difference in cardiovascular mortality, non-fatal myocardial infarction, non-fatal stroke, or all-cause mortality between canagliflozin and placebo.
- High-quality evidence from 1 RCT containing 10,142 people diagnosed with type 2 diabetes and with history of symptomatic atherosclerotic cardiovascular disease or with 2 or more risk factors for cardiovascular disease found that more people randomised to canagliflozin had lower limb amputations at a median follow-up of 126.1 weeks compared to people randomised to placebo irrespective of their history of amputations.

Empagliflozin versus placebo (EMPA-REG study)

- High-quality evidence from 1 RCT containing 7,020 people diagnosed with type 2 diabetes and with established cardiovascular disease found that fewer people randomised to empagliflozin (pooled doses[1], 10mg/d, or 25mg/d) died from cardiovascular causes at a median observation time of 161.6 weeks compared to people randomised to placebo.
- Moderate- to high-quality evidence from 1 RCT containing 7,020 people diagnosed with type 2 diabetes and with established cardiovascular disease found that fewer people randomised to empagliflozin (pooled doses) died from cardiovascular causes at a median observation time of 161.6 weeks compared to people randomised to placebo in subgroups of participants with the following characteristics at baseline: without heart failure; with only coronary artery disease; with 2 or 3 high cardiovascular risk categories; HbA1c <8.5%; BMI <30 kg/m^2; White population, Asian population; ≥65 years old; eGFR 60 to <90 mL/min/1.73 m^2. However, it could not detect a difference in cardiovascular mortality between empagliflozin and placebo in subgroups of participants with the following characteristics at baseline: with heart failure; with only cerebrovascular disease or peripheral artery disease; HbA1c ≥8.5%; BMI ≥30 kg/m^2; Black/African-American

[1] Pooled doses group meant that both 10mg/d and 25md/d groups were analysed together.

population; <65 years old; eGFR >90 mL/min/1.73 m^2 or eGFR <60 mL/min/1.73 m^2.

- Moderate-quality evidence from 1 RCT containing 7,020 people diagnosed with type 2 diabetes and with established cardiovascular disease could not detect a difference in fatal acute myocardial infarction at a median observation time of 161.6 weeks between people randomised to empagliflozin (pooled doses, 10mg/d, or 25mg/d) compared to people randomised to placebo and in subgroups of participants with or without heart failure at baseline.
- Low- to moderate-quality evidence from 1 RCT containing 7,020 people diagnosed with type 2 diabetes and with established cardiovascular disease could not detect a difference in non-fatal myocardial infarction (excluding silent myocardial infarction) at a median observation time of 161.6 weeks between people randomised to empagliflozin (pooled doses, 10mg/d, or 25mg/d) compared to people randomised to placebo and in an Asian population subgroup analysis.
- Low- to moderate-quality evidence from 1 RCT containing 7,020 people diagnosed with type 2 diabetes and with established cardiovascular disease could not detect a difference in non-fatal silent myocardial infarction at a median observation time of 161.6 weeks between people randomised to empagliflozin (pooled doses, 10mg/d, or 25mg/d) compared to people randomised to placebo.
- Moderate-quality evidence from 1 RCT containing 7,020 people diagnosed with type 2 diabetes and with established cardiovascular disease could not detect a difference in fatal stroke at a median observation time of 161.6 weeks between people randomised to empagliflozin (pooled doses, 10mg/d, or 25mg/d) compared to people randomised to placebo and in subgroups of participants with or without heart failure at baseline.
- Low- to moderate-quality evidence from 1 RCT containing 7,020 people diagnosed with type 2 diabetes and with established cardiovascular disease could not detect a difference in non-fatal stroke at a median observation time of 161.6 weeks between people randomised to empagliflozin (pooled doses, 10mg/d, or 25mg/d) compared to people randomised to placebo and in an Asian population subgroup analysis.
- Moderate- to high-quality evidence from 1 RCT containing 7,020 people diagnosed with type 2 diabetes and with established cardiovascular disease found that fewer people randomised to empagliflozin died of heart failure at a median observation time of 161.6 weeks compared to people randomised to placebo in the following subgroups: empagliflozin (pooled doses or 25mg/d); with or without heart failure at baseline. However, it could not detect a difference in fatal heart failure between empagliflozin 10mg/d and placebo.
- Moderate- to high-quality evidence from 1 RCT containing 7,020 people diagnosed with type 2 diabetes and with established cardiovascular disease found that fewer people randomised to empagliflozin (pooled doses) had non-fatal heart failure (investigator-reported) at a median observation time of 161.6 weeks compared to people randomised to placebo. However, it could not detect a difference in non-fatal heart failure (investigator-reported) between empagliflozin either 10mg/d or 25mg/d and placebo.
- Low- to high-quality evidence from 1 RCT containing 7,020 people diagnosed with type 2 diabetes and with established cardiovascular disease found that fewer people randomised to empagliflozin (pooled doses) were hospitalised for heart failure at a median observation time of 161.6 weeks compared to people randomised to placebo if they did not have heart failure at baseline. However, it could not detect a difference in hospitalisation for heart failure between

empagliflozin either 10mg/d or 25mg/d and placebo; for the subgroup of people with heart failure at baseline and in an Asian population subgroup analysis.

- Low- to high-quality evidence from 1 RCT containing 7,020 people diagnosed with type 2 diabetes and with established cardiovascular disease found that fewer people randomised to empagliflozin (pooled doses) had incident or worsening nephropathy at a median observation time of 161.6 weeks compared to people randomised to placebo irrespective of their eGFR at baseline. However, it could not detect a difference in initiation of laser therapy for retinopathy between empagliflozin and placebo.
- Low- to moderate-quality evidence from 1 RCT containing 7,020 people diagnosed with type 2 diabetes and with established cardiovascular disease could not detect a difference in coronary revascularisation procedure at a median observation time of 161.6 weeks between people randomised to empagliflozin (pooled doses, 10mg/d, or 25mg/d) compared to people randomised to placebo.
- Moderate- to high-quality evidence from 1 RCT containing 7,020 people diagnosed with type 2 diabetes and with established cardiovascular disease found that fewer people randomised to empagliflozin (pooled doses, 10mg/d, or 25mg/d) died from any cause at a median observation time of 161.6 weeks compared to people randomised to placebo and in participants without heart failure at baseline. However, it could not detect a difference in all-cause mortality between empagliflozin and placebo in subgroup of participants with heart failure at baseline and in an Asian population subgroup analysis.

Health economics

- Exploratory modelling suggests that the UKPDS model, and therefore the NG28 model, may be inaccurate at predicting the incidence of CV events and mortality in high-risk people receiving canagliflozin or empagliflozin, particularly MI and all-cause mortality, and the relative incidence of those events compared with placebo.

Recommendations

No recommendations were made for this review question.

Rationale and impact

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The committee agreed that reduction on cardiovascular and all-cause mortality on people with type 2 diabetes were the most important outcomes to address for this question. The committee highlighted that in previous years, diabetes management as driven by the prescription of drugs on the basis of HbA1c benefits. However, diabetes management is now moving towards the prescription of drugs based on cardiovascular benefits.

The committee noted that the largest included trials recruited people with established cardiovascular disease at baseline, and therefore, it was important to note that the impact of SGLT-2 inhibitors on decreasing cardiovascular and microvascular

outcomes has been estimated for this high risk population, and not the full population of people with type 2 diabetes.

The committee agreed that in clinical practice, it is sometimes difficult to differentiate fatal acute myocardial infarction from fatal stroke. However, the trials provided a clear definition for each cardiovascular outcome. The committee decided to exclude composite outcome measures from their decision making, as it was agreed these are less easy to interpret than specific individual events and therefore can be misleading.

The quality of the evidence

Overall, the quality of the evidence ranged from low to high, with imprecision in effect estimates the main reason for downgrading. Two large trials which focused on cardiovascular and microvascular outcomes, CANVAS (evaluating canagliflozin, Neal 2017) and EMPA-REG-OUTCOME (evaluating empagliflozin, Zinman 2015), were included and these trials were in a population with high risk of cardiovascular disease or with established cardiovascular disease. The committee agreed that this population was directly relevant to this guideline update, but the results cannot be generalised to a population of type 2 diabetes at low risk of or without cardiovascular disease. The remaining trials included in this update reported cardiovascular and microvascular outcomes as adverse events and were included in the analysis, but were not taken into account for decision making as the event rates in these trials were too low to provide meaningful estimates of benefit.

No evidence was identified assessing cardiovascular and microvascular outcomes with dapagliflozin apart from the report of these outcomes as adverse events. However, a large trial is expected to be published in 2019 aiming to estimate the effect of dapagliflozin on cardiovascular outcomes and the results of this trial should be available for consideration in the next update of this guideline.

The committee noted that the number of events of non-fatal silent myocardial infarction and non-fatal stroke were higher with empagliflozin compared to placebo but the difference was not significant and the sample sizes were smaller for these outcomes.

The committee agreed to include outcomes directly related to the list of outcomes listed in the PICO table but those were downgraded if overall rates of the primary outcome were not reported. For example, hospitalisation for heart failure is directly related to heart failure, and therefore it was not downgraded for indirectness, provided overall rates of heart failure (fatal or non-fatal) were also reported. The committee also agreed to exclude outcomes when it was unclear whether those were directly related to the outcomes in the PICO table. For example, renal replacement therapy was excluded because it was not clear how many participants received this therapy for nephropathy.

Benefits and harms

The committee highlighted that previously, diabetes drug management was primarily driven by blood glucose control. However, diabetes management is now moving towards the prescription of drugs based on cardiovascular benefits. More evidence is now available reporting cardiovascular and microvascular outcomes which can be used to develop recommendations based on this evidence.

The committee agreed that evidence showed a clinically significant reduction in cardiovascular and all-cause mortality with empagliflozin but not with canagliflozin. Therefore, benefits on cardiovascular and all-cause mortality can not be assumed for all SGLT-2 inhibitors as a class until more evidence is available.

The committee noted that in clinical practice, SGLT-2 inhibitors have been shown to have a good effect on blood pressure and weight control and that there is a differential use of SGLT-2 inhibitors based on amputations and diabetic ketoacidosis where clinicians choose a SGLT-2 inhibitor based on its lower risk for amputations or diabetic ketoacidosis. The committee also noted that common reasons for discontinuation of SGLT-2 inhibitors are genital and urinary infections.

The committee highlighted that the Medicines and Healthcare products Regulatory Agency (MHRA) published a drug safety update for SGLT-2 inhibitors in 2017, and that it was appropriate to add this as a footnote to the recommendation. The drug safety update was about canagliflozin, which may increase the risk of lower-limb amputation (mainly toes) in patients with type 2 diabetes. Although there was no evidence of an increased risk for dapagliflozin and empagliflozin, the MHRA warned about a possible class effect. The CANVAS trial found an increased risk of lower-limb amputations in participants receiving canagliflozin. However, EMPA-REG trial did not look at lower-limb amputations.

The committee agreed that there is limited evidence from large trials focusing on cardiovascular, macrovascular, and microvascular outcomes in type 2 diabetes and that, historically, the focus has been on glucose control. The committee agreed that, of all the antidiabetic drugs and combination of drugs, healthcare professionals and patients do not know which drug or combination of drugs is best at improving macrovascular and microvascular outcomes.

The committee noted that in current clinical practice, there is a patient-focused and individualised approach to choice of single, or combination of, antidiabetic drugs. It was noted that patients and healthcare professionals are not only considering glucose management, but also the benefits of treatment of other aspects of health. These include cardiovascular, macrovascular, and microvascular outcomes; weight management; and adverse events, such as risk of hypoglycaemia, genital infections and nausea. Additionally, patients take into account frequency of monitoring and how the drug is administered (injectable or oral) when considering choice of drug. The choice of antidiabetic drugs can be restricted by the presence of chronic kidney disease (for example, metformin and SGLT-2 inhibitors). There is currently a lack of information among healthcare professionals about which factors are the most important to discuss with patients when planning treatment. Because of the many available options of drugs and combinations of drugs, there is also a lack of clarity among patients as to why a specific drug or combinations of drugs are offered to them.

Cost effectiveness and resource use

The committee noted there were no cost-effectiveness studies on SGLT-2 inhibitors based directly on cardiovascular outcomes reported in randomised trials. In the absence of robust cost-effectiveness evidence, the committee agreed it would not be appropriate to make specific recommendations about the place of SGLT-2 inhibitors in the diabetes management pathway, as to do so would involve a comparison to all the other available antidiabetic drug options, something that it is currently not possible to do based on cardiovascular outcomes. It was therefore agreed that no recommendations should be made until the remaining ongoing large trials were published, to maximise the evidence available to feed in to making robust decisions. Committee members were aware that SGLT-2 inhibitors currently have the same price per dose, and noted that the existing technology appraisals for these drugs remained a relevant source of advice on their usage.

The committee noted that the UKPDS equations, used by the health economic model in the original NICE diabetes management guideline (NG28), appeared to underestimate the cardiovascular benefits seen with empagliflozin, based on an exploratory analysis using results from the EMPA-REG and CANVAS trials. The results of this model were primarily based on the effects of drugs on HbA1c, and the committee agreed such an approach may no longer be appropriate to assess antidiabetic drugs, now robust evidence exists that blood glucose control and mortality may not be highly correlated in all cases. The committee therefore agreed it was appropriate that a larger scale update of the antidiabetic drug pathway in the original NICE diabetes management guideline be considered, and that this should be timed to also take in to account the evidence from the large upcoming trial on dapagliflozin, so all the relevant drugs from this class can be considered.

Other factors the committee took into account

The committee noted that in clinical practice, empagliflozin is usually initially prescribed as 10mg but that it can be increased to 25mg. Both doses are currently licensed doses in the UK.

The committee noted that the Asian population subgroup reported for empagliflozin by the EMPA-REG trial (Zinman 2015) included the following countries: Hong Kong, India, Indonesia, Japan, Korea, Malaysia, Philippines, Singapore, Sri Lanka, Taiwan, and Thailand. The committee noted that South Asian populations (people from India, Pakistan, and Bangladesh) may have different characteristics in terms of diabetes compared to other Asian populations. Therefore, the results of the Asian subgroup analyses might not reflect this difference. It was also noted that Asian population was analysed as a subgroup which covered a smaller sample size with large confidence intervals, and therefore agreed it was not appropriate to make a different recommendation for this subgroup.

The committee was aware that a large trial (DECLARE-TIMI58) is expected to be published in 2019 aiming to determine the effect of dapagliflozin on cardiovascular outcomes when added to current background therapy in participants with type 2 diabetes with either established cardiovacular disease or cardiovascular risk factors. The results of this trial should be available for consideration in a future update of this guideline.

The committee were aware of a large multinational observational study evaluating the effectiveness of SGLT-2 inhibitors compared to other glucose lowering drugs on cardiovascular outcomes (Kosiborod 2017). However, the study was not randomised, and therefore did not meet the criteria for this review.

GLP1 mimetics

Review questions

In adults with Type 2 diabetes, what is the clinical effectiveness of GLP-1 mimetics on cardiovascular outcomes?

In adults with Type 2 diabetes, what are the differences between a). The assumptions used in the HE model that informed NG28 and b). The empirical evidence from RCTs?

Introduction

The aim of this topic, regarding the cardiovascular benefits of GLP-1 mimetics for people with Type 2 diabetes, was to identify whether there any important discrepancies between the assumptions used in the health economic model that informed NG28 and the empirical evidence from RCTs. The first of these questions was intended to review the evidence on cardiovascular outcomes for GLP-1 mimetics.

The second of these questions was intended to compare the results of the evidence review with the economic modelling that was undertaken for NG28, to establish whether the assumptions made in the NG28 model are in agreement with recent empirical data. The approach for this question was therefore primarily to be exploratory analysis of the existing economic model, rather than a separate evidence review. This analysis was not necessarily intended to lead to new recommendations; but if it was found that the assumptions made in the health economic model in NG28 are not in agreement with empirical evidence on the cardiovascular outcomes associated with GLP-1 mimetics, then a substantial update of this area may be required to identify whether there is an extended role for glucagon-like peptide-1 receptor agonists (GLP-1 mimetics), which would be done separately from this piece of work.

PICO table

Population	Adults (aged 18 years and older) with Type 2 diabetes mellitus.
Intervention	1. GLP-1 mimetics alone: • Albiglutide • Dulaglutide • Liraglutide 2. GLP-1 mimetics, in combination with other treatments: • Exenatide • Lixisenatide • Dulaglutide • Liraglutide • Albiglutide
Comparison	There will be a stepwise approach to comparators: 1. Studies that compare GLP-1 mimetics to each other (active comparators within class) 2. If no studies that identify GLP-1 mimetics v another GLP-1 mimetic, then comparators of usual care, no treatment or placebo will be used.
Outcomes	Cardiovascular outcomes:

	• Cardiovascular mortality • Fatal MI • Non-fatal MI • Fatal stroke • Non-fatal stroke • Heart failure • Lower limb amputation Microvascular patient oriented outcomes: • Retinopathy • Nephropathy • End-stage renal disease • Neuropathy

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A.

Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy.

Meta-analyses of the evidence were conducted with reference to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011). A pooled relative risk was calculated for dichotomous outcomes (using the Mantel–Haenszel method). Forest plots are presented in Appendix E – Forest plots. Minimal important differences for clinical significance were discussed and the committee agreed that a difference of 25% (which is the GRADE default when no other dichotomous MID is specified) was too high. The committee decided that it was appropriate to use the line of no effect for mortality outcomes, and an MID of a 10% increase or decrease for other outcomes.

Clinical evidence

Included studies

A systematic literature search was carried out to identify randomised controlled trials or systematic reviews of randomised controlled trials (see Appendix B for literature search strategy). The search identified 5,620 articles, which were screened at the title and abstract level. Of these, 263 articles were screened in full. Of these, 57 studies were included based on their relevance to the review protocol (Appendix A – Review protocols). The clinical evidence study selection is available in Appendix C – Clinical evidence study selection.

Fifty seven studies which met the inclusion criteria defined in the review protocol were included in the clinical evidence review. None of these trials compared GLP1 mimetics to each other (active comparators within class). Included trials compared GLP1 mimetics to other active treatments or placebo. Of these, 17 studies reported that no cardiovascular deaths occurred and 1 study reported that no renal failure events occurred. These trials were agreed to not provide useful data as they were all small studies reporting outcomes as adverse events and provided no information on relative risks between the two groups, and therefore they were not incorporated into the statistical analysis. A summary of all included trials is presented in Appendix D – Clinical evidence tables.

Excluded studies

The excluded studies table is available in Appendix J – Excluded studies.

Summary of clinical studies included in the evidence review, and reporting at least 1 event

Study ID	Population	Intervention	Comparison	Outcomes
Araki 2015	- Adults aged ≥20 years with T2D. - Taking stable doses of sulphonylureas (2.5 to 5 mg of glibenclamide; 60 to 80 mg of glicazide; or 2 to 3 mg of glimepiride) and/or biguanides (750 to 1,500 mg of metformin or 100 to 150 of buformin) - N = 361	Sc injections of once-weekly dulaglutide 0.75 mg	Sc injections of once daily glargine with initial dose between 4.0 and 8.0 IU	• Cerebral infarction • Acute myocardial infarction
Bergenstal 2010	- Adults aged ≥18 years with with T2D. - Taking stable doses of metformin. - N = 491	Exenatide 2mg/week	- Sitagliptin 100mg once daily - Pioglitazone 45mg/day	• Cerebrovascular accident • Acute renal failure
Blonde 2015	- Adults aged ≥18 years with with T2D. - Background therapy: metformin 1,500 mg per day or more. - N = 884	- Once-weekly dulaglutide 1.5 mg and insulin lispro using a dosing algorithm - Once-weekly dulaglutide 0.75 mg and insulin lispro using a dosing algorithm	Daily bedtime insulin glargine adjusted to a treat-to-target strategy and insulin lispro using a dosing algorithm	• Fatal cardiovascular event
Buse 2004	- Adults with T2D, between 22 – 76 years - Background therapy: sulfonylurea - N = 252	Exenatide 10ug twice daily	Placebo	• Myocardial infarction
Buse 2013	- Adults aged ≥18 years with T2D. - Background therapy: oral antihyperglycaemic (metformin, sulfonylurea, metformin plus sulfonylurea or metformin plus pioglitazone)	- Exenatide 2mg/week	- Liraglutide 1.8 mg/day	• Myocardial infarction • Brain stem infarction

Study ID	Population	Intervention	Comparison	Outcomes
	- N = 911			
D'Alessio 2015	- Adults aged 35 – 75 years with T2D. - Metformin at a minimum dose of 1g/day alone or in combination with suphonylurea and lifestyle programme. Sulphonylurea reduced or discontinued at start of trial. - N = 965	Liraglutide 1.8 mg/day	Insulin glargine, instructed on a titration schedule, adjusted every 3 days, to attain fasting plasma glucose levels of ≥4.0 and ≤5.5mmol/l	• Cerebrovascular accidents • Ischaemic stroke • Chronic cardiac failure
Davies 2009	Adults with T2D aged ≥18 years Background therapy: two or more of: metformin, sulphonylurea and thiazolidinedione - N = 234	Exenatide 10ug twice daily	Insulin glargine	• Acute myocardial infarction • Acute renal failure
Davies 2015	- Adults with T2D aged ≥18 years. - Background therapy: 500 kcal/d dietary deficit and increased physical activity (≥150 min/wk). - N = 846	- Once-daily sc liraglutide 3.0 mg - Once-daily sc liraglutide 1.8 mg	Once-daily placebo	• Cerebrovascular event • Heart failure • Renal failure
Davies 2016	- Adults aged 18–80 years with T2D Background therapy: monotherapy or dual-therapy combinations of metformin and/or SU and/or pioglitazone, monotherapy with basal or premix insulin, or any combination of basal or premix insulin with metformin and/or pioglitazone. - N = 279	Liraglutide 1.8 mg/day	Insulin glargine	• Cardiovascular mortality
de Wit 2016	- Adults with T2D, mean age = 58 years	Liraglutide up to 1.8 mg added to insulin	Insulin (dose adjusted to fasting glucose target of 4.0 to 6.5 mmol L-1) without liraglutide	• Myocardial infarction

Study ID	Population	Intervention	Comparison	Outcomes
	- Background therapy: glucose-lowering treatment (only metformin and sulfonylurea were allowed) - N = 50			
Diamant 2010, Diamant 2014	- Adults with T2D, mean age = 58 years - Background therapy: metformin with or without sulfonylurea - N = 456	Once weekly exenatide 2 mg injected into abdominal sc tissue	Once daily insulin glargine starting at 10 IU per day and adjusted to achieve target glucose of 4.0 to 5.5 mmol/L	• Cerebrovascular accident • Mortality • Myocardial infarction •
Dungan 2014	- Adults with T2D, 18 years or older - Background therapy: metformin ≥1500 mg/day up to the highest dose allowed per local label - N = 599	Sc injections of once-weekly dulaglutide 1.5 mg	Sc injections of once-daily liraglutide 1.8 mg	• Myocardial infarction • Mortality
Dungan 2016	- Adults aged ≥ 18 years wit T2D not optimally controlled with diet and exercise - Background therapy: glimepride - N = 299	Dulaglutide 1.5mg once weekly	Placebo	• Myocardial infarction • Mortality
Frias 2016	- Adults aged ≥ 18 years with T2D and inadequate glycaemic control - Background therapy: metformin - N = 464	Exenatide 2mg once weekly	Dapagliflozin 10 mg	• CV mortality • Renal failure
Garber 2011	- Adults aged 18 – 80 years with T2D - Background therapy: monotherapy oral antidiabetic - N = 499	Liraglutide 1.2 mg	glimepiride 8 mg/day	• Myocardial infarction
Giorgino 2015	- Adults with T2D, mean age = 57 years	-Sc injection of once-weekly dulaglutide 1.5 mg	Once-daily glargine started at 10 units once daily	• Mortality (death due to heart failure)

Study ID	Population	Intervention	Comparison	Outcomes
	- Background therapy: metformin and glimepiride maximally tolerated doses but not higher than the maximum locally approved doses. - N = 807	- Scinjection ofonce-weekly dulaglutide 0.75 mg	adjusted according to a standard titration algorithm	
Gough 2014	- Adults with T2D, mean age = 55 years - Background therapy: Metformin with or without pioglitazone - N = 828	Liraglutide 1.8 mg	insulin degludec	• Myocardial infarction
Inagaki 2012	- Adults with T2D, aged ≥20 years - Background therapy: current oral antidiabetes drugs (biguanide or biguanide plus thiazolidine derivative - N = 427	Exenatide 2 mg once weekly by sc injection	Insulin glargine once daily before bedtime by sc injection, dose started at 4 U and adjusted to achieve target fasting blood glucose of <100 mg/dL	• Mortality (death due to cardiac failure)
Jaiswal 2015	- Adults with T2D aged between 18 and 70 years. - Background therapy: prior oral agents to optimize blood glucose control. - N = 46	Exenatide up to 10 µg	Insulin glargine initiated with 10 units daily and titrated in 2-unit increments to achieve a fasting blood glucose target level of 5.6 mmol/L (100 mg/dL)	• Left toe amputation
Kaku 2016	- Adults with T2D, aged ≥20 years - Background therapy: oral antidiabetes drugs: glinide, metformin, a-glucosidase inhibitor or thiazolinedione) - N = 360	Liraglutide 0.9mg/day	Another oral antidiabetic	• Diabetic retinopathy
Lind 2015	- Adults with T2D, mean age = 63.6 years	liraglutide 1.8 mg/day	Placebo	• Cardiac failure

Study ID	Population	Intervention	Comparison	Outcomes
	- Treated with multiple daily insulin injections - Background therapy: multiple insulin injections - N = 124			
Marso 2016 (LEADER trial)	- Adults with T2D aged 50 years or more with at least one cardiovascular coexisting condition - Background therapy: standard care which could include metformin, add-on therapy (thiazolidinediones, sulfonylureas, alpha glucosidase inhibitors), and insulin therapy (basal, basal/bolus, premix, and mealtime bolus). - N = 9340	Liraglutide 1.8 mg once daily as a sc injection	Matching placebo once daily as a sc injection	• Fatal MI • Nonfatal MI • Silent MI • Fatal stroke • Nonfatal stroke • Transient ischemic attack • Hospitalization for heart failure • Retinopathy • Nephropathy • Mortality (death from cardiovascular causes)
Meier 2015	- Adults aged 18 to 75 years with T2D - Background therapy: optimised insulin glargine with/without metformin - N = 142	Lixisenatide 20 µg sc once daily	-Liraglutide 1.2 mg sc once daily - Liraglutide 1.8 mg sc once daily	• Myocardial infarction requiring hospitalisation • Mortality
Meneilly 2017	- Adults with T2D, aged ≥70 years - Background therapy: Permitted antidiabetic therapies were metformin, sulfonylurea (except glibenclamide >10 mg and gliclazide >160 mg), meglitinide (except repaglinide >6 mg), pioglitazone, and basal insulin.	Lixisenatide up to 20 µg self-administered once daily by sc injection 30–60 min before breakfast	Placebo	• Mortality (death due to aortic aneurysm)

Study ID	Population	Intervention	Comparison	Outcomes
	- N = 350			
Nauck 2016	- Adults with T2D, aged ≥18 years - Background therapy: metformin - N = 404	Liraglutide 1.8 mg once daily scinjection	Lixisenatide 20 µg once daily sc injection	• Myocardial ischemia • Cardiac failure • Ischemic stroke
Pfeffer 2015 (ELIXA trial)	- Adults with T2D, age <30 years - Background therapy: concomitant glucose-lowering agents or addition of new antidiabetic medications with the exception of other incretin therapies to achieve glycaemic control. - N = 6068	Once-daily sc injections of lixisenatide up to 20 µg	Placebo	• Myocardial infarction • Stroke • Hospitalization for heart failure • Death from cardiovascular causes
Pinget 2013	- Adults with T2D - pioglitazone with/without metformin - N = 484	Lixisenatide 20ug/day	Placebo	• Mortality (death due to myocardial infarction)
Pratley 2010, Pratley 2011	- Adults with T2D, mean age = 55 years - Background therapy: metformin - N = 665	liraglutide 1.2 mg and 1.8 mg	Sitagliptin	• CV mortality • Myocardial infarction • Heart failure • Diabetic retinopathy
Riddle 2013a	- Adults with T2D, mean age = 57 years - Background therapy: If used at enrolment, metformin was continued at a stable dose throughout the study and basal insulin dosage was to remain relatively stable throughout the study. - N = 495	Once-daily lixisenatide in a two-step dose-increase regimen from 10 µg up to 20 µg sc injection within 1 h before the morning meal	Once-daily placebo	• Mortality (sudden cardiac death)
Riddle 2013b	- Adults with T2D, mean age = 56 years	Lixisenatide up to 20ug	Placebo	• Mortality (myocardial infarction leading to death)

Study ID	Population	Intervention	Comparison	Outcomes
	- Background therapy: insulin glargine with or without metformin - N = 446			
Rosenstock 2016a	- Adults with T2D, mean age = 59 years - Background therapy: stable dose of basal insulin (≥ 20 units/day) with or without metformin - N = 890	Lixisenatide up to 20ug/day	- Insulin glulisine once daily - Insulin glulisine 3 times daily	• Mortality (death due to chronic heart failure) •
Seino 2012	- Adults with T2D aged 25 to 81 years. - Background therapy: established doses of basal insulin with or without sulfonylureas - N = 311	Lixisenatide up to 20 µg sc injection once daily within 1 hour before breakfast	Placebo	• Nonfatal ischemic stroke
Weinstock 2015	- Adults aged 18 to 75 years with T2D - Background therapy: metformin - N = 619	Dulaglutide 1.5 mg	Sitagliptin 100 mg	• Cardiovascular mortality
Yu Pan 2014	- Adult participants with T2D, mean age = 55 years, diagnosed for at least 1 year - Background therapy: metformin with or without sulphonylurea - N = 390	Lixisenatide 20 ug	Placebo	• Stroke • Myocardial infarction • Cardiovascular mortality

Abbreviations: sc = subcutaneous, T2D = type 2 diabetes.

See appendix D for full evidence tables.

Quality assessment of clinical studies included in the evidence review

See appendix F for full GRADE tables. Both hazard ratios and relative risks are reported where available, with imprecision calculated based on relative risks if both measures were presented. Because a significant proportion of the included studies did not contain sufficient events to produce meaningful results, GRADE tables are only presented for studies where at least 5 events occurred.

Economic evidence

Included studies

A literature search was conducted to identify cost–utility analyses that included at least one GLP-1 mimetic therapy. The MEDLINE, Embase, EconLit and PubMed databases were searched, along with the Health Technology Assessment database and the NHS Economic Evaluation Database (EED). A total of 1,208 studies was retrieved. After review of titles and abstracts, 38 studies were ordered for full-text review.

The first part of this topic is concerned with the clinical effectiveness of GLP-1 mimetics on CV outcomes. We sought to include any cost–utility analyses that used treatment effects on CV outcomes directly to calculate cost–utility outcomes, rather than using a prediction model that uses effects on intermediate outcomes to predict subsequent CV outcomes. After review of the 38 full texts, no studies were included for this part of the topic.

The second part of this topic involved identifying the key clinical assumptions used in the economic model that was developed to support the existing NICE guideline for type 2 diabetes management (NG28). Outcomes from the NG28 model were determined largely by treatment effects on HbA1c, body weight and the rate of hypoglycaemic events. To identify whether there are important alternative effects, we sought to include any cost–utility analyses that included different treatment effect parameters to those used by the NG28 model, and that tested the sensitivity of cost-effectiveness results to exclusion of (or variation in) those parameters. After review of full texts, 12 studies were included for this part of the topic.

Excluded studies

Studies excluded from the review of economic evaluations are listed in Appendix J, including reasons for exclusion.

Summary of studies included in the economic evidence review

Cost–utility analyses from the GLP-1 mimetics economic evidence search were included if they included (1) different treatment effect parameters to those used in the NG28 model, for example change in SBP or lipid levels, or that modelled using observed CV event data directly; and (2) sensitivity analysis on the exclusion of (or variation in) those parameters. After review of 38 full texts, 12 studies were included.

All 12 were modelling studies, using intermediate outcomes (e.g. change in HbA1c) to predict differences in CV event rates, and thereafter costs and QALYs. No studies estimated cost-effectiveness using empirical evidence on CV event rates directly. Four studies were UK analyses; 5 contained analyses from different European

countries; 2 were from the US and 1 was from China. Studies included albiglutide, exenatide, liraglutide and lixisenatide as GLP-1 interventions, in various combination therapies (e.g. with metformin) and in various comparisons (including versus insulin and versus each other).

Ten studies found their cost-effectiveness results to be robust to exclusion of (or variation in) relative effects on SBP. No studies found that exclusion of (or variation in) lipid markers had an impact on the cost-effectiveness decision. All used the CORE Diabetes Model to determine the incidence of CV events based on intermediate outcomes from several GLP-1 mimetic trials.

Two studies found cost-effectiveness results to be sensitive to the exclusion of relative effects on SBP. In one case, the decision rule regarding which intervention is cost-effective changed if the relative effects on SBP were excluded from the model.

Bruhn et al. (2016) compared albiglutide with 3 alternatives: sitagliptin, insulin glargine, and insulin lispro both with insulin glargine, chosen to reflect different stages of the treatment pathway. The analysis used the CORE Diabetes Model, with relative effects on intermediate outcomes informed by the HARMONY trials (3, 4 & 6). The base case ICER compared with insulin lispro was $43,541 per QALY gained. Excluding relative effects on SBP reduced the incremental QALYs associated with albiglutide, increasing its ICER to $51,027 per QALY gained. This change would potentially change the decision rule relative to a cited lower US cost-effectiveness threshold of $50,000 per QALY gained. In the comparison with insulin glargine, omitting SBP effects increased the ICER from $79,166 to $152,400 per QALY gained. This would potentially change the decision rule relative to a cited upper US cost-effectiveness threshold of $100,000 per QALY gained.

Gao et al. (2012) found that excluding SBP effects reduced the incremental QALYs from liraglutide 1.8 mg compared with glimepride significantly, from 0.168 to 0.060 per patient. This was a much more substantial change than other sensitivity analyses. The analysis used the UKPDS outcomes model (1) to determine relative CV event rates. The Asian trial used to inform treatment effects was not published in English. The ICER remained above the cited cost-effectiveness threshold in China of 3x gross domestic product per capita.

Economic evidence tables are provided in Appendix H.

Economic model

New economic modelling was not conducted for this topic. However, to explore the clinical assumptions used in the NG28 cost–utility model, the original model was re-simulated over a 5-year time horizon for 2 reasons:

1. To provide an estimate of the rate of CV events predicted by the model over a relatively short time horizon;
2. To identify which treatment effect parameters are most strongly correlated with CV event rates.

The NG28 model predicted CV events using the UKPDS Outcomes Model 1, which utilises intermediate outcome measures, such as HbA1c, to predict the incidence of CV events and mortality. This analysis identified that myocardial infarction is the CV event that occurs most often in the model, having happened to 8.4% to 8.5% of modelled patients at first treatment intensification after 5 years. Congestive heart failure and stroke were each predicted to occur in 3.7% to 3.8% of patients. Amputation (0.4%) and renal failure (0.3%) were the least common CV events after 5 years. The incidence of CV events was compared with the model input treatment

effects on intermediate outcomes, to identify which clinical inputs were the most influential at predicting ultimate cost–utility outcomes. This analysis found CV events and mortality to be almost perfectly correlated with the absolute 1-year treatment effects on HbA1c used in the original model. Glucose control was therefore identified as the key clinical driver of the model, with weight, treatment dropout and hypoglycaemic events being less influential. Other intermediate measures, such as systolic blood pressure and lipid levels, were not included in the NG28 model, such that any interventions causing improvements in those parameters had no impact on model results.

A further modelling analysis was conducted, to explore how accurately the UKPDS model (and therefore the NG28 model) predicts the number of CV events reported in the 2 recent GLP-1 mimetic trials (ELIXA, LEADER). The health economic model for the original guideline (NG28), and indeed most diabetes models to date, was driven by the UKPDS prediction equations, therefore this analysis explores the extent to which the CV outcomes in the high-risk ELIXA and LEADER poulations would be captured by the original model.

The NG28 model was used to create a cohort of 5,000 patients, whose population-level characteristics matched the ELIXA and LEADER study participants in characteristics used by the UKPDS model that were reported. Where such information was not reported, the original NG28 model characteristics from the THIN database were applied. Results suggest that when applying treatment effects on either HbA1c alone or HbA1c and SBP simultaneously, the UKPDS equations may underpredict the magnitude of benefit of liraglutide, and potentially overpredict the benefit of lixisenatide. It may be that they influence the risk of CV events via a mechanism that is not captured by changes in HbA1c or SBP reduction. The UKPDS model also appears to overpredict mortality in the LEADER population. It may therefore be poorly suited for modelling populations with high baseline CV risk, such as those in the ELIXA and LEADER studies.

Details of these exploratory analyses are provided in Appendix I.

Evidence statements

When results other than mortality are reported below, these are based on defined minimal important differences of a 10% change, so the result needs to be statistically significant, and the point estimate needs to correspond to an increase or decrease of greater than 10%. For mortality outcomes, it was only needed that the outcome be statistically significant.

Liraglutide versus placebo (LEADER study)

- High-quality evidence from 1 RCT containing 9,340 people with type 2 diabetes and high risk of cardiovascular events found that fewer people randomised to liraglutide (1.8 mg per day) died from cardiovascular causes and died from all causes compared to people randomised to placebo.
- Moderate-quality evidence from 1 RCT containing 9,340 people with type 2 diabetes and high risk of cardiovascular events could not detect a difference in myocardial infarction mortality or stroke mortality between people randomised to liraglutide (1.8 mg per day) compared to people randomised to placebo.
- Low- to moderate-quality evidence from 1 RCT containing 9,340 people with type 2 diabetes and high risk of cardiovascular events could not detect a difference in:
  - myocardial infarction
  - stroke

- transient ischaemic attack or
- diabetic retinopathy

between people randomised to liraglutide (1.8 mg per day) compared to people randomised to placebo.

- Low-quality evidence from 1 RCT containing 9,340 people with type 2 diabetes and high risk of cardiovascular events found that fewer people randomised to liraglutide (1.8 mg per day) had nephropathy compared to people randomised to placebo.

Lixisenatide versus placebo (ELIXA study)

- Moderate-quality evidence from 1 RCT containing 6,068 people with type 2 diabetes and high risk of cardiovascular events could not detect a difference in cardiovascular mortality and mortality from all causes between people randomised to lixisenatide (up to 20 µg per day) compared to people randomised to placebo.
- Low-quality evidence from 1 RCT containing 6,068 people with type 2 diabetes and high risk of cardiovascular events could not detect a difference in:
  - myocardial infarction or
  - stroke

  between people randomised to lixisenatide (up to 20 µg per day) compared to people randomised to placebo.
- Very low-quality evidence from 1 RCT containing 6,068 people with type 2 diabetes and high risk of cardiovascular events could not detect a difference in hospitalisation for heart failure between people randomised to lixisenatide (up to 20 µg per day) compared to people randomised to placebo.

Health economics

- Ten cost–utility analyses found their cost-effectiveness decisions to be insensitive to the use of relative treatment effects on SBP and lipids – 4 were directly applicable (6 partially), 9 had potentially serious limitations (1 very serious). Two partially applicable cost–utility analysis with potentially serious limitations found cost-effectiveness results to be sensitive to the use of relative effects on SBP.
- Exploratory modelling suggests that the UKPDS model, and therefore the NG28 model, may be inaccurate at predicting the incidence of CV events and mortality in high-risk people receiving liraglutide or lixisenatide, particularly MI, heart failure and all-cause mortality, and the relative incidence of those events compared with placebo.

Recommendations

No recommendations were made for this review question.

Rationale and impact

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The committee agreed that cardiovascular outcomes (in particular cardiovascular and all-cause mortality) is the focus of this guideline update, but considered microvascular outcomes including nephropathy, retinopathy and renal failure.

The committee noted that the largest included trials recruited people with established cardiovascular disease or a high risk of cardiovascular disease at baseline, and therefore, it was important to note that the impact of GLP-1 mimetics on decreasing cardiovascular and microvascular outcomes has been estimated for this high risk population, and not the full population of people with type 2 diabetes.

The quality of the evidence

Overall, the quality of the evidence ranged from very low to high. Two large trials which focused on cardiovascular outcomes, LEADER (Marso et al. 2016) and ELIXA (Pfeffer et al. 2015), were included and these trials were in a population with high risk of cardiovascular disease or with established cardiovascular disease. The committee agreed that this population was directly relevant to this guideline update, but the results cannot be generalised to a population of type 2 diabetes at low risk of or without cardiovascular disease. The remaining trials included in this update reported cardiovascular and microvascular outcomes as adverse events and were included in the analysis, but were not taken into account for decision making as the event rates in these trials were too low to provide meaningful estimates of benefit.

No evidence was identified assessing cardiovascular and microvascular outcomes with GLP-1 mimetics other than liragutide and lixisenatide, apart from the report of these outcomes as adverse events.

Benefits and harms

The committee noted that the results of the LEADER trial found a clinically meaningful reduction of nephropathy, cardiovascular mortality and mortality from all causes in participants treated with liraglutide compared to placebo. The committee discussed that the beneficial effect of liraglutide on cardiovascular mortality and mortality from all causes could be because a high dose of liraglutide (1.8 mg) was used in the trial, and this may not be applicable to the majority of patients who are prescribed 1.2 mg in clinical practice. Additionally, the LEADER trial had no restrictions on BMI, and a higher dose may be more beneficial in reducing cardiovascular disease risk in patients with a higher BMI.

The committee noted that previous recommendations based on GLP-1 mimetics considered liraglutide at a dose of 1.2 mg and that the LEADER trial is not sufficient evidence by itself to recommend a dosage of 1.8 mg. Additionally, it was noted that a brand of liraglutide, Saxenda, is licensed at a maintenance dose of 3.0 mg for weight reduction in adults with a BMI of 30 kg/m2 or more or from 27 to 30 kg/m2 in the presence of at least one weight-related comorbidity, such as type 2 diabetes. The committee noted that liraglutide at the higher dose of 3.0 mg may have cardiovascular benefits in a population of overweight or obese patients with type 2 diabetes, but there is a lack of research in this area.

The committee discussed the results of the ELIXA trial, which found no difference in cardiovascular mortality, all-cause mortality, myocardial infarction, stroke and hospitalisation for heart failure between lixisenatide and placebo, and queried why a beneficial effect on cardiovascular outcomes was found for liraglutide in the LEADER trial. The committee discussed that, theoretically, there could be a difference in the mechanism of different GLP-1 mimetics and it could not be assumed that the cardiovascular benefit of liraglutide can be extended to all GLP-1 mimetics until more evidence is available. Additionally, the populations of both trials varied. The LEADER trial had a population of adults with type 2 diabetes aged 50 years or older with mostly (81.3%) established cardiovascular disease or a high risk of cardiovascular disease. In contrast, the ELIXA trial had a population of adults with type 2 diabetes aged 30 years or older with a high risk cardiovascular disease. While liraglutide was administered at a 1.8 mg, which is higher than what is usually prescribed (1.2 mg), lixisenatide was administered up to the maximum dose of 20 µg. The committee agreed that the potential differences within the drug class, the difference in population, alongside the possible dose effect of liraglutide, could be the reason why a cardiovascular benefit was observed in the LEADER trial, but not ELIXA. It was noted that the population of both trials were treated with different background therapies and the additive effect of these therapies with GLP-1 mimetics are not known. The committee agreed not to make a specific recommendation on the cardiovascular benefit to using lixisenatide in people with type 2 diabetes and high risk of cardiovascular disease; as the ELIXA trial provided no evidence of cardiovascular benefit.

The committee agreed that there is limited evidence from large trials focusing on cardiovascular outcomes, other macrovascular outcomes, and microvascular outcomes in type 2 diabetes and that, historically, the focus has been on glucose control. The committee agreed that, of all the antidiabetic drugs and combination of drugs, healthcare professionals and patients do not know which drug or combination of drug is best at improving macrovascular and microvascular outcomes.

The committee noted that in current clinical practice, there is a patient-focused and individualised approach to choice of single, or combination of, antidiabetic drugs. Patients and healthcare professionals are not only considering glucose management, but also the benefits of treatment other aspects of health. These include cardiovascular, macrovascular, and microvascular outcomes; weight management; and adverse events, such as risk of hypoglycaemia, genital infections and nausea. Additionally, patients take into account frequency of monitoring and how the drug is administered (injectable or oral) when considering adherence. There is currently a lack of information among healthcare professionals about which factors are the most important to discuss with patients when planning treatment. Because of the many available options of drugs and combinations of drugs, there is also a lack of clarity among patients as to why a specific drug or combinations of drugs are offered to them.

Cost effectiveness and resource use

The committee noted there were no cost-effectiveness studies on GLP-1 mimetics based directly on cardiovascular outcomes reported in randomised trials. In the absence of robust cost-effectiveness evidence, the committee agreed it would not be appropriate to make specific recommendations about the place of GLP-1 mimetics in the diabetes management pathway, as to do so would involve a comparison to all the other available antidiabetic drug options, something that it is currently not possible to do based on cardiovascular outcomes. It was therefore agreed that no

recommendations should be made until the remaining ongoing large trials were published, to maximise the evidence available to feed in to making robust decisions.

The committee noted that the UKPDS prediction equations, used by the health economic model used in the original NICE diabetes management guideline (NG28), appeared to underestimate the cardiovascular benefits seen with liraglutide, and overestimate the benefit of lixisenatide, based on an exploratory analysis using results from the ELIXA and LEADER trials. The estimates in the original NG28 model were primarily based on the effects of drugs on HbA1c, and the committee agreed such an approach may no longer be appropriate to assess antidiabetic drugs, now robust evidence exists that blood glucose control and mortality may not be highly correlated in all cases. The committee also noted that other models which had included systolic blood pressure generally did not provide meaningfully different results to those based on HbA1c only, as described in Appendix H, such that increasing the number of intermediate endpoints used as predictors of cardiovascular events is unlikely to solve this problem. The committee therefore agreed it was appropriate that a larger scale update of the antidiabetic drug pathway in the original NICE diabetes management guideline be considered, and that this should be timed to also take in to account the evidence from the other large upcoming trials on GLP-1 mimetics, so all the relevant drugs from this class can be considered.

Other factors the committee took into account

The committee discussed the results of a recent trial, SUSTAIN-6, on semaglutide, a GLP-1 mimetic which has been submitted for licensing, and therefore was not included or assessed in this review. The trial showed that in participants aged 50 years or older with type 2 diabetes and clinical or subclinical evidence of cardiovascular disease, fewer people offered semaglutide had non-fatal stroke than placebo. However, there was no difference in cardiovascular mortality, non-fatal myocardial infarction, hospitalisation for heart failure and all-cause mortality. The trial also found that more people offered semaglutide (3%) had diabetic retinopathy compared to placebo (1.8%). The committee noted that this trial provided inconclusive evidence of the cardiovascular benefits of semaglutide.

The committee noted that they are aware of 3 large trials on GLP-1 mimetics: HARMONY (albiglutide, due to complete in 2018), EXSCEL (exenatide, due to complete in late 2017) and REWIND (dulaglutide, due to complete in 2018) trials which are yet to publish. The results of these trials should be available for consideration in a future update of this guideline.

Appendices

Appendix A – Review protocols

SGLT-2 inhibitors

Review Protocol	
Components	Details
Review question	In adults with Type 2 diabetes, what is the clinical effectiveness of SGLT-2 inhibitors on cardiovascular outcomes?
Background/ objectives	The aim here is to provide recommendations to supplement NICE's TA guidance on SGLT-2 inhibitors, which is reproduced in NG28. This work will not update any of the TAs (these have not looked at cardiovascular outcomes), so no permission to update is required although the TA team will be informed the work is happening. Any recommendations that result from the CGUT work cannot affect the interpretation of the TA guidance.
Population	Adults (aged 18 years and older) with type 2 Diabetes mellitus
Intervention	Sodium-glucose cotransporter-2 inhibitors (SGLT-2), including: • Canaglifozin • Dapaglifozin • Empaglifozin In mono, dual or triple therapy or as an add-on to insulin therapy.
Comparator	There will be a stepwise approach to comparators: 1. Studies that compare SGLT-2 inhibitors to each other (active comparators within class) 2. If no studies that identify SGLT-2 inhibitor v another SGLT-2 inhibitor, then comparators of usual care, no treatment or placebo will be used.
Outcomes	Cardiovascular outcomes: • Cardiovascular mortality • Fatal MI • Non-fatal MI • Fatal stroke • Non-fatal stroke • Heart failure • Lower limb amputation Microvascular patient oriented outcomes: • Retinopathy • Nephropathy • End-stage renal disease • Neuropathy
Type of review question	Intervention
Types of study to be included	RCT
Language	English language only
Status	Published studies, full text only.

Review Protocol	
Any other information or criteria for inclusion/exclusion	The committee will be sent the list of included and excluded studies prior to the committee meeting. The committee will be requested to check whether any studies have been excluded inappropriately, and whether there are any relevant studies they know of which haven't been picked up by the searches or have been wrongly sifted out.
Analysis of subgroups or subsets	The following subgroup analyses will be undertaken: • People in specific cardiovascular risk groups • Baseline glycaemic control (<59 mmol/mol (<7.5%), ≥59 - <69 mmol/mol (≥7.5% - <8.5%), and ≥ 69 mmol/mol (≥8.5%) glycosylated HbA1c) • BMI (<25, ≥25-<30, ≥30- <35, ≥35) • People in specific ethnic groups • Age <65 yr, ≥65 yr • People with renal impairment
Data extraction and quality assessment	Sifting Relevant studies will be identified through sifting the abstracts and excluding studies clearly not relevant to the review question (measured against the review protocol). In the case of relevant or potentially relevant studies, the full paper will be ordered and reviewed; studies that do not match the review protocol will be excluded. Relevant information from included studies will be extracted into standardised evidence tables. Critical appraisal The risk of bias of each included study will be assessed using standardised checklists available in the NICE manual, appropriate for the design of each included study. GRADE methodology will be used to assess the quality of evidence for each outcome: i. Risk of bias will be assessed for the evidence as a whole, based on the findings of the critical appraisal checklists applied to each of the individual studies ii. Inconsistency will be assessed by visual inspection, and taking I^2 and Tau^2 into account; iii. Indirectness will be assessed by considering the population, intervention and outcomes of the included studies, relative to the target population, intervention, comparator and outcomes as specified in the review protocol; iv. Imprecision will be assessed using the confidence intervals around point estimates and whether they cross the MIDs for each outcome. COMET and published literature including related NICE guidelines were checked for established / published appropriate minimal important differences (MIDs) for each outcome. None were identified; therefore the committee were consulted on the appropriateness of using default MIDs (0.8, 1.25) for dichotomous outcomes as suggested by the GRADE working group. It was agreed that 25% was too high, and that it was appropriate to use the line of no effect for mortality outcomes and use an MID of 10% as a starting point for discussion of effectiveness for other outcomes. The same parameters will be used as a starting point to assess imprecision. No continuous outcomes were specififed in the review. Quality assurance i. Sifting and data extraction

Review Protocol	
	A full double-sifting of titles and abstracts will not be conducted because this is a narrow intervention question with clearly defined straightforward inclusion and exclusion criteria. However in cases of uncertainty the following step-wise mechanisms will be in place: • technical analyst will discuss with a support technical analyst • comparison with included studies of other current (within 5 years) systematic reviews • members of the committee will be asked to comment on whether the paper is appropriate to include in a review; providing justification for their decision. A full double-selecting of full papers for inclusion/exclusion will not be conducted (see above). However in cases of uncertainty the same mechanisms stated above will be followed. ii. Quality assessment A full double-scoring quality assessment will not be conducted due to the nature of the review question (see above). Internal QA (10% of studies) by CGUT technical adviser on the risk of bias and quality assessment that is being conducted. Any disagreement will be resolved through discussion. The Committee will be sent the evidence synthesis prior to the committee meeting and will be requested to comment on the quality assessment, which will serve as another QA function.
Strategy for data synthesis	If possible a meta-analysis of available study data will be carried out to provide a more complete picture of the evidence body as a whole. A fixed effects model will be used as it is expected that the studies will be homogenous in terms of population and we can assume a similar effect size across studies. If unexplained heterogeneity is present despite subgroup analysis, a random effects model will be used. Narrative evidence statements outlining key issues such as volume and quality of evidence (GRADE) and presenting the key findings from the evidence will be produced.
Searches	Sources to be searched • Clinical searches - Medline, Medline in Process, PubMed, Embase, Cochrane databases (CDSR, CENTRAL, DARE (legacy records) and HTA) • Economic searches - Medline, Medline in Process, PubMed, Embase, EconLit, NHS EED (legacy records) and HTA, with economic evaluations and quality of life filters applied. Supplementary search techniques • None identified Limits • Studies reported in English • Study design RCT and Systematic Review filters will be applied • Animal studies will be excluded from the search results • Conference abstracts will be excluded from the search results • No date limit (all years)
Key papers	Studies identified by Medicines and Prescribing Centre EMPA-REG-OUTCOME (2015)-empaglifozin Studies in progress CANVAS safety trial – estimated study completion date February 2017

Review Protocol	
	DECLAR-TIMI 58 – estimated completion date 2019 Relevant NICE guidance TAs on combination therapy with Canaglifozin (TA315), Dapaglifozin (TA288) and Empaglifozin (TA336), Canaglifozin, Dapaglifozin and Empaglifozin as monotherapies for treating type 2 diabetes (TA390), and Dapaglifozin triple therapy (TA418)

GLP-1 mimetics

Review Protocol	
Components	Details
Review question	2a. In adults with Type 2 diabetes, what is the clinical effectiveness of GLP-1 mimetics on cardiovascular outcomes? 2b. In adults with Type 2 diabetes, what are the differences between a). The assumptions used in the HE model that informed NG28 and b). The empirical evidence from RCTs?
Background/ objectives	The original commission was worded thus: Regarding the cardiovascular benefits of GLP-1 mimetics for people with Type 2 diabetes, are there any important discrepancies between a) the assumptions used in the HE model that informed NG28 and b) the empirical evidence from RCTs. The decision was made to split the review into 2 parts: part 2a. To review the evidence on cardiovascular outcomes for GLP-1 mimetics and part 2b. To compare the results of the evidence review to the economic model inputs for NG28. The aim here is to investigate the validity of the current restrictive NG28 position on GLP-1 mimetics. It is possible that no new recommendations will be made, although the findings of the work will be published. If the answer to question 2b is that there is no difference between RCT data and the health economic assumptions, then the recommendations in NG28 will remain valid. If a difference is found between RCT data and the health economic assumptions, then NICE will consider a substantial update of NG28 separate from this piece of work.
Population	Adults (aged 18 years and older) with Type 2 diabetes mellitus.
Intervention	1. GLP-1 mimetics alone: • Albiglutide • Dulaglutide • Liraglutide 2.GLP-1 mimetics, in combination with other treatments: • Exenatide • Lixisenatide • Dulaglutide • Liraglutide • Albiglutide
Comparator	There will be a stepwise approach to comparators: 1. Studies that compare GLP1 mimetics to each other (active comparators within class) 2. If no studies that identify GLP1 mimetics v another GLP1 mimetic, then comparators of usual care, no treatment or placebo will be used.
Outcomes	Cardiovascular outcomes:

Review Protocol	
	• Cardiovascular mortality • Fatal MI • Non-fatal MI • Fatal stroke • Non-fatal stroke • Heart failure • Lower limb amputation Microvascular patient oriented outcomes: • Retinopathy • Nephropathy • End-stage renal disease • Neuropathy
Type of review question	Intervention
Types of study to be included	RCT
Language	English language only
Status	Published studies, full text only.
Any other information or criteria for inclusion/exclusion	The committee will be sent the list of included and excluded studies prior to the committee meeting. The committee will be requested to check whether any studies have been excluded inappropriately, and whether there are any relevant studies they know of which haven't been picked up by the searches or have been wrongly sifted out.
Analysis of subgroups or subsets	The following subgroup analyses will be undertaken: • People in specific cardiovascular risk groups • Baseline glycaemic control (<59 mmol/mol (<7.5%), ≥59 - <69 mmol/mol (≥7.5% - <8.5%), and ≥ 69 mmol/mol (≥8.5%) glycosylated HbA1c) • BMI (<25, ≥25-<30, ≥30- <35, ≥35) • People in specific ethnic groups • Age <65 yr, ≥65 yr • People with renal impairment
Data extraction and quality assessment	Sifting Relevant studies will be identified through sifting the abstracts and excluding studies clearly not relevant to the review question (measured against the review protocol). In the case of relevant or potentially relevant studies, the full paper will be ordered and reviewed; studies that do not match the review protocol will be excluded. Data extraction Relevant information from included studies will be extracted into standardised evidence tables. Critical appraisal The risk of bias of each included study will be assessed using standardised checklists available in the NICE manual, appropriate for the design of each included study. GRADE methodology will be used to assess the quality of evidence for each outcome:

Review Protocol	
	i. Risk of bias will be assessed for the evidence as a whole, based on the findings of the critical appraisal checklists applied to each of the individual studies ii. Inconsistency will be assessed by visual inspection, and taking I^2 and Tau^2 into account; iii. Indirectness will be assessed by considering the population, intervention and outcomes of the included studies, relative to the target population, intervention, comparator and outcomes as specified in the review protocol; iv. Imprecision will be assessed using the confidence intervals around point estimates and whether they cross the MIDs for each outcome. COMET and published literature including related NICE guidelines were checked for established / published appropriate minimal important differences (MIDs) for each outcome. None were identified; therefore the committee were consulted on the appropriateness of using default MIDs (0.8, 1.25) for dichotomous outcomes as suggested by the GRADE working group. It was agreed that 25% was too high, and that it was appropriate to use the line of no effect for mortality outcomes and use an MID of 10% as a starting point for discussion of effectiveness for other outcomes. The same parameters will be used as a starting point to assess imprecision. No continuous outcomes were specififed in the review. Quality assurance i. Sifting and data extraction A full double-sifting of titles and abstracts will not be conducted because this is a narrow intervention question with clearly defined straightforward inclusion and exclusion criteria. However in cases of uncertainty the following step-wise mechanisms will be in place: • technical analyst will discuss with a support technical analyst • comparison with included studies of other current (within 5 years) systematic reviews • members of the committee will be asked to comment on whether the paper is appropriate to include in a review; providing justification for their decision. A full double-selecting of full papers for inclusion/exclusion will not be conducted (see above). However in cases of uncertainty the same mechanisms stated above will be followed. ii. Quality assessment A full double-scoring quality assessment will not be conducted due to the nature of the review question (see above). Internal QA (10% of studies) by CGUT technical adviser on the risk of bias and quality assessment that is being conducted. Any disagreement will be resolved through discussion. The Committee will be sent the evidence synthesis prior to the committee meeting and will be requested to comment on the quality assessment, which will serve as another QA function.
Strategy for data synthesis	If possible a meta-analysis of available study data will be carried out to provide a more complete picture of the evidence body as a whole. A fixed effects model will be used as it is expected that the studies will be homogenous in terms of population and we can assume a similar effect size across studies. If heterogeneity is found, subgroup analysis will be undertaken. If heterogeneity is present despite subgroup analysis, a random effects model will be used.

Review Protocol	
	Narrative evidence statements outlining key issues such as volume and quality of evidence and presenting the key findings from the evidence will be produced.
Searches	Sources to be searched • Clinical searches - Medline, Medline in Process, PubMed, Embase, Cochrane databases (CDSR, CENTRAL, DARE (legacy records) and HTA) • Economic searches - Medline, Medline in Process, PubMed, Embase, EconLit, NHS EED (legacy records) and HTA, with economic evaluations and quality of life filters applied. Supplementary search techniques • None identified Limits • Studies reported in English • Study design RCT and Systematic Review filters will be applied • Animal studies will be excluded from the search results • Conference abstracts will be excluded from the search results • No date limit (all years)
Key papers	Studies identified by surveillance process This referral did not go through surveillance process – n/a Studies identified by Medicines and Prescribing Centre LEADER (Marso et al. 2016) assessed the cardiovascular effects of the glucagon-like-peptide-1 (GLP-1) mimetic liraglutide as an add-on to standard care in people with type 2 diabetes who had established cardiovascular disease or were at high risk of developing it. ELIXA (Evaluation of Lixisenatide in Acute Coronary Syndrome) – 2015. Studies in progress EXSEL- due to complete 2018 REWIND – due to complete 2018 HARMONY outcomes – due to complete 2019

Appendix B – Literature search strategies

Search summary

The clinical searches were conducted in February 2017.

Databases	Date searched	Version/files
Cochrane Central Register of Controlled Trials (CENTRAL)	21/2/2017	Issue 1 of 12, January 2017
Cochrane Database of Systematic Reviews (CDSR)	21/2/2017	2 of 12, February 2017
Database of Abstracts of Reviews of Effect (DARE)	21/2/2017	Issue 2 of 4, April 2015
Embase (Ovid)	21/2/2017	1980 to 2017 Week 08
Health Technology Assessment Database (HTA)	21/02/2017	Issue 4 of 4, October 2016
MEDLINE (Ovid)	21/2/2017	1946 to February Week 2 2017
MEDLINE In-Process (Ovid)	21/2/2017	February 17, 2017
PubMed	21/2/2017	n/a

Clinical search terms (Medline)

The MEDLINE search strategy is presented below. It was translated for use in all other databases.

Database: Medline
1 Diabetes Mellitus, Type 2/
2 (Type* adj4 ("2" or "II" or two*) adj4 (diabete* or diabetic* or DM)).tw.
3 ((Type2 or T2 or TII) adj4 (diabete* or diabetic* or DM)).tw.
4 ((Maturit* or adult* or slow*) adj4 onset* adj4 (diabete* or diabetic* or DM)).tw.
5 ((Keto* or stable* or acidi* or gastropare*) adj4 (diabete* or diabetic* or DM)).tw.
6 ((Non-insulin* or Non insulin* or Noninsulin*) adj4 depend* adj4 (diabete* or diabetic* or DM)).tw.
7 (DM2 or T2D* or DKA or T2DM or NIDDM or LADA or MODY).tw.
8 or/1-7
9 Sodium-Glucose Transporter 2/
10 (Sodium* adj2 Glucose* adj2 Transporter* adj2 "2").tw.
11 (Sodium* adj2 Glucose* adj2 (co-transporter* or cotransporter* or co transporter*) adj2 "2").tw.
12 SGLT*.tw.
13 Canagliflozin/ or (Canagliflozin* or Invokana* or Vokanamet*).tw.
14 (Dapagliflozin* or Forxiga* or Farxiga* or Xigduo* or Edistride*).tw.
15 (Empagliflozin* or Jardiance* or Synjardy* or Glyxambi*).tw.
16 or/9-15
17 8 and 16
18 Glucagon-Like Peptide 1/ or Glucagon-Like Peptide-1 Receptor/
19 (Glucagon* adj Like adj Peptide* adj "1").tw.
20 GLP*.tw.
21 (Albiglutide* or Eperzan* or Tanzeum* or Albugon* or Naliglutide* or Syncria*).tw.
22 (Dulaglutide* or Trulicity*).tw.
23 Liraglutide/ or (Liraglutide* or Victoza* or Saxenda*).tw.
24 (Exenatide* or Exendin* or Byetta* or Bydureon*).tw.
25 (Lixisenatide* or Lyxumia* or Adlyxin*).tw.
26 or/18-25
27 8 and 26

Database: Medline	
28	Randomized Controlled Trial.pt.
29	Controlled Clinical Trial.pt.
30	Clinical Trial.pt.
31	exp Clinical Trials as Topic/
32	Placebos/
33	Random Allocation/
34	Double-Blind Method/
35	Single-Blind Method/
36	Cross-Over Studies/
37	((random$ or control$ or clinical$) adj3 (trial$ or stud$)).tw.
38	(random$ adj3 allocat$).tw.
39	placebo$.tw.
40	((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw.
41	(crossover$ or (cross adj over$)).tw.
42	or/28-41
43	Meta-Analysis.pt.
44	Network Meta-Analysis/
45	Meta-Analysis as Topic/
46	Review.pt.
47	exp Review Literature as Topic/
48	(metaanaly$ or metanaly$ or (meta adj3 analy$)).tw.
49	(review$ or overview$).ti.
50	(systematic$ adj5 (review$ or overview$)).tw.
51	((quantitative$ or qualitative$) adj5 (review$ or overview$)).tw.
52	((studies or trial$) adj2 (review$ or overview$)).tw.
53	(integrat$ adj3 (research or review$ or literature)).tw.
54	(pool$ adj2 (analy$ or data)).tw.
55	(handsearch$ or (hand adj3 search$)).tw.
56	(manual$ adj3 search$).tw.
57	or/43-56
58	42 or 57
59	Animals/ not Humans/
60	58 not 59
61	Comment/ or Letter/ or Editorial/ or Historical article/ or (conference abstract or conference paper or "conference review" or letter or editorial or case report).pt.
62	60 not 61
63	17 and 62
64	limit 63 to english language
65	27 and 62
66	limit 65 to english language

Health economics search strategies

Searches to retrieve economic evaluations and quality of life papers were conducted in February 2017.

Databases	Date searched	Version/files
EconLit (Ovid)	28/2/2017	1886 to January 2017
Embase (Ovid)	28/2/2017	1980 to 2017 Week 09
Health Technology Assessment Database (HTA)	28/2/2017	Issue 4 of 4, October 2016
MEDLINE (Ovid)	28/2/2017	1946 to February Week 3 2017
MEDLINE In-Process (Ovid)	28/2/2017	February 27, 2017

Databases	Date searched	Version/files
NHS Economic Evaluation Database – NHS EED (Wiley)	28/2/2017	Issue 2 of 4, April 2015
PubMed	28/2/2017	n/a
HTA	28/2/2017	Issue 4 of 4, October 2016

The MEDLINE economic evaluations and quality of life search filters are presented below. They were translated for use in the MEDLINE In-Process and the EMBASE databases.

Database: Medline

Economic evaluations

1 Economics/
2 exp "Costs and Cost Analysis"/
3 Economics, Dental/
4 exp Economics, Hospital/
5 exp Economics, Medical/
6 Economics, Nursing/
7 Economics, Pharmaceutical/
8 Budgets/
9 exp Models, Economic/
10 Markov Chains/
11 Monte Carlo Method/
12 Decision Trees/
13 econom$.tw.
14 cba.tw.
15 cea.tw.
16 cua.tw.
17 markov$.tw.
18 (monte adj carlo).tw.
19 (decision adj2 (tree$ or analys$)).tw.
20 (cost or costs or costing$ or costly or costed).tw.
21 (price$ or pricing$).tw.
22 budget$.tw.
23 expenditure$.tw.
24 (value adj2 (money or monetary)).tw.
25 (pharmacoeconomic$ or (pharmaco adj economic$)).tw.
26 or/1-25

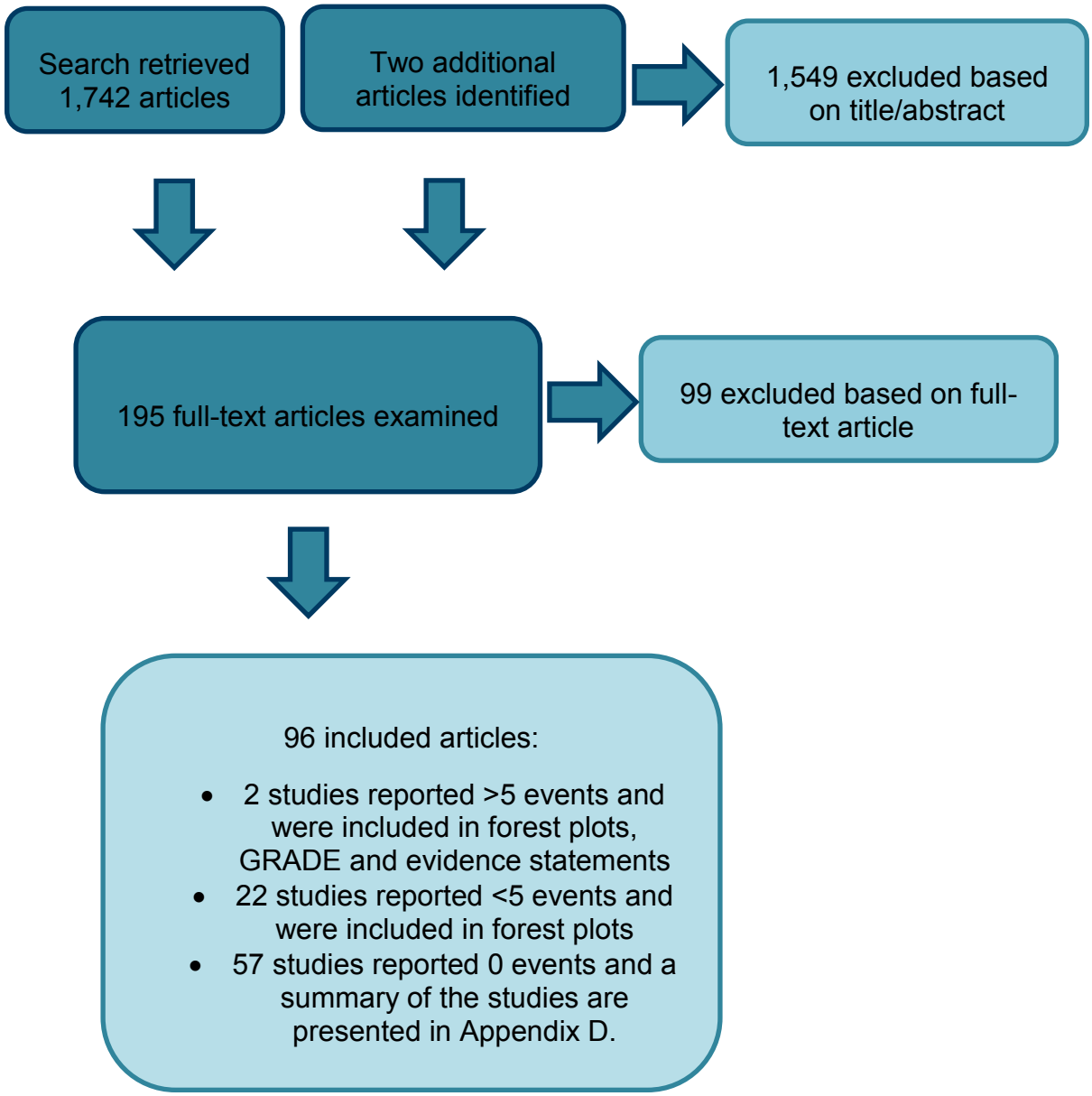
Quality of life

1 "Quality of Life"/
2 quality of life.tw.
3 "Value of Life"/
4 Quality-Adjusted Life Years/
5 quality adjusted life.tw.
6 (qaly$ or qald$ or qale$ or qtime$).tw.
7 disability adjusted life.tw.
8 daly$.tw.
9 Health Status Indicators/
10 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.

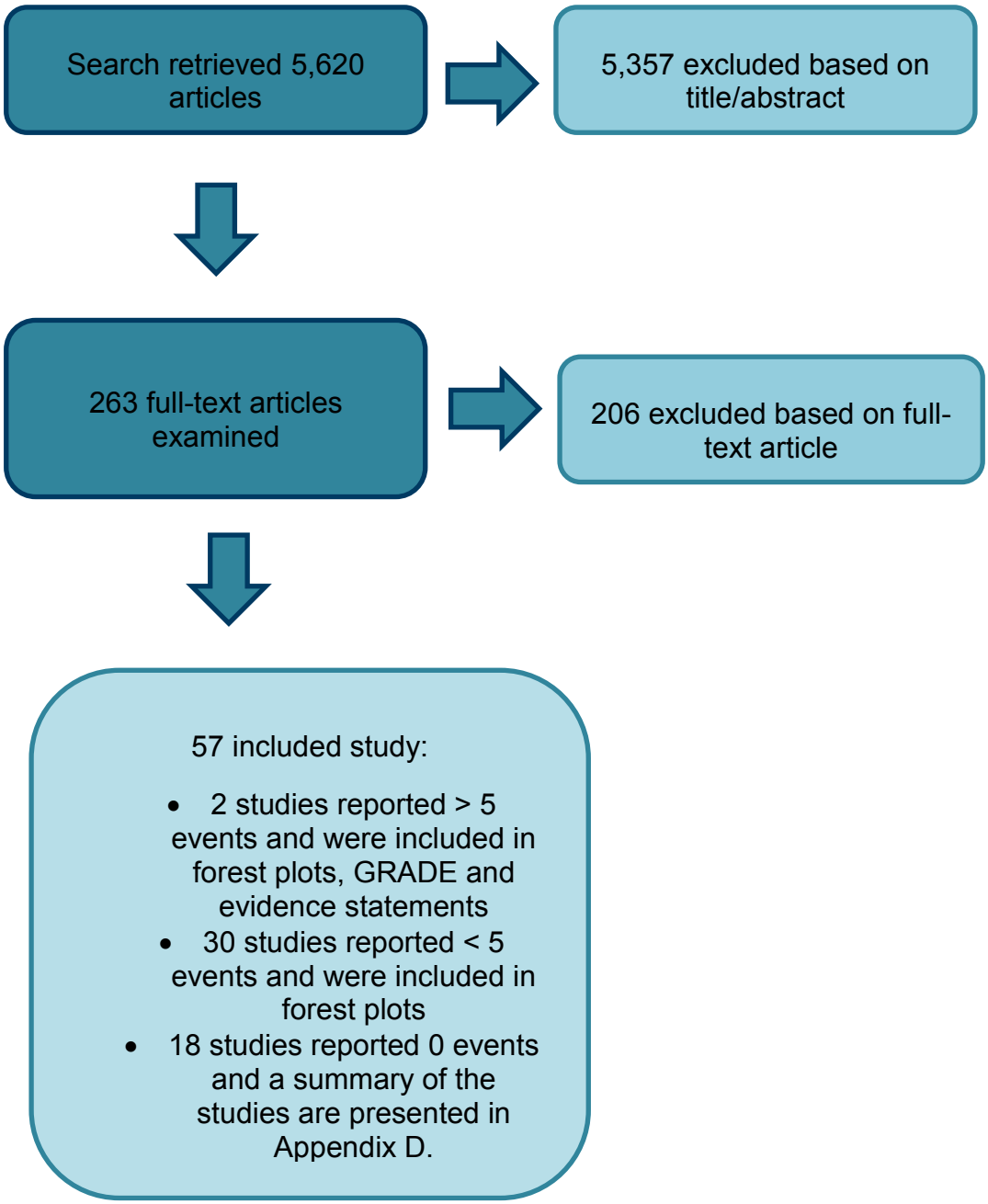
Database: Medline
11 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
12 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
13 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.
14 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
15 (euroqol or euro qol or eq5d or eq 5d).tw.
16 (qol or hql or hqol or hrqol).tw.
17 (hye or hyes).tw.
18 health$ year$ equivalent$.tw.
19 utilit$.tw.
20 (hui or hui1 or hui2 or hui3).tw.
21 disutili$.tw.
22 rosser.tw.
23 quality of wellbeing.tw.
24 quality of well-being.tw.
25 qwb.tw.
26 willingness to pay.tw.
27 standard gamble$.tw.
28 time trade off.tw.
29 time tradeoff.tw.
30 tto.tw.
31 or/1-30

Appendix C – Clinical evidence study selection

SGLT-2 inhibitors



GLP-1 mimetics



Appendix D – Clinical evidence tables

SGLT-2 inhibitors

Bibliographic reference	**Amin N B, Wang X, Jain S M, et al. (2015) Dose-ranging efficacy and safety study of ertugliflozin, a sodium-glucose co-transporter 2 inhibitor, in patients with type 2 diabetes on a background of metformin. Diabetes, and obesity & metabolism 17(6):591-8.**
Study type	RCT to investigate the efficacy and safety of ertugliflozin in people with type 2 diabetes inadequately controlled on metformin. Follow-up: 12 weeks.
Participants	Inclusion criteria Men and women aged 18 to 70 years Type 2 diabetes Body mass index (BMI) 23 to 45 kg/m^2 Exclusion criteria Type 1 diabetes History of significant renal or urinary disease <6 months before screening Persistent severe uncontrolled hypertension (seated blood pressure ≥180/105 mmHg) Congestive heart failure Abnormalities in clinical chemistry at screening (such as C-peptide, fasting serum triglycerides, aspartate aminotransferase or alanine aminotransferase, or total bilirubin) Any other unstable disease or medical condition/history considered clinically relevant by the investigator Upper arm circumference >50 cm Any abnormalities on electrocardiogram (ECG) at screening
Patient characteristics	Gender = male 36.0% (ertugliflozin 1mg/d); 74.5% (ertugliflozin 5mg/d); 56.4% (ertugliflozin 10mg/d); 67.3% (ertugliflozin 25mg/d); 72.7% (sitagliptin); 55.6% (placebo) Age = mean (standard deviation [SD]) 53.1 years (9.1) (ertugliflozin 1mg/d); 54.7 years (7.7) (ertugliflozin 5mg/d); 57.3 years (6.5) (ertugliflozin 10mg/d); 54.2 years (8.8) (ertugliflozin 25mg/d); 53.3 years (10.7) (sitagliptin); 54 years (8.1) (placebo)

<table>
<tr><td>Bibliographic reference</td><td>Amin N B, Wang X, Jain S M, et al. (2015) Dose-ranging efficacy and safety study of ertugliflozin, a sodium-glucose co-transporter 2 inhibitor, in patients with type 2 diabetes on a background of metformin. Diabetes, and obesity & metabolism 17(6):591-8.</td></tr>
<tr><td></td><td>BMI = mean (standard error [SE]) 29.8 kg/m^2 (0.67) (ertugliflozin 1mg/d); 31.1 kg/m^2 (0.85) (ertugliflozin 5mg/d); 30.7 kg/m^2 (0.80) (ertugliflozin 10mg/d); 29.8 kg/m^2 (0.67) (ertugliflozin 25mg/d); 30.4 kg/m^2 (0.77) (sitagliptin); 30.6 kg/m^2 (0.61) (placebo)
Weight = not reported
Risk of cardiovascular diseases (e.g. previous myocardial infarction [MI]) = not reported</td></tr>
<tr><td>Intervention</td><td>Intervention: ertugliflozin 1 mg/d (n=54 participants), 5 mg/d (n=55 participants), 10 mg/d (n=55 participants), or 25 mg/d (n=55 participants)
Background therapy: metformin up to 3,000 mg/d</td></tr>
<tr><td>Comparison</td><td>Comparison: sitagliptin 100 mg/d (n=55 participants) or placebo (n=54 participants)
Background therapy: metformin up to 3,000 mg/d</td></tr>
<tr><td>Outcome measures</td><td>Non-fatal acute myocardial infarction (considered as a serious adverse event)
Adverse events were coded according to the Medical Dictionary for Regulatory Activities (MedDRA version 13.1).</td></tr>
<tr><td>Study dates</td><td>Enrolment was between March 2010 and January 2011.</td></tr>
<tr><td>Comments (Risk of bias)</td><td>
<table>
<tr><th>Bias</th><th>Authors judgment</th><th>Support for judgment</th></tr>
<tr><td>Random sequence generation (selection bias)</td><td>Low risk</td><td>Patients were randomised using a computer-generated random permuted block method.</td></tr>
<tr><td>Allocation concealment (selection bias)</td><td>Low risk</td><td>Patients were randomised using a computer-generated random permuted block method.</td></tr>
<tr><td>Blinding of participants and researchers (performance bias)</td><td>Low risk</td><td>The trial was double-blinded.</td></tr>
<tr><td>Blinding of outcome assessment (detection bias)</td><td>Low risk</td><td>There was no information about who performed safety assessments but these assessments are unlikely to be influenced by lack of blinding.</td></tr>
<tr><td>Incomplete outcome data (attrition bias)</td><td>Low risk</td><td>Missing outcome data balanced in numbers across groups with similar reasons for missing outcome data across groups.</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Amin N B, Wang X, Jain S M, et al. (2015) Dose-ranging efficacy and safety study of ertugliflozin, a sodium-glucose co-transporter 2 inhibitor, in patients with type 2 diabetes on a background of metformin. Diabetes, and obesity & metabolism 17(6):591-8.**		
	Selective reporting (reporting bias)	Low risk	The study protocol is available (NCT01059825) and the outcomes of interest are reported in the pre-specified way.

Bibliographic reference	**AstraZeneca & Bristol-Myers Squibb (2010) A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Phase 3 Trial to Evaluate the Safety and Efficacy of Dapagliflozin in Subjects With Type 2 Diabetes With Inadequately Controlled Hypertension on an Angiotensin-Converting Enzyme Inhibitor (ACEI) or Angiotensin Receptor Blocker (ARB). ClinicalTrials.gov NCT01137474 [http://clinicaltrials.gov].**
Study type	RCT to evaluate the safety and efficacy of dapagliflozin in subjects with type 2 diabetes with inadequately controlled hypertension on an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB). Follow-up: 12 weeks.
Participants	Inclusion criteria Men and women aged 18 to 89 years Type 2 diabetes Inadequate glycaemic control (HbA1c 7% to 10.5%) Uncontrolled hypertension (seated systolic blood pressure of 140 to 165 mm Hg and seated diastolic blood pressure 85 to 105 mm Hg) Mean 24-hour BP>=130/80 mmHg determined by ambulatory blood pressure monitoring Stable dose of oral antidiabetic agent for at least 6 weeks (12 weeks for thiazolidinedione) or a stable daily dose of insulin as monotherapy or in combination with another oral antidiabetic agent, for 8 weeks, and a stable dose of an angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker for at least 4 weeks C-peptide level ≥0.8 ng/mL BMI ≤45.0 kg/m^2 Exclusion criteria History of diabetes insipidus Symptoms of poorly controlled diabetes that would preclude participation in this trial, including but not limited to, marked polyuria and polydipsia with greater than 10% weight loss during the 3 months prior to enrolment History of diabetic ketoacidosis or hyperosmolar non-ketotic coma History of malignant and accelerated hypertension

Bibliographic reference	**AstraZeneca & Bristol-Myers Squibb (2010) A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Phase 3 Trial to Evaluate the Safety and Efficacy of Dapagliflozin in Subjects With Type 2 Diabetes With Inadequately Controlled Hypertension on an Angiotensin-Converting Enzyme Inhibitor (ACEI) or Angiotensin Receptor Blocker (ARB). ClinicalTrials.gov NCT01137474 [http://clinicaltrials.gov].**
	Known or suspected secondary hypertension Any of the following within 6 months of enrolment visit: - Myocardial infarction - Cardiac surgery or revascularisation (coronary artery bypass surgery /percutaneous transluminal coronary angioplasty) - Unstable angina - Unstable congestive heart disease or New York Heart Association Class III or IV - Transient ischemic attack or significant cerebrovascular disease - Unstable or previously undiagnosed arrhythmia A complete list of exclusion criteria can be seen in the registration trial website.
Patient characteristics	Gender = male 54.2% (dapagliflozin 2.5mg/d); 53.9% (dapagliflozin 5mg/d); 59.3% (dapagliflozin 10mg/d); 55.0% (placebo) Age = ≥65 years 15.1% (dapagliflozin 2.5mg/d); 13.9% (dapagliflozin 5mg/d); 13.9% (dapagliflozin 10mg/d); 16.7% (placebo) BMI = ≥25 kg/m^2 87.9% (dapagliflozin 2.5mg/d); 89.1% (dapagliflozin 5mg/d); 88.7% (dapagliflozin 10mg/d); 90.9% (placebo) Weight = not reported Risk of cardiovascular diseases (e.g. previous MI) = people with cardiovascular events were excluded
Intervention	Intervention: dapagliflozin 2.5mg/d (n=166 participants), dapagliflozin 5mg/d (n=165 participants), dapagliflozin 10mg/d (n=302 participants) Background therapy: oral antidiabetic drug with or without insulin.
Comparison	Comparison: placebo (n=311 participants) Background therapy: oral antidiabetic drug with or without insulin.
Outcome measures	Non-fatal ischaemic stroke (considered as adverse event) The term 'ischaemic stroke' was from vocabulary MedDRA 15.1. Results were extracted from the trial registration https://clinicaltrials.gov/ct2/show/results/NCT01137474
Study dates	July 2010 to February 2013.
Comments (Risk of bias)	Bias | Authors judgment | Support for judgment

Bibliographic reference	**AstraZeneca & Bristol-Myers Squibb (2010) A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Phase 3 Trial to Evaluate the Safety and Efficacy of Dapagliflozin in Subjects With Type 2 Diabetes With Inadequately Controlled Hypertension on an Angiotensin-Converting Enzyme Inhibitor (ACEI) or Angiotensin Receptor Blocker (ARB). ClinicalTrials.gov NCT01137474 [http://clinicaltrials.gov].**

Random sequence generation (selection bias)	Unclear risk	Sequence generation process was not described.
Allocation concealment (selection bias)	Unclear risk	Method of concealment was not described.
Blinding of participants and researchers (performance bias)	Low risk	This study was double-blind.
Blinding of outcome assessment (detection bias)	Low risk	There was no information about who performed safety assessments but these assessments are unlikely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias)	Low risk	Missing outcome data balanced in numbers across groups with similar reasons for missing outcome data across groups.
Selective reporting (reporting bias)	Low risk	The study protocol is available (NCT01137474) and the outcomes of interest are reported in the pre-specified way.

Bibliographic reference	**Bailey CJ, Gross JL, Pieters A, et al. (2010) Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with metformin: a randomised, double-blind, placebo-controlled trial. Lancet 375(9733):2223-33.** **Bailey CJ, Gross JL, Hennicken D, et al. (2013) Dapagliflozin add-on to metformin in type 2 diabetes inadequately controlled with metformin: a randomized, double-blind, placebo-controlled 102-week trial. BMC medicine 11, 43.**
Study type	RCT to assess the efficacy and safety of dapagliflozin when added to metformin in adults with type 2 diabetes who were not adequately controlled with metformin alone. Follow-up: 24 and 102 weeks.

Bibliographic reference	**Bailey CJ, Gross JL, Pieters A, et al. (2010) Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with metformin: a randomised, double-blind, placebo-controlled trial. Lancet 375(9733):2223-33.** **Bailey CJ, Gross JL, Hennicken D, et al. (2013) Dapagliflozin add-on to metformin in type 2 diabetes inadequately controlled with metformin: a randomized, double-blind, placebo-controlled 102-week trial. BMC medicine 11, 43.**
Participants	Inclusion criteria Men and women aged 18 to 77 years Type 2 diabetes HbA1c 7 to 10% C-peptide concentration ≥0.34 nmol/L BMI ≤45 kg/m^2 Taking a stable dose of metformin (≥1500 mg/d) for at least 8 weeks before enrolment Exclusion criteria Serum creatinine ≥133 µmol/L for men or ≥124 µmol/L for women (consistent with metformin labelling) Urine albumin/creatinine ratio >203.4 mg/mmol Aspartate aminotransferase or alanine aminotransferase more than three times the upper limit of normal Creatine kinase more than three times the upper limit of normal Symptoms of poorly controlled diabetes Clinically significant renal, hepatic, haematological, oncological, endocrine, psychiatric, or rheumatic disease Recent cardiovascular event (within 6 months) or New York Heart Association class III or IV congestive heart failure Systolic blood pressure ≥180 mm Hg or diastolic blood pressure ≥110 mm Hg.
Patient characteristics	Gender = male 51% (dapagliflozin 2.5mg/d); 50% (dapagliflozin 2.5mg/d); 57% (dapagliflozin 2.5mg/d); 55% (placebo) Age = mean (SD) 55.0 years (9.3) (dapagliflozin 2.5mg/d); 54.3 years (9.4) (dapagliflozin 2.5mg/d); 52.7 years (9.9) (dapagliflozin 2.5mg/d); 53.7 (10.3) (placebo) BMI = mean (SD) 31.6 kg/m^2 (4.8) (dapagliflozin 2.5mg/d); 31.4 kg/m^2 (5.0) (dapagliflozin 2.5mg/d); 31.2 kg/m^2 (5.1) (dapagliflozin 2.5mg/d); 31.8 kg/m^2 (5.3) (placebo) Weight = not reported Risk of cardiovascular diseases (e.g. previous MI) = participants with a recent cardiovascular event or congestive heart failure were excluded.
Intervention	Intervention: dapagliflozin 2.5mg/d (n=137 participants), 5mg/d (n=137 participants), 10mg/d (n=135 participants) Background therapy: metformin ≥1,500 mg/d as well as diet and exercise counselling

<table>
<tr><td>Bibliographic reference</td><td>Bailey CJ, Gross JL, Pieters A, et al. (2010) Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with metformin: a randomised, double-blind, placebo-controlled trial. Lancet 375(9733):2223-33.
Bailey CJ, Gross JL, Hennicken D, et al. (2013) Dapagliflozin add-on to metformin in type 2 diabetes inadequately controlled with metformin: a randomized, double-blind, placebo-controlled 102-week trial. BMC medicine 11, 43.</td></tr>
<tr><td>Comparison</td><td>Comparison: placebo (n=135 participants)
Background therapy: metformin ≥1,500 mg/d as well as diet and exercise counselling</td></tr>
<tr><td>Outcome measures</td><td>Acute myocardial infarction (this data will not be reported because it was not presented in a extractable way [from Bailey et al. 2010])
Fatal myocardial infarction (considered as a serious adverse event; extracted from Bailey et al. 2013)
A serious adverse event was defined as an adverse event that was fatal, life threatening, required admission to hospital, prolonged an existing hospital stay, resulted in persistent or significant disability or incapacity, was a cancer or a congenital anomaly, resulted in the development of drug dependency or drug abuse, or was an important medical event that jeopardised the patient or required intervention to prevent a serious outcome.</td></tr>
<tr><td>Study dates</td><td>Recruitment was from September 2007 to April 2008.</td></tr>
<tr><td>Comments (Risk of bias)</td><td>
<table>
<tr><th>Bias</th><th>Authors judgment</th><th>Support for judgment</th></tr>
<tr><td>Random sequence generation (selection bias)</td><td>Low risk</td><td>Randomisation schedules were computer-generated by the sponsor and stored in a secure location.</td></tr>
<tr><td>Allocation concealment (selection bias)</td><td>Low risk</td><td>Randomisation was done using a central interactive voice response system.</td></tr>
<tr><td>Blinding of participants and researchers (performance bias)</td><td>Low risk</td><td>Participants, investigators, and sponsor personnel were blinded to treatment allocation. The film-coated placebo and active tablets were similar in colour, shape, size, texture, and taste.</td></tr>
<tr><td>Blinding of outcome assessment (detection bias)</td><td>Low risk</td><td>There was no information about who performed safety assessments but these assessments are unlikely to be influenced by lack of blinding.</td></tr>
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</td></tr>
</table>

Bibliographic reference	**Bailey CJ, Gross JL, Pieters A, et al. (2010) Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with metformin: a randomised, double-blind, placebo-controlled trial. Lancet 375(9733):2223-33.** **Bailey CJ, Gross JL, Hennicken D, et al. (2013) Dapagliflozin add-on to metformin in type 2 diabetes inadequately controlled with metformin: a randomized, double-blind, placebo-controlled 102-week trial. BMC medicine 11, 43.**

Incomplete outcome data (attrition bias)	Low risk	Missing outcome data balanced in numbers across groups with similar reasons for missing outcome data across groups.
Selective reporting (reporting bias)	Low risk	The study protocol is available (NCT00528879) and the outcomes of interest are reported in the pre-specified way.

Bibliographic reference	**Bode B, Stenlof K, Sullivan D, et al. (2013) Efficacy and safety of canagliflozin treatment in older subjects with type 2 diabetes mellitus: a randomized trial. Hospital practice (1995) 41(2):72-84.** **Bode B, Stenlof K, Harris S, et al. (2015) Long-term efficacy and safety of canagliflozin over 104 weeks in patients aged 55-80 years with type 2 diabetes. Diabetes, obesity & metabolism 17(3):294-303.**
Study type	RCT to evaluate the long-term efficacy and safety of canagliflozin in people with type 2 diabetes inadequately controlled on a stable antihyperglycaemic agent regimen. Follow-up: 104 weeks.
Participants	Inclusion criteria Men and women aged 55 to 80 years Type 2 diabetes HbA1c ≥7.0 to ≤10.0% Either not on antihyperglycaemic agent therapy or on a stable regimen of antihyperglycaemic agents as monotherapy or combination therapy BMI 20 to 40 kg/m^2 Fasting plasma glucose <270 mg/dL (15.0 mmol/L) Exclusion criteria History of type 1 diabetes Repeated fasting plasma glucose ≥270 mg/dL (15.0 mmol/L) during pre-treatment phase

<table>
<tr><td>Bibliographic reference</td><td>Bode B, Stenlof K, Sullivan D, et al. (2013) Efficacy and safety of canagliflozin treatment in older subjects with type 2 diabetes mellitus: a randomized trial. Hospital practice (1995) 41(2):72-84.
Bode B, Stenlof K, Harris S, et al. (2015) Long-term efficacy and safety of canagliflozin over 104 weeks in patients aged 55-80 years with type 2 diabetes. Diabetes, obesity & metabolism 17(3):294-303.</td></tr>
<tr><td></td><td>History of myocardial infarction, unstable angina, revascularisation procedure, or cerebrovascular accident within 3 months before screening
History of New York Heart Association Class III–IV cardiac disease
Uncontrolled hypertension
Estimated glomerular filtration rate <50 mL/min/1.73 m^2</td></tr>
<tr><td>Patient characteristics</td><td>Gender = male 51.5% (canagliflozin 100mg/d); 54.7% (canagliflozin 300mg/d); 60.3% (placebo)
Age = mean (SD) 64.3 years (6.5) (canagliflozin 100mg/d); 63.4 years (6.0) (canagliflozin 300mg/d); 63.2 years (6.2) (placebo)
BMI = mean (SD) 31.4 kg/m^2 (4.4) (canagliflozin 100mg/d); 31.5 kg/m^2 (4.6) (canagliflozin 300mg/d); 31.8 kg/m^2 (4.7) (placebo)
Weight = mean (SD) 88.4 kg (15.6) (canagliflozin 100mg/d); 88.8 kg (17.1) (canagliflozin 300mg/d); 91.1 kg (17.5) (placebo)
Risk of cardiovascular diseases (e.g. previous MI) = not reported.</td></tr>
<tr><td>Intervention</td><td>Intervention: canagliflozin 100mg/d (n=241 participants) or 300mg/d (n=236 participants)
Background therapy: add-on to their ongoing stable diabetes treatment regimen.</td></tr>
<tr><td>Comparison</td><td>Comparison: placebo (n=237 participants)
Background therapy: add-on to their ongoing stable diabetes treatment regimen.</td></tr>
<tr><td>Outcome measures</td><td>Fatal stroke (extracted from Bode et al. 2015)
This outcome was considered as an adverse event but a definition was not provided.</td></tr>
<tr><td>Study dates</td><td>The double-blind treatment period took place between April 2010 and November 2011.</td></tr>
<tr><td>Comments (Risk of bias)</td><td>
<table>
<tr><th>Bias</th><th>Authors judgment</th><th>Support for judgment</th></tr>
<tr><td>Random sequence generation (selection bias)</td><td>Low risk</td><td>Randomisation was performed using an interactive voice response system/interactive web response system with a computer-generated randomisation schedule prepared by the sponsor before the study.</td></tr>
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</table>

Bibliographic reference	**Bode B, Stenlof K, Sullivan D, et al. (2013) Efficacy and safety of canagliflozin treatment in older subjects with type 2 diabetes mellitus: a randomized trial. Hospital practice (1995) 41(2):72-84.** **Bode B, Stenlof K, Harris S, et al. (2015) Long-term efficacy and safety of canagliflozin over 104 weeks in patients aged 55-80 years with type 2 diabetes. Diabetes, obesity & metabolism 17(3):294-303.**

Allocation concealment (selection bias)	Low risk	Randomisation was performed using an interactive voice response system/interactive web response system with a computer-generated randomisation schedule prepared by the sponsor before the study.
Blinding of participants and researchers (performance bias)	Low risk	The trial was double-blinded.
Blinding of outcome assessment (detection bias)	Low risk	Subjects, investigators, and local sponsor personnel were to remain blinded to treatment assignment until the final database lock.
Incomplete outcome data (attrition bias)	Low risk	Missing outcome data balanced in numbers across groups with similar reasons for missing outcome data across groups.
Selective reporting (reporting bias)	Low risk	The study protocol is available (NCT01106651) and the outcomes of interest are reported in the pre-specified way.

Bibliographic reference	**Cefalu WT, Leiter LA, de Bruin TWA, et al. (2015) Dapagliflozin's Effects on Glycemia and Cardiovascular Risk Factors in High-Risk Patients With Type 2 Diabetes: A 24-Week, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study With a 28-Week Extension. Diabetes care 38(7):1218-27.**
Study type	RCT to assess the efficacy and safety of dapagliflozin compared with placebo in people with type 2 diabetes, documented pre-existing cardiovascular disease, and a history of hypertension. Follow-up: 52 weeks.
Participants	Inclusion criteria

Bibliographic reference	Cefalu WT, Leiter LA, de Bruin TWA, et al. (2015) Dapagliflozin's Effects on Glycemia and Cardiovascular Risk Factors in High-Risk Patients With Type 2 Diabetes: A 24-Week, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study With a 28-Week Extension. Diabetes care 38(7):1218-27.
	Men aged ≥45 years or women ≥50 years (not of childbearing potential) Type 2 diabetes Cerebrovascular disease Hypertension Stable monotherapy or dual combination therapy with oral antidiabetic drugs (OADs), insulin therapy in combination with OADs, or insulin monotherapy Inadequate glycaemic control (HbA1c ≥7.2% [55 mmol/mol] ≤10.5% [91 mmol/mol]) Exclusion criteria Type 1 diabetes mellitus Use of >3 oral antidiabetic medications Fasting plasma glucose >15 mmol/l at randomization History of diabetic ketoacidosis Recent cardiovascular event (acute coronary syndrome, hospitalization for unstable angina or acute myocardial infarction, acute stroke or transient ischemic attack, coronary artery revascularization) within 2 months prior to enrolment Systolic blood pressure (BP) ≥165 mmHg, diastolic BP ≥100 mmHg Congestive heart failure (CHF) defined as New York Heart Association class IV, unstable or acute CHF Calculated creatinine clearance <60 ml/min Severe hepatic insufficiency and/or significant abnormal liver function (defined as aspartate aminotransferase >3× upper limit of normal (ULN) and/or alanine aminotransferase >3× ULN) or creatine kinase >3× ULN.
Patient characteristics	Gender = male 67.9% (dapagliflozin); 68.6% (placebo) Age = mean (SD) 62.8 years (7.0) (dapagliflozin); 63.0 years (7.7) (placebo) BMI = mean (SD) 32.6 kg/m^2 (5.9) (dapagliflozin); 32.9 kg/m^2 (6.1) (placebo) Weight = mean (SD) 92.6 kg (20.5) (dapagliflozin); 93.6 kg (19.5) (placebo) Risk of cardiovascular diseases (e.g. previous MI) = stroke or transient ischemic attack 22.0% (dapagliflozin); 19.4% (placebo)
Intervention	Intervention: dapagliflozin 10mg/d Background therapy: pre-existing stable background treatment, excluding rosiglitazone.
Comparison	Comparison: matched placebo dose Background therapy: pre-existing stable background treatment, excluding rosiglitazone.

Bibliographic reference	**Cefalu WT, Leiter LA, de Bruin TWA, et al. (2015) Dapagliflozin's Effects on Glycemia and Cardiovascular Risk Factors in High-Risk Patients With Type 2 Diabetes: A 24-Week, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study With a 28-Week Extension. Diabetes care 38(7):1218-27.**
Outcome measures	Fatal myocardial infarction Non-fatal myocardial infarction Non-fatal acute myocardial infarction These outcomes were reported as adverse events but a definition was not provided.
Study dates	Not reported.

Comments (Risk of bias)

Bias	Authors judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Participants were randomised to the treatment groups using the method of randomly permuted blocks.
Allocation concealment (selection bias)	Low risk	Patients were assigned a unique enrolment number using interactive web response system or interactive voice response system.
Blinding of participants and researchers (performance bias)	Low risk	The trial was double-blinded.
Blinding of outcome assessment (detection bias)	Low risk	There was no information about who performed safety assessments but these assessments are unlikely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias)	Low risk	Missing outcome data balanced in numbers across groups with similar reasons for missing outcome data across groups.
Selective reporting (reporting bias)	Low risk	The study protocol is available (NCT01031680) and the outcomes of interest are reported in the pre-specified way.

Bibliographic reference	**Ferrannini E, Seman L, Seewaldt-Becker E, et al. (2013) A Phase IIb, randomized, placebo-controlled study of the SGLT2 inhibitor empagliflozin in patients with type 2 diabetes. Diabetes, obesity & metabolism 15(8):721-8.**
Study type	RCT to evaluate the efficacy, safety, tolerability and pharmacokinetics of empagliflozin in people with type 2 diabetes. Follow-up: 12 weeks.
Participants	Inclusion criteria Men and women aged 18 to 79 years Type 2 diabetes Treatment-naïve (no antidiabetic medication for ≥10 weeks prior screening) or on one antidiabetic drug (except thiazolidinediones, glucagon-like peptide-1 [GLP-1] analogues or insulin) at a stable dose for ≥10 weeks prior screening HbA1c ≥6.5 to ≥9.0% for people treated with other antidiabetic drug or HbA1c >7.0 to 10.0% for treatment-naïve people BMI ≤40 kg/m^2 Exclusion criteria Myocardial infraction, stroke or transient ischaemic attack ≤6 months prior to informed consent Impaired hepatic function Renal insufficiency or impaired renal function defined as calculated creatinine clearance <0.84 ml/s/m^2 or serum creatinine levels ≥132.6 µmol/l for men and ≥123.8 µmol/l for women Unstable or acute congestive heart failure (a longer list of exclusion criteria can be seen in Ferrannini 2013).
Patient characteristics	Gender = male 56.8% (empagliflozin 5mg/d); 49.4% (empagliflozin 10mg/d); 50.0% (empagliflozin 25mg/d); 54.9% (placebo) Age = median (range) 59.0 years (37 to 78) (empagliflozin 5mg/d); 58.0 years (30 to 76) (empagliflozin 10mg/d); 57.0 years (30 to 79) (empagliflozin 25mg/d); 58.0 years (28 to 80) (placebo) BMI = median (range) 28.5 kg/m^2 (20.5 to 38.8) (empagliflozin 5mg/d); 28.1 kg/m^2 (21.5 to 39.3) (empagliflozin 10mg/d); 28.3 kg/m^2 (20.1 to 38.8) (empagliflozin 25mg/d); 28.8 kg/m^2 (20.7 to 39.6) (placebo) Weight = median (range) 82.8 kg (51.9 to 116.0) (empagliflozin 5mg/d); 76.8 kg (45.5 to 118.0) (empagliflozin 10mg/d); 81.2 kg (49.1 to 130.0) (empagliflozin 25mg/d); 82.2 kg (49.0 to 152.3) (placebo) Risk of cardiovascular diseases (e.g. previous MI) = participants with myocardial infarction or stroke were excluded.
Intervention	Intervention: empagliflozin 5mg/d (n=81 participants), 10mg/d (n=81 participants), or 25mg/d (n=82 participants) Background therapy:
Comparison	Comparison: placebo (n=82 participants)

<table>
<tr><td>Bibliographic reference</td><td>Ferrannini E, Seman L, Seewaldt-Becker E, et al. (2013) A Phase IIb, randomized, placebo-controlled study of the SGLT2 inhibitor empagliflozin in patients with type 2 diabetes. Diabetes, obesity & metabolism 15(8):721-8.</td></tr>
<tr><td></td><td>Open-label immediate release metformin up to a maximum of 1,000 mg twice daily or the maximum tolerated dose (n=80 participants)
Background therapy:</td></tr>
<tr><td>Outcome measures</td><td>Non-fatal myocardial infarction
Non-fatal acute myocardial infarction
Diabetic nephropathy
These outcomes were considered as serious adverse events but a definition was not provided.</td></tr>
<tr><td>Study dates</td><td>Not reported.</td></tr>
<tr><td>Comments (Risk of bias)</td><td>
<table>
<tr><th>Bias</th><th>Authors judgment</th><th>Support for judgment</th></tr>
<tr><td>Random sequence generation (selection bias)</td><td>Low risk</td><td>Randomisation was performed using an interactive voice response system by which participants were assigned to treatment groups using a computer-generated random sequence.</td></tr>
<tr><td>Allocation concealment (selection bias)</td><td>Low risk</td><td>Randomisation was performed using an interactive voice response system by which participants were assigned to treatment groups using a computer-generated random sequence.</td></tr>
<tr><td>Blinding of participants and researchers (performance bias)</td><td>Low risk</td><td>The trial was double-blinded.</td></tr>
<tr><td>Blinding of outcome assessment (detection bias)</td><td>Low risk</td><td>There was no information about who performed safety assessments but these assessments are unlikely to be influenced by lack of blinding.</td></tr>
<tr><td>Incomplete outcome data (attrition bias)</td><td>Low risk</td><td>No missing outcome data.</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Ferrannini E, Seman L, Seewaldt-Becker E, et al. (2013) A Phase IIb, randomized, placebo-controlled study of the SGLT2 inhibitor empagliflozin in patients with type 2 diabetes. Diabetes, obesity & metabolism 15(8):721-8.**		
	Selective reporting (reporting bias)	Low risk	The study protocol is available (NCT00789035) and the outcomes of interest are reported in the pre-specified way.

Bibliographic reference	**Frias JP, Guja C, Hardy E, et al. (2017) Exenatide once weekly plus dapagliflozin once daily versus exenatide or dapagliflozin alone in patients with type 2 diabetes inadequately controlled with metformin monotherapy (DURATION-8): a 28 week, multicentre, double-blind, phase 3, randomised controlled trial. The lancet diabetes and endocrinology 4(12):1004-1016.**
Study type	RCT to compare efficacy and safety of co-initiation of dapagliflozin and exenatide with that of dapagliflozin or exenatide alone in people with type 2 diabetes inadequately controlled by metformin. Follow-up: 28 weeks.
Participants	Inclusion criteria Men and women aged ≥18 years Type 2 diabetes Inadequate glycaemic control (HbA1c 8.0 to 12.0% [64 to 108 mmol/mol]) Exclusion criteria Receiving any glucose-lowering drugs other than metformin for >14 days during the 12 weeks before enrolment Known active proliferative retinopathy Clinically significant cardiovascular disease or procedure within 3 months of screening including, but not limited to, myocardial infarction, clinically significant arrhythmia, unstable angina, coronary artery bypass surgery, or angioplasty; or are expected to require coronary artery bypass surgery or angioplasty during the course of the study Presence or history of severe congestive heart failure (New York Heart Association Class IV).
Patient characteristics	Gender = male 45% (dapagliflozin plus exenatide); 48% (dapagliflozin); 51% (exenatide) Age = mean (SD) 54 years (10) (dapagliflozin plus exenatide); 55 years (9) (dapagliflozin); 54 years (10) (exenatide) BMI = mean (SD) 33.2 kg/m^2 (6.8) (dapagliflozin plus exenatide); 33.0 kg/m^2 (6.1) (dapagliflozin); 32.0 kg/m^2 (5.9) (exenatide) Weight = mean (SD) 91.8 kg (22.2) (dapagliflozin plus exenatide); 91.1 kg (19.7) (dapagliflozin); 89.8 kg (20.2) (exenatide)

<table>
<tr><td>Bibliographic reference</td><td>Frias JP, Guja C, Hardy E, et al. (2017) Exenatide once weekly plus dapagliflozin once daily versus exenatide or dapagliflozin alone in patients with type 2 diabetes inadequately controlled with metformin monotherapy (DURATION-8): a 28 week, multicentre, double-blind, phase 3, randomised controlled trial. The lancet diabetes and endocrinology 4(12):1004-1016.</td></tr>
<tr><td></td><td>Risk of cardiovascular diseases (e.g. previous myocardial infarction [MI]) = people with previous cardiovascular disease were excluded.</td></tr>
<tr><td>Intervention</td><td>Intervention: Dapagliflozin 10mg/d plus exenatide 2mg once weekly (n=228 participants) or dapagliflozin 10mg/d plus placebo injections once weekly (n=230 participants)
Background therapy: metformin</td></tr>
<tr><td>Comparison</td><td>Comparison: Exenatide 2mg once weekly plus placebo (n=227 participants)
Background therapy: metformin</td></tr>
<tr><td>Outcome measures</td><td>Adjudicated cardiovascular events including:
Cause of death (cardiovascular related vs non-cardiovascular)
Myocardial infarction
Stroke
Acute coronary syndrome
Ventricular fibrillation/tachycardia
Congestive heart failure requiring hospitalization.</td></tr>
<tr><td>Study dates</td><td>Participants were randomised between September 2014 and October 2015.</td></tr>
<tr><td>Comments (Risk of bias)</td><td>
<table>
<tr><th>Bias</th><th>Authors judgment</th><th>Support for judgment</th></tr>
<tr><td>Random sequence generation (selection bias)</td><td>Low risk</td><td>Participants were randomly assigned centrally via an interactive voice and web-response system.</td></tr>
<tr><td>Allocation concealment (selection bias)</td><td>Low risk</td><td>Participants were randomly assigned centrally via an interactive voice and web-response system.</td></tr>
<tr><td>Blinding of participants and researchers (performance bias)</td><td>Low risk</td><td>Participants, investigators, and data analysts were masked to treatment assignment. Placebo was supplied as oral tablets matching those of dapagliflozin or as powder</td></tr>
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Bibliographic reference	**Frias JP, Guja C, Hardy E, et al. (2017) Exenatide once weekly plus dapagliflozin once daily versus exenatide or dapagliflozin alone in patients with type 2 diabetes inadequately controlled with metformin monotherapy (DURATION-8): a 28 week, multicentre, double-blind, phase 3, randomised controlled trial. The lancet diabetes and endocrinology 4(12):1004-1016.**

Blinding of outcome assessment (detection bias)	Low risk	A blinded independent cardiology adjudication committee adjudicated cardiovascular events.
Incomplete outcome data (attrition bias)	Low risk	Missing outcome data balanced in numbers across groups with similar reasons for missing outcome data across groups.
Selective reporting (reporting bias)	Low risk	The study protocol is available (NCT02229396) and the outcomes of interest are reported in the pre-specified way.

Bibliographic reference	**Haring HU, Merker L, Seewaldt-Becker E, et al. (2013) Empagliflozin as add-on to metformin plus sulfonylurea in patients with type 2 diabetes: a 24-week, randomized, double-blind, placebo-controlled trial. Diabetes care 36(11):3396-404.** **Haering HU, Merker L, Christiansen AV, et al. (2015) Empagliflozin as add-on to metformin plus sulphonylurea in patients with type 2 diabetes. Diabetes research and clinical practice 110(1):82-90.**
Study type	RCT to investigate the efficacy and tolerability of empagliflozin as add-on to metformin and sulfonylurea in patients with type 2 diabetes. Follow-up: 24 weeks (EMPA-REG METSU) and 76 weeks (EMPA-REG EXTEND™ METSU).
Participants	Inclusion criteria Men and women aged ≥18 years Type 2 diabetes BMI ≤45 kg/m^2 Inadequately controlled type 2 diabetes (HbA1c ≥7 to ≤10%) despite a diet and exercise program and a stable regimen of metformin immediate release plus a sulfonylurea Exclusion criteria

Bibliographic reference	**Haring HU, Merker L, Seewaldt-Becker E, et al. (2013) Empagliflozin as add-on to metformin plus sulfonylurea in patients with type 2 diabetes: a 24-week, randomized, double-blind, placebo-controlled trial. Diabetes care 36(11):3396-404.** **Haering HU, Merker L, Christiansen AV, et al. (2015) Empagliflozin as add-on to metformin plus sulphonylurea in patients with type 2 diabetes. Diabetes research and clinical practice 110(1):82-90.**
	Uncontrolled hyperglycaemia (glucose level >13.3 mmol/L) after an overnight fast, confirmed by a second measurement) Acute coronary syndrome Stroke or transient ischemic attack within 3 months prior to consent Indication of liver disease Impaired kidney function during screening or run-in Contraindications to metformin or sulfonylurea according to the local label Gastrointestinal surgeries that induce chronic malabsorption History of cancer (except basal cell carcinoma) or treatment for cancer within 5 years Blood dyscrasias or any disorders causing haemolysis or unstable erythrocytes Treatment with anti-obesity drugs 3 months prior to consent Use of any treatment at screening that leads to unstable body weight Treatment with systemic steroids at time of consent Change in dosage of thyroid hormones within 6 weeks of consent Alcohol or drug abuse within 3 months of consent Investigational drug intake within 30 days of the trial.
Patient characteristics	Gender = male 50% (empagliflozin 10mg); 53% (empagliflozin 25mg); 50% (placebo) Age = mean (SD) 57.0 years (9.2) (empagliflozin 10mg); 57.4 years (9.4) (empagliflozin 25mg); 56.9 years (9.2) (placebo) BMI = mean (SD) 28.3 kg/m^2 (5.4) (empagliflozin 10mg); 28.3 kg/m^2 (5.5) (empagliflozin 25mg); 27.9 kg/m^2 (4.9) (placebo) Weight = mean (SD) 77.1 kg (18.3) (empagliflozin 10mg); 77.5 kg (18.8) (empagliflozin 25mg); 76.2 kg (16.9) (placebo) Risk of cardiovascular diseases (e.g. previous MI) = participants with prior stroke were excluded.
Intervention	Intervention: once daily empagliflozin 10mg (n=226 participants) or 25mg (n=218 participants) Background therapy: metformin (≥1,500 mg/day or maximum tolerated dose or maximum dose according to local label) plus a sulfonylurea (greater than or equal to half the maximum recommended dose, or the maximum tolerated dose, or the maximum dose according to local label) for 24 weeks.

<table>
<tr><td>Bibliographic reference</td><td>Haring HU, Merker L, Seewaldt-Becker E, et al. (2013) Empagliflozin as add-on to metformin plus sulfonylurea in patients with type 2 diabetes: a 24-week, randomized, double-blind, placebo-controlled trial. Diabetes care 36(11):3396-404.
Haering HU, Merker L, Christiansen AV, et al. (2015) Empagliflozin as add-on to metformin plus sulphonylurea in patients with type 2 diabetes. Diabetes research and clinical practice 110(1):82-90.</td></tr>
<tr><td>Comparison</td><td>Comparison: once daily placebo (n=225 participants)
Background therapy: metformin (≥1,500 mg/day or maximum tolerated dose or maximum dose according to local label) plus a sulfonylurea (greater than or equal to half the maximum recommended dose, or the maximum tolerated dose, or the maximum dose according to local label) for 24 weeks.</td></tr>
<tr><td>Outcome measures</td><td>Fatal acute myocardial infarction (considered as an adverse event and reported by Haering et al. 2015)
Adverse events: preferred terms coded according to the MedDRA version 16.0.</td></tr>
<tr><td>Study dates</td><td>The study was conducted between July 2010 and February 2012.</td></tr>
<tr><td>Comments (Risk of bias)</td><td>
<table>
<tr><th>Bias</th><th>Authors judgment</th><th>Support for judgment</th></tr>
<tr><td>Random sequence generation (selection bias)</td><td>Low risk</td><td>Randomisation was performed using a third-party interactive voice and web response system.</td></tr>
<tr><td>Allocation concealment (selection bias)</td><td>Low risk</td><td>Randomisation was performed using a third-party interactive voice and web response system.</td></tr>
<tr><td>Blinding of participants and researchers (performance bias)</td><td>Low risk</td><td>The trial was double-blinded.</td></tr>
<tr><td>Blinding of outcome assessment (detection bias)</td><td>Low risk</td><td>There was no information about who performed safety assessments but these assessments are unlikely to be influenced by lack of blinding.</td></tr>
<tr><td>Incomplete outcome data (attrition bias)</td><td>Low risk</td><td>Missing outcome data balanced in numbers across groups with similar reasons for missing outcome data across groups.</td></tr>
<tr><td>Selective reporting (reporting bias)</td><td>Low risk</td><td>The study protocol is available (NCT01159600) and the outcomes of interest are reported in the pre-specified way.</td></tr>
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Bibliographic reference	**Henry RR, Murray AV, Marmolejo MH, et al. (2012) Dapagliflozin, metformin XR, or both: initial pharmacotherapy for type 2 diabetes, a randomised controlled trial. International journal of clinical practice 66(5):446-56.**
Study type	Two RCTs to compare dapagliflozin plus metformin, dapagliflozin alone, and metformin alone. Follow-up: 24 weeks.*
Participants	Inclusion criteria Men and women aged 18 to 77 years Type 2 diabetes uncontrolled with diet and exercise HbA1c 7.5 to 12% BMI ≤45 kg/m^2 C-peptide concentration ≥0.33 nmol/l Exclusion criteria Serum creatinine ≥132.60 µmol/l (men) or ≥123.76 µmol/l (women) consistent with metformin labelling Urine albumin:creatinine ratio >1,800 mg/g Serum aspartate transaminase or alanine transaminase >3 times upper limit of normal (ULN) Creatine kinase >3 times ULN History of diabetes insipidus Symptoms of poorly controlled diabetes Clinically significant renal, hepatic, haematological, oncological, endocrine, psychiatric or rheumatic disease A cardiovascular event within 6 months or New York Heart Association Class III or IV congestive heart failure Systolic blood pressure ≥180 or diastolic blood pressure ≥110 mmHg.
Patient characteristics	Study 2 Gender = male 50.2% (dapagliflozin plus metformin); 47.9% (dapagliflozin plus placebo); 46.6% (metformin plus placebo) Age = mean (SD) 51.0 years (10.1) (dapagliflozin plus metformin); 51.1 years (11.5) (dapagliflozin plus placebo); 52.7 years (10.4) (metformin plus placebo) BMI = not reported Weight = mean (SD) 88.4 kg (19.7) (dapagliflozin plus metformin); 88.5 kg (19.3) (dapagliflozin plus placebo); 87.2 kg (19.4) (metformin plus placebo) Risk of cardiovascular diseases (e.g. previous MI) = participants with cardiovascular events or congestive heart failure were excluded.

Bibliographic reference	**Henry RR, Murray AV, Marmolejo MH, et al. (2012) Dapagliflozin, metformin XR, or both: initial pharmacotherapy for type 2 diabetes, a randomised controlled trial. International journal of clinical practice 66(5):446-56.**
Intervention	Intervention: Study 2 Dapagliflozin 10mg/d plus metformin XR up to 2,000 mg/d Dapagliflozin 10mg/d plus placebo Background therapy: not reported.
Comparison	Comparison: Study 2 Metformin XR up to 2,000 mg/d plus placebo Background therapy: not reported.
Outcome measures	Fatal myocardial infarction (considered as an adverse event) Adverse events were coded by preferred terms (MedDRA version 13 [Study 2]).
Study dates	Study 2 was initiated in April 2009 and completed in November 2010.
Comments (Risk of bias)	

Bias	Authors judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	A central interactive voice system assigned participants unique numbers and a single-blind placebo kit.
Allocation concealment (selection bias)	Low risk	A central interactive voice system assigned participants unique numbers and a single-blind placebo kit.
Blinding of participants and researchers (performance bias)	Low risk	The trial was double-blinded.
Blinding of outcome assessment (detection bias)	Low risk	There was no information about who performed safety assessments but these assessments are unlikely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias)	Low risk	Missing outcome data balanced in numbers across groups with similar reasons for missing outcome data across groups.

Bibliographic reference	**Henry RR, Murray AV, Marmolejo MH, et al. (2012) Dapagliflozin, metformin XR, or both: initial pharmacotherapy for type 2 diabetes, a randomised controlled trial. International journal of clinical practice 66(5):446-56.**		
	Selective reporting (reporting bias)	Low risk	The study protocol is available (NCT00859898) and the outcomes of interest are reported in the pre-specified way.

* Only Study 2 reported an outcome of interest for this review. Therefore, no details are given about Study 1.

Bibliographic reference	**Kadowaki T, Inagaki N, Kondo K, et al. (2017) Efficacy and safety of canagliflozin as add-on therapy to teneligliptin in Japanese patients with type 2 diabetes mellitus: results of a 24-week, randomised, double-blind, placebo-controlled trial. Diabetes Obes Metab doi: 10.1111/dom.12898. [Epub ahead of print]**
Study type	RCT to investigate efficacy and safety of canagliflozin administered as add-on therapy to the dipeptidyl peptidase-4 (DPP-4) inhibitor teneligliptin in people with type 2 diabetes. Follow-up: 24 weeks.
Participants	Inclusion criteria Men and women aged 20 to 75 years Type 2 diabetes Diet and exercise regimen and teneligliptin 20 mg monotherapy once daily for at least 8 weeks prior to initiation of run-in period HbA1c ≥7.0 and <10% Exclusion criteria Treatment for arrhythmia History of ventricular tachycardia or ventricular fibrillation Findings by standard 12-lead electrocardiogram at rest of paroxysmal tachycardia, atrioventricular block, sick sinus syndrome, ventricular fibrillation, QTc prolongation Heart failure (New York Heart Association class III or IV) Myocardial infarction, congestive heart failure, unstable angina, cerebrovascular disorder (excluding lacunar infarction) within 6 months before the run-in period History of transient ischemic attacks or brain infarction with clear neurological symptoms Serious diabetic complications (proliferative retinopathy, Stage 4 or later diabetic nephropathy, or serious diabetic neuropathy)

<table>
<tr><td>Bibliographic reference</td><td>Kadowaki T, Inagaki N, Kondo K, et al. (2017) Efficacy and safety of canagliflozin as add-on therapy to teneligliptin in Japanese patients with type 2 diabetes mellitus: results of a 24-week, randomised, double-blind, placebo-controlled trial. Diabetes Obes Metab doi: 10.1111/dom.12898. [Epub ahead of print]</td></tr>
<tr><td></td><td>Serious concurrent liver or kidney disease (e.g., requiring hospitalization for treatment or for which surgery is indicated)
Estimated glomerular filtration rate <45 mL/min/1.73 m^2</td></tr>
<tr><td>Patient characteristics</td><td>77.9
Age = mean (SD) 58.4 years (8.9) (canagliflozin); 56.0 years (9.5) (placebo)
BMI = mean (SD) 25.5 kg/m^2 (4.2) (canagliflozin); 26.4 kg/m^2 (3.8) (placebo)
Weight = mean (SD) 71.3 kg (15.9) (canagliflozin); 73.2 kg (12.9) (placebo)
Risk of cardiovascular diseases (e.g. previous MI) = diabetes complications:
Retinopathy 21.4% (canagliflozin); 11.8% (placebo)
Neuropathy 18.6% (canagliflozin); 8.8% (placebo)
Nephropathy 21.4% (canagliflozin); 25.0% (placebo)</td></tr>
<tr><td>Intervention</td><td>Intervention: canagliflozin 100mg/d (n=70 participants)
Background therapy: add-on to teneligliptin.</td></tr>
<tr><td>Comparison</td><td>Comparison: placebo (n=68 participants)
Background therapy: add-on to teneligliptin.</td></tr>
<tr><td>Outcome measures</td><td>Cardiovascular-related events (considered as adverse events)
Adverse events were classified according to MedDRA version 18.1.</td></tr>
<tr><td>Study dates</td><td>Not reported.</td></tr>
<tr><td>Comments (Risk of bias)</td><td>
<table>
<tr><th>Bias</th><th>Authors judgment</th><th>Support for judgment</th></tr>
<tr><td>Random sequence generation (selection bias)</td><td>Low risk</td><td>Randomisation was done by a permuted block method.</td></tr>
<tr><td>Allocation concealment (selection bias)</td><td>Unclear risk</td><td>Allocation was not described.</td></tr>
<tr><td>Blinding of participants and researchers (performance bias)</td><td>Low risk</td><td>The trial was double-blinded.</td></tr>
<tr><td>Blinding of outcome assessment (detection bias)</td><td>Low risk</td><td>There was no information about who performed safety assessments but these assessments are unlikely to be influenced by lack of blinding.</td></tr>
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Bibliographic reference	**Kadowaki T, Inagaki N, Kondo K, et al. (2017) Efficacy and safety of canagliflozin as add-on therapy to teneligliptin in Japanese patients with type 2 diabetes mellitus: results of a 24-week, randomised, double-blind, placebo-controlled trial. Diabetes Obes Metab doi: 10.1111/dom.12898. [Epub ahead of print]**

Incomplete outcome data (attrition bias)	Low risk	There was no missing outcome data.
Selective reporting (reporting bias)	Low risk	The study protocol is available (NCT02354235) and the outcomes of interest are reported in the pre-specified way.

Bibliographic reference	**Kashiwagi A, Akiyama N, Shiga T, et al. (2015) Efficacy and safety of ipragliflozin as an add-on to a sulfonylurea in Japanese patients with inadequately controlled type 2 diabetes: results of the randomized, placebo-controlled, double-blind, phase III EMIT study. Diabetology International 6(2):125-138.**
Study type	RCT to examine the efficacy and safety of ipragliflozin as an add-on to a sulfonylurea in Japanese people with type 2 diabetes and inadequate glycaemic control. Follow-up: 24 weeks. EMIT study.
Participants	Inclusion criteria Men and women aged ≥20 years Type 2 diabetes HbA1c 7.4 to 9.9% Fasting plasma glucose ≥126 mg/dl BMI 20.0 to 45.0 kg/m^2 Treatment with sulfonylurea alone at a stable dose (≥1.25 mg/d glibenclamide, ≥40 mg/d glicazide, or ≥1 mg/d glimepiride) for ≥4 weeks before the screening period Exclusion criteria Proliferative diabetic retinopathy Dysuria Symptomatic urinary tract or genital infection A serious cardiovascular event within 12 weeks New York Heart Association class III or IV congestive heart failure (a full list of exclusion criteria can be seen in the methods section of the article).

<table>
<tr><td>Bibliographic reference</td><td>Kashiwagi A, Akiyama N, Shiga T, et al. (2015) Efficacy and safety of ipragliflozin as an add-on to a sulfonylurea in Japanese patients with inadequately controlled type 2 diabetes: results of the randomized, placebo-controlled, double-blind, phase III EMIT study. Diabetology International 6(2):125-138.</td></tr>
<tr><td>Patient characteristics</td><td>Gender = male 67.3% (ipragliflozin); 62.7% (placebo)
Age = mean (SD) 59.6 years (10.0) (ipragliflozin); 59.8 years (8.5) (placebo)
BMI = mean (SD) 25.8 kg/m^2 (3.6) (ipragliflozin); 24.1 kg/m^2 (2.9) (placebo)
Weight = mean (SD) 68.8 kg (12.4) (ipragliflozin); 63.9 kg (11.3) (placebo)
Risk of cardiovascular diseases (e.g. previous MI) = people with serious cardiovascular events (not defined) and congestive heart failure were excluded.</td></tr>
<tr><td>Intervention</td><td>Intervention: ipragliflozin 50mg/d
Background therapy: Add-on to sulfonylurea</td></tr>
<tr><td>Comparison</td><td>Comparison: placebo once daily
Background therapy: Add-on to sulfonylurea</td></tr>
<tr><td>Outcome measures</td><td>Proliferative retinopathy
This outcome was considered as a serious treatment emergent adverse event.
Treatment emergent adverse events were recorded according to system organ class and preferred term (MedDRA version 12.1), along with the severity and relationship to the study drug.</td></tr>
<tr><td>Study dates</td><td>The study was conducted between September 2010 and April 2012.</td></tr>
<tr><td>Comments (Risk of bias)</td><td>
<table>
<tr><th>Bias</th><th>Authors judgment</th><th>Support for judgment</th></tr>
<tr><td>Random sequence generation (selection bias)</td><td>Low risk</td><td>The randomisation schedule was prepared by a central registration centre.</td></tr>
<tr><td>Allocation concealment (selection bias)</td><td>Low risk</td><td>The randomisation schedule was prepared by a central registration centre.</td></tr>
<tr><td>Blinding of participants and researchers (performance bias)</td><td>Low risk</td><td>Participants and clinicians were kept blind to the treatment received in treatment period I until data for treatment period I had been entered into the study database and locked. The placebo drug was identical in appearance and packaging to the active drug.</td></tr>
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Bibliographic reference	**Kashiwagi A, Akiyama N, Shiga T, et al. (2015) Efficacy and safety of ipragliflozin as an add-on to a sulfonylurea in Japanese patients with inadequately controlled type 2 diabetes: results of the randomized, placebo-controlled, double-blind, phase III EMIT study. Diabetology International 6(2):125-138.**

Blinding of outcome assessment (detection bias)	Low risk	There was no information about who performed safety assessments but these assessments are unlikely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias)	Low risk	Missing outcome data balanced in numbers across groups with similar reasons for missing outcome data across groups.
Selective reporting (reporting bias)	Low risk	The study protocol is available (NCT01242215) and the outcomes of interest are reported in the pre-specified way.

Bibliographic reference	**Kohan DE, Fioretto P, Tang W, et al. (2014) Long-term study of patients with type 2 diabetes and moderate renal impairment shows that dapagliflozin reduces weight and blood pressure but does not improve glycemic control. Kidney international 85(4):962-71.**
Study type	RCT to examine the efficacy and safety of dapagliflozin in people with type 2 diabetes and moderate renal impairment. Follow-up: 104 weeks.
Participants	Inclusion criteria Men and women aged ≥18 years Type 2 diabetes Inadequate glycaemic control defined as HbA1c ≥7.0 and ≤11.0% eGFR 30 to 59 ml/min per 1.73 m^2 BMI ≤45.0 kg/m^2 Exclusion criteria Aspartate or alanine aminotransferases >3.0 times the upper limit of normal Serum total bilirubin >2.0 mg/dl History of diabetes insipidus or diabetic ketoacidosis or hyperosmolar non-ketotic coma

<table>
<tr><td>Bibliographic reference</td><td>Kohan DE, Fioretto P, Tang W, et al. (2014) Long-term study of patients with type 2 diabetes and moderate renal impairment shows that dapagliflozin reduces weight and blood pressure but does not improve glycemic control. Kidney international 85(4):962-71.</td></tr>
<tr><td></td><td>Uncontrolled hypertension defined as systolic blood pressure ≥180 mmHg and/or diastolic blood pressure ≥110mmHg
Specified cardiovascular/vascular diseases within 6 months of enrolment visit
Renal exclusion criteria: need for haemodialysis or renal replacement therapy, history of rapidly progressing renal disease, lupus nephritis, renal or systemic vasculitis, renal artery stenosis, renal transplant, or hepatic disease
Diabetic nephropathy.</td></tr>
<tr><td>Patient characteristics</td><td>Gender = male 66.3% (dapagliflozin 5mg/d); 65.9% (dapagliflozin 10 mg/d); 63.1% (placebo)
Age = mean (SD) 66 years (8.9) (dapagliflozin 5mg/d); 68 years (7.7) (dapagliflozin 10 mg/d); 67 years (8.6) (placebo)
BMI ≥30 kg/m^2 = 71.1% (dapagliflozin 5mg/d); 63.5% (dapagliflozin 10 mg/d); 59.5% (placebo)
Weight = mean (SD) 95.2 kg (20.9) (dapagliflozin 5mg/d); 93.2 kg (17.3) (dapagliflozin 10 mg/d); 89.6 kg (20.0) (placebo)
Risk of cardiovascular diseases (e.g. previous MI) = people with cardiovascular disease were excluded.</td></tr>
<tr><td>Intervention</td><td>Intervention: dapagliflozin 5mg/d (n=83 participants) or 10mg/d (n=85 participants)
Background therapy: add-on to original pre-enrolment antidiabetic regimen.</td></tr>
<tr><td>Comparison</td><td>Comparison: placebo (n=84 participants)
Background therapy: add-on to original pre-enrolment antidiabetic regimen.</td></tr>
<tr><td>Outcome measures</td><td>Fatal acute myocardial infarction
Fatal myocardial infarction
These outcomes were considered as adverse events but a definition was not provided.</td></tr>
<tr><td>Study dates</td><td>Participants were enrolled from June 2008 to May 2009.</td></tr>
<tr><td>Comments (Risk of bias)</td><td>
<table>
<tr><td>Bias</td><td>Authors judgment</td><td>Support for judgment</td></tr>
<tr><td>Random sequence generation (selection bias)</td><td>Unclear risk</td><td>Randomisation was not described.</td></tr>
<tr><td>Allocation concealment (selection bias)</td><td>Unclear risk</td><td>Allocation was not described.</td></tr>
<tr><td>Blinding of participants and researchers (performance bias)</td><td>Low risk</td><td>The trial was double-blinded.</td></tr>
<tr><td>Blinding of outcome assessment (detection bias)</td><td>Low risk</td><td>There was no information about who performed safety</td></tr>
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Bibliographic reference	**Kohan DE, Fioretto P, Tang W, et al. (2014) Long-term study of patients with type 2 diabetes and moderate renal impairment shows that dapagliflozin reduces weight and blood pressure but does not improve glycemic control. Kidney international 85(4):962-71.**

		assessments but these assessments are unlikely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias)	Low risk	Missing outcome data balanced in numbers across groups with similar reasons for missing outcome data across groups.
Selective reporting (reporting bias)	Low risk	The study protocol is available (NCT00663260) and the outcomes of interest are reported in the pre-specified way.

Bibliographic reference	**Kovacs CS, Seshiah V, Swallow R, et al. (2014) Empagliflozin improves glycaemic and weight control as add-on therapy to pioglitazone or pioglitazone plus metformin in patients with type 2 diabetes: A 24-week, randomized, placebo-controlled trial. Diabetes, Obesity & Metabolism 16(2):147-158.** **Kovacs CS, Seshiah V, Merker L, et al. (2015) Empagliflozin as Add-on Therapy to Pioglitazone With or Without Metformin in Patients With Type 2 Diabetes Mellitus. Clinical therapeutics 37(8):1773-88.**
Study type	RCT to assess the efficacy, safety and tolerability of empagliflozin compared with placebo as add-on therapy to pioglitazone alone or pioglitazone plus metformin in people with type 2 diabetes and insufficient glycaemic control. Follow-up: 24 and 76 weeks. EMPA-REG PIO™ trial.
Participants	Inclusion criteria Men and women aged ≥18 years Type 2 diabetes BMI ≤45 kg/m^2 HbA1c ≥7 and ≤10% Diet and exercise regimen Receiving unchanged doses of pioglitazone monotherapy (≥30 mg/day, or maximum tolerated dose, or the maximum dose according to the local label) or pioglitazone plus metformin (≥1,500 mg/day or maximum tolerated dose, or the maximum dose according to the local label)

Bibliographic reference	**Kovacs CS, Seshiah V, Swallow R, et al. (2014) Empagliflozin improves glycaemic and weight control as add-on therapy to pioglitazone or pioglitazone plus metformin in patients with type 2 diabetes: A 24-week, randomized, placebo-controlled trial. Diabetes, Obesity & Metabolism 16(2):147-158.** **Kovacs CS, Seshiah V, Merker L, et al. (2015) Empagliflozin as Add-on Therapy to Pioglitazone With or Without Metformin in Patients With Type 2 Diabetes Mellitus. Clinical therapeutics 37(8):1773-88.**
	Exclusion criteria Uncontrolled hyperglycaemia (plasma glucose >13.3 mmol/l after an overnight fast and confirmed by a second measurement) Severe renal impairment (estimated glomerular filtration rate [eGFR] <30 ml/min/1.73m^2 using the Modification of Diet in Renal Disease [MDRD] equation) Contraindication of pioglitazone and/or metformin according to the local label Indication of liver disease Acute coronary syndrome, stroke or transient ischaemic attack, receiving anti-obesity drugs within 3 months of consent Undergone bariatric surgery within 2 years Change in dose of thyroid hormones within 6 weeks of consent Any uncontrolled endocrine disorder.
Patient characteristics	Gender = male 50.3% (empagliflozin 10mg); 50.6% (empagliflozin 25mg); 44.2% (placebo) Age = mean (SD) 54.7 years (9.9) (empagliflozin 10mg); 54.2 years (8.9) (empagliflozin 25mg); 54.6 years (10.5) (placebo) BMI = mean (SD) 29.2 kg/m^2 (5.6) (empagliflozin 10mg); 29.1 kg/m^2 (5.5) (empagliflozin 25mg); 29.3 kg/m^2 (5.4) (placebo) Weight = mean (SD) 78.0 kg (19.1) (empagliflozin 10mg); 78.9 kg (19.9) (empagliflozin 25mg); 78.1 kg (20.1) (placebo) Risk of cardiovascular diseases (e.g. previous MI) = participants with stroke were excluded.
Intervention	Intervention: once daily empagliflozin 10 mg (n=165 participants) or empagliflozin 25 mg (n=168 participants) Background therapy: add-on to pioglitazone with or without metformin.
Comparison	Comparison: once daily placebo (n=165 participants) Background therapy: add-on to pioglitazone with or without metformin.
Outcome measures	Fatal myocardial infarction (reported by Kovacs et al. 2015) Fatal stroke (reported by Kovacs et al. 2015) Non-fatal heart failure (reported by Kovacs et al. 2014)

Bibliographic reference	**Kovacs CS, Seshiah V, Swallow R, et al. (2014) Empagliflozin improves glycaemic and weight control as add-on therapy to pioglitazone or pioglitazone plus metformin in patients with type 2 diabetes: A 24-week, randomized, placebo-controlled trial. Diabetes, Obesity & Metabolism 16(2):147-158.** **Kovacs CS, Seshiah V, Merker L, et al. (2015) Empagliflozin as Add-on Therapy to Pioglitazone With or Without Metformin in Patients With Type 2 Diabetes Mellitus. Clinical therapeutics 37(8):1773-88.**
	Adverse events were coded according to the Medical Dictionary for Drug Regulatory Activities (MedDRA) version 15.0 As participants were receiving pioglitazone, a dedicated examination for signs and symptoms of heart failure was performed at 6 weeks after randomisation, in addition to the standard physical examination performed at week 24.
Study dates	Not reported.
Comments (Risk of bias)	

Bias	Authors judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Randomisation was done using a computer-generated random sequence and an interactive voice and web response system.
Allocation concealment (selection bias)	Low risk	Randomisation was done using a computer-generated random sequence and an interactive voice and web response system.
Blinding of participants and researchers (performance bias)	Low risk	The trial was double-blinded.
Blinding of outcome assessment (detection bias)	Low risk	There was no information about who performed safety assessments but these assessments are unlikely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias)	Low risk	Missing outcome data balanced in numbers across groups with similar reasons for missing outcome data across groups.
Selective reporting (reporting bias)	Low risk	The study protocol is available (NCT01210001) and the outcomes of interest are reported in the pre-specified way.

Bibliographic reference	**Leiter LA, Cefalu WT, de Bruin TWA, et al. (2014) Dapagliflozin added to usual care in individuals with type 2 diabetes mellitus with preexisting cardiovascular disease: a 24-week, multicenter, randomized, double-blind, placebo-controlled study with a 28-week extension. Journal of the American Geriatrics Society 62(7):1252-62.**
Study type	RCT assess the efficacy and safety of dapagliflozin in people with inadequately controlled type 2 diabetes and documented pre-existing cardiovascular disease. Follow-up: 24 weeks.
Participants	Inclusion criteria Uncontrolled type 2 diabetes (HbA1c 7.0 to 10.0%) Pre-existing cardiovascular disease defined as (1) prior documented coronary heart disease, including history of myocardial infarction or revascularization or coronary artery stenosis >50%, confirmed with angiography or abnormal stress test imaging, compatible with ischemia or prior myocardial infarction; (2) prior documented stroke or transient ischemic attack; or (3) prior documented peripheral artery disease treated with revascularization (excluding amputation) Exclusion criteria Type 1 diabetes Use of rosiglitazone or three or more oral antihyperglycaemic drugs Symptoms of poorly controlled diabetes such as marked polyuria, polydipsia, and/or >10% weight loss, fasting plasma glucose (FPG) >270 mg/dL Cardiovascular events within 2 months of enrolment New York Association class IV congestive heart failure Unstable or acute congestive heart failure Systolic blood pressure (BP) ≥160 mmHg and/or diastolic BP ≥100 mmHg at randomization Calculated creatinine clearance <60 mL/min; urine albumin:creatinine ratio >1,800 mg/g History of unstable or rapidly progressing renal disease.
Patient characteristics	Gender = male 66.9% (dapagliflozin); 67.0% (placebo) Age = mean (SD) 63.9 years (7.6) (dapagliflozin); 63.6 years (7.0) (placebo) BMI = mean (SD) 33.0 kg/m^2 (5.3) (dapagliflozin); 32.7 kg/m^2 (5.7) (placebo) Weight = mean (SD) 94.5 kg (17.8) (dapagliflozin); 93.2 kg (16.8) (placebo) Risk of cardiovascular diseases (e.g. previous MI) = Stroke or transient ischemic attack = 21.9% (dapagliflozin); 17.4% (placebo) Congestive heart failure = 17.9% (dapagliflozin); 13.7% (placebo)
Intervention	Intervention: once-daily dapagliflozin 10 mg (n=480 participants)

<table>
<tr><td>Bibliographic reference</td><td>Leiter LA, Cefalu WT, de Bruin TWA, et al. (2014) Dapagliflozin added to usual care in individuals with type 2 diabetes mellitus with preexisting cardiovascular disease: a 24-week, multicenter, randomized, double-blind, placebo-controlled study with a 28-week extension. Journal of the American Geriatrics Society 62(7):1252-62.</td></tr>
<tr><td></td><td>Background therapy: add-on to pre-existing stable antidiabetic therapy including insulin.</td></tr>
<tr><td>Comparison</td><td>Comparison: matched placebo (n=482 participants)
Background therapy: add-on to pre-existing stable antidiabetic therapy including insulin.</td></tr>
<tr><td>Outcome measures</td><td>Fatal myocardial infarction
Fatal heart failure
These outcomes were considered as adverse events but a definition was not provided.</td></tr>
<tr><td>Study dates</td><td>Not reported.</td></tr>
<tr><td>Comments (Risk of bias)</td><td>
<table>
<tr><th>Bias</th><th>Authors judgment</th><th>Support for judgment</th></tr>
<tr><td>Random sequence generation (selection bias)</td><td>Low risk</td><td>Randomisation was done using interactive web response system or interactive voice response system.</td></tr>
<tr><td>Allocation concealment (selection bias)</td><td>Low risk</td><td>Randomisation was done using interactive web response system or interactive voice response system.</td></tr>
<tr><td>Blinding of participants and researchers (performance bias)</td><td>Low risk</td><td>The trial was double-blinded.</td></tr>
<tr><td>Blinding of outcome assessment (detection bias)</td><td></td><td>There was no information about who performed safety assessments but these assessments are unlikely to be influenced by lack of blinding.</td></tr>
<tr><td>Incomplete outcome data (attrition bias)</td><td></td><td>Missing outcome data balanced in numbers across groups with similar reasons for missing outcome data across groups.</td></tr>
<tr><td>Selective reporting (reporting bias)</td><td></td><td>The study protocol is available (NCT01042977) and the</td></tr>
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Bibliographic reference	**Leiter LA, Cefalu WT, de Bruin TWA, et al. (2014) Dapagliflozin added to usual care in individuals with type 2 diabetes mellitus with preexisting cardiovascular disease: a 24-week, multicenter, randomized, double-blind, placebo-controlled study with a 28-week extension. Journal of the American Geriatrics Society 62(7):1252-62.**
	outcomes of interest are reported in the pre-specified way.

Bibliographic reference	**Leiter LA, Yoon KH, Arias P, et al. (2015) Canagliflozin provides durable glycemic improvements and body weight reduction over 104 weeks versus glimepiride in patients with type 2 diabetes on metformin: a randomized, double-blind, phase 3 study. Diabetes care 38(3):355-64.** **Patel CA, Bailey RA, Vijapurkar U, et al. (2016) A post-hoc analysis of the comparative efficacy of canagliflozin and glimepiride in the attainment of type 2 diabetes-related quality measures. BMC Health Services Research 16(a):356.**
Study type	RCT to assess the efficacy and safety of canagliflozin compared with glimepiride over 104 weeks in people with type 2 diabetes inadequately controlled with metformin. Follow-up: 104 weeks. CANaglifl ozin Treatment And Trial Analysis versus SUlphonylurea (CANTATA-SU) study.
Participants	Inclusion criteria Men and women ≥18 and ≤80 years of age Type 2 diabetes HbA1c ≥7.0% (53 mmol/mol) and ≤9.5% (80 mmol/mol) Receiving metformin therapy (≥2,000 mg/day, or ≥1,500 mg/day if unable to tolerate a higher dose) for ≥10 weeks Exclusion criteria Repeated fasting plasma glucose or self-monitored blood glucose measurements of ≥15.0 mmol/L (270 mg/dL) during the pre-treatment phase History of type 1 diabetes History of more than one severe hypoglycaemia episode within 6 months before screening Estimated glomerular filtration rate (eGFR) <55 mL/min/1.73 m^2 (or <60 mL/min/1.73 m^2 if based upon the restriction of metformin use in local label) Taking thiazolidinediones within 16 weeks before screening.
Patient characteristics	Gender = 52.2% (canagliflozin 100mg); 49.7% (canagliflozin 300mg); 54.6% (glimepiride)

<table>
<tr><td>Bibliographic reference</td><td>Leiter LA, Yoon KH, Arias P, et al. (2015) Canagliflozin provides durable glycemic improvements and body weight reduction over 104 weeks versus glimepiride in patients with type 2 diabetes on metformin: a randomized, double-blind, phase 3 study. Diabetes care 38(3):355-64.
Patel CA, Bailey RA, Vijapurkar U, et al. (2016) A post-hoc analysis of the comparative efficacy of canagliflozin and glimepiride in the attainment of type 2 diabetes-related quality measures. BMC Health Services Research 16(a):356.</td></tr>
<tr><td></td><td>Age = mean (SD) 56.4 years (9.5) (canagliflozin 100mg); 55.8 years (9.2) (canagliflozin 300mg); 56.3 years (9.0) (glimepiride)
BMI = mean (SD) 31.0 kg/m^2 (5.3) (canagliflozin 100mg); 31.2 kg/m^2 (5.4) (canagliflozin 300mg); 30.9 kg/m^2 (5.5) (glimepiride)
Weight = mean (SD) 86.9 kg (20.1) (canagliflozin 100mg); 86.6 kg (19.5) (canagliflozin 300mg); 86.5 kg (19.8) (glimepiride)
Risk of cardiovascular diseases (e.g. previous MI) = not reported.</td></tr>
<tr><td>Intervention</td><td>Intervention: canagliflozin 100 mg (n=483 participants) or canagliflozin 300 mg (n=485 participants)
Background therapy: metformin.</td></tr>
<tr><td>Comparison</td><td>Comparison: glimepiride up to 8 mg (n=482 participants)
Background therapy: metformin.</td></tr>
<tr><td>Outcome measures</td><td>Cardiovascular mortality (reported by Patel et al. 2016)
Non-fatal myocardial infarction (reported by Patel et al. 2016)
Non-fatal stroke (reported by Patel et al. 2016)
These outcomes were listed as adverse events without providing a definition.</td></tr>
<tr><td>Study dates</td><td>The study was conducted from August 2009 to January 2013.</td></tr>
<tr><td>Comments (Risk of bias)</td><td>
<table>
<tr><th>Bias</th><th>Authors judgment</th><th>Support for judgment</th></tr>
<tr><td>Random sequence generation (selection bias)</td><td>Low risk</td><td>The sponsor prepared the computer-generated randomisation schedule before the study.</td></tr>
<tr><td>Allocation concealment (selection bias)</td><td>Low risk</td><td>The sponsor prepared the computer-generated randomisation schedule before the study.</td></tr>
<tr><td>Blinding of participants and researchers (performance bias)</td><td>Low risk</td><td>Patients, study investigators, and local sponsor personnel were masked to treatment assignment</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Leiter LA, Yoon KH, Arias P, et al. (2015) Canagliflozin provides durable glycemic improvements and body weight reduction over 104 weeks versus glimepiride in patients with type 2 diabetes on metformin: a randomized, double-blind, phase 3 study. Diabetes care 38(3):355-64.** **Patel CA, Bailey RA, Vijapurkar U, et al. (2016) A post-hoc analysis of the comparative efficacy of canagliflozin and glimepiride in the attainment of type 2 diabetes-related quality measures. BMC Health Services Research 16(a):356.**

		until final database lock. To maintain masked treatment, study drug was supplied in levels (levels one to five) to allow for masked increases and decreases of glimepiride throughout the double-blind treatment period.
Blinding of outcome assessment (detection bias)	Low risk	There was no information about who performed safety assessments but these assessments are unlikely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias)	Low risk	Missing outcome data balanced in numbers across groups with similar reasons for missing outcome data across groups.
Selective reporting (reporting bias)	Low risk	The study protocol is available (NCT00968812) and the outcomes of interest are reported in the pre-specified way.

Bibliographic reference	**Lewin A, DeFronzo RA, Patel S, et al. (2015) Initial combination of empagliflozin and linagliptin in subjects with type 2 diabetes. Diabetes care 38(3):394-402.**
Study type	RCT to evaluate the efficacy and safety of the initial combination of empagliflozin/linagliptin in people with type 2 diabetes. Follow-up: 52 weeks.
Participants	Inclusion criteria

Bibliographic reference	**Lewin A, DeFronzo RA, Patel S, et al. (2015) Initial combination of empagliflozin and linagliptin in subjects with type 2 diabetes. Diabetes care 38(3):394-402.**
	Men and women aged ≥18 years Type 2 diabetes BMI ≤45 kg/m^2 HbA1c >7 to ≤10.5% (>53 to ≤91 mmol/l) at screening despite a diet and exercise regimen Had not received treatment with oral antidiabetes therapy, GLP-1 analogue, or insulin for ≥12 weeks prior randomisation Exclusion criteria Uncontrolled hyperglycaemia (glucose level >240 mg/dL) Estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 Acute coronary syndrome, stroke, or transient ischemic attack within 3 months prior to consent Bariatric surgery in the last 2 years Treatment with antiobesity drugs within 3 months prior to consent.
Patient characteristics	Gender = male 52.2% (empagliflozin 25mg and linagliptin 5mg); 54.1% (empagliflozin 10mg and linagliptin 5mg); 57.9% (empagliflozin 25mg); 48.5% (empagliflozin 10mg); 56.4% (linagliptin 5mg) Age = mean (SD) 54.2 years (10.0) (empagliflozin 25mg and linagliptin 5mg); 55.2 years (9.8) (empagliflozin 10mg and linagliptin 5mg); 56.0 years (9.3) (empagliflozin 25mg); 53.9 years (10.5) (empagliflozin 10mg); 53.8 years (11.5) (linagliptin 5mg) BMI = mean (SD) 31.8 kg/m^2 (5.3) (empagliflozin 25mg and linagliptin 5mg); 31.5 kg/m^2 (5.6) (empagliflozin 10mg and linagliptin 5mg); 31.2 kg/m^2 (5.7) (empagliflozin 25mg); 31.5 kg/m^2 (5.7) (empagliflozin 10mg); 31.9 kg/m^2 (5.9) (linagliptin 5mg) Weight = mean (SD) 87.9 kg (18.2) (empagliflozin 25mg and linagliptin 5mg); 87.3 kg (18.4) (empagliflozin 10mg and linagliptin 5mg); 86.7 kg (19.7) (empagliflozin 25mg); 87.8 kg (24.0) (empagliflozin 10mg); 89.5 kg (20.1) (linagliptin 5mg) Risk of cardiovascular diseases (e.g. previous MI) = people with stroke were excluded.
Intervention	Intervention: once daily empagliflozin 25mg and linagliptin 5mg (n=134 participants), empagliflozin 10mg and linagliptin 5mg (n=135 participants), empagliflozin 25mg (n=133 participants), or empagliflozin 10mg (n=132 participants) Background therapy: none.
Comparison	Comparison: once daily linagliptin 5mg (n=133 participants) Background therapy: none.
Outcome measures	Fatal haemorrhagic stroke This outcome was considered as an adverse event.

<table>
<tr><td>Bibliographic reference</td><td>Lewin A, DeFronzo RA, Patel S, et al. (2015) Initial combination of empagliflozin and linagliptin in subjects with type 2 diabetes. Diabetes care 38(3):394-402.</td></tr>
<tr><td></td><td>Adverse events were preferred terms coded according to the Medical Dictionary for Regulatory Activities (MedDRA), version 16.0.</td></tr>
<tr><td>Study dates</td><td>This study was conducted between August 2011 and September 2013.</td></tr>
<tr><td>Comments (Risk of bias)</td><td>
<table>
<tr><th>Bias</th><th>Authors judgment</th><th>Support for judgment</th></tr>
<tr><td>Random sequence generation (selection bias)</td><td>Low risk</td><td>Randomisation was performed using a third-party interactive voice and web response system.</td></tr>
<tr><td>Allocation concealment (selection bias)</td><td>Low risk</td><td>Randomisation was performed using a third-party interactive voice and web response system.</td></tr>
<tr><td>Blinding of participants and researchers (performance bias)</td><td>Low risk</td><td>The trial was double-blinded.</td></tr>
<tr><td>Blinding of outcome assessment (detection bias)</td><td>Low risk</td><td>There was no information about who performed safety assessments but these assessments are unlikely to be influenced by lack of blinding.</td></tr>
<tr><td>Incomplete outcome data (attrition bias)</td><td>Low risk</td><td>Missing outcome data balanced in numbers across groups with similar reasons for missing outcome data across groups.</td></tr>
<tr><td>Selective reporting (reporting bias)</td><td>Low risk</td><td>The study protocol is available (NCT01422876) and the outcomes of interest are reported in the pre-specified way.</td></tr>
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Bibliographic reference	**Ljunggren O, Bolinder J, Johansson L, et al. (2012) Dapagliflozin has no effect on markers of bone formation and resorption or bone mineral density in patients with inadequately controlled type 2 diabetes mellitus on metformin. Diabetes, obesity & metabolism 14(11):990-9.**
Study type	RCT to evaluate markers of bone formation and resorption and bone mineral density in people with type 2 diabetes after 50 weeks of dapagliflozin treatment.

Bibliographic reference	**Ljunggren O, Bolinder J, Johansson L, et al. (2012) Dapagliflozin has no effect on markers of bone formation and resorption or bone mineral density in patients with inadequately controlled type 2 diabetes mellitus on metformin. Diabetes, obesity & metabolism 14(11):990-9.**
	Follow-up: 50 weeks.
Participants	Inclusion criteria Women aged 55 to 75 years who were post-menopausal for at least 5 years Men aged 30 to 75 years Type 2 diabetes HbA1c 6.5 to 8.5% Fasting plasma glucose ≤13.2 mmol/l BMI ≥25 kg/m^2 Body weight ≤120 kg (due to limitations imposed by equipment to measure bone mineral density) Treatment with metformin at a stable dose of ≥1,500 mg/d for ≥12 weeks prior enrolment Exclusion criteria Poor glycaemic control (HbA1c >8.5%) Treatment known to significantly influence bone metabolism (e.g. bisphosphonates, calcitonin, corticosteroids or hormone replacement therapy).
Patient characteristics	Gender = male 55.1% (dapagliflozin); 56.0% (placebo) Age = mean (SD) 60.6 years (8.2) (dapagliflozin); 60.8 years (6.9) (placebo) BMI = mean (SD) 32.1 kg/m^2 (3.9) (dapagliflozin); 31.7 kg/m^2 (3.9) (placebo) Weight = mean (SD) 92.1 kg (14.1) (dapagliflozin); 90.9 kg (13.7) (placebo) Risk of cardiovascular diseases (e.g. previous MI) = prior history of cardiovascular disease 23.6% (dapagliflozin); 28.6% (placebo)
Intervention	Intervention: dapagliflozin 10mg/d (n=89 participants) Background therapy: add-on to metformin.
Comparison	Comparison: once daily placebo (n=91 participants) Background therapy: add-on to metformin.
Outcome measures	Non-fatal acute myocardial infarction This outcome was considered as a serious adverse event. Serious adverse events were not defined.
Study dates	This study started in February 2009 and was ongoing in 2012 (publication date).
Comments (Risk of bias)	Bias | Authors judgment | Support for judgment

Bibliographic reference	Ljunggren O, Bolinder J, Johansson L, et al. (2012) Dapagliflozin has no effect on markers of bone formation and resorption or bone mineral density in patients with inadequately controlled type 2 diabetes mellitus on metformin. Diabetes, obesity & metabolism 14(11):990-9.		
	Random sequence generation (selection bias)	Low risk	Participants were allocated to study treatments according to a predefined computer-generated randomisation scheme provided by AstraZeneca.
	Allocation concealment (selection bias)	Low risk	Participants were allocated to study treatments according to a predefined computer-generated randomisation scheme provided by AstraZeneca.
	Blinding of participants and researchers (performance bias)	Low risk	Participants and investigators were blinded to study treatment. All investigational products (dapagliflozin and placebo) were identical in appearance, smell, and taste, and packaged into identical bottles.
	Blinding of outcome assessment (detection bias)	Low risk	There was no information about who performed safety assessments but these assessments are unlikely to be influenced by lack of blinding.
	Incomplete outcome data (attrition bias)	Low risk	Missing outcome data balanced in numbers across groups with similar reasons for missing outcome data across groups.
	Selective reporting (reporting bias)	Low risk	The study protocol is available (NCT00855166) and the outcomes of interest are reported in the pre-specified way.

Bibliographic reference	**Mathieu C, Ranetti AE, Li D, et al. (2015) Randomized, Double-Blind, Phase 3 Trial of Triple Therapy With Dapagliflozin Add-on to Saxagliptin Plus Metformin in Type 2 Diabetes. Diabetes care 38(11):2009-17.** **Mathieu C, Herrera Marmolejo M, Gonzalez Gonzalez JG, et al. (2016) Efficacy and safety of triple therapy with dapagliflozin add-on to saxagliptin plus metformin over 52weeks in patients with type 2 diabetes. Diabetes, obesity & metabolism 18(11):1134-1137.**
Study type	RCT to compare the safety and efficacy of dapagliflozin therapy versus placebo add-on to saxagliptin plus metformin therapy in people with type 2 diabetes who had inadequate glycaemic control with saxagliptin plus metformin therapy. Follow-up: 24 and 52 weeks.
Participants	Inclusion criteria Men and women aged ≥18 years Type 2 diabetes HbA1c 8.0 to 11.5% with stable metformin therapy (immediate release or extended release ≥1,500 mg/d) or HbA1c 7.5 to 10.5% with stable metformin therapy (immediate release or extended release ≥1,500 mg/d) and a DPP-4 inhibitor at the maximum approved dose Exclusion criteria Pregnancy Cardiovascular events within 3 months of screening An estimated glomerular filtration rate of <60 mL/min/1.73 m^2 or a serum creatinine level of ≥1.5 mg/dL in men or ≥1.4 mg/dL in women Microscopic haematuria with no known cause in men Significant hepatic disease Receiving any antidiabetes medication, other than metformin and DPP-4 inhibitors, for >14 days during the 12 weeks before screening.
Patient characteristics	Gender = male 43.7% (dapagliflozin); 47.5% (placebo) Age = mean (SD) 55.2 years (8.6) (dapagliflozin); 55.0 years (9.6) (placebo) BMI = mean (SD) 31.2 kg/m^2 (4.7) (dapagliflozin); 32.2 kg/m^2 (5.3) (placebo) Weight = not reported Risk of cardiovascular diseases (e.g. previous MI) = people with cardiovascular events were excluded.
Intervention	Intervention: dapagliflozin 10mg/d (n=160 participants) Background therapy: add-on to saxagliptin plus metformin.
Comparison	Comparison: placebo (n=160 participants) Background therapy: add-on to saxagliptin plus metformin.

<table>
<tr><td>Bibliographic reference</td><td>Mathieu C, Ranetti AE, Li D, et al. (2015) Randomized, Double-Blind, Phase 3 Trial of Triple Therapy With Dapagliflozin Add-on to Saxagliptin Plus Metformin in Type 2 Diabetes. Diabetes care 38(11):2009-17.
Mathieu C, Herrera Marmolejo M, Gonzalez Gonzalez JG, et al. (2016) Efficacy and safety of triple therapy with dapagliflozin add-on to saxagliptin plus metformin over 52weeks in patients with type 2 diabetes. Diabetes, obesity & metabolism 18(11):1134-1137.</td></tr>
<tr><td>Outcome measures</td><td>Non-fatal heart failure (reported by Mathieu et al. 2016)
Suspected cardiovascular adverse events were blindly adjudicated by a clinical event committee managed by the Montreal Heart Institute.</td></tr>
<tr><td>Study dates</td><td>The 24-week followed was from September 2012 to August 2014.</td></tr>
<tr><td>Comments (Risk of bias)</td><td>
<table>
<tr><th>Bias</th><th>Authors judgment</th><th>Support for judgment</th></tr>
<tr><td>Random sequence generation (selection bias)</td><td>Low risk</td><td>Participants were randomly assigned by an interactive voice response system.</td></tr>
<tr><td>Allocation concealment (selection bias)</td><td>Low risk</td><td>Participants were randomly assigned by an interactive voice response system.</td></tr>
<tr><td>Blinding of participants and researchers (performance bias)</td><td>Low risk</td><td>The trial was double-blinded.</td></tr>
<tr><td>Blinding of outcome assessment (detection bias)</td><td>Low risk</td><td>Suspected cardiovascular adverse events were blindly adjudicated by a clinical event committee managed by the Montreal Heart Institute.</td></tr>
<tr><td>Incomplete outcome data (attrition bias)</td><td>Low risk</td><td>Missing outcome data balanced in numbers across groups with similar reasons for missing outcome data across groups.</td></tr>
<tr><td>Selective reporting (reporting bias)</td><td>Low risk</td><td>The study protocol is available (NCT01646320) and the outcomes of interest are reported in the pre-specified way.</td></tr>
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Bibliographic reference	**Nauck MA, Del Prato S, Meier JJ, et al. (2011) 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 34(9):2015-22.** **Nauck MA, Del Prato S, Duran-Garcia S, et al. (2014) Durability of glycaemic efficacy over 2 years with dapagliflozin versus glipizide as add-on therapies in patients whose type 2 diabetes mellitus is inadequately controlled with metformin. Diabetes, obesity & metabolism 16(11):1111-20.**
Study type	RCT to assess the long-term glycaemic durability, safety and tolerability of dapagliflozin versus glipizide as add-on therapies in people with type 2 diabetes inadequately controlled by metformin alone. Follow-up: 52 weeks and 104 weeks.
Participants	Inclusion criteria Men and women aged ≥18 years Type 2 diabetes HbA1c >6.5 and ≤10% Fasting plasma glucose ≤15 mmol/l C-peptide concentration of ≥0.33 mmol/l Metformin or metformin plus one other oral antidiabetic drug administered up to half-maximum dose for at least 8 weeks before enrolment Exclusion criteria BMI >45.0 kg/m^2 Calculated creatinine clearance <60 mL/min; urine albumin:creatinine ratio >203.4 mg/mmol Cardiovascular event within 6 months of enrolment Congestive heart failure A complete list of exclusion criteria can be found in Nauck (2011).
Patient characteristics	Gender = male 55.3% (dapagliflozin); 54.9% (glipizide) Age = mean (SD) 58 years (9) (dapagliflozin); 59 years (10) (glipizide) BMI = mean (SD) 31.7 kg/m^2 (5.1) (dapagliflozin); 31.2 kg/m^2 (5.1) (glipizide) Weight = not reported Risk of cardiovascular diseases (e.g. previous MI) = prior history of cardiovascular disease 18.0% (dapagliflozin); 19.5% (glipizide)
Intervention	Intervention: dapagliflozin up to 10mg/d (n=406 participants) Background therapy: add-on to metformin ≥1,500 mg/d.
Comparison	Comparison: glipizide up to 20mg/d (n=408 participants) Background therapy: add-on to metformin ≥1,500 mg/d.

<table>
<tr><td>Bibliographic reference</td><td>Nauck MA, Del Prato S, Meier JJ, et al. (2011) 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 34(9):2015-22.
Nauck MA, Del Prato S, Duran-Garcia S, et al. (2014) Durability of glycaemic efficacy over 2 years with dapagliflozin versus glipizide as add-on therapies in patients whose type 2 diabetes mellitus is inadequately controlled with metformin. Diabetes, obesity & metabolism 16(11):1111-20.</td></tr>
<tr><td>Outcome measures</td><td>Fatal acute myocardial infarction (extracted from Nauck et al. 2014)</td></tr>
<tr><td>Study dates</td><td>This outcome was considered as an adverse event.
Adverse events were classified using the Medical Dictionary for Regulatory Activities version 12.1.</td></tr>
<tr><td>Comments (Risk of bias)</td><td>
<table>
<tr><th>Bias</th><th>Authors judgment</th><th>Support for judgment</th></tr>
<tr><td>Random sequence generation (selection bias)</td><td>Low risk</td><td>Participants were randomised sequentially at study level according to a predefined computer-generated randomisation scheme provided by AstraZeneca.</td></tr>
<tr><td>Allocation concealment (selection bias)</td><td>Low risk</td><td>Allocation of study treatments was performed via an interactive web response system.</td></tr>
<tr><td>Blinding of participants and researchers (performance bias)</td><td>Low risk</td><td>Blinding of patients and investigators to study treatment was achieved using a double-dummy technique.</td></tr>
<tr><td>Blinding of outcome assessment (detection bias)</td><td>Low risk</td><td>There was no information about who performed safety assessments but these assessments are unlikely to be influenced by lack of blinding.</td></tr>
<tr><td>Incomplete outcome data (attrition bias)</td><td>Low risk</td><td>Missing outcome data balanced in numbers across groups with similar reasons for missing outcome data across groups.</td></tr>
<tr><td>Selective reporting (reporting bias)</td><td>Low risk</td><td>The study protocol is available (NCT00660907) and the</td></tr>
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Bibliographic reference	**Nauck MA, Del Prato S, Meier JJ, et al. (2011) 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 34(9):2015-22.** **Nauck MA, Del Prato S, Duran-Garcia S, et al. (2014) Durability of glycaemic efficacy over 2 years with dapagliflozin versus glipizide as add-on therapies in patients whose type 2 diabetes mellitus is inadequately controlled with metformin. Diabetes, obesity & metabolism 16(11):1111-20.**
	outcomes of interest are reported in the pre-specified way.

Bibliographic reference	**Neal B, Perkovic V, Mahaffey KW, et al. (2017) Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. The New England Journal of Medicine 1-14.**
Study type	RCT to assess the cardiovascular safety and efficacy of canagliflozin and to evaluate the balance between any potential benefits of the drug and the risks associated with it. Follow-up: mean of 188.2 weeks. CANVAS and CANVAS-R trial.
Participants	Inclusion criteria Men and women Type 2 diabetes HbA1c ≥7.0% and ≤10.5% Either 30 years of age or older with a history of symptomatic atherosclerotic cardiovascular disease or 50 years of age or older with two or more of the following risk factors for cardiovascular disease: duration of diabetes of at least 10 years, systolic blood pressure higher than 140 mm Hg while they were receiving one or more antihypertensive agents, current smoking, microalbuminuria or macroalbuminuria, or high-density lipoprotein cholesterol level of less than 1 mmol per litre (38.7 mg per decilitre) Estimated glomerular filtration rate (eGFR) at entry of more than 30 ml per minute per 1.73 m^2 of body-surface area and to meet a range of other criteria Exclusion criteria History of diabetic ketoacidosis, type 1 diabetes, pancreas or beta-cell transplantation, or diabetes secondary to pancreatitis or pancreatectomy. A longer list of inclusion and exclusion criteria is reported in the supplementary appendix of Neal et al. (2017).
Patient characteristics	Gender = male 64.9% (canagliflozin); 63.3% (placebo) Age = mean (SD) 63.2 years (8.3) (canagliflozin); 63.4 years (8.2) (placebo) BMI kg/m^2 = mean (SD) 31.9 kg/m^2 (5.9) (canagliflozin); 32.0 kg/m^2 (6.0) (placebo)

<table>
<tr><td>Bibliographic reference</td><td>Neal B, Perkovic V, Mahaffey KW, et al. (2017) Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. The New England Journal of Medicine 1-14.</td></tr>
<tr><td></td><td>Weight = not reported
Risk of cardiovascular diseases (e.g. previous MI) = history of cardiovascular disease 64.8% (canagliflozin); 66.7% (placebo)</td></tr>
<tr><td>Intervention</td><td>Intervention: canagliflozin 100 mg/d or 300 mg/d (n=5,795 participants)
Background therapy: Use of other background therapy for glycaemic management and other control of risk factors were guided by best practice instituted in line with local guidelines.</td></tr>
<tr><td>Comparison</td><td>Comparison: placebo (n=4,347 participants)
Background therapy: Use of other background therapy for glycaemic management and other control of risk factors were guided by best practice instituted in line with local guidelines.</td></tr>
<tr><td>Outcome measures</td><td>Cardiovascular mortality
Non-fatal myocardial infarction
Non-fatal stroke
Hospitalisation for heart failure
Lower limb amputation
All-cause mortality
See Appendix L for definitions of each outcome.</td></tr>
<tr><td>Study dates</td><td>CANVAS initiated in December 2009. Follow-up ended in February 2017.</td></tr>
<tr><td>Comments (Risk of bias)</td><td>
<table>
<tr><th>Bias</th><th>Authors judgment</th><th>Support for judgment</th></tr>
<tr><td>Random sequence generation (selection bias)</td><td>Low risk</td><td>Randomisation was performed centrally through an interactive Web-based response system with the use of a computer-generated randomisation schedule with randomly permuted blocks that was prepared by the trial sponsor.</td></tr>
<tr><td>Allocation concealment (selection bias)</td><td>Low risk</td><td>Randomisation was performed centrally through an interactive Web-based response system with the use of a computer-generated randomisation schedule with randomly</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Neal B, Perkovic V, Mahaffey KW, et al. (2017) Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. The New England Journal of Medicine 1-14.**		
			permuted blocks that was prepared by the trial sponsor.
	Blinding of participants and researchers (performance bias)	Low risk	Participants and all trial staff were unaware of the individual treatment assignments until completion of the trial.
	Blinding of outcome assessment (detection bias)	Low risk	All major cardiovascular events, renal outcomes, and deaths, plus selected safety outcomes, were adjudicated by end-point adjudication committees. The members of the committees and the definitions that were used for the clinical events are listed in the Supplementary Appendix.
	Incomplete outcome data (attrition bias)	Low risk	Missing outcome data balanced in numbers across groups with similar reasons for missing outcome data across groups.
	Selective reporting (reporting bias)	Low risk	The study protocol is available (NCT01032629 and NCT01989754) and the outcomes of interest are reported in the pre-specified way.

Bibliographic reference	**Rosenstock J, Vico M, Wei L, et al. (2012) Effects of dapagliflozin, an SGLT2 inhibitor, on HbA(1c), body weight, and hypoglycemia risk in patients with type 2 diabetes inadequately controlled on pioglitazone monotherapy. Diabetes care 35(7):1473-8.**
Study type	RCT to examine the safety and efficacy of dapagliflozin added on to pioglitazone in type 2 diabetes inadequately controlled on pioglitazone. Follow-up: 48 weeks.
Participants	Inclusion criteria

<table>
<tr><td>Bibliographic reference</td><td>Rosenstock J, Vico M, Wei L, et al. (2012) Effects of dapagliflozin, an SGLT2 inhibitor, on HbA(1c), body weight, and hypoglycemia risk in patients with type 2 diabetes inadequately controlled on pioglitazone monotherapy. Diabetes care 35(7):1473-8.</td></tr>
<tr><td></td><td>Men and women aged ≥18 years
Type 2 diabetes
Fasting C-peptide ≥1.0 ng/mL
BMI ≤45.0 kg/m^2
Exclusion criteria
Aspartate or alanine aminotransferases >2.5 times the upper limit of normal
Total bilirubin >2.0 mg/dL
Serum creatinine ≥2.0mg/dL
Urine albumin/creatinine ratio >1,800 mg/g
Calculated creatinine clearance <50 mL/min
Congestive heart failure class III and IV.</td></tr>
<tr><td>Patient characteristics</td><td>Gender = male 55.3% (dapagliflozin 5mg/d); 42.1% (dapagliflozin 10mg/d); 51.1% (placebo)
Age = mean (SD) 53.2 years (10.9) (dapagliflozin 5mg/d); 53.8 years (10.4) (dapagliflozin 10mg/d); 53.5 years (11.4) (placebo)
BMI ≥25 kg/m^2 = 86.5% (dapagliflozin 5mg/d); 92.9% (dapagliflozin 10mg/d); 87.8% (placebo)
Weight = mean (SD) 87.8 kg (20.7) (dapagliflozin 5mg/d); 84.8 kg (22.2) (dapagliflozin 10mg/d); 86.4 kg (21.3) (placebo)
Risk of cardiovascular diseases (e.g. previous MI) = people with congestive heart failure were excluded.</td></tr>
<tr><td>Intervention</td><td>Intervention: dapagliflozin 5mg/d (n=141 participants) or 10mg/d (n=140 participants)
Background therapy: add-on to pioglitazone 30 or 45 mg/d.</td></tr>
<tr><td>Comparison</td><td>Comparison: placebo (n=139 participants)
Background therapy: add-on to pioglitazone 30 or 45 mg/d.</td></tr>
<tr><td>Outcome measures</td><td>Non-fatal heart failure
This outcome was considered as an adverse event.
Adverse events were not defined.</td></tr>
<tr><td>Study dates</td><td>Participants were enrolled between July 2008 and July 2009 and study was completed in June 2010.</td></tr>
<tr><td>Comments (Risk of bias)</td><td>
<table>
<tr><td>Bias</td><td>Authors judgment</td><td>Support for judgment</td></tr>
<tr><td>Random sequence generation (selection bias)</td><td>Unclear risk</td><td>Not described.</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Rosenstock J, Vico M, Wei L, et al. (2012) Effects of dapagliflozin, an SGLT2 inhibitor, on HbA(1c), body weight, and hypoglycemia risk in patients with type 2 diabetes inadequately controlled on pioglitazone monotherapy. Diabetes care 35(7):1473-8.**

Allocation concealment (selection bias)	Unclear risk	Allocation was not described.
Blinding of participants and researchers (performance bias)	Low risk	The trial was double-blinded.
Blinding of outcome assessment (detection bias)	Low risk	There was no information about who performed safety assessments but these assessments are unlikely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias)	Low risk	Missing outcome data balanced in numbers across groups with similar reasons for missing outcome data across groups.
Selective reporting (reporting bias)	Low risk	The study protocol is available (NCT00683878) and the outcomes of interest are reported in the pre-specified way.

Bibliographic reference	**Strojek K, Yoon KH, Hruba V, et al. (2011). Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with glimepiride: a randomized, 24-week, double-blind, placebo-controlled trial. Diabetes, Obesity and Metabolism, 13(10):928-938.** **Strojek K, Yoon KH, Hruba V, et al. (2014) Dapagliflozin Added to Glimepiride in Patients with Type 2 Diabetes Mellitus Sustains Glycemic Control and Weight Loss Over 48 Weeks: A Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Trial. Diabetes Therapy 5(1):267-83.**
Study type	RCT to assess the efficacy, safety and tolerability of dapagliflozin added to glimepiride in people with uncontrolled type 2 diabetes. Follow-up: 24 and 48 weeks.
Participants	Inclusion criteria Men and women aged ≥18 years Type 2 diabetes

Bibliographic reference	**Strojek K, Yoon KH, Hruba V, et al. (2011). Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with glimepiride: a randomized, 24-week, double-blind, placebo-controlled trial. Diabetes, Obesity and Metabolism, 13(10):928-938.** **Strojek K, Yoon KH, Hruba V, et al. (2014) Dapagliflozin Added to Glimepiride in Patients with Type 2 Diabetes Mellitus Sustains Glycemic Control and Weight Loss Over 48 Weeks: A Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Trial. Diabetes Therapy 5(1):267-83.**
	HbA1c ≥7.0 and ≤10.0% Receiving a stable dose of sulfonylurea monotherapy at a level of at least half the maximum recommended dose for at least 8 weeks prior to enrolment Fasting plasma glucose ≤15 mmol/L C-peptide ≥0.33 nmol/L Exclusion criteria Use of glimepiride >4 mg/day during the 8 weeks up to and including enrolment BMI >45.0 kg/m^2 Calculated creatinine clearance <50 mL/min or serum creatinine >177 µmol/L Urine albumin/creatinine ratio >203.4 mg/mmol Aspartate aminotransferase and/or alanine aminotransferase and/or creatine kinase ≥3 x upper limit of normal range Serum total bilirubin >34 µmol/L Hb ≤10 g/dL for men and ≤9.5 g/dL for women Systolic blood pressure ≥180 mmHg and/or diastolic blood pressure ≥110 mmHg Cardiovascular event within 6 months of enrolment A full list of exclusion criteria can be seen in Strojek 2011.
Patient characteristics	Gender = male 50.0% (dapagliflozin 2.5mg/d); 50.0% (dapagliflozin 5mg/d); 43.7% (dapagliflozin 10 mg/d); 49.0% (placebo) Age = mean (SD) 59.9 years (10.1) (dapagliflozin 2.5mg/d); 60.2 years (9.7) (dapagliflozin 5mg/d); 58.9 years (8.3) (dapagliflozin 10 mg/d); 60.3 years (10.2) (placebo) BMI = mean (SD) 30.0 kg/m^2 (5.1) (dapagliflozin 2.5mg/d); 29.8 kg/m^2 (5.2) (dapagliflozin 5mg/d); 29.8 kg/m^2 (5.6) (dapagliflozin 10 mg/d); 29.7 kg/m^2 (4.6) (placebo) Weight = not reported Risk of cardiovascular diseases (e.g. previous MI) = prior history of cardiovascular disease
Intervention	Intervention: dapagliflozin 2.5mg/d (n=154 participants), 5mg/d (n=145 participants), or 10mg/d (n=151 participants) Background therapy: add-on to glimepiride up to 4 mg/d, dietary and lifestyle counselling.
Comparison	Comparison: placebo (n=146 participants)

<table>
<tr><td>Bibliographic reference</td><td>Strojek K, Yoon KH, Hruba V, et al. (2011). Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with glimepiride: a randomized, 24-week, double-blind, placebo-controlled trial. Diabetes, Obesity and Metabolism, 13(10):928-938.
Strojek K, Yoon KH, Hruba V, et al. (2014) Dapagliflozin Added to Glimepiride in Patients with Type 2 Diabetes Mellitus Sustains Glycemic Control and Weight Loss Over 48 Weeks: A Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Trial. Diabetes Therapy 5(1):267-83.</td></tr>
<tr><td></td><td>Background therapy: add-on to glimepiride up to 4 mg/d, dietary and lifestyle counselling.</td></tr>
<tr><td>Outcome measures</td><td>Non-fatal stroke (extracted from Strojek et al. 2014)
This outcome was considered as a serious adverse event leading to discontinuation.
Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA version 12.1).</td></tr>
<tr><td>Study dates</td><td>This study was conducted from April 2008 to November 2009.</td></tr>
<tr><td>Comments (Risk of bias)</td><td>
<table>
<tr><th>Bias</th><th>Authors judgment</th><th>Support for judgment</th></tr>
<tr><td>Random sequence generation (selection bias)</td><td>Low risk</td><td>A computer-generated randomisation schedule was provided by Astra-Zeneca.</td></tr>
<tr><td>Allocation concealment (selection bias)</td><td>Low risk</td><td>A computer-generated randomisation schedule was provided by Astra-Zeneca.</td></tr>
<tr><td>Blinding of participants and researchers (performance bias)</td><td>Low risk</td><td>Blinding of dapagliflozin tablets was achieved by double-blind allocation and use of a double-dummy technique because the dapagliflozin 10 mg tablet size was slightly larger than that for the 2.5 and 5 mg doses.</td></tr>
<tr><td>Blinding of outcome assessment (detection bias)</td><td>Low risk</td><td>There was no information about who performed safety assessments but these assessments are unlikely to be influenced by lack of blinding.</td></tr>
<tr><td>Incomplete outcome data (attrition bias)</td><td>Low risk</td><td>Missing outcome data balanced in numbers across groups with similar reasons for missing outcome data across groups.</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Strojek K, Yoon KH, Hruba V, et al. (2011). Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with glimepiride: a randomized, 24-week, double-blind, placebo-controlled trial. Diabetes, Obesity and Metabolism, 13(10):928-938.** **Strojek K, Yoon KH, Hruba V, et al. (2014) Dapagliflozin Added to Glimepiride in Patients with Type 2 Diabetes Mellitus Sustains Glycemic Control and Weight Loss Over 48 Weeks: A Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Trial. Diabetes Therapy 5(1):267-83.**		
	Selective reporting (reporting bias)	Low risk	The study protocol is available (NCT00680745) and the outcomes of interest are reported in the pre-specified way.

Bibliographic reference	**Wilding JPH, Woo V, Soler NG, et al. (2012) Long-term efficacy of dapagliflozin in patients with type 2 diabetes mellitus receiving high doses of insulin: a randomized trial. Annals of internal medicine 156(6):405-15.** **Wilding JPH, Woo V, Rohwedder K, et al. (2014) Dapagliflozin in patients with type 2 diabetes receiving high doses of insulin: Efficacy and safety over 2 years. Diabetes, Obesity and Metabolism 16(2):124-136.**
Study type	RCT to evaluate the efficacy and safety adding dapagliflozin therapy in people with type 2 diabetes inadequately controlled with insulin with or without oral antidiabetic drugs. Follow-up: 48 and 104 weeks.
Participants	Inclusion criteria Men and women aged 18 to 80 years Type 2 diabetes BMI ≤45 kg/m^2 Inadequate glycaemic control (HbA1c ≥7.5 and ≤10.5%) Stable insulin regimen with a mean daily insulin dose of ≥30 U for at least 8 weeks, with daily insulin requirements varying by no more than 10% or no more than 1 occasion in the 7 days before randomisation Receiving at least 1,500 mg/d or their maximum tolerated dose of metformin or at least half of the daily maximum dose of other oral antidiabetic drugs for at least 8 weeks before enrolment Exclusion criteria Type 1 diabetes Symptoms of poorly controlled diabetes Calculated creatinine clearance <50 mL/min per 1.73 m^2

<table>
<tr><td>Bibliographic reference</td><td>Wilding JPH, Woo V, Soler NG, et al. (2012) Long-term efficacy of dapagliflozin in patients with type 2 diabetes mellitus receiving high doses of insulin: a randomized trial. Annals of internal medicine 156(6):405-15.
Wilding JPH, Woo V, Rohwedder K, et al. (2014) Dapagliflozin in patients with type 2 diabetes receiving high doses of insulin: Efficacy and safety over 2 years. Diabetes, Obesity and Metabolism 16(2):124-136.</td></tr>
<tr><td></td><td>Measured serum creatinine level >177 µmol/L (>2 mg/dL) or if receiving metformin, >133 µmol/L (>1.5 mg/dL) for men and at least 124 µmol/L (≥1.4 mg/dL) for women.</td></tr>
<tr><td>Patient characteristics</td><td>Gender = male 49.5% (dapagliflozin 2.5mg/d); 47.4% (dapagliflozin 5mg/d); 44.8% (dapagliflozin 10 mg/d); 49.2% (placebo)
Age = mean (SD) 59.8 years (7.6) (dapagliflozin 2.5mg/d); 59.3 years (7.9) (dapagliflozin 5mg/d); 59.3 years (8.8) (dapagliflozin 10 mg/d); 58.8 years (8.6) (placebo)
BMI = mean (SD) 33.0 kg/m^2 (5.0) (dapagliflozin 2.5mg/d); 33.0 kg/m^2 (5.3) (dapagliflozin 5mg/d); 33.4 kg/m^2 (5.1) (dapagliflozin 10 mg/d); 33.1 kg/m^2 (5.9) (placebo)
Weight = mean (SD) 93.0 kg (16.7) (dapagliflozin 2.5mg/d); 93.3 kg (17.4) (dapagliflozin 5mg/d); 94.5 kg (16.8) (dapagliflozin 10 mg/d); 94.5 kg (19.8) (placebo)
Risk of cardiovascular diseases (e.g. previous MI) = history of cardiovascular disease 40.6% (dapagliflozin 2.5mg/d); 31.8% (dapagliflozin 5mg/d); 42.8% (dapagliflozin 10 mg/d); 33.2% (placebo)</td></tr>
<tr><td>Intervention</td><td>Intervention: dapagliflozin 2.5mg/d (n=202 participants), 5mg/d (n=212 participants), or 10mg/d(n=196 participants)
Background therapy: add-on to daily insulin, existing oral antidiabetic drugs, and a stable diet and exercise regimen.</td></tr>
<tr><td>Comparison</td><td>Comparison: placebo (n=197 participants)
Background therapy: add-on to daily insulin, existing oral antidiabetic drugs, and a stable diet and exercise regimen.</td></tr>
<tr><td>Outcome measures</td><td>Fatal acute myocardial infarction (extracted from Wilding et al. 2014)
A definition for this outcome was not provided.</td></tr>
<tr><td>Study dates</td><td>This study was conducted from April 2008 to November 2009.</td></tr>
<tr><td>Comments (Risk of bias)</td><td>
<table>
<tr><th>Bias</th><th>Authors judgment</th><th>Support for judgment</th></tr>
<tr><td>Random sequence generation (selection bias)</td><td>Low risk</td><td>A computer-generated, stratified, block-randomisation schedule containing stratum, randomisation code, and treatment was provided by AstraZeneca.</td></tr>
<tr><td>Allocation concealment (selection bias)</td><td>Low risk</td><td>A computer-generated, stratified, block-randomisation schedule containing stratum,</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	Wilding JPH, Woo V, Soler NG, et al. (2012) Long-term efficacy of dapagliflozin in patients with type 2 diabetes mellitus receiving high doses of insulin: a randomized trial. Annals of internal medicine 156(6):405-15. Wilding JPH, Woo V, Rohwedder K, et al. (2014) Dapagliflozin in patients with type 2 diabetes receiving high doses of insulin: Efficacy and safety over 2 years. Diabetes, Obesity and Metabolism 16(2):124-136.

		randomisation code, and treatment was provided by AstraZeneca.
Blinding of participants and researchers (performance bias)	Low risk	Participants, investigators, and study monitors were blinded during the 24-week treatment and extension periods. A double-dummy technique was used because the 10 mg dapagliflozin tablets were slightly larger than the 2.5 or 5 mg tablets. All placebos were identical in appearance, odour, and taste to their corresponding investigational products.
Blinding of outcome assessment (detection bias)	Low risk	There was no information about who performed safety assessments but these assessments are unlikely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias)	Low risk	Missing outcome data balanced in numbers across groups with similar reasons for missing outcome data across groups.
Selective reporting (reporting bias)	Low risk	The study protocol is available (NCT00673231) and the outcomes of interest are reported in the pre-specified way.

Bibliographic reference	**Zinman B, Wanner C, Lachin JM, et al. (2015) Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. The New England journal of medicine 373(22):2117-28.** **Fitchett D, Zinman B, Wanner C, et al. (2016) Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: Results of the EMPA-REG OUTCOME trial. European heart journal 37(19):1526-34.** **Wanner C, Inzucchi SE, Lachin JM, et al. (2016). Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes. The New England journal of medicine 375(4):323-34.** **Kaku K, Lee J, Mattheus M, Kaspers S, et al. (2017) Empagliflozin and cardiovascular outcomes in Asian patients with type 2 diabetes and established cardiovascular disease - results from EMPA-REG OUTCOME. Circulation Journal 81(2):227-234.**
Study type	RCT to examine the effects of empagliflozin, as compared with placebo, on cardiovascular morbidity and mortality in patients with type 2 diabetes at high risk for cardiovascular events who were receiving standard care. Follow-up: median observation time 3.1 years. EMPA-REG OUTCOME trial.
Participants	Inclusion criteria Adults ≥18 years Type 2 diabetes BMI 45 kg/m^2 or less Estimated glomerular filtration rate (eGFR) of at least 30 ml per minute per 1.73 m^2 of body-surface area Established cardiovascular disease No glucose-lowering agents for at least 12 weeks before randomization and HbA1c level of at least 7.0% and no more than 9.0% or stable glucose-lowering therapy for at least 12 weeks before randomization and HbA1c level of at least 7.0% and no more than 10.0% Exclusion criteria Other key exclusion criteria are provided in Section D in the Supplementary Appendix.
Patient characteristics	Gender = male 71.2% (empagliflozin); 72.0% (placebo) Age = mean (SD) 63.1 years (8.6) (empagliflozin); 63.2 years (8.8) (placebo) BMI = mean (SD) 30.6 kg/m^2 (5.3) (empagliflozin); 30.7 kg/m^2 (5.2) (placebo) Weight = mean (SD) 86.2 kg (18.9) (empagliflozin); 86.6 kg (19.1) (placebo) Risk of cardiovascular diseases (e.g. previous MI) = cardiovascular risk factor 99.4% (empagliflozin); 98.9% (placebo). Cardiovascular risk factors included coronary artery disease, multi-vessel coronary artery disease, history of myocardial infarction, coronary artery bypass graft, history of stroke, peripheral artery disease, single vessel coronary artery disease, and cardiac failure. Kaku (2017) reported baseline characteristics of Asian population*:

Bibliographic reference	**Zinman B, Wanner C, Lachin JM, et al. (2015) Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. The New England journal of medicine 373(22):2117-28.** **Fitchett D, Zinman B, Wanner C, et al. (2016) Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: Results of the EMPA-REG OUTCOME trial. European heart journal 37(19):1526-34.** **Wanner C, Inzucchi SE, Lachin JM, et al. (2016). Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes. The New England journal of medicine 375(4):323-34.** **Kaku K, Lee J, Mattheus M, Kaspers S, et al. (2017) Empagliflozin and cardiovascular outcomes in Asian patients with type 2 diabetes and established cardiovascular disease - results from EMPA-REG OUTCOME. Circulation Journal 81(2):227-234.**
	Empagliflozin 10mg (n=505 participants) Empagliflozin 25 mg (n=501 participants) Placebo (n=511 participants) Gender = male 73.1% (empagliflozin 10mg); 73.9% (empagliflozin 25mg); 74.2% (placebo) Age = mean (SD) 61.1 years (8.8) (empagliflozin 10mg); 61.1 years (9.4) (empagliflozin 25mg); 60.7 years (9.4) (placebo) BMI = mean (SD) 26.8 kg/m^2 (4.2) (empagliflozin 10mg); 26.5 kg/m^2 (4.0) (empagliflozin 25mg); 26.6 kg/m^2 (3.9) (placebo) Weight = mean (SD) 71.1 kg (13.6) (empagliflozin 10mg); 70.5 kg (13.2) (empagliflozin 25mg); 70.7 kg (13.2) (placebo) Risk of cardiovascular diseases (e.g. previous MI) = 99.6% (empagliflozin 10mg); 98.8% (empagliflozin 25mg); 99.2% (placebo)
Intervention	Intervention: once-daily empagliflozin 10mg (n=2,345 participants) or 25 mg (n=2,342 participants) Background therapy: add-on to background glucose-lowering therapy.
Comparison	Comparison: once daily placebo (n=2,333 participants) Background therapy: add-on to background glucose-lowering therapy.
Outcome measures	The following outcomes were extracted from Zinman et al. (2015), Fitchett et al. (2016), or Wanner et al. (2016) Cardiovascular mortality Fatal acute myocardial infarction Non-fatal myocardial infarction Non-fatal silent myocardial infarction Fatal stroke Non-fatal stroke Fatal heart failure

<table>
<tr><td>Bibliographic reference</td><td>Zinman B, Wanner C, Lachin JM, et al. (2015) Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. The New England journal of medicine 373(22):2117-28.
Fitchett D, Zinman B, Wanner C, et al. (2016) Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: Results of the EMPA-REG OUTCOME trial. European heart journal 37(19):1526-34.
Wanner C, Inzucchi SE, Lachin JM, et al. (2016). Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes. The New England journal of medicine 375(4):323-34.
Kaku K, Lee J, Mattheus M, Kaspers S, et al. (2017) Empagliflozin and cardiovascular outcomes in Asian patients with type 2 diabetes and established cardiovascular disease - results from EMPA-REG OUTCOME. Circulation Journal 81(2):227-234.</td></tr>
<tr><td></td><td>Non-fatal heart failure (investigator-reported)
Hospitalisation for heart failure
Incident or worsening nephropathy
Initiation of laser therapy for retinopathy
Coronary revascularisation procedure
All-cause mortality
See Appendix M for definitions of each outcome.
All cardiovascular outcome events and deaths were prospectively adjudicated by two Clinical Events Committees (for cardiac and neurological events).</td></tr>
<tr><td>Study dates</td><td>Participants were randomised between September 2010 and April 2013.</td></tr>
<tr><td>Comments (Risk of bias)</td><td>
<table>
<tr><th>Bias</th><th>Authors judgment</th><th>Support for judgment</th></tr>
<tr><td>Random sequence generation (selection bias)</td><td>Low risk</td><td>Randomisation was performed with the use of a computer-generated random-sequence and interactive voice- and Web-response system.</td></tr>
<tr><td>Allocation concealment (selection bias)</td><td>Low risk</td><td>Randomisation was performed with the use of a computer-generated random-sequence and interactive voice- and Web-response system.</td></tr>
<tr><td>Blinding of participants and researchers (performance bias)</td><td>Low risk</td><td>The trial was double-blinded.</td></tr>
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</td></tr>
</table>

Bibliographic reference	**Zinman B, Wanner C, Lachin JM, et al. (2015) Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. The New England journal of medicine 373(22):2117-28.** **Fitchett D, Zinman B, Wanner C, et al. (2016) Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: Results of the EMPA-REG OUTCOME trial. European heart journal 37(19):1526-34.** **Wanner C, Inzucchi SE, Lachin JM, et al. (2016). Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes. The New England journal of medicine 375(4):323-34.** **Kaku K, Lee J, Mattheus M, Kaspers S, et al. (2017) Empagliflozin and cardiovascular outcomes in Asian patients with type 2 diabetes and established cardiovascular disease - results from EMPA-REG OUTCOME. Circulation Journal 81(2):227-234.**		
	Blinding of outcome assessment (detection bias)	Low risk	Cardiovascular outcome events and deaths were prospectively adjudicated by two clinical-events committees (one for cardiac events and the other for neurologic events), as recommended by the Food and Drug Administration (FDA) guidelines.
	Incomplete outcome data (attrition bias)	Low risk	Missing outcome data balanced in numbers across groups with similar reasons for missing outcome data across groups.
	Selective reporting (reporting bias)	Low risk	The study protocol is available (NCT01131676) and the outcomes of interest are reported in the pre-specified way. Subgroup analysis on race was considered in the published protocol (Zinman 2014).

* Participating countries from Asia: Hong Kong, India, Indonesia, Japan, Korea, Malaysia, Philippines, Singapore, Sri Lanka, Taiwan, Thailand.

A number of studies did not report any relevant events taking place within the study, but did report that no cardiovascular deaths occurred in either arm of the trial. These studies cannot be included in the meta-analysis because it is not possible to calculate a relative risk when no events occur in either arm. A brief summary of these studies is reported below. All interventions and comparators were given once daily.

Study	Sample size	Intervention	Comparator	Background treatment
Araki E, Onishi Y, Asano M, et al. (2016) Efficacy and safety of dapagliflozin in addition to insulin therapy in Japanese patients with type 2 diabetes: Results of the interim analysis of 16-week double-blind treatment period. Journal of Diabetes Investigation 7(4):555-64.	182	Dapagliflozin and insulin	Placebo and insulin	With or without DPP-4 inhibitor
Bailey CJ, Iqbal N, T'Joen C, et al. (2012) Dapagliflozin monotherapy in drug-naive patients with diabetes: a randomized-controlled trial of low-dose range. Diabetes, obesity & metabolism 14(10):951-9.	282	Dapagliflozin	Placebo	None
Barnett AH, Mithal A, Manassie J, et al. (2014) Efficacy and safety of empagliflozin added to existing antidiabetes treatment in patients with type 2 diabetes and chronic kidney disease: A randomised, double-blind, placebo-controlled trial. The Lancet Diabetes and Endocrinology 2(5):369-384.	741	Empagliflozin	Placebo	Background antidiabetes medication
Bolinder J, Ljunggren O, Kullberg J, et al. (2012) Effects of dapagliflozin on body weight, total fat mass, and regional adipose tissue distribution in patients with type 2 diabetes mellitus with inadequate glycemic control on metformin. The Journal of clinical endocrinology and metabolism 97(3):1020-31. Bolinder J, Ljunggren O, Johansson L, et al. (2014) Dapagliflozin maintains glycaemic control while reducing weight and body fat mass over 2 years in patients with type 2 diabetes mellitus inadequately controlled on metformin. Diabetes, obesity & metabolism 16(2):159-69.	182	Dapagliflozin	Placebo	Metformin
DeFronzo RA, Lewin A, Patel S, et al. (2015) Combination of empagliflozin and linagliptin as second-line therapy in subjects with type 2 diabetes inadequately controlled on metformin. Diabetes care 38(3):384-93.	686	Empagliflozin and linagliptin or Empagliflozin alone	Linagliptin	Add-on to metformin

Study	Sample size	Intervention	Comparator	Background treatment
Del Prato S, Nauck M, Duran-Garcia S, 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, and obesity & metabolism 17(6):581-90.	816	Dapagliflozin	Glipizide	Add-on to metformin
Devineni D, Morrow L, Hompesch M, et al. (2012) Canagliflozin improves glycaemic control over 28 days in subjects with type 2 diabetes not optimally controlled on insulin. Diabetes, obesity & metabolism 14(6):539-45.	29	Canagliflozin	Placebo	Insulin therapy and fixed stable doses of oral antidiabetic agents
Ferrannini E, Jimenez Ramos S, Salsali A, et al. (2010) Dapagliflozin monotherapy in type 2 diabetic patients with inadequate glycemic control by diet and exercise: a randomized, double-blind, placebo-controlled, phase 3 trial. Diabetes care 33(10):2217-24. Bailey CJ, Morales Villegas EC, Woo V, et al. (2015) Efficacy and safety of dapagliflozin monotherapy in people with Type 2 diabetes: a randomized double-blind placebo-controlled 102-week trial. Diabetic medicine : a journal of the British Diabetic Association 32(4):531-41.	485	Dapagliflozin	Placebo	Metformin
Forst T, Guthrie R, Goldenberg R, et al. (2014) Efficacy and safety of canagliflozin over 52 weeks in patients with type 2 diabetes on background metformin and pioglitazone. Diabetes, obesity & metabolism 16(5):467-77.	342	Canagliflozin	Placebo up to 26 weeks Sitagliptin last 26 weeks	Metformin and pioglitazone
Fulcher G, Matthews DR, Perkovic V, et al. (2015) Efficacy and Safety of Canagliflozin Used in Conjunction with Sulfonylurea in Patients with Type 2 Diabetes Mellitus: A Randomized, Controlled Trial. Diabetes therapy: research, and treatment and education of diabetes and related disorders 6(3):289-302.	127	Dapagliflozin	Placebo	Add-on to sulfonylurea
Haring HU, Merker L, Seewaldt-Becker E, et al. (2014) Empagliflozin as add-on to metformin in patients with type 2 diabetes: a 24-week, randomized, double-blind, placebo-controlled trial. Diabetes care 37(6):1650-9.	638	Empagliflozin	Placebo	Add-on to metformin

Study	Sample size	Intervention	Comparator	Background treatment
Heerspink HJ, Desai M, Jardine M, et al. (2017) Canagliflozin Slows Progression of Renal Function Decline Independently of Glycemic Effects. Journal of the American Society of Nephrology: JASN 28(1):368-375.	1,450	Canagliflozin	Glimepiride	Metformin
Heise T, Seman L, Macha S, et al. (2013) Safety, tolerability, pharmacokinetics, and pharmacodynamics of multiple rising doses of empagliflozin in patients with type 2 diabetes mellitus. Diabetes Therapy 4(2):331-45.	48	Empagliflozin	Placebo	Unclear
Ikeda S, Takano Y, Cynshi O, et al. (2015) A novel and selective sodium-glucose cotransporter-2 inhibitor, tofogliflozin, improves glycaemic control and lowers body weight in patients with type 2 diabetes mellitus. Diabetes, obesity & metabolism 17(10):984-993.	394	Tofogliflozin	Placebo	None
Inagaki N, Kondo K, Yoshinari T, et al. (2013) Efficacy and safety of canagliflozin in Japanese patients with type 2 diabetes: a randomized, double-blind, placebo-controlled, 12-week study. Diabetes, obesity & metabolism 15(12):1136-45.	383	Canagliflozin	Placebo	Antihyperglycaemic drugs were prohibited until end of follow-up
Jabbour SA, Hardy E, Sugg J, et al. (2014) Dapagliflozin is effective as add-on therapy to sitagliptin with or without metformin: a 24-week, multicenter, randomized, double-blind, placebo-controlled study. Diabetes care 37(3):740-50.	451	Dapagliflozin	Placebo	Sitagliptin or metformin
Ji L, Ma J, Li H, et al. (2014) Dapagliflozin as monotherapy in drug-naive Asian patients with type 2 diabetes mellitus: a randomized, blinded, prospective phase III study. Clinical therapeutics 36(1):84-100.e9.	393	Dapagliflozin	Placebo	None
Ji L, Han P, Liu Y, et al. (2015) Canagliflozin in Asian patients with type 2 diabetes on metformin alone or metformin in combination with sulphonylurea. Diabetes, obesity & metabolism 17(1):23-31.	678	Canagliflozin	Placebo	Metformin alone or metformin plus sulfonylurea
Kadowaki T, Haneda M, Inagaki N, et al. (2014) Empagliflozin monotherapy in Japanese patients with type 2 diabetes mellitus: a randomized, 12-week, double-	547	Empagliflozin	Placebo	None

Study	Sample size	Intervention	Comparator	Background treatment
blind, placebo-controlled, phase II trial. Advances in therapy 31(6):621-38. Kadowaki T, Haneda M, Inagaki N, et al. (2015) Efficacy and safety of empagliflozin monotherapy for 52 weeks in Japanese patients with type 2 diabetes: a randomized, double-blind, parallel-group study. Advances in therapy 32(4):306-318.				
Kaku K, Inoue S, Matsuoka O, et al. (2013) Efficacy and safety of dapagliflozin as a monotherapy for type 2 diabetes mellitus in Japanese patients with inadequate glycaemic control: A phase II multicentre, randomized, double-blind, placebo-controlled trial. Diabetes, Obesity and Metabolism 15(5):432-440.	279	Dapagliflozin	Placebo	None
Kaku K, Watada H, Iwamoto Y, et al. (2014) Efficacy and safety of monotherapy with the novel sodium/glucose cotransporter-2 inhibitor tofogliflozin in Japanese patients with type 2 diabetes mellitus: a combined Phase 2 and 3 randomized, placebo-controlled, double-blind, parallel-group comparative study. Cardiovascular diabetology 13:65.	235	Tofogliflozin	Placebo	None
Kanada S, Koiwai K, Taniguchi A, et al. (2013) Pharmacokinetics, pharmacodynamics, safety and tolerability of 4 weeks' treatment with empagliflozin in Japanese patients with type 2 diabetes mellitus. Journal of Diabetes Investigation 4(6):613-7.	100	Empagliflozin	Placebo	Not reported
Kapur A, O'Connor-Semmes R, Hussey EK, et al. (2013) First human dose-escalation study with remogliflozin etabonate, a selective inhibitor of the sodium-glucose transporter 2 (SGLT2), in healthy subjects and in subjects with type 2 diabetes mellitus. BMC Pharmacology and Toxicology 14.	6	Remogliflozin etabonate	Placebo	None
Kashiwagi A, Kazuta K, Yoshida S, et al. (2014) Randomized, placebo-controlled, double-blind glycemic control trial of novel sodium-dependent glucose cotransporter 2 inhibitor ipragliflozin in Japanese patients	361	Ipragliflozin	Placebo	None

Study	Sample size	Intervention	Comparator	Background treatment
with type 2 diabetes mellitus. Journal of Diabetes Investigation 5(4):382-91.				
Kashiwagi A, Kazuta K, Goto K, et al. (2015) Ipragliflozin in combination with metformin for the treatment of Japanese patients with type 2 diabetes: ILLUMINATE, a randomized, double-blind, placebo-controlled study. Diabetes, obesity & metabolism 17(3):304-8.	235	Tofogliflozin	Placebo	None
Kasichayanula S, Chang M, Hasegawa M, et al. (2011) Pharmacokinetics and pharmacodynamics of dapagliflozin, a novel selective inhibitor of sodium-glucose co-transporter type 2, in Japanese subjects without and with type 2 diabetes mellitus. Diabetes, obesity & metabolism 13(4):357-65.	36	Dapagliflozin	Placebo	None
Komoroski B, Vachharajani N, Feng Y, et al. (2009) Dapagliflozin, a novel, selective SGLT2 inhibitor, improved glycemic control over 2 weeks in patients with type 2 diabetes mellitus. Clinical pharmacology and therapeutics 85(5):513-9.	47	Dapagliflozin	Placebo	Metformin
Lambers Heerspink HJ, de Zeeuw D, Wie L, et al. (2013) Dapagliflozin a glucose-regulating drug with diuretic properties in subjects with type 2 diabetes. Diabetes, obesity & metabolism 15(9):853-62.	75	Dapagliflozin	Placebo Hydrochlorothiazide	Not reported
Leiter LA, Yoon KH, Arias P, et al. (2015) Canagliflozin provides durable glycemic improvements and body weight reduction over 104 weeks versus glimepiride in patients with type 2 diabetes on metformin: a randomized, double-blind, phase 3 study. Diabetes care 38(3):355-64.	1,151	Canagliflozin	Glimepiride	Metformin
List JF, Woo V, Morales E, et al. (2009) Sodium-glucose cotransport inhibition with dapagliflozin in type 2 diabetes. Diabetes care 32(4):650-7.	389	Dapagliflozin	Placebo Metformin XR	None
Matthaei S, Bowering K, Rohwedder K, et al. (2015) Dapagliflozin improves glycemic control and reduces body weight as add-on therapy to metformin plus	218	Dapagliflozin	Placebo	Metformin plus sulfonylurea

Study	Sample size	Intervention	Comparator	Background treatment
sulfonylurea: a 24-week randomized, double-blind clinical trial. Diabetes care 38(3):365-72. Matthaei S, Bowering K, Rohwedder K, et al. (2015) Durability and tolerability of dapagliflozin over 52weeks as add-on to metformin and sulphonylurea in type 2 diabetes. Diabetes, and Obesity and Metabolism 17(11):1075-1084.				
Mudaliar S, Henry RR, Boden G, et al. (2014) Changes in insulin sensitivity and insulin secretion with the sodium glucose cotransporter 2 inhibitor dapagliflozin. Diabetes Technology and Therapeutics 16(3):137-144.	44	Dapagliflozin	Placebo	Metformin, insulin secretagogue, diet and exercise
Nishimura R, Osonoi T, Kanada S, et al. (2015) Effects of luseogliflozin, a sodium-glucose co-transporter 2 inhibitor, on 24-h glucose variability assessed by continuous glucose monitoring in Japanese patients with type 2 diabetes mellitus: a randomized, double-blind, placebo-controlled, crossover study. Diabetes, obesity & metabolism 17(8):800-4.	37	Luseogliflozin	Placebo	Not reported
Rodbard HW, Seufert J, Aggarwal N, et al. (2016) Efficacy and safety of titrated canagliflozin in patients with type 2 diabetes mellitus inadequately controlled on metformin and sitagliptin. Diabetes, obesity & metabolism 18(8):812-9.	218	Canagliflozin	Placebo	Metformin and sitagliptin
Roden M, Weng J, Eilbracht J, et al. (2013) Empagliflozin monotherapy with sitagliptin as an active comparator in patients with type 2 diabetes: A randomised, double-blind, placebo-controlled, phase 3 trial. The Lancet Diabetes and Endocrinology 1(3):208-219. Roden M, Merker L, Christiansen AV, et al. (2015) Safety, tolerability and effects on cardiometabolic risk factors of empagliflozin monotherapy in drug-naïve patients with type 2 diabetes: a double-blind extension of a Phase III randomized controlled trial. Cardiovascular diabetology 14:154.	899	Empagliflozin	Placebo or Sitagliptin	Diet and exercise counselling

Study	Sample size	Intervention	Comparator	Background treatment
Rosenstock J, Seman L J, Jelaska A, et al. (2013) Efficacy and safety of empagliflozin, a sodium glucose cotransporter 2 (SGLT2) inhibitor, as add-on to metformin in type 2 diabetes with mild hyperglycaemia. Diabetes, obesity & metabolism 15(12):1154-60.	495	Empagliflozin	Placebo or Sitagliptin	Metformin
Rosenstock J, Jelaska A, Frappin G, et al. (2014) Improved glucose control with weight loss, lower insulin doses, and no increased hypoglycemia with empagliflozin added to titrated multiple daily injections of insulin in obese inadequately controlled type 2 diabetes. Diabetes care 37(7):1815-23.	563	Empagliflozin	Placebo	Insulin with or without metformin
Rosenstock J, Hansen L, Zee P, et al. (2015) Dual add-on therapy in type 2 diabetes poorly controlled with metformin monotherapy: a randomized double-blind trial of saxagliptin plus dapagliflozin addition versus single addition of saxagliptin or dapagliflozin to metformin. Diabetes care 38(3):376-83.	534	Dapagliflozin and saxagliptin Dapagliflozin and placebo	Saxagliptin and placebo	Metformin
Ross S, Thamer C, Cescutti J, et al. (2015) Efficacy and safety of empagliflozin twice daily versus once daily in patients with type 2 diabetes inadequately controlled on metformin: a 16-week, randomized, placebo-controlled trial. Diabetes, obesity & metabolism 17(7), 699-702	983	Empagliflozin	Placebo	Metformin immediate release
Schernthaner G, Gross JL, Rosenstock J, et al. (2013) Canagliflozin compared with sitagliptin for patients with type 2 diabetes who do not have adequate glycemic control with metformin plus sulfonylurea: a 52-week randomized trial. Diabetes care 36(9):2508-15.	756	Canagliflozin	Sitagliptin	Metformin and sulfonylurea
Schumm-Draeger PM, Burgess L, Koranyi L, et al. (2015) Twice-daily dapagliflozin co-administered with metformin in type 2 diabetes: a 16-week randomized, placebo-controlled clinical trial. Diabetes, obesity & metabolism 17(1);42-51.	520	Dapagliflozin	Placebo	Metformin
Schwartz SL, Akinlade B, Klasen S, et al. (2011) Safety, pharmacokinetic, and pharmacodynamic profiles of ipragliflozin (ASP1941), a novel and selective inhibitor of	61	Ipragliflozin	Placebo	None

Study	Sample size	Intervention	Comparator	Background treatment
sodium-dependent glucose co-transporter 2, in patients with type 2 diabetes mellitus. Diabetes technology & therapeutics 13(12):1219-27.				
Seino Y, Sasaki T, Fukatsu A, et al. (2014) Efficacy and safety of luseogliflozin monotherapy in Japanese patients with type 2 diabetes mellitus: a 12-week, randomized, placebo-controlled, phase II study. Current medical research and opinion 30(7):1219-30.	239	Luseogliflozin	Placebo	Diet therapy Oral antidiabetic drugs and insulin were prohibited for the entire study duration
Seino Y, Sasaki T, Fukatsu A, et al. (2014) Efficacy and safety of luseogliflozin as monotherapy in Japanese patients with type 2 diabetes mellitus: a randomized, double-blind, placebo-controlled, phase 3 study. Current medical research and opinion 30(7):1245-55.	158	Luseogliflozin	Placebo	Diet therapy Antidiabetic drugs were prohibited during the study period
Sha S, Devineni D, Ghosh A, et al. (2014) Pharmacodynamic effects of canagliflozin, a sodium glucose co-transporter 2 inhibitor, from a randomized study in patients with type 2 diabetes. PloS one 9(9):e110069.	116	Canagliflozin	Placebo	Standard diet
Sha S, Polidori D, Heise T, et al. (2014) Effect of the sodium glucose co-transporter 2 inhibitor canagliflozin on plasma volume in patients with type 2 diabetes mellitus. Diabetes, obesity & metabolism 16(11):1087-95.	36	Canagliflozin	Placebo	Standardised diet and metformin
Softeland E, Meier JJ, Vangen B, et al. (2017) Empagliflozin as Add-on Therapy in Patients With Type 2 Diabetes Inadequately Controlled With Linagliptin and Metformin: A 24-Week Randomized, Double-Blind, Parallel-Group Trial. Diabetes care 40(2):201-209.	333	Empagliflozin	Placebo	Linagliptin and metformin
Stein P, Berg JK, Morrow L, et al. (2014) Canagliflozin, a sodium glucose co-transporter 2 inhibitor, reduces post-meal glucose excursion in patients with type 2 diabetes by a non-renal mechanism: results of a randomized trial. Metabolism: clinical and experimental 63(10):1296-303.	37	Canagliflozin	Placebo	Metformin
Stenlof K, Cefalu WT, Kim KA, et al. (2013) Efficacy and safety of canagliflozin monotherapy in subjects with type 2 diabetes mellitus inadequately controlled with diet and	587	Canagliflozin	Placebo	None

Study	Sample size	Intervention	Comparator	Background treatment
exercise. Diabetes, Obesity and Metabolism 15(4):372-382. Stenlof K, Cefalu WT, Kim KA, et al. (2014) Long-term efficacy and safety of canagliflozin monotherapy in patients with type 2 diabetes inadequately controlled with diet and exercise: findings from the 52-week CANTATA-M study. Current medical research and opinion 30(2):163-75.				
Terra SG, Focht K, Davies M, et al. (2017) A Phase 3, Efficacy and Safety Study of Ertugliflozin Monotherapy in Patients with Type 2 Diabetes Mellitus Inadequately Controlled with Diet and Exercise Alone. Diabetes Obes Metab 19:721-28.	461	Ertugliflozin	Placebo	None
Weber MA, Mansfield TA, Alessi F, et al. (2016) Effects of dapagliflozin on blood pressure in hypertensive diabetic patients on renin-angiotensin system blockade. Blood pressure 25(2):93-103.	613	Dapagliflozin plus ACEi or ARB	Placebo plus ACEi or ARB	Stable doses of antidiabetic drugs including insulin
Weber MA, Mansfield TA, Cain VA, et al. (2016) Blood pressure and glycaemic effects of dapagliflozin versus placebo in patients with type 2 diabetes on combination antihypertensive therapy: a randomised, double-blind, placebo-controlled, phase 3 study. The lancet Diabetes & endocrinology 4(3):211-20.	449	Dapagliflozin	Placebo	Background antihyperglycaemic drugs
Wilding JP, Norwood P, T'Joen C, et al. (2009) A study of dapagliflozin in patients with type 2 diabetes receiving high doses of insulin plus insulin sensitizers: applicability of a novel insulin-independent treatment. Diabetes care 32(9):1656-62.	71	Dapagliflozin	Placebo	Diet and exercise program Insulin and oral antidiabetic agents
Wilding JP, Charpentier G, Hollander P, et al. (2013) Efficacy and safety of canagliflozin in patients with type 2 diabetes mellitus inadequately controlled with metformin and sulphonylurea: a randomised trial. International journal of clinical practice 67(12):1267-82.	469	Canagliflozin	Placebo	Metformin and sulfonylurea
Yang W, Han P, Min KW, et al. (2016) Efficacy and safety of dapagliflozin in Asian patients with type 2	445	Dapagliflozin	Placebo	Metformin

Study	Sample size	Intervention	Comparator	Background treatment
diabetes after metformin failure: A randomized controlled trial. Journal of diabetes 8(6):796-808.				

ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker.

GLP-1 mimetics

Bibliographic reference	**Araki E, Inagaki N, Tanizawa Y, et al. (2015) Efficacy and safety of once-weekly dulaglutide in combination with sulphonylurea and/or biguanide compared with once-daily insulin glargine in Japanese patients with type 2 diabetes: a randomized, open-label, phase III, non-inferiority study. Diabetes Obes Metab; 17(10):994-1002.**
Study type	Randomised controlled trial to compare once-weekly dulaglutide and once-daily basal insulin therapy in Japanese patients who were inadequately controlled by sulphonylureas and/or biguanides. Follow-up: 26 weeks. Safety follow-up further 30 days after end of treatment.
Participants	Inclusion criteria • Japanese men and women with type 2 diabetes • Aged ≥20 years • BMI ≥18.5 and <35.0 kg/m^2 • HbA1c at screening ≥7.0 and ≤10.0% • Taking stable doses of sulphonylureas (2.5 to 5 mg of glibenclamide; 60 to 80 mg of glicazide; or 2 to 3 mg of glimepiride) and/or biguanides (750 to 1,500 mg of metformin or 100 to 150 of buformin) Exclusion criteria • Patients with type 1 diabetes • Previously treated with any GLP-1 receptor agonist • Previously treated with an α-glucosidase inhibitor, thiazolidinedione, glinide or dipeptidyl peptidase-4 (DPP-4) inhibitor, or insulin within 3 months before screening • Undergoing chronic systemic glucocorticoid therapy • Patients who had a clinically significant gastric emptying abnormality, cardiovascular disease, liver disease, renal disease, active or untreated malignancy, poorly controlled hypertension, a history of chronic or acute pancreatitis, obvious clinical signs or symptoms of pancreatitis, or a self or family history of medullary C-cell hyperplasia, focal hyperplasia or medullary thyroid carcinoma.
Patient characteristics	Gender = male 69% (dulaglutide); 74% (insulin glargine) Age = mean (SD) 57.5 years (10.5) (dulaglutide); 56.1 years (11.3) (insulin glargine) BMI = mean (SD) 26.1 kg/m^2 (3.6) (dulaglutide); 25.9 kg/m^2 (3.9) (insulin glargine)

<table>
<tr><td>Bibliographic reference</td><td>Araki E, Inagaki N, Tanizawa Y, et al. (2015) Efficacy and safety of once-weekly dulaglutide in combination with sulphonylurea and/or biguanide compared with once-daily insulin glargine in Japanese patients with type 2 diabetes: a randomized, open-label, phase III, non-inferiority study. Diabetes Obes Metab; 17(10):994-1002.</td></tr>
<tr><td></td><td>Weight = mean (SD) 70.9 kg (13.7) (dulaglutide); 71.1 kg (13.8) (insulin glargine)
Risk of cardiovascular diseases (e.g. previous MI) = participants with cardiovascular disease were excluded.</td></tr>
<tr><td>Intervention</td><td>Intervention: subcutaneous injections of once-weekly dulaglutide 0.75 mg (181 participants)
Background therapy: sulphonylureas and/or biguanides</td></tr>
<tr><td>Comparison</td><td>Comparison: subcutaneous injections of once daily glargine with initial dose between 4.0 and 8.0 IU (180 participants)
Background therapy: sulphonylureas and/or biguanides</td></tr>
<tr><td>Outcome measures</td><td>Cerebral infarction
Acute myocardial infarction</td></tr>
<tr><td>Study dates</td><td>June 2012 to July 2013.</td></tr>
<tr><td>Comments (Risk of bias)</td><td>
<table>
<tr><th>Bias</th><th>Authors judgment</th><th>Support for judgment</th></tr>
<tr><td>Random sequence generation (selection bias)</td><td>Low risk</td><td>Patients were randomised using a computer-generated random sequence with an interactive voice response system.</td></tr>
<tr><td>Allocation concealment (selection bias)</td><td>Low risk</td><td>Patients were randomised using a computer-generated random sequence with an interactive voice response system.</td></tr>
<tr><td>Blinding of participants and researchers (performance bias)</td><td>High risk</td><td>An open-label design was used. Patients, investigators and site staff were not masked to treatment allocation.</td></tr>
<tr><td>Blinding of outcome assessment (detection bias)</td><td>Low risk</td><td>An independent external committee adjudicated deaths and non-fatal cardiovascular adverse events in a masked manner with pre-specified event</td></tr>
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Bibliographic reference	**Araki E, Inagaki N, Tanizawa Y, et al. (2015) Efficacy and safety of once-weekly dulaglutide in combination with sulphonylurea and/or biguanide compared with once-daily insulin glargine in Japanese patients with type 2 diabetes: a randomized, open-label, phase III, non-inferiority study. Diabetes Obes Metab; 17(10):994-1002.**

		criteria based on the preponderance of evidence and clinical knowledge and experience.
Incomplete outcome data (attrition bias)	Low risk	Missing outcome data balanced in numbers across groups with similar reasons for missing outcome data across groups.
Selective reporting (reporting bias)	Low risk	The study protocol is available (NCT01584232) and the outcomes of interest are reported in the pre-specified way.

Bibliographic reference	**Bergenstal R, Wysham C, Macconell L, et al. (2010). Efficacy and safety of exenatide once weekly versus sitagliptin or pioglitazone as an adjunct to metformin for treatment of type 2 diabetes (DURATION-2): a randomised trial. Lancet (London, and England), 376(9739), pp.431-9.**
Study type	Randomised controlled trial
Participants	Inclusion criteria: - Adults aged 18 years or over with type 2 diabetes but otherwise healthy - Had been treated with stable metformin regimen for at least 2 months before screening. - HbA1c of 7.1 to 11% - BMI of 25-45 kg/m^2 Exclusion criteria: - Women who were pregnant.
Patient characteristics	Gender = men: 56% (exenatide), 86% (sitagliptin), 79% (pioglitazone) Age (mean years) = 52 (exenatide), 52 (sitagliptin), 53 (pioglitazone) BMI (kg/m^2 mean) = 32 (exenatide), 32 (sitagliptin), 32 (pioglitazone) Weight (kg mean) = 89 (exenatide), 87 (sitagliptin), 88 (pioglitazone)

<table>
<tr><td>Bibliographic reference</td><td>Bergenstal R, Wysham C, Macconell L, et al. (2010). Efficacy and safety of exenatide once weekly versus sitagliptin or pioglitazone as an adjunct to metformin for treatment of type 2 diabetes (DURATION-2): a randomised trial. Lancet (London, and England), 376(9739), pp.431-9.</td></tr>
<tr><td></td><td>Risk of cardiovascular disease = not reported</td></tr>
<tr><td>Intervention</td><td>Exenatide 2mg/week (160 participants)
Background therapy: metformin</td></tr>
<tr><td>Comparison</td><td>- Sitagliptin 100mg once daily (166 participants)
- Pioglitazone 45mg/day (165 participants)
Background therapy: metformin</td></tr>
<tr><td>Outcome measures</td><td>Cerebrovascular accident
Acute renal failure</td></tr>
<tr><td>Study dates</td><td>January 2008 – August 2008</td></tr>
<tr><td>Comments (Risk of bias)</td><td>
<table>
<tr><th>Bias</th><th>Authors judgment</th><th>Support for judgment</th></tr>
<tr><td>Random sequence generation (selection bias)</td><td>Low risk</td><td>Interactive voice response computer generated system to conceal allocation.</td></tr>
<tr><td>Allocation concealment (selection bias)</td><td>Low risk</td><td>Interactive voice response computer generated system to conceal allocation.</td></tr>
<tr><td>Blinding of participants and researchers (performance bias)</td><td>Low risk</td><td>Double-blinded.</td></tr>
<tr><td>Blinding of outcome assessment (detection bias)</td><td>Low risk</td><td>All patients, study-site staff, investigators and the sponser were masked to treatment allocation.</td></tr>
<tr><td>Incomplete outcome data (attrition bias)</td><td>Low risk</td><td>Missing outcome data balanced in numbers across groups with similar reasons for missing outcome data across groups.</td></tr>
<tr><td>Selective reporting (reporting bias)</td><td>Low risk</td><td>The study protocol is available (NCT00637273) and the</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Bergenstal R, Wysham C, Macconell L, et al. (2010). Efficacy and safety of exenatide once weekly versus sitagliptin or pioglitazone as an adjunct to metformin for treatment of type 2 diabetes (DURATION-2): a randomised trial. Lancet (London, and England), 376(9739), pp.431-9.**
	outcomes of interest are reported in the pre-specified way.

Bibliographic reference	**Blonde L, Jendle J, Gross J, et al. (2015) Once-weekly dulaglutide versus bedtime insulin glargine, both in combination with prandial insulin lispro, in patients with type 2 diabetes (AWARD-4): a randomised, open-label, phase 3, non-inferiority study. Lancet; 385(9982):2057-66.**
Study type	A randomised controlled trial to assess the efficacy and safety of prandial insulin combined with dulaglutide as an alternative to basal-bolus treatment in patients with late-stage type 2 diabetes inadequately controlled with conventional insulin treatment. Follow-up: 52 weeks.
Participants	Inclusion criteria • Age 18 years and older • Receiving one or two stable daily insulin doses (any combination of basal, basal with prandial, or premixed insulin, with or without oral antihyperglycaemia drugs) • HbA1c 7.0% or more (≥53 mmol/mol) and 11.0% or less (≤97 mmol/mol) • BMI 23 to 45 kg/m^2 Exclusion criteria • Not reported
Patient characteristics	Gender = male 54% (dulaglutide 1.5 mg); 50% (dulaglutide 0.75 mg); 56% (insulin glargine) Age = mean (SD) 58.9 years (9.6) (dulaglutide 1.5 mg); 59.3 years (9.0) (dulaglutide 0.75 mg); 59.9 years (9.1) (insulin glargine) BMI = mean (SD) 32.0 kg/m^2 (5.1) (dulaglutide 1.5 mg); 33.1 kg/m^2 (5.2) (dulaglutide 0.75 mg); 32.4 kg/m^2 (5.3) (insulin glargine) Weight = mean (SD) 91.0 kg (18.2) (dulaglutide 1.5 mg); 91.7 kg (18.0) (dulaglutide 0.75 mg); 90.8 kg (18.9) (insulin glargine) Risk of cardiovascular diseases (e.g. previous MI) = not reported.
Intervention	Interventions Once-weekly dulaglutide 1.5 mg and insulin lispro using a dosing algorithm (295 participants)

<table>
<tr><td>Bibliographic reference</td><td>Blonde L, Jendle J, Gross J, et al. (2015) Once-weekly dulaglutide versus bedtime insulin glargine, both in combination with prandial insulin lispro, in patients with type 2 diabetes (AWARD-4): a randomised, open-label, phase 3, non-inferiority study. Lancet; 385(9982):2057-66.</td></tr>
<tr><td></td><td>Once-weekly dulaglutide 0.75 mg and insulin lispro using a dosing algorithm (293 participants)
Background therapy: metformin 1,500 mg per day or more.</td></tr>
<tr><td>Comparison</td><td>Comparison: daily bedtime insulin glargine adjusted to a treat-to-target strategy and insulin lispro using a dosing algorithm (296 participants)
Background therapy: metformin 1,500 mg per day or more.</td></tr>
<tr><td>Outcome measures</td><td>Fatal cardiovascular event</td></tr>
<tr><td>Study dates</td><td>December 2010 to September 2012.</td></tr>
<tr><td>Comments (Risk of bias)</td><td>
<table>
<tr><th>Bias</th><th>Authors judgment</th><th>Support for judgment</th></tr>
<tr><td>Random sequence generation (selection bias)</td><td>Low risk</td><td>Randomisation was done via a computer-generated randomisation sequence with an interactive voice-response system.</td></tr>
<tr><td>Allocation concealment (selection bias)</td><td>Low risk</td><td>Randomisation was done via a computer-generated randomisation sequence with an interactive voice-response system.</td></tr>
<tr><td>Blinding of participants and researchers (performance bias)</td><td>High risk</td><td>Participants and study investigators were not masked to treatment allocation, but were aware of dulaglutide dose assignment.</td></tr>
<tr><td>Blinding of outcome assessment (detection bias)</td><td>Low risk</td><td>Independent committees adjudicated investigator-reported deaths, and pre-specified non-fatal cardiovascular adverse events.</td></tr>
<tr><td>Incomplete outcome data (attrition bias)</td><td>Low risk</td><td>Missing outcome data balanced in numbers across groups with</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Blonde L, Jendle J, Gross J, et al. (2015) Once-weekly dulaglutide versus bedtime insulin glargine, both in combination with prandial insulin lispro, in patients with type 2 diabetes (AWARD-4): a randomised, open-label, phase 3, non-inferiority study. Lancet; 385(9982):2057-66.**

		similar reasons for missing outcome data across groups.
Selective reporting (reporting bias)	Low risk	The study protocol is available (NCT01191268) and the outcomes of interest are reported in the pre-specified way.

Bibliographic reference	**Buse J, Henry R, Han J, et al. (2004). Effects of exenatide (exendin-4) on glycemic control over 30 weeks in sulfonylurea-treated patients with type 2 diabetes. Diabetes Care, 27(11), pp.2628-35.**
Study type	Randomised controlled trial
Participants	Inclusion criteria: - Adults with type 2 diabetes, between 22 – 76 years - Treated with maximally effective dose of a sulfonylurea as monotherapy for at least 3 months before screening - Fasting plasma glucose concentration <240 mg/ dl, BMI 27–45 kg/m^2, - HbA1c 7.1 – 11% - Stable weight for 3 months Exclusion criteria: - Metformin, TZD, meglitinides, a-glucosidase inhibitos, exogenous insulin therapy or weight loss drugs within 3 months prior. - Corticosteroid use - Evidence of clinically significant comorbid conditions
Patient characteristics	Gender: male (%): 62.6% (placebo), 57.4% (exenatide) Age (mean years): 55 (placebo), 56 (exenatide) BMI (kg/m^2 mean): 34 ± 5 (placebo), 33 ± 6 (exenatide) Weight (kg): 99 ± 18 (placebo), 95 ± 18 (exenatide) Risk of cardiovascular disease: not reported

<table>
<tr><td>Bibliographic reference</td><td>Buse J, Henry R, Han J, et al. (2004). Effects of exenatide (exendin-4) on glycemic control over 30 weeks in sulfonylurea-treated patients with type 2 diabetes. Diabetes Care, 27(11), pp.2628-35.</td></tr>
<tr><td>Intervention</td><td>Intervention: Exenatide 10ug twice daily n = 129
Background therapy: sulphonylurea</td></tr>
<tr><td>Comparison</td><td>Intervention: Placebo n = 123
Background therapy: sulfonylurea</td></tr>
<tr><td>Outcome measures</td><td>Myocardial infarction</td></tr>
<tr><td>Study dates</td><td>2002 - 2003</td></tr>
<tr><td>Comments (Risk of bias)</td><td>
<table>
<tr><td>Bias</td><td>Authors judgment</td><td>Support for judgment</td></tr>
<tr><td>Random sequence generation (selection bias)</td><td>Unclear risk</td><td>Randomization was stratified according to screening HbA1c values. Method of randomisation (i.e. computer generated) unclear.</td></tr>
<tr><td>Allocation concealment (selection bias)</td><td>Unclear risk</td><td>Allocation concealment not reported.</td></tr>
<tr><td>Blinding of participants and researchers (performance bias)</td><td>High risk</td><td>Single blinded.</td></tr>
<tr><td>Blinding of outcome assessment (detection bias)</td><td>Unclear risk</td><td>Unclear if outcome assessment is blinded.</td></tr>
<tr><td>Incomplete outcome data (attrition bias)</td><td>Low risk</td><td>Missing outcome data balanced in numbers across groups with similar reasons for missing outcome data across groups.</td></tr>
<tr><td>Selective reporting (reporting bias)</td><td>Unclear risk</td><td>Study protocol could not be found.</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Buse J, Bergenstal R, Glass L C, et al (2011). Use of twice-daily exenatide in Basal insulin-treated patients with type 2 diabetes: a randomized, controlled trial. Annals of Internal Medicine, 154(2), pp.103-12.**
Study type	Randomised controlled trial, 59 centers in: Greece, Israel, Mexico, UK and US.
Participants	Inclusion criteria: - Adults with type 2 diabetes, at least 18 years of age - Insulin glargine at a maximum of 20 U/d alone or in combination with metformin or pioglitazone for at least 3 months - HbA1c level of 7.1% – 10.5% and stable body weight Exclusion criteria: - Clinically significant haematologic disease - In weight loss program in the 3 months prior to the study - Received systemic glucocorticosteriod therapy in the 8 weeks priori to the study - Had more than 1 episode of major hypoglycaemia in 6 months prior to the study - Had irregular sleep-wake cycle - History of pancreatitis
Patient characteristics	Gender: male (%): 51% (exenatide), 64% (placebo) Age (mean years): 59 (exenatide), 59 (placebo) BMI (kg/m^2 mean): 33.8 (exenatide), 33.1 (placebo) Weight (kg): 95.4 (exenatide), 93.4 (placebo) Risk of cardiovascular disease: not reported
Intervention	Intervention: Exenatide 10ug twice daily n = 137 Background therapy: insulin glargine
Comparison	Placebo n - 122 Background therapy: insulin glargine
Outcome measures	Cardiovascular mortality (due to myocardial infarction)
Study dates	2008 - 2010
Comments (Risk of bias)	Bias | Authors judgment | Support for judgment

Bibliographic reference	Buse J, Bergenstal R, Glass L C, et al (2011). Use of twice-daily exenatide in Basal insulin-treated patients with type 2 diabetes: a randomized, controlled trial. Annals of Internal Medicine, 154(2), pp.103-12.		
	Random sequence generation (selection bias)	Low risk	A computer generated, random sequence interactive voice-response system was used to assign participants in blocks of 4, stratified by HbA1c level.
	Allocation concealment (selection bias)	Unclear	Allocation concealment not reported.
	Blinding of participants and researchers (performance bias)	Low risk	Participants, investigators and other personnel involved in the conduct of the study were blinded to individual treatment assignments for the duration of the study.
	Blinding of outcome assessment (detection bias)	Low risk	Participants, investigators and other personnel involved in the conduct of the study were blinded to individual treatment assignments for the duration of the study.
	Incomplete outcome data (attrition bias)	Low risk	Missing outcome data balanced in numbers across groups with similar reasons for missing outcome data across groups.
	Selective reporting (reporting bias)	Low risk	The study protocol is available (NCT00765817) and the outcomes of interest are reported in the pre-specified way.

Bibliographic reference	**Buse J, Nauck M, Forst T, et al. (2013). Exenatide once weekly versus liraglutide once daily in patients with type 2 diabetes (DURATION-6): a randomised, open-label study. Lancet (London, and England), 381(9861), pp.117-24.**
Study type	Randomised controlled trial Follow-up: 26 weeks
Participants	Inclusion criteria: - Adults with type 2 diabetes, at least 18 years of age - Suboptimum glycaemic control despite lifestyle modification (diet and exercise) - Maximum or near maximum dose of oral antihyperglycaemic drugs (metformin, sulfonylurea, metformin, metformin plus pioglitazone) - HbA1c between 7.1% and 11% (54 mmol/mol to 97 mmol/mol) - BMI of 45 kg/m^2 or less - Stable bodyweight for at least 3 months Exclusion criteria: - Active cardiac disease within 3 months of screening - Inflammatory bowel disease or other sever gastrointestinal disease - Medulla carcinoma or multiple endocrine neoplasm type2 syndrome - Liver or renal disease - Creatinine clearance less than 60 mL/min - Active or untreated malignancy - Acute or chronic anaemia - 2 or more episodes of major hyperglycaemia within 6 months - Use of excluded drugs(insulin, a-glucosidase inhibitors, meglitinides, DPP-4 inhibitors, GLP-1 receptor agonists or rosiglitazone)
Patient characteristics	Gender: male (%): 55% (exenatide), 54% (liraglutide) Age (mean years): 57 (exenatide), 57 (liraglutide) BMI (kg/m^2 mean): 32.3 (exenatide), 32.3 (liraglutide) Weight (kg): 90.9 (exenatide), 91.9 (liraglutide) Risk of cardiovascular disease: not reported
Intervention	Intervention: Exenatide 2mg/week (461 participants)

<table>
<tr><td>Bibliographic reference</td><td>Buse J, Nauck M, Forst T, et al. (2013). Exenatide once weekly versus liraglutide once daily in patients with type 2 diabetes (DURATION-6): a randomised, open-label study. Lancet (London, and England), 381(9861), pp.117-24.</td></tr>
<tr><td></td><td>Background therapy: oral antihyperglycaemic (metformin, sulfonylurea, metformin plus sulfonylurea or metformin plus pioglitazone)</td></tr>
<tr><td>Comparison</td><td>Liraglutide 1.8 mg/day (450 participants)
Background therapy: oral antihyperglycaemic (metformin, sulfonylurea, metformin plus sulfonylurea or metformin plus pioglitazone)</td></tr>
<tr><td>Outcome measures</td><td>Myocardial infarction
Brain stem infarction</td></tr>
<tr><td>Study dates</td><td>January 2010 – January 2011</td></tr>
<tr><td>Comments (Risk of bias)</td><td>
<table>
<tr><td>Bias</td><td>Authors judgment</td><td>Support for judgment</td></tr>
<tr><td>Random sequence generation (selection bias)</td><td>Low risk</td><td>Computer generated interactive voice response system,</td></tr>
<tr><td>Allocation concealment (selection bias)</td><td>Unclear risk</td><td>Not reported.</td></tr>
<tr><td>Blinding of participants and researchers (performance bias)</td><td>High risk</td><td>Open-labelled.</td></tr>
<tr><td>Blinding of outcome assessment (detection bias)</td><td>Unclear risk</td><td>Not reported.</td></tr>
<tr><td>Incomplete outcome data (attrition bias)</td><td>Low risk</td><td>Missing outcome data balanced in numbers across groups with similar reasons for missing outcome data across groups.</td></tr>
<tr><td>Selective reporting (reporting bias)</td><td>Low risk</td><td>The study protocol is available (NCT01029886) and the outcomes of interest are reported in the pre-specified way.</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**D'Alessio D, Haring H, Charbonnel B, et al. (2015). Comparison of insulin glargine and liraglutide added to oral agents in patients with poorly controlled type 2 diabetes. Diabetes, and Obesity & Metabolism, 17(2), pp.170-8.**
Study type	Randomised controlled trial
Participants	Inclusion criteria: - Men and women aged 35 – 75 years with a diagnosis of type 2 diabetes for at least 1 year. - HbA1c level >7.5 and ≤12% (>58 and ≤108mmol/mol) - body mass index between 25 and 40 kg/m^2. - Taking metformin at a minimum dose of 1 g/day, alone or in combination with sulphonylurea, glinides or a dipeptidyl peptidase-4 inhibitor for > 3 months. Exclusion criteria: - Those treated with GLP-1 receptor agonists or insulin in the previous year, or with thiazolidinediones or α-glucosidase inhibitors in the previous 3 months. - Impaired renal (estimated glomerular filtration rate<60 ml/min) or hepatic (alanine aminotransferase/ aspartate aminotransferase >2.5 × upper limit of normal) function. - Any condition that investigators felt would compromise the patient's safety or participation in the study.
Patient characteristics	Gender: women – 44% (liraglutide), 47.3 (insulin glargine) Age (mean years): 57.4 (liraglutide), 57.1 (insulin glargine) BMI (mean kg/m^2): 31.8 (liraglutide), 32(insulin glargine) Weight (mean kg): 90.1 (liraglutide), 90.8 (insulin glargine) Risk of cardiovascular disease: previous myocardial infarction – 4%(liraglutide), 4% (insulin glargine)
Intervention	Liraglutide 1.8 mg/day (481 participants) Background treatment: Metformin at a minimum dose of 1g/day alone or in combination with suphonylurea and lifestyle programme. Sulphonylurea reduced or discontinued at start of trial.
Comparison	Insulin glargine, instructed on a titration schedule, adjusted every 3 days, to attain fasting plasma glucose levels of ≥4.0 and ≤5.5mmol/l (484 participants) Background treatment: Metformin at a minimum dose of 1g/day alone or in combination with suphonylurea and lifestyle programme. Sulphonylurea reduced or discontinued at start of trial.
Outcome measures	Cerebrovascular accidence Ischaemic stroke Chronic cardiac failure

<table>
<tr><td>Bibliographic reference</td><td>D'Alessio D, Haring H, Charbonnel B, et al. (2015). Comparison of insulin glargine and liraglutide added to oral agents in patients with poorly controlled type 2 diabetes. Diabetes, and Obesity & Metabolism, 17(2), pp.170-8.</td></tr>
<tr><td>Study dates</td><td>August 2010 to October 2012</td></tr>
<tr><td>Comments (Risk of bias)</td><td>
<table>
<tr><td>Bias</td><td>Authors judgment</td><td>Support for judgment</td></tr>
<tr><td>Random sequence generation (selection bias)</td><td>Unclear risk</td><td>Method of random sequence generation not reported.</td></tr>
<tr><td>Allocation concealment (selection bias)</td><td>High risk</td><td>Neither participants nor investigators were masked to group assignment.</td></tr>
<tr><td>Blinding of participants and researchers (performance bias)</td><td>High risk</td><td>Open-labelled.</td></tr>
<tr><td>Blinding of outcome assessment (detection bias)</td><td>Unclear risk</td><td>Blinding of outcome assessment not reported.</td></tr>
<tr><td>Incomplete outcome data (attrition bias)</td><td>High risk</td><td>Completion rate was higher with insulin glargine than liraglutide.</td></tr>
<tr><td>Selective reporting (reporting bias)</td><td>Low risk</td><td>Protocol not available but all specified outcomes were reported.</td></tr>
</table>
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Bibliographic reference	**Davies M, Bain S, Atkin S, et al. (2016). Efficacy and Safety of Liraglutide Versus Placebo as Add-on to Glucose-Lowering Therapy in Patients With Type 2 Diabetes and Moderate Renal Impairment (LIRA-RENAL): A Randomized Clinical Trial. Diabetes Care, 39(2), pp.222-30.**
Study type	Randomised controlled trial
Participants	Inclusion criteria: • Adults aged 18–80 years with T2D • had HbA1c 7–10% (53–86 mmol/mol) • on stable diabetes treatment for .90 days before screening. Exclusion criteria

<table>
<tr><td>Bibliographic reference</td><td>Davies M, Bain S, Atkin S, et al. (2016). Efficacy and Safety of Liraglutide Versus Placebo as Add-on to Glucose-Lowering Therapy in Patients With Type 2 Diabetes and Moderate Renal Impairment (LIRA-RENAL): A Randomized Clinical Trial. Diabetes Care, 39(2), pp.222-30.</td></tr>
<tr><td></td><td>• hypoglycemic unawareness and/or recurrent severe hypoglycaemia as judged by the investigator
• impaired liver function
• history of chronic pancreatitis or idiopathic acute pancreatitis
• New York Heart Association Functional Classification IV heart failure; episode of unstable angina, acute coronary event, cerebral stroke/transient ischemic attack, or other significant cardiovascular event within the past 180 days
• Systolic blood pressure (SBP) ≥180 mmHg or diastolic blood pressure (DBP) ≤100 mmHg
• A screening calcitonin value ≥50 ng/L
• Personal or family history ofmedullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2.</td></tr>
<tr><td>Patient characteristics</td><td>Gender, males = 53% (liraglutide), 47% (placebo)
Age, mean years= 68 (liraglutide), 66 (placebo)
BMI, mean kg/m^2 = 33.4 (liraglutide), 34.5 (placebo)
Weight mean kg= 93.6 (liraglutide), 95.6 (placebo)
Risk of cardiovascular diseases (e.g. previous MI) = not reported.</td></tr>
<tr><td>Intervention</td><td>Interventions: Liraglutide 1.8 mg/day n = 140
Background therapy: monotherapy or dual-therapy combinations of metformin and/or SU and/or pioglitazone, monotherapy with basal or premix insulin, or any combination of basal or premix insulin with metformin and/or pioglitazone.</td></tr>
<tr><td>Comparison</td><td>Comparison: Insulin glargine n = 139
Background therapy: monotherapy or dual-therapy combinations of metformin and/or SU and/or pioglitazone, monotherapy with basal or premix insulin, or any combination of basal or premix insulin with metformin and/or pioglitazone.</td></tr>
<tr><td>Outcome measures</td><td>Cardiovascular mortality</td></tr>
<tr><td>Study dates</td><td>June 2006 to January 2008</td></tr>
<tr><td>Comments (Risk of bias)</td><td>
<table>
<tr><td>Bias</td><td>Authors judgment</td><td>Support for judgment</td></tr>
<tr><td>Random sequence generation (selection bias)</td><td>Low risk</td><td>Telephone or web-based randomization system</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Davies M, Bain S, Atkin S, et al. (2016). Efficacy and Safety of Liraglutide Versus Placebo as Add-on to Glucose-Lowering Therapy in Patients With Type 2 Diabetes and Moderate Renal Impairment (LIRA-RENAL): A Randomized Clinical Trial. Diabetes Care, 39(2), pp.222-30.**

Allocation concealment (selection bias)	Low risk	Trial site personnel, patients, and the sponsor remained blinded until trial completion.
Blinding of participants and researchers (performance bias)	Low risk	Trial site personnel, patients, and the sponsor remained blinded until trial completion.
Blinding of outcome assessment (detection bias)	Low risk	Trial site personnel, patients, and the sponsor remained blinded until trial completion.
Incomplete outcome data (attrition bias)	Low risk	Missing outcome data balanced in numbers across groups with similar reasons for missing outcome data across groups.
Selective reporting (reporting bias)	High risk	The study protocol is available (NCT01620489) and the outcomes of interest are reported in the pre-specified way.

Bibliographic reference	**Davies MJ, Bergenstal R, Bode B, et al. (2015) Efficacy of Liraglutide for Weight Loss Among Patients With Type 2 Diabetes: The SCALE Diabetes Randomized Clinical Trial. JAMA; 314(7):687-99.**
Study type	Randomised controlled trial to investigate the efficacy and safety of liraglutide, as an adjunct to diet and exercise, for weight management in adults with overweight or obesity and type 2 diabetes. Follow-up: 56 weeks. Treatment cessation effects were assessed at a 12-week observational off-drug follow-up period (total study length was 68 weeks).
Participants	Inclusion criteria • Adults with overweight or obesity (BMI ≥27 kg/m^2) • Adults (age ≥18 years) with a stable body weight (<5kg change in the last 3 months) • Diagnosed of type 2 diabetes (HbA1c 7.0% to 10.0%)

Bibliographic reference	**Davies MJ, Bergenstal R, Bode B, et al. (2015) Efficacy of Liraglutide for Weight Loss Among Patients With Type 2 Diabetes: The SCALE Diabetes Randomized Clinical Trial. JAMA; 314(7):687-99.**
	• Treated with diet and exercise alone or in combination with 1 to 3 oral hypoglycaemic agents (metformin, thiazolidinedione, sulfonylurea) Exclusion criteria • Treatment with GLP-1, DPP-4 inhibitors, insulin, or any other hypoglycaemic agent other than metformin, thiazolidinedione and sulfonylurea within the last 3 months • Known proliferative retinopathy or maculopathy requiring acute treatment, as judged by the investigator • Supplement 1 includes a longer list of exclusion criteria.
Patient characteristics	Gender = male 52.0% (liraglutide 3.0 mg); 51.2% (liraglutide 1.8 mg); 45.8% (placebo) Age = mean (SD) 55.0 years (10.8) (liraglutide 3.0 mg); 54.9 years (10.7) (liraglutide 1.8 mg); 54.7 years (9.8) (placebo) BMI = mean (SD) 37.1 kg/m^2 (6.5) (liraglutide 3.0 mg); 37.0 kg/m^2 (6.9) (liraglutide 1.8 mg); 37.4 kg/m^2 (7.1) (placebo) Weight = mean (SD) 105.7 kg (21.9) (liraglutide 3.0 mg); 105.8 kg (21.0) (liraglutide 1.8 mg); 106.5 kg (21.3) (placebo) Risk of cardiovascular diseases (e.g. previous MI) = cardiovascular disease* at screening 16.4% (liraglutide 3.0 mg); 14.8% (liraglutide 1.8 mg); 12.3% (placebo) *Cardiovascular disease defined as ischemic heart disease, cardiac failure and central nervous system haemorrhages, and cerebrovascular conditions and embolic and thrombotic events based on a predefined search on Standard MedDRA Queries (further information see eTable 2 in Supplement 1 of Davies et al. [2015]).
Intervention	Interventions: Once-daily subcutaneous liraglutide 3.0 mg (423 participants) Once-daily subcutaneous liraglutide 1.8 mg (211 participants) Background therapy: 500 kcal/d dietary deficit and increased physical activity (≥150 min/wk).
Comparison	Comparison: once-daily placebo (212 participants) Background therapy: 500 kcal/d dietary deficit and increased physical activity (≥150 min/wk).
Outcome measures	Cerebrovascular event Heart failure Renal failure
Study dates	June 2011 to January 2013

Bibliographic reference	Davies MJ, Bergenstal R, Bode B, et al. (2015) Efficacy of Liraglutide for Weight Loss Among Patients With Type 2 Diabetes: The SCALE Diabetes Randomized Clinical Trial. JAMA; 314(7):687-99.

Comments (Risk of bias)

Bias	Authors judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Treatments were allocated in a centralised manner via an interactive voice/web response system.
Allocation concealment (selection bias)	Low risk	Treatments were allocated in a centralised manner.
Blinding of participants and researchers (performance bias)	Unclear risk	Although participants were randomly assigned in a blinded fashion and trial drug was administered using a modified insulin pen device, it is unclear whether key study personnel was blinded.
Blinding of outcome assessment (detection bias)	Low risk	Unclear if there was blinding of outcome assessment but cardiovascular and microvascular outcomes are not likely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias)	High risk	Reasons for missing outcome data were imbalance between placebo and active treatments.
Selective reporting (reporting bias)	High risk	The study protocol is available (NCT01272232) but safety outcomes are not mentioned.

Bibliographic reference	**Davies M, Donnelly R, Barnett A, et al. (2009). Exenatide compared with long-acting insulin to achieve glycaemic control with minimal weight gain in patients with type 2 diabetes: results of the Helping Evaluate Exenatide in patients with diabetes compared with Long-Acting insulin (HEELA) study. Diabetes, and Obesity & Metabolism, 11(12), pp.1153-62.**
Study type	Randomised controlled trial Follow-up: 26 weeks
Participants	Inclusion criteria: • Type 2 diabetes • BMI > 27 kg/m^2 • Inadequate glycaemic control (HbA1c 7.5–10.0%), despite treatment with stable doses of two or three OADs (metformin, sulphonylurea and thiazolidinedione) for at least 3 months before randomization. • Patients had at least 1 cardiocascular risk factor, defined as either a previous cardiovascular event, peripheral vascular disease, or an abnormal risk factor. Exclusion criteria • history of malignancy • Class III or IV heart disease • uncontrolled hypertension (systolic BP ≥180 mmHg, diastolic BP ≥105 mmHg), • renal transplantation or dialysis, chronic renal impairment • liver disease
Patient characteristics	Gender, males = 70% (exenatide) 66% (insulin) Age = 56.8 (exenatide) 56.2 (insulin) BMI, mean kg/m^2 = 34.6 (exenatide) 33.7 (insulin) Weight, mean kg = 101.4 (exenatide) 97.6 (insulin) Risk of cardiovascular diseases (e.g. previous MI) = not reported, majority of patients had hypertention
Intervention	Interventions: exenatide 10ug twice daily n = 118 Background therapy: two or more of: metformin, sulphonylurea and thiazolidinedione
Comparison	Comparison: Insulin glargine n = 116 Background therapy: two or more of: metformin, sulphonylurea and thiazolidinedione

<table>
<tr><td>Bibliographic reference</td><td>Davies M, Donnelly R, Barnett A, et al. (2009). Exenatide compared with long-acting insulin to achieve glycaemic control with minimal weight gain in patients with type 2 diabetes: results of the Helping Evaluate Exenatide in patients with diabetes compared with Long-Acting insulin (HEELA) study. Diabetes, and Obesity & Metabolism, 11(12), pp.1153-62.</td></tr>
<tr><td>Outcome measures</td><td>Acute myocardial infarction
Acute renal failure</td></tr>
<tr><td>Study dates</td><td>June 2011 to January 2013</td></tr>
<tr><td>Comments (Risk of bias)</td><td>
<table>
<tr><th>Bias</th><th>Authors judgment</th><th>Support for judgment</th></tr>
<tr><td>Random sequence generation (selection bias)</td><td>Unclear risk</td><td>Method of randomisation not reported.</td></tr>
<tr><td>Allocation concealment (selection bias)</td><td>Unclear risk</td><td>Not reported.</td></tr>
<tr><td>Blinding of participants and researchers (performance bias)</td><td>High risk</td><td>Open labelled.</td></tr>
<tr><td>Blinding of outcome assessment (detection bias)</td><td>High risk</td><td>Open labelled.</td></tr>
<tr><td>Incomplete outcome data (attrition bias)</td><td>Low risk</td><td>Missing outcome data balanced in numbers acs groups with similar reasons for missing outcome data across groups.</td></tr>
<tr><td>Selective reporting (reporting bias)</td><td>Unclear risk</td><td>Unclear if protocol was pre-specified.</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td>de Wit HM, Vervoort GM, Jansen HJ, et al. (2016) Durable efficacy of liraglutide in patients with type 2 diabetes and pronounced insulin-associated weight gain: 52-week results from the Effect of Liraglutide on insulin-associated wEight GAiN in patients with Type 2 diabetes' (ELEGANT) randomized controlled trial. J Intern Med; 279(3):283-92.</td></tr>
<tr><td>Study type</td><td>A randomised controlled trial to investigate whether the beneficial effects of liraglutide were sustained up to 52 weeks and whether similar effects could be obtained when liraglutide is added to insulin 6 months later.
Follow-up 52 weeks.</td></tr>
<tr><td>Participants</td><td>Inclusion criteria</td></tr>
</table>

Bibliographic reference	**de Wit HM, Vervoort GM, Jansen HJ, et al. (2016) Durable efficacy of liraglutide in patients with type 2 diabetes and pronounced insulin-associated weight gain: 52-week results from the Effect of Liraglutide on insulin-associated wEight GAiN in patients with Type 2 diabetes' (ELEGANT) randomized controlled trial. J Intern Med; 279(3):283-92.**
	• Adult people with type 2 diabetes • BMI ≥25 kg/m^2 • HbA1c between 6.5% and 8.5% • Recent insulin therapy (between 3 and 16 months, all types and regimens allowed) • Body weight gain ≥4% since start of insulin treatment Exclusion criteria* • Recurrent hypoglycaemia • Diabetic gastroparesis • Use of oral glucose-lowering agents or drugs known to interfere with blood glucose levels other than sulfonylurea or metformin • Recent start of diuretics • Heart failure • Inflammatory bowel disease • Recent history of pancreatitis • Uncontrolled thyroid disease • Liver enzymes ≥3.0 times upper normal limit • Plasma creatinine >130 µmol/l • Pregnancy * From de Wit HM, Vervoort GM, Jansen HJ, et al. (2014) Liraglutide reverses pronounced insulin-associated weight gain, improves glycaemic control and decreases insulin dose in patients with type 2 diabetes: a 26 week, randomised clinical trial (ELEGANT). Diabetologia; 57(9):1812-9
Patient characteristics	Gender = male 61.5% (liraglutide); 62.5% (insulin) Age = mean (SD) 57 years (10) (liraglutide); 59 years (8) (insulin) BMI = mean (SD) 34 kg/m^2 (7) (liraglutide); 32 kg/m^2 (5) (insulin) Weight = mean (SD) 102.3 kg (20.1) (liraglutide); 97.7 kg (18.5) (insulin) Risk of cardiovascular diseases (e.g. previous MI) = not reported.
Intervention	Intervention: liraglutide up to 1.8 mg added to insulin (26 participants)

<table>
<tr><td>Bibliographic reference</td><td>de Wit HM, Vervoort GM, Jansen HJ, et al. (2016) Durable efficacy of liraglutide in patients with type 2 diabetes and pronounced insulin-associated weight gain: 52-week results from the Effect of Liraglutide on insulin-associated wEight GAiN in patients with Type 2 diabetes' (ELEGANT) randomized controlled trial. J Intern Med; 279(3):283-92.</td></tr>
<tr><td></td><td>Background therapy: glucose-lowering treatment (only metformin and sulfonylurea were allowed)</td></tr>
<tr><td>Comparison</td><td>Comparison: insulin (dose adjusted to fasting glucose target of 4.0 to 6.5 mmol L^{-1}) without liraglutide (24 participants)
Background therapy:</td></tr>
<tr><td>Outcome measures</td><td>Myocardial infarction</td></tr>
<tr><td>Study dates</td><td>February 2012 to April 2014.</td></tr>
<tr><td>Comments (Risk of bias)</td><td>
<table>
<tr><th>Bias</th><th>Authors judgment</th><th>Support for judgment</th></tr>
<tr><td>Random sequence generation (selection bias)</td><td>Low risk</td><td>Randomisation was performed using a computer-generated random number list.*</td></tr>
<tr><td>Allocation concealment (selection bias)</td><td>Unclear risk</td><td>Randomisation was used but further description of allocation was not included.</td></tr>
<tr><td>Blinding of participants and researchers (performance bias)</td><td>High risk</td><td>Open-label trial.</td></tr>
<tr><td>Blinding of outcome assessment (detection bias)</td><td>Low risk</td><td>Unclear if there was blinding of outcome assessment but cardiovascular and microvascular outcomes are not likely to be influenced by lack of blinding.</td></tr>
<tr><td>Incomplete outcome data (attrition bias)</td><td>Low risk</td><td>Missing outcome data balanced in numbers acs groups with similar reasons for missing outcome data across groups.</td></tr>
<tr><td>Selective reporting (reporting bias)</td><td>Low risk</td><td>The study protocol is available (NCT01392898) and the outcomes of interest are reported in the pre-specified way.</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Diamant M, Van Gaal L, Stranks S, et al. (2010) Once weekly exenatide compared with insulin glargine titrated to target in patients with type 2 diabetes (DURATION-3): an open-label randomised trial. Lancet; 375(9733):2234-43.** **Diamant M, Gaal L, Guerci B, et al. (2014). Exenatide once weekly versus insulin glargine for type 2 diabetes (DURATION-3): 3-year results of an open-label randomised trial. The lancet. Diabetes & endocrinology, 2(6), pp.464-73.**
Study type	Randomised controlled trial to test the hypothesis that improvement in HbA1c achieved with once-weekly exenatide was better than that achieved with the existing standard second-line treatment for patients not responding to oral blood-glucose-lowering agents, insulin glargine titrated to glucose targets. Follow-up: 26 weeks.
Participants	Inclusion criteria • Adults • HbA1c 7.1% to 11.0% • BMI 25 kg/m^2 to 45 kg/m^2 • Stable bodyweight for 3 months or more • Being treated with a stable dose of metformin of 1,500 mg or more per day for 8 or more weeks before screening Exclusion criteria • More than 3 episodes of major hypoglycaemia within 6 months of screening • Treatment within 4 weeks of screening with systemic glucocorticoids • Treatment for longer than 2 weeks with insulin, thiazolidinediones, α-glucosidase inhibitors meglitinides, exenatide twice-a-day formulation, DPP-4 inhibitors, or pramlintide acetate within 3 months of screening • Prescription and non-prescription weight-loss drugs were excluded within 3 months of screening and during the entire 26-week study.
Patient characteristics	Gender = male 52.0% (exenatide); 55.0% (insulin glargine) Age = mean (SD) 58 years (10) (exenatide); 58 years (9) (insulin glargine) BMI = mean (SD) 32 kg/m^2 (5) (exenatide); 32 kg/m^2 (5) (insulin glargine) Weight = mean (SD) 91.2 kg (18.6) (exenatide); 90.6 kg (16.4) (insulin glargine) Risk of cardiovascular diseases (e.g. previous MI) = not reported
Intervention	Intervention: once weekly exenatide 2 mg injected into abdominal subcutaneous tissue (233 participants)

<table>
<tr><td>Bibliographic reference</td><td>Diamant M, Van Gaal L, Stranks S, et al. (2010) Once weekly exenatide compared with insulin glargine titrated to target in patients with type 2 diabetes (DURATION-3): an open-label randomised trial. Lancet; 375(9733):2234-43.

Diamant M, Gaal L, Guerci B, et al. (2014). Exenatide once weekly versus insulin glargine for type 2 diabetes (DURATION-3): 3-year results of an open-label randomised trial. The lancet. Diabetes & endocrinology, 2(6), pp.464-73.</td></tr>
<tr><td></td><td>Background therapy: metformin with or without sulfonylurea</td></tr>
<tr><td>Comparison</td><td>Comparison: once daily insulin glargine starting at 10 IU per day and adjusted to achieve target glucose of 4.0 to 5.5 mmol/L (223 participants)
Background therapy: metformin with or without sulfonylurea</td></tr>
<tr><td>Outcome measures</td><td>Cerebrovascular accident
Mortality (zero events)
Myocardial infarction – reported in Diamant 2014</td></tr>
<tr><td>Study dates</td><td>May 2008 to May 2009.</td></tr>
<tr><td>Comments (Risk of bias)</td><td>
<table>
<tr><td>Bias</td><td>Authors judgment</td><td>Support for judgment</td></tr>
<tr><td>Random sequence generation (selection bias)</td><td>Low risk</td><td>Random assignment was done with a computer-generated randomisation sequence via an automated voice-response system.</td></tr>
<tr><td>Allocation concealment (selection bias)</td><td>Low risk</td><td>Randomisation was administered by the sponsor via an automated voice-response system.</td></tr>
<tr><td>Blinding of participants and researchers (performance bias)</td><td>High risk</td><td>Study participants and clinical investigators were not masked to treatment assignment, but investigators analysing data were.</td></tr>
<tr><td>Blinding of outcome assessment (detection bias)</td><td>Low risk</td><td>Unclear if there was blinding of outcome assessment but cardiovascular and microvascular</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Diamant M, Van Gaal L, Stranks S, et al. (2010) Once weekly exenatide compared with insulin glargine titrated to target in patients with type 2 diabetes (DURATION-3): an open-label randomised trial. Lancet; 375(9733):2234-43.** **Diamant M, Gaal L, Guerci B, et al. (2014). Exenatide once weekly versus insulin glargine for type 2 diabetes (DURATION-3): 3-year results of an open-label randomised trial. The lancet. Diabetes & endocrinology, 2(6), pp.464-73.**

		outcomes are not likely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias)	High risk	There was imbalance in numbers and reasons for missing outcome data across groups.
Selective reporting (reporting bias)	High risk	The study protocol is available (NCT00641056) and the outcomes of interest are reported in the pre-specified way.

Bibliographic reference	**Dungan K, Povedano S, Forst T, et al. (2014) Once-weekly dulaglutide versus once-daily liraglutide in metformin-treated patients with type 2 diabetes (AWARD-6): a randomised, open-label, phase 3, non-inferiority trial. Lancet; 384(9951):1349-57.**
Study type	A randomised controlled trial to assess the non-inferiority of once-weekly dulaglutide compared with once-daily liraglutide in patients with type 2 diabetes receiving concomitant metformin therapy. Follow-up: 26 weeks. Safety data were collected for a further 4 weeks' follow-up.
Participants	Inclusion criteria • Type 2 diabetes at screening (HbA1c ≥7.0% [≥53 mmol/mol] and ≤10.0% [≤86 mmol/mol]) • 18 years or older • Body mass index (BMI) of 45 kg/m^2 or less • Receiving a stable dose of metformin (≥1500 mg/day) for 3 months or longer Exclusion criteria • Use of other antihyperglycaemic drugs

<table>
<tr><td>Bibliographic reference</td><td>Dungan K, Povedano S, Forst T, et al. (2014) Once-weekly dulaglutide versus once-daily liraglutide in metformin-treated patients with type 2 diabetes (AWARD-6): a randomised, open-label, phase 3, non-inferiority trial. Lancet; 384(9951):1349-57.</td></tr>
<tr><td></td><td>• Serum calcitonin concentration of 5.79 pmol/L or higher
• Serum creatinine concentration of 132.6 µmol/L or higher (men) or 123.8 µmol/L or higher (women)
• Creatinine clearance of less than 60 mL/min
• History of pancreatitis
• Recent cardiovascular event
Full inclusion and exclusion criteria can be found in the appendix of Dungan et al. (2014).</td></tr>
<tr><td>Patient characteristics</td><td>Gender = male 46.0% (dulaglutide); 50.0% (liraglutide)
Age = mean (SD) 56.5 years (9.3) (dulaglutide); 56.8 years (9.9) (liraglutide)
BMI = mean (SD) 33.5 kg/m^2 (5.1) (dulaglutide); 33.6 kg/m^2 (5.2) (liraglutide)
Weight = mean (SD) 93.8 kg (18.2) (dulaglutide); 94.4 kg (19.0) (liraglutide)
Risk of cardiovascular diseases (e.g. previous MI) = participants with a recent cardiovascular event were excluded.</td></tr>
<tr><td>Intervention</td><td>Intervention: subcutaneous injections of once-weekly dulaglutide 1.5 mg (299 participants)
Background therapy: metformin ≥1500 mg/day up to the highest dose allowed per local label</td></tr>
<tr><td>Comparison</td><td>Comparison: subcutaneous injections of once-daily liraglutide 1.8 mg (300 participants)
Background therapy: metformin ≥1500 mg/day up to the highest dose allowed per local label</td></tr>
<tr><td>Outcome measures</td><td>Myocardial infarction
Mortality</td></tr>
<tr><td>Study dates</td><td>June 2012 to November 2013</td></tr>
<tr><td>Comments (Risk of bias)</td><td>
<table>
<tr><td>Bias</td><td>Authors judgment</td><td>Support for judgment</td></tr>
<tr><td>Random sequence generation (selection bias)</td><td>Low risk</td><td>Participants were randomised with a computer-generated random sequence using an interactive voice response system.</td></tr>
<tr><td>Allocation concealment (selection bias)</td><td>Low risk</td><td>The study statistician and medical personnel from the sponsor were masked to the treatment allocation until after</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Dungan K, Povedano S, Forst T, et al. (2014) Once-weekly dulaglutide versus once-daily liraglutide in metformin-treated patients with type 2 diabetes (AWARD-6): a randomised, open-label, phase 3, non-inferiority trial. Lancet; 384(9951):1349-57.**

		database lock and analyses were completed.
Blinding of participants and researchers (performance bias)	High risk	An open-label design was used and participants, treating physicians, investigators, and site staff were not masked to treatment allocation.
Blinding of outcome assessment (detection bias)	Low risk	An independent external committee adjudicated deaths and non-fatal cardiovascular adverse events in a masked manner, with prespecified event criteria based on the preponderance of the evidence and clinical knowledge and experience.
Incomplete outcome data (attrition bias)	Low risk	Missing outcome data balanced in numbers across groups with similar reasons for missing outcome data across groups.
Selective reporting (reporting bias)	Low risk	The study protocol is available (NCT01624259) and the outcomes of interest are reported in the pre-specified way.

Bibliographic reference	**Dungan K M, Weitgasser R, Perez Mi, et al. (2016). A 24-week study to evaluate the efficacy and safety of once-weekly dulaglutide added on to glimepiride in type 2 diabetes (AWARD-8). Diabetes, and Obesity & Metabolism, 18(5), pp.475-82.**
Study type	A randomised controlled trial
Participants	Inclusion criteria

<table>
<tr><td>Bibliographic reference</td><td>Dungan K M, Weitgasser R, Perez Mi, et al. (2016). A 24-week study to evaluate the efficacy and safety of once-weekly dulaglutide added on to glimepiride in type 2 diabetes (AWARD-8). Diabetes, and Obesity & Metabolism, 18(5), pp.475-82.</td></tr>
<tr><td></td><td>• Adults aged ≥ 18 years wit T2D not optimally controlled with diet and exercise
• BMI ≤45 kg/m^2
• on a stable dose of SU that was at least 50% of themaximum dose per country-specific label for at least 3months before screening
Exclusion criteria
• Patients treated with any other antihyperglycaemic medication (including nsulin) <3 months before screening
• history of pancreatitis
• signs or symptoms of liver disease,
• impaired renal function
• elevated serum calcitonin concentration
• recent history of severe hypoglycaemia</td></tr>
<tr><td>Patient characteristics</td><td>Gender, male = 43.5% (dulaglutide), 46.7% (placebo)
Age, mean yrs = 57.7 (dulaglutide), 58.2 (placebo)
BMI kg/m^2= 30.9 (dulaglutide), 32.4 (placebo)
Weight = 84.4 (dulaglutide), 89.5 (placebo)
Risk of cardiovascular diseases (e.g. previous MI) = not reported</td></tr>
<tr><td>Intervention</td><td>Intervention: Dulaglutide 1.5mg once weekly n = 239
Background therapy: glimepride</td></tr>
<tr><td>Comparison</td><td>Comparison: placebo n = 60
Background therapy: glimepride</td></tr>
<tr><td>Outcome measures</td><td>Myocardial infarction
Mortality</td></tr>
<tr><td>Study dates</td><td></td></tr>
<tr><td>Comments (Risk of bias)</td><td>
<table>
<tr><td>Bias</td><td>Authors judgment</td><td>Support for judgment</td></tr>
<tr><td>Random sequence generation (selection bias)</td><td>Unclear risk</td><td>Randomisation method not reported.</td></tr>
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</td></tr>
</table>

Bibliographic reference	**Dungan K M, Weitgasser R, Perez Mi, et al. (2016). A 24-week study to evaluate the efficacy and safety of once-weekly dulaglutide added on to glimepiride in type 2 diabetes (AWARD-8). Diabetes, and Obesity & Metabolism, 18(5), pp.475-82.**

Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported.
Blinding of participants and researchers (performance bias)	Low risk	Double-blinded.
Blinding of outcome assessment (detection bias)	Unclear risk	Outcome assessment blinding not reported.
Incomplete outcome data (attrition bias)	Low risk	Missing outcome data balanced in numbers across groups with similar reasons for missing outcome data across groups.
Selective reporting (reporting bias)	Low risk	The study protocol is available (NCT01769378) and the outcomes of interest are reported in the pre-specified way.

Bibliographic reference	**Frias J, Guja C, Hardy E, et al. (2016). Exenatide once weekly plus dapagliflozin once daily versus exenatide or dapagliflozin alone in patients with type 2 diabetes inadequately controlled with metformin monotherapy (DURATION-8): a 28 week, multicentre, double-blind, phase 3, randomised controlled trial. The Lancet Diabetes and Endocrinology, 4(12), pp.1004-1016.**
Study type	randomised controlled trial, 28 week follow-up
Participants	Inclusion criteria • Adults aged ≥ 18 years wit T2D and inadequate glycaemic control despite at least 2 months of treatment with stable dose of metformin Exclusion criteria • any glucose-lowering drugs other than metformin for more than 14 days in the 12 weeks before enrolment.
Patient characteristics	Gender, male = 51% (exenatide), 48% (placebo) Age, mean yrs = 54 (exenatide), 55 (placebo) BMI kg/m^2= 32 (exenatide), 33 (placebo)

<table>
<tr><td>Bibliographic reference</td><td>Frias J, Guja C, Hardy E, et al. (2016). Exenatide once weekly plus dapagliflozin once daily versus exenatide or dapagliflozin alone in patients with type 2 diabetes inadequately controlled with metformin monotherapy (DURATION-8): a 28 week, multicentre, double-blind, phase 3, randomised controlled trial. The Lancet Diabetes and Endocrinology, 4(12), pp.1004-1016.</td></tr>
<tr><td></td><td>Weight = 89·8 (exenatide), 91.1 (placebo)
Risk of cardiovascular diseases (e.g. previous MI) = not reported</td></tr>
<tr><td>Intervention</td><td>Intervention: Exenatide 2mg once weekly (231 participants)
Background therapy: metformin</td></tr>
<tr><td>Comparison</td><td>Comparison: dapagliflozin 10 mg (233 participants)
Background therapy: metformin</td></tr>
<tr><td>Outcome measures</td><td>CV mortality
Renal failure</td></tr>
<tr><td>Study dates</td><td>Not reported</td></tr>
<tr><td>Comments (Risk of bias)</td><td>
<table>
<tr><td>Bias</td><td>Authors judgment</td><td>Support for judgment</td></tr>
<tr><td>Random sequence generation (selection bias)</td><td>Low risk</td><td>Randomisation via an interactive voice and web-response system</td></tr>
<tr><td>Allocation concealment (selection bias)</td><td>Unclear risk</td><td>Allocation concealment not reported.</td></tr>
<tr><td>Blinding of participants and researchers (performance bias)</td><td>Low risk</td><td>Double-blinded.</td></tr>
<tr><td>Blinding of outcome assessment (detection bias)</td><td>Low risk</td><td>Patients, investigators, and data analysts were masked to treatment assignment.</td></tr>
<tr><td>Incomplete outcome data (attrition bias)</td><td>Low risk</td><td>Missing outcome data balanced in numbers across groups with similar reasons for missing outcome data across groups.</td></tr>
<tr><td>Selective reporting (reporting bias)</td><td>Low risk</td><td>The study protocol is available (NCT02229396) and the outcomes of interest are reported in the pre-specified way.</td></tr>
</table>
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</table>

Bibliographic reference	**Garber A, Henry R, Ratner R, et al. (2011). Liraglutide, a once-daily human glucagon-like peptide 1 analogue, provides sustained improvements in glycaemic control and weight for 2 years as monotherapy compared with glimepiride in patients with type 2 diabetes. Diabetes, and Obesity and Metabolism, 13(4), pp.348-356.**
Study type	A randomised controlled trial Follow-up: 104 week (52 week randomised, 52 week open extension)
Participants	Inclusion criteria • 18 – 80 years • BMI ≤ 45 kg/m^2 • Treated with diet and exercise or up to half the highest dose of oral antidiabetic drug monotherapy (63·5%) including sulphonylureas, meglitinides, aminoacid derivatives, biguanides, α-glucosidase inhibitors, and thiazolidinediones (1500 mg metformin or 30 mg pioglitazone were allowed) for at least 2 months • screening HbA1c value of 7–11% if treated with diet and exercise or 7–10% with oral antidiabetic monotherapy Exclusion criteria • insulin treatment during the previous 3 months (except short-term treatment for intercurrent illness • treatment with systemic corticosteroids • hypoglycaemia unawareness or recurrent severe hypoglycaemia • impaired liver function
Patient characteristics	Gender, male = 47% (liraglutide 1.2), 49% (liraglutide 1.8), 54% (glimepride) Age = 53.7 (liraglutide 1.2), 52 (liraglutide 1.8), 53.4 (glimepride) BMI = 33.2 (liraglutide 1.2), 32.8 (liraglutide 1.8), 33.2 (glimepride) Weight = 92.1 (liraglutide 1.2), 92.6 (liraglutide 1.8), 93.3 (glimepride) Risk of cardiovascular diseases (e.g. previous MI) = not reported.
Intervention	Interventions Subcutaneously injected once-daily liraglutide 1.2 mg n = 251 Subcutaneously injected once-daily liraglutide 1.8 mg n = 247 Background therapy: monotherapy oral antidiabetic
Comparison	Comparison: glimepiride 8 mg/day orally n = 248

Bibliographic reference	**Garber A, Henry R, Ratner R, et al. (2011). Liraglutide, a once-daily human glucagon-like peptide 1 analogue, provides sustained improvements in glycaemic control and weight for 2 years as monotherapy compared with glimepiride in patients with type 2 diabetes. Diabetes, and Obesity and Metabolism, 13(4), pp.348-356.**
	Background therapy: monotherapy oral antidiabetic
Outcome measures	Myocardial infarction
Study dates	February 2006 to November 2008

Comments (Risk of bias)

Bias	Authors judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Randomisation was done with telephone-based or web-based systems. Participants were randomly assigned to the lowest available number
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported.
Blinding of participants and researchers (performance bias)	Low risk	Double-blinded
Blinding of outcome assessment (detection bias)	Unclear risk	Blinding of outcome assessment not reported.
Incomplete outcome data (attrition bias)	Low risk	Missing outcome data balanced in numbers across groups with similar reasons for missing outcome data across groups.
Selective reporting (reporting bias)	Low risk	The study protocol is available (NCTC00294723) and the outcomes of interest are reported in the pre-specified way.

Bibliographic reference	**Giorgino F, Benroubi M, Sun JH, et al. (2015) Efficacy and Safety of Once-Weekly Dulaglutide Versus Insulin Glargine in Patients With Type 2 Diabetes on Metformin and Glimepiride (AWARD-2). Diabetes Care; 38(12):2241-9.**
Study type	A randomised controlled trial to compare the efficacy and safety of once-weekly dulaglutide with once-daily insulin glargine in patients not optimally controlled on oral antihyperglycaemic medications (OAMs) during a 78-week treatment period. Follow-up: 78 weeks.
Participants	Inclusion criteria • Adults with an HbA1c of ≥7.0%(≥53mmol/mol) and ≤11.0% (≤97 mmol/mol) • BMI ≥23 and ≤45 kg/m^2 • Stable weight for ≥3 months • Not optimally controlled with one, two, or three OAMs (of which one had to be metformin or a sulfonylurea) for at least 3 months Exclusion criteria • Chronic insulin therapy at any time in the past or had taken GLP-1 receptor agonists within 3 months of screening.
Patient characteristics	Gender = male 53% (dulaglutide 1.5 mg); 50% (dulaglutide 0.75 mg); 51% (insulin glargine) Age = mean (SD) 56 years (10) (dulaglutide 1.5 mg); 57 years (9) (dulaglutide 0.75 mg); 57 years (9) (insulin glargine) BMI = mean (SD) 31 kg/m^2 (5) (dulaglutide 1.5 mg); 32 kg/m^2 (5) (dulaglutide 0.75 mg); 31 kg/m^2 (6) (insulin glargine) Weight = mean (SD) 85 kg (18) (dulaglutide 1.5 mg); 86 kg (18) (dulaglutide 0.75 mg); 88 kg (20) (insulin glargine) Risk of cardiovascular diseases (e.g. previous MI) = not reported.
Intervention	Interventions Subcutaneously injected once-weekly dulaglutide 1.5 mg (273 participants) Subcutaneously injected once-weekly dulaglutide 0.75 mg (272 participants) Background therapy: metformin and glimepiride maximally tolerated doses but not higher than the maximum locally approved doses.
Comparison	Comparison: once-daily glargine started at 10 units once daily adjusted according to a standard titration algorithm (262 participants) Background therapy: metformin and glimepiride maximally tolerated doses but not higher than the maximum locally approved doses.

Bibliographic reference	**Giorgino F, Benroubi M, Sun JH, et al. (2015) Efficacy and Safety of Once-Weekly Dulaglutide Versus Insulin Glargine in Patients With Type 2 Diabetes on Metformin and Glimepiride (AWARD-2). Diabetes Care; 38(12):2241-9.**
Outcome measures	Death due to heart failure
Study dates	Not reported

Comments (Risk of bias)

Bias	Authors judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Randomisation was done using a computer generated random sequence using an interactive voice response system.
Allocation concealment (selection bias)	Low risk	Randomisation was done using a computer generated random sequence using an interactive voice response system.
Blinding of participants and researchers (performance bias)	High risk	Open-label trial.
Blinding of outcome assessment (detection bias)	Low risk	Deaths and nonfatal cardiovascular adverse events were adjudicated by a committee of physicians external to Eli Lilly and Company.
Incomplete outcome data (attrition bias)	Low risk	Missing outcome data balanced in numbers across groups with similar reasons for missing outcome data across groups.
Selective reporting (reporting bias)	Low risk	The study protocol is available (NCT01075282) and the outcomes of interest are reported in the pre-specified way.

<table>
<tr><td>Bibliographic reference</td><td>Gough S. L, Bode B, Woo V, et al. (2014). Efficacy and safety of a fixed-ratio combination of insulin degludec and liraglutide (IDegLira) compared with its components given alone: Results of a phase 3, open-label, randomised, 26-week, treat-to-target trial in insulin-naive patients with type 2 diabetes. The Lancet Diabetes and Endocrinology, 2(11), pp.885-893.</td></tr>
<tr><td>Study type</td><td>A randomised controlled trial
Follow-up: 26 week</td></tr>
<tr><td>Participants</td><td>Inclusion criteria
Adults 18 yrs and older with T2D
HbA1c of 7.0-10%
BMI ≤40 kg/m^2
had been previously treated with metformin with or without pioglitazone for at least 90 days before screening were eligible for enrolment.
Exclusion criteria
treated with GLP-1 receptor agonists, DPP4 inhibitors or sulfonylureas within 90 days of screening.</td></tr>
<tr><td>Patient characteristics</td><td>Gender, female = 52% (Liraglutide);48% (insulin degludec)
Age = mean 55 (Liraglutide);54.9 (insulin degludec)
BMI = mean 31.3 kg/m^2 (Liraglutide); 31.2 (insulin degludec)
Weight = mean 87.4 (Liraglutide); 87.4(insulin degludec)
Risk of cardiovascular diseases (e.g. previous MI) = not reported.</td></tr>
<tr><td>Intervention</td><td>Interventions
once-daily liraglutide 1.8 mg n = 414
Background therapy: Metformin with or without pioglitazone</td></tr>
<tr><td>Comparison</td><td>Comparison: insulin degludec n = 414
Background therapy: Metformin with or without pioglitazone</td></tr>
<tr><td>Outcome measures</td><td>Myocardial infarction</td></tr>
<tr><td>Study dates</td><td>Not reported</td></tr>
<tr><td>Comments (Risk of bias)</td><td><table><tr><td>Bias</td><td>Authors judgment</td><td>Support for judgment</td></tr><tr><td>Random sequence generation (selection bias)</td><td>Low risk</td><td>An interactive voice or web system, with stratification by concomitant oral antidiabetic treatment.</td></tr></table></td></tr>
</table>

Bibliographic reference	Gough S. L, Bode B, Woo V, et al. (2014). Efficacy and safety of a fixed-ratio combination of insulin degludec and liraglutide (IDegLira) compared with its components given alone: Results of a phase 3, open-label, randomised, 26-week, treat-to-target trial in insulin-naive patients with type 2 diabetes. The Lancet Diabetes and Endocrinology, 2(11), pp.885-893.		
	Allocation concealment (selection bias)	Low risk	Treatment assignment was masked for a safety committee (responsible for safety surveillance), an independent external committee that adjudicated selected adverse events and personnel involved in defi ning the analysis sets until the database was released for statistical analysis.
	Blinding of participants and researchers (performance bias)	High risk	Open-label.
	Blinding of outcome assessment (detection bias)	Low risk	Treatment assignment was masked for a safety committee (responsible for safety surveillance), an independent external committee that adjudicated selected adverse events and personnel involved in defi ning the analysis sets until the database was released for statistical analysis.
	Incomplete outcome data (attrition bias)	High risk	A higher proportion of participants withdrew from the liraglutide group (18% [73/414]) than from insulin degludec (12% [48/413]).
	Selective reporting (reporting bias)	Low risk	The study protocol is available (NCT01336023) and the outcomes of interest are reported in the pre-specified way.

Bibliographic reference	**Inagaki N, Atsumi Y, Oura T, et al. (2012) Efficacy and safety profile of exenatide once weekly compared with insulin once daily in Japanese patients with type 2 diabetes treated with oral antidiabetes drug(s): results from a 26-week, randomized, open-label, parallel-group, multicenter, noninferiority study. Clin Ther; 34(9):1892-908.**
Study type	A randomised controlled trial to test the hypothesis that exenatide once weekly is non-inferior to insulin glargine in patients with type 2 diabetes who had inadequate glycaemic control with oral antidiabetes drugs. Follow-up 26 weeks.
Participants	Inclusion criteria • Aged ≥20 years • Type 2 diabetes diagnosis based on WHO criteria • Insufficient control at screening with HbA1c between 7.1% and 11.0% • BMI >18 kg/m^2 and <35 kg/m^2 • History of stable weight (not varying by >5% for at least 90 days before screening) Exclusion criteria • Fasting serum glucose >250 mg/dL or occasional serum glucose >350 mg/dL at screening • >2 episodes of hypoglycaemia requiring another person's support within 180 days before screening • Treatment for >2 consecutive weeks with insulin, DPP-4 inhibitors, or GLP-1 analogues within 90 days before screening.
Patient characteristics	Gender = male 66.0% (exenatide); 69.8% (insulin glargine) Age = mean (SD) 57.07 years (10.44) (exenatide); 56.44 years (11.16) (insulin glargine) BMI = mean (SD) 26.11 kg/m^2 (exenatide); 26.18 kg/m^2 (3.77) (insulin glargine) Weight = mean (SD) 69.95 kg (13.25) (exenatide); 71.03 kg (13.93) (insulin glargine) Risk of cardiovascular diseases (e.g. previous MI) = not reported.
Intervention	Intervention: exenatide 2 mg once weekly by subcutaneous injection (215 participants) Background therapy: current oral antidiabetes drugs (biguanide or biguanide plus thiazolidine derivative)
Comparison	Comparison: insulin glargine once daily before bedtime by subcutaneous injection, dose started at 4 U and adjusted to achieve target fasting blood glucose of <100 mg/dL (212 participants) Background therapy: current oral antidiabetes drugs (biguanide or biguanide plus thiazolidine derivative)
Outcome measures	Death due to cardiac failure
Study dates	Not reported.

Bibliographic reference	**Inagaki N, Atsumi Y, Oura T, et al. (2012) Efficacy and safety profile of exenatide once weekly compared with insulin once daily in Japanese patients with type 2 diabetes treated with oral antidiabetes drug(s): results from a 26-week, randomized, open-label, parallel-group, multicenter, noninferiority study. Clin Ther; 34(9):1892-908.**
Comments (Risk of bias)	

Bias	Authors judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Randomisation was done using a computer-generated random sequence with an interactive voice response system.
Allocation concealment (selection bias)	Low risk	Randomisation was done using a computer-generated random sequence with an interactive voice response system.
Blinding of participants and researchers (performance bias)	High risk	Open-label trial.
Blinding of outcome assessment (detection bias)	Low risk	Unclear if there was blinding of outcome assessment but cardiovascular and microvascular outcomes are not likely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias)	Low risk	Missing outcome data balanced in numbers across groups with similar reasons for missing outcome data across groups.
Selective reporting (reporting bias)	Low risk	The study protocol is available (NCT00935532) and the outcomes of interest are reported in the pre-specified way.

Bibliographic reference	**Jaiswal M, Martin CL, Brown MB, et al. (2015) Effects of exenatide on measures of diabetic neuropathy in subjects with type 2 diabetes: results from an 18-month proof-of-concept open-label randomized study. J Diabetes Complications; 29(8):1287-94.**
Study type	A randomised controlled trial to evaluate the effects of exenatide on measures of diabetic peripheral neuropathy and cardiovascular autonomic neuropathy in subjects with type 2 diabetes. Follow-up 18 months.
Participants	Inclusion criteria • Aged between 18 and 70 years old • Type 2 diabetes with HbA1c >7% and fasting blood glucose >140 mg/dl • Prior stable glucose lowering regimen that did not include insulin or a GLP-1 receptor agonist • No contraindications to treatment with either exenatide or insulin glargine based on FDA prescribing guidelines • Having mild-to-moderate diabetic peripheral neuropathy as defined by a score of 6 or more on the Michigan Diabetes Neuropathy Scale Exclusion criteria • History of kidney, pancreas, or cardiac transplantation, neuropathy independent of diabetes, or any condition other than diabetes associated with neuropathy (e.g. hepatitis C, end stage renal disease, lupus), any lower extremity amputation or severe deformity of lower extremity • HbA1c > 10% • Participation in an experimental medication trial within 3 months of starting this study • Undergoing therapy for malignant disease other than basal or squamous cell carcinoma • Requiring long-term glucocorticoid therapy • Inability or unwillingness to comply with the protocol • Nursing mothers or pregnant women.
Patient characteristics	Gender = male 59% (exenatide); 54% (insulin glargine) Age = mean (SD) 51 years (13) (exenatide); 54 years (9) (insulin glargine) BMI = mean (SD) 35 kg/m^2 (3) (exenatide); 37 kg/m^2 (6) (insulin glargine) Weight = mean (SD) 107 kg (13) (exenatide); 110 kg (21) (insulin glargine) Risk of cardiovascular diseases (e.g. previous MI) Confirmed clinical neuropathy 67% (exenatide); 75% (insulin glargine)
Intervention	Intervention: exenatide up to 10 µg (22 participants) Background therapy: prior oral agents to optimize blood glucose control.

Bibliographic reference	**Jaiswal M, Martin CL, Brown MB, et al. (2015) Effects of exenatide on measures of diabetic neuropathy in subjects with type 2 diabetes: results from an 18-month proof-of-concept open-label randomized study. J Diabetes Complications; 29(8):1287-94.**
Comparison	Comparison: insulin glargine initiated with 10 units daily and titrated in 2-unit increments to achieve a fasting blood glucose target level of 5.6 mmol/L (100 mg/dL) without recurrent or severe hypoglycaemia (24 participants) Background therapy: prior oral agents to optimize blood glucose control.
Outcome measures	Left toe amputation
Study dates	July 2008 to June 2014.

Comments (Risk of bias)

Bias	Authors judgment	Support for judgment
Random sequence generation (selection bias)	Unclear risk	Randomisation was used without sufficient information about the sequence generation process.
Allocation concealment (selection bias)	Unclear risk	Allocation was not described.
Blinding of participants and researchers (performance bias)	High risk	Open-label trial.
Blinding of outcome assessment (detection bias)	Low risk	Unclear if there was blinding of outcome assessment but the outcome is not likely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias)	Low risk	Most participants completed the study in both groups.
Selective reporting (reporting bias)	High risk	The study protocol is available (NCT00855439) but adverse events outcomes are not mentioned.

Bibliographic reference	**Kaku K, Kiyosue A, Ono Y, et al. (2016) Liraglutide is effective and well tolerated in combination with an oral antidiabetic drug in Japanese patients with type 2 diabetes: A randomized, 52-week, open-label, parallel-group trial. J Diabetes Investig; 7(1):76-84.**
Study type	A randomised controlled trial to assess the safety and efficacy of liraglutide in combination with oral antidiabetic drugs (glinide, metformin, a-glucosidase inhibitor or thiazolidinedione) compared to a combination of 2 oral antidiabetic drugs (OAD), in patients with type 2 diabetes insufficiently controlled with OAD monotherapy. Follow-up 52 weeks.
Participants	Inclusion criteria • Male and female • Aged ≥20 years • Having type 2 diabetes for at least 6 months • HbA1c 7.0 to 10.0% • BMI <40.0 kg/ Exclusion criteria • Use of the following drugs within the past 12 weeks: a GLP-1 receptor agonist, a DPP-4 inhibitor or insulin • Personal history of non-familial medullary thyroid carcinoma • Family or personal history of multiple endocrine neoplasia type 2 or familial medullary thyroid carcinoma, malignant tumour (either known or previous and strongly suspected of recurrence) • History of chronic pancreatitis or idiopathic acute pancreatitis • Calcitonin ≥160 pg/mL (radioimmunoassay-2 method) • Contraindications to liraglutide or any of the OADs (according to Japanese labelling) • Recurrent severe hypoglycaemia, hypoglycaemia unawareness or hospitalization for diabetic ketoacidosis during the previous 6 months.
Patient characteristics	Gender = male 75.8% (liraglutide); 66.7% (additional OAD) Age = mean (SD) 59.6 years (11.6) (liraglutide); 59.2 years (10.2) (additional OAD) BMI = mean (SD) 25.7 kg/m^2 (4.2) (liraglutide); 25.5 kg/m^2 (3.7) (additional OAD) Weight = 69.4 kg (14.2) (liraglutide); 68.2 kg (13.6) (additional OAD) Risk of cardiovascular diseases (e.g. previous MI) = not reported
Intervention	Intervention: liraglutide up to 0.9 mg/day subcutaneously (240 participants) Background therapy: one OAD (glinide, metformin, a-glucosidase inhibitor or thiazolidinedione)

<table>
<tr><td>Bibliographic reference</td><td>Kaku K, Kiyosue A, Ono Y, et al. (2016) Liraglutide is effective and well tolerated in combination with an oral antidiabetic drug in Japanese patients with type 2 diabetes: A randomized, 52-week, open-label, parallel-group trial. J Diabetes Investig; 7(1):76-84.</td></tr>
<tr><td>Comparison</td><td>Comparison: addition of an OAD (DPP-4 inhibitor, sulfonylurea, glinide, metformin, α-glucosidase inhibitor or thiazolidinedione) (120 participants)
Background therapy: one OAD (glinide, metformin, a-glucosidase inhibitor or thiazolidinedione)</td></tr>
<tr><td>Outcome measures</td><td>Diabetic retinopathy
Mortality</td></tr>
<tr><td>Study dates</td><td>January 2012 to April 2013.</td></tr>
<tr><td>Comments (Risk of bias)</td><td>
<table>
<tr><th>Bias</th><th>Authors judgment</th><th>Support for judgment</th></tr>
<tr><td>Random sequence generation (selection bias)</td><td>Low risk</td><td>Randomisation was done using an interactive voice/web response service.</td></tr>
<tr><td>Allocation concealment (selection bias)</td><td>Low risk</td><td>Randomisation was done using an interactive voice/web response service.</td></tr>
<tr><td>Blinding of participants and researchers (performance bias)</td><td>High risk</td><td>Open-label trial.</td></tr>
<tr><td>Blinding of outcome assessment (detection bias)</td><td>Low risk</td><td>Unclear if there was blinding of outcome assessment but cardiovascular and microvascular outcomes are not likely to be influenced by lack of blinding.</td></tr>
<tr><td>Incomplete outcome data (attrition bias)</td><td>Low risk</td><td>Missing outcome data balanced in numbers across groups with similar reasons for missing outcome data across groups.</td></tr>
<tr><td>Selective reporting (reporting bias)</td><td>Low risk</td><td>The study protocol is available (NCT01512108) and the outcomes of interest are reported in the pre-specified way.</td></tr>
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</table>

<table>
<tr><td>Bibliographic reference</td><td>Lind M, Hirsch I, Tuomilehto J, et al. (2015). Liraglutide in people treated for type 2 diabetes with multiple daily insulin injections: randomised clinical trial (MDI Liraglutide trial). BMJ (Clinical research ed.), 351, pp.h5364.</td></tr>
<tr><td>Study type</td><td>A randomised controlled trial
Follow-up: 24 weeks</td></tr>
<tr><td>Participants</td><td>Inclusion criteria
people with type 2 diabetes treated with multiple daily insulin injections
HbA1c concentrations ≥ 58 mmol/mol (7.5%) and ≤102 mmol/mol (11.5%)
body mass index of 27.5 - 45 kg/m^2
Exclusion criteria
people using premixed insulin</td></tr>
<tr><td>Patient characteristics</td><td>Gender, male = 62.5% (liraglutide) 66% (placebo)
Age mean yrs = 63.7 (liraglutide) 63.5 (placebo)
BMI = 33.7 (liraglutide) 33.5 (placebo)
Weight mean kg= 98.9 (liraglutide) 100 (placebo)
Risk of cardiovascular diseases (e.g. previous MI) = previous MI: 9.4% (liraglutide), 16.7% (placebo)</td></tr>
<tr><td>Intervention</td><td>Intervention: liraglutide 1.8 mg/day (n=64)
Background therapy: multiple insulin injections</td></tr>
<tr><td>Comparison</td><td>Comparison: Placebo (n=60)
Background therapy: multiple insulin injections</td></tr>
<tr><td>Outcome measures</td><td>Cardiac failure</td></tr>
<tr><td>Study dates</td><td>Not reported.</td></tr>
<tr><td>Comments (Risk of bias)</td><td><table>
<tr><td>Bias</td><td>Authors judgment</td><td>Support for judgment</td></tr>
<tr><td>Random sequence generation (selection bias)</td><td>unclear risk</td><td>Method of randomisation unclear.</td></tr>
<tr><td>Allocation concealment (selection bias)</td><td>Low risk</td><td>Minimisation allocation used.</td></tr>
<tr><td>Blinding of participants and researchers (performance bias)</td><td>Low risk</td><td>Double-blinded.</td></tr>
</table></td></tr>
</table>

Bibliographic reference	**Lind M, Hirsch I, Tuomilehto J, et al. (2015). Liraglutide in people treated for type 2 diabetes with multiple daily insulin injections: randomised clinical trial (MDI Liraglutide trial). BMJ (Clinical research ed.), 351, pp.h5364.**

Blinding of outcome assessment (detection bias)	Low risk	During masking the receiver does not display the values but rather stores them for downloading.
Incomplete outcome data (attrition bias)	Low risk	Missing outcome data balanced in numbers across groups with similar reasons for missing outcome data across groups.
Selective reporting (reporting bias)	Low risk	The study protocol is available (EudraCT 2012-001941-42.) and the outcomes of interest are reported in the pre-specified way.

Bibliographic reference	**Marso S, Daniels G, Brown-Frandsen K, et al. (2016) Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med; 375(4):311-22.**
Study type	A randomised controlled trial to assess the long-term effects of liraglutide on cardiovascular outcomes and other clinically important events. Follow-up 3.5 to 5 years.
Participants	Inclusion criteria • Age 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) • Age 60 years or more with at least one cardiovascular risk factor, as determined by the investigator (microalbuminuria or proteinuria, hypertension and left ventricular hypertrophy, left ventricular systolic or diastolic dysfunction, or an ankle–brachial index [the ratio of the systolic blood pressure at the ankle to the systolic blood pressure in the arm] of less than 0.9). Exclusion criteria • Type 1 diabetes • Use of GLP-1–receptor agonists, DPP-4 inhibitors, pramlintide, or rapid-acting insulin

Bibliographic reference	**Marso S, Daniels G, Brown-Frandsen K, et al. (2016) Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med; 375(4):311-22.**
	• A familial or personal history of multiple endocrine neoplasia type 2 or medullary thyroid cancer • Occurrence of an acute coronary or cerebrovascular event within 14 days before screening and randomization. • Complete inclusion and exclusion criteria can be seen in the Supplementary Appendix of Marso et al. (2016).
Patient characteristics	Gender = male 64.5% (liraglutide); 64.0% (placebo) Age = mean (SD) 64.2 years (7.2) (liraglutide); 64.4 years (7.2) (placebo) BMI = mean (SD) 32.5 kg/m^2 (6.3) (liraglutide); 32.5 kg/m^2 (6.3) (placebo) Weight = mean (SD) 91.9 kg (21.2) (liraglutide); 91.6 kg (20.8) (placebo) Risk of cardiovascular diseases (e.g. previous MI) = all participants were considered to be at high risk of cardiovascular disease.
Intervention	Intervention: liraglutide 1.8 mg once daily as a subcutaneous injection (4,668 participants) Background therapy: standard care which could include metformin, add-on therapy (thiazolidinediones, sulfonylureas, alpha glucosidase inhibitors), and insulin therapy (basal, basal/bolus, premix, and mealtime bolus).
Comparison	Comparison: matching placebo once daily as a subcutaneous injection (4,672 participants) Background therapy: standard care which could include metformin, add-on therapy (thiazolidinediones, sulfonylureas, alpha glucosidase inhibitors), and insulin therapy (basal, basal/bolus, premix, and mealtime bolus).
Outcome measures	Fatal MI Nonfatal MI Silent MI Fatal stroke Nonfatal stroke Transient ischemic attack Hospitalization for heart failure Retinopathy Nephropathy Death from cardiovascular causes Definitions:

Bibliographic reference	Marso S, Daniels G, Brown-Frandsen K, et al. (2016) Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med; 375(4):311-22.
	Transient Ischemic Attack: Transient ischemic attack (TIA) is defined as a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction. Ischemic Stroke: Ischemic stroke is defined as an acute episode of focal cerebral, spinal, or retinal dysfunction caused by an infarction of central nervous system tissue that results from a thrombus or embolus impairing central nervous system perfusion (not due to hemorrhage) and is documented by imaging. Evidence of ischemic stroke obtained from autopsy can also confirm the diagnosis. Findings on lumbar puncture can be supportive to the diagnosis. Hemorrhagic stroke: Hemorrhagic stroke is defined as an acute episode of focal or global cerebral, spinal, or retinal dysfunction caused by a nontraumatic intraparenchymal, intraventricular, or subarachnoid hemorrhage with documentation of cerebral hemorrhage on imaging (eg, CT or MRI scan), ie, intraparenchymal, intraparenchymal with penetration into the ventricles, intraventricular, or subarachnoidal hemorrhage. Subdural and epidural bleedings are not included. Evidence of hemorrhagic stroke obtained from autopsy can also confirm the diagnosis. Findings on lumbar puncture can be supportive to the diagnosis. MI is diagnosed based on any of the following criteria, based on the redefinitions suggested by the ESC (European Society of Cardiology)/ACCF (American College of Cardiology Foundation)/AHA (American Heart Association)/WHF (World Heart Federation) task force. Heart failure (HF) requiring hospitalization is defined as an event that meets the following criteria: 1. Requires hospitalization defined as an admission to an inpatient unit or a visit to an emergency department that results in at least a 12 hour stay (or a date change if the time of admission/discharge is not available). AND 2. Clinical manifestations of heart failure including at least one of the following: New or worsening dyspnea, orthopnea, paroxysmal nocturnal dyspnea, edema, pulmonary basilar crackles, jugular venous distension, new or worsening third heart sound or gallop rhythm, or radiological evidence of worsening heart failure. AND Additional/Increased therapy, initiation of intravenous diuretic, inotrope, or vasodilator therapy, uptitration of intravenous therapy, if already on therapy, initiation of mechanical or surgical intervention (mechanical circulatory support, heart transplantation or ventricular pacing to improve cardiac function), or the use of ultrafiltration, hemofiltration, or dialysis that is specifically directed at treatment of heart failure, or biomarker results (e.g., brain natriuretic peptide) consistent with congestive heart failure will be supportive of this diagnosis.

Bibliographic reference	**Marso S, Daniels G, Brown-Frandsen K, et al. (2016) Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med; 375(4):311-22.**
Study dates	September 2010 to April 2012
Comments (Risk of bias)	

Bias	Authors judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Randomisation was carried out using the interactive voice/web response system.*
Allocation concealment (selection bias)	Low risk	Randomisation was carried out using the interactive voice/web response system.*
Blinding of participants and researchers (performance bias)	Low risk	Trial registration defines masking as double blind (participant, investigator) and outcomes of interest are not likely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias)	Low risk	Outcomes were adjudicated in a blinded fashion by an external, independent event-adjudication committee.
Incomplete outcome data (attrition bias)	Low risk	Missing outcome data balanced in numbers across groups with similar reasons for missing outcome data across groups.
Selective reporting (reporting bias)	Low risk	The study protocol is available (NCT01179048) and the outcomes of interest are reported in the pre-specified way.
* From Marso SP, Poulter NR, Nissen SE, et al. (2013) Design of the Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results (LEADER) trial. Am Heart J; 166(5):823–30.		

Bibliographic reference	**Meier J, Rosenstock J, Hincelin-Méry A, et al. (2015) Contrasting Effects of Lixisenatide and Liraglutide on Postprandial Glycemic Control, Gastric Emptying, and Safety Parameters in Patients With Type 2 Diabetes on Optimized Insulin Glargine With or Without Metformin: A Randomized, Open-Label Trial. Diabetes Care;38(7):1263-73.**
Study type	A randomised controlled trial to compare the pharmacodynamics and safety of lixisenatide and liraglutide in combination with optimised insulin glargine with/without metformin in type 2 diabetes. Follow-up: 8 weeks

Bibliographic reference	**Meier J, Rosenstock J, Hincelin-Méry A, et al. (2015) Contrasting Effects of Lixisenatide and Liraglutide on Postprandial Glycemic Control, Gastric Emptying, and Safety Parameters in Patients With Type 2 Diabetes on Optimized Insulin Glargine With or Without Metformin: A Randomized, Open-Label Trial. Diabetes Care;38(7):1263-73.**
Participants	Inclusion criteria • Men and women aged 18 to 75 years with type 2 diabetes for at least 1 year • BMI 20.0 to 40.0 kg/m^2 • HbA1c ≥6.5% to ≤9.5% (≥48 to ≤80 mmol/mol) Exclusion criteria • A clinically relevant history of gastrointestinal disease associated with prolonged nausea or vomiting • A history of unexplained/chronic pancreatitis • Patients with alanine aminotransferase, amylase, or lipase more than 3 times the upper limit of normal (3 X ULN) or calcitonin ≥20 pg/mL
Patient characteristics	Gender = male 68.8% (lixisenatide); 83.0% (liraglutide 1.2 mg); 70.2% (liraglutide 1.8 mg) Age = mean (SD) 61.6 years (7.4) (lixisenatide); 61.4 years (7.9) (liraglutide 1.2 mg); 62.6 years (9.4) (liraglutide 1.8 mg) BMI = mean (SD) 30.7 kg/m^2 (4.3) (lixisenatide); 30.5 kg/m^2 (4.0) (liraglutide 1.2 mg); 31.2 kg/m^2 (4.3) (liraglutide 1.8 mg) Weight = mean (SD) 90.3 kg (13.3) (lixisenatide); 91.4 kg (14.0) (liraglutide 1.2 mg); 93.1 kg (15.4) (liraglutide 1.8 mg) Risk of cardiovascular diseases (e.g. previous MI) = not reported
Intervention	Intervention: lixisenatide 20 µg subcutaneous once daily (48 participants) Background therapy: optimised insulin glargine with/without metformin
Comparison	Comparisons: liraglutide 1.2 mg subcutaneous once daily (47 participants) liraglutide 1.8 mg subcutaneous once daily (47 participants) Background therapy: optimised insulin glargine with/without metformin
Outcome measures	Myocardial infarction requiring hospitalisation Mortality
Study dates	May 2012 to May 2013
Comments (Risk of bias)	Bias | Authors judgment | Support for judgment

Bibliographic reference	**Meier J, Rosenstock J, Hincelin-Méry A, et al. (2015) Contrasting Effects of Lixisenatide and Liraglutide on Postprandial Glycemic Control, Gastric Emptying, and Safety Parameters in Patients With Type 2 Diabetes on Optimized Insulin Glargine With or Without Metformin: A Randomized, Open-Label Trial. Diabetes Care;38(7):1263-73.**

Random sequence generation (selection bias)	Low risk	Participants were centrally randomised by interactive voice response system.
Allocation concealment (selection bias)	Low risk	Participants were centrally randomised by interactive voice response system.
Blinding of participants and researchers (performance bias)	High risk	Open-label study.
Blinding of outcome assessment (detection bias)	Low risk	Unclear if there was blinding of outcome assessment but cardiovascular and microvascular outcomes are not likely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias)	Low risk	Missing outcome data balanced in numbers across groups with similar reasons for missing outcome data across groups.
Selective reporting (reporting bias)	Low risk	The study protocol is not available but it seems that all expected outcomes were reported.

Bibliographic reference	**Meneilly G, Roy-Duval C, Alawi H, et al. (2017) Lixisenatide Therapy in Older Patients With Type 2 Diabetes Inadequately Controlled on Their Current Antidiabetic Treatment: The GetGoal-O Randomized Trial. Diabetes Care; 40(4):485-493.**
Study type	A randomised controlled trial to evaluate the efficacy and safety of lixisenatide compared to placebo on glycaemic control in older people with type 2 diabetes uncontrolled on their current antidiabetic treatment. Follow-up 24 weeks.
Participants	Inclusion criteria • Type 2 diabetes inadequately controlled with a current antidiabetic treatment regimen • Age ≥70 years

Bibliographic reference	**Meneilly G, Roy-Duval C, Alawi H, et al. (2017) Lixisenatide Therapy in Older Patients With Type 2 Diabetes Inadequately Controlled on Their Current Antidiabetic Treatment: The GetGoal-O Randomized Trial. Diabetes Care; 40(4):485-493.**
	• At least 3 months on the current antidiabetic treatment regimen • Ability to be compliant and to complete study procedures, including self-injection Exclusion criteria • HbA1c ≤7% (≤53 mmol/mol) and >10% (>86 mmol/mol) • FPG >13.9 mmol/L at screening • Basal insulin therapy combined with either a sulfonylurea or meglitinides • Severe renal impairment (eGFR <30 mL/min/1.73 m^2) at visit 6 (week21) • Amylase and/or lipase >3 times the upper limit of normal at visit 6 (week 21) • History of severe hypoglycaemia associated with unawareness of symptoms or leading to unconsciousness, coma, or seizure ≤6 months before screening • Risk for malnutrition • Moderate to severe cognitive impairment.
Patient characteristics	Gender = male 52.3% (lixisenatide); 51.7% (placebo) Age = mean (SD) 74.4 years (4.0) (lixisenatide); 74.4 years (3.8) (placebo) BMI = mean (SD) 29.9 kg/m^2 (3.7) (lixisenatide); 30.1 kg/m^2 (4.5) (placebo) Weight = mean (SD) 80.8 kg (14.5) (lixisenatide); 80.1 kg (16.8) (placebo) Risk of cardiovascular diseases (e.g. previous MI) = history of cardiovascular/cerebrovascular disorder 93.2% (lixisenatide); 93.1% (placebo)
Intervention	Intervention: lixisenatide up to 20 µg self-administered once daily by subcutaneous injection 30–60 min before breakfast (176 participants) Background therapy: Permitted antidiabetic therapies were metformin, sulfonylurea (except glibenclamide >10 mg and gliclazide >160 mg), meglitinide (except repaglinide >6 mg), pioglitazone, and basal insulin.
Comparison	Comparison: placebo self-administered once daily by subcutaneous injection 30–60 min before breakfast (174 participants) Background therapy: Permitted antidiabetic therapies were metformin, sulfonylurea (except glibenclamide >10 mg and gliclazide >160 mg), meglitinide (except repaglinide >6 mg), pioglitazone, and basal insulin.
Outcome measures	Death due to aortic aneurysm
Study dates	Not reported.

Bibliographic reference	**Meneilly G, Roy-Duval C, Alawi H, et al. (2017) Lixisenatide Therapy in Older Patients With Type 2 Diabetes Inadequately Controlled on Their Current Antidiabetic Treatment: The GetGoal-O Randomized Trial. Diabetes Care; 40(4):485-493.**
Comments (Risk of bias)	

Bias	Authors judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	An interactive voice/Web response system generated patient randomisation.
Allocation concealment (selection bias)	Low risk	An interactive voice/Web response system generated patient randomisation.
Blinding of participants and researchers (performance bias)	Low risk	The trial was double blinded with regard to active and placebo treatments.
Blinding of outcome assessment (detection bias)	Low risk	Unclear if there was blinding of outcome assessment but cardiovascular and microvascular outcomes are not likely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias)	Low risk	Missing outcome data balanced in numbers across groups with similar reasons for missing outcome data across groups.
Selective reporting (reporting bias)	Low risk	The study protocol is not available but it seems that all expected outcomes were reported.

Bibliographic reference	**Nauck M, Rizzo M, Johnson A, et al. (2016) Once-Daily Liraglutide Versus Lixisenatide as Add-on to Metformin in Type 2 Diabetes: A 26-Week Randomized Controlled Clinical Trial. Diabetes Care; 39(9):1501-9.**
Study type	Randomised controlled trial to compare the efficacy and safety of liraglutide versus lixisenatide as add-on to metformin in patients with type 2 diabetes not achieving adequate glycaemic control on metformin alone. Follow-up: 26 weeks.

Bibliographic reference	**Nauck M, Rizzo M, Johnson A, et al. (2016) Once-Daily Liraglutide Versus Lixisenatide as Add-on to Metformin in Type 2 Diabetes: A 26-Week Randomized Controlled Clinical Trial. Diabetes Care; 39(9):1501-9.**
Participants	Inclusion criteria • Males and females with type 2 diabetes • Aged ≥18 years • HbA1c 7.5 to 10.5% (58 to 91 mmol/mol) • BMI ≥20 kg/m^2 • Unchanged metformin treatment at the maximum tolerated dose (1,000 to 3,000 mg/day) for at least 90 days prior to screening Exclusion criteria • Females of child-bearing potential who was pregnant, breast-feeding, or intending to become pregnant or not using adequate contraception • Previous treatment with a GLP-1 RA • Treated with glucose-lowering agents other than metformin within 90 days of screening • History of chronic pancreatitis or idiopathic acute pancreatitis • Screening calcitonin value ≥50 ng/L • Personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2 • Impaired liver function (alanine aminotransferase ≥2.5 times the upper normal limit [UNL]) • Impaired renal function (estimated glomerular filtration rate <60 mL/min/1.73 m2 per MDRD formula) • Any chronic disorder or severe disease that in the opinion of the investigator might jeopardize the patient's safety or compliance with the protocol.
Patient characteristics	Gender = male 65% (liraglutide); 55% (lixisenatide) Age = mean (SD) 56.3 years (10.6) (liraglutide); 56.1 years (10.0) (lixisenatide) BMI = mean (SD) 34.5 kg/m^2 (6.8) (liraglutide); 34.9 kg/m^2 (6.6) (lixisenatide) Weight = mean (SD) 101.9 kg (23.3) (liraglutide); 100.6 kg (19.9) (lixisenatide) Risk of cardiovascular diseases (e.g. previous MI) = not reported
Intervention	Intervention: liraglutide 1.8 mg once daily subcutaneously (202 participants) Background therapy: metformin
Comparison	Comparison: lixisenatide 20 µg once daily subcutaneously (202 participants) Background therapy: metformin

Bibliographic reference	**Nauck M, Rizzo M, Johnson A, et al. (2016) Once-Daily Liraglutide Versus Lixisenatide as Add-on to Metformin in Type 2 Diabetes: A 26-Week Randomized Controlled Clinical Trial. Diabetes Care; 39(9):1501-9.**
Outcome measures	Myocardial ischemia Cardiac failure Ischemic stroke
Study dates	October 2013 to November 2014.

Comments (Risk of bias)

Bias	Authors judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Patients were randomised using the interactive voice/web response system to receive the interventions.
Allocation concealment (selection bias)	Low risk	Patients were randomised using the interactive voice/web response system to receive the interventions.
Blinding of participants and researchers (performance bias)	High risk	Open-label trial.
Blinding of outcome assessment (detection bias)	Low risk	Unclear if there was blinding of outcome assessment but cardiovascular and microvascular outcomes are not likely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias)	Low risk	Missing outcome data balanced in numbers across groups with similar reasons for missing outcome data across groups.
Selective reporting (reporting bias)	Low risk	The study protocol is available (NCT01973231) and the outcomes of interest are reported in the pre-specified way.
Other bias	High risk	More participants allocated to lixisenatide received rescue medication compared to participants allocated to liraglutide (16 and 5, respectively).

Bibliographic reference	**Pfeffer M, Claggett B, Diaz R, et al. (2015) Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome. N Engl J Med; 373(23):2247-57.**
Study type	A randomised controlled trial to assess the effects of lixisenatide on cardiovascular morbidity and mortality. Follow-up: median of 25 months
Participants	Inclusion criteria • Type 2 diabetes • Acute coronary event within 180 days before screening Exclusion criteria • Age <30 years • Percutaneous coronary intervention within the previous 15 days • Coronary-artery bypass graft surgery for the qualifying event • Planned coronary revascularization procedure within 90 days after screening • Estimated glomerular filtration rate (eGFR) of less than 30 ml per minute per 1.73 m2 of body surface area • Glycated haemoglobin level <5.5% or >11.0% • Inability to provide written informed consent.
Patient characteristics	Gender = male 69.6% (lixisenatide); 69.1% (placebo) Age = mean (SD) 59.9 years (9.7) (lixisenatide); 60.6 years (9.6) (placebo) BMI = mean (SD) 30.1 kg/m^2 (5.6) (lixisenatide); 30.2 kg/m^2 (5.8) (placebo) Weight = mean (SD) 84.6 kg (19.2) (lixisenatide); 85.1 kg (19.6) (placebo) Risk of cardiovascular diseases (e.g. previous MI) Myocardial infarction 22.1% (lixisenatide); 22.1% (placebo) Heart failure 22.5% (lixisenatide); 22.3% (placebo) Stroke 4.7% (lixisenatide); 6.2% (placebo)
Intervention	Intervention: once-daily subcutaneous injections of lixisenatide up to 20 µg (3,034 participants) Background therapy: concomitant glucose-lowering agents or addition of new antidiabetic medications with the exception of other incretin therapies to achieve glycaemic control.
Comparison	Comparison: volume-matched placebo (3,034 participants) Background therapy: concomitant glucose-lowering agents or addition of new antidiabetic medications with the exception of other incretin therapies to achieve glycaemic control.
Outcome measures	Myocardial infarction

Bibliographic reference	**Pfeffer M, Claggett B, Diaz R, et al. (2015) Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome. N Engl J Med; 373(23):2247-57.**
	Stroke Hospitalization for heart failure Death from cardiovascular causes Defiitions of MI, stroke and heart failure were not reported.
Study dates	July 2010 to February 2015
Comments (Risk of bias)	

Bias	Authors judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Randomisation was performed with the use of a centralized assignment system.
Allocation concealment (selection bias)	Low risk	Randomisation was performed with the use of a centralised assignment system.
Blinding of participants and researchers (performance bias)	Low risk	Trial registration defines masking as double blind (participant, investigator, outcomes assessor) and outcomes of interest are not likely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias)	Low risk	Separate independent committees whose members were unaware of the study group assignments adjudicated potential cardiovascular, pancreatic, and allergic events.
Incomplete outcome data (attrition bias)	Low risk	CONSORT diagram was not reported but most participants completed the study in both groups 96% in each group.
Selective reporting (reporting bias)	Low risk	The study protocol is available (NCT01147250) and the outcomes of interest are reported in the pre-specified way.

Bibliographic reference	**Pinget M, Goldenberg R, Niemoeller E, Muehlen-Bartmer I, Guo H, and Aronson R. (2013). Efficacy and safety of lixisenatide once daily versus placebo in type 2 diabetes insufficiently controlled on pioglitazone (GetGoal-P). Diabetes, and Obesity & Metabolism, 15(11), pp.1000-7.**
Study type	Randomised controlled trial
Participants	Inclusion criteria - Adults with T2DM for at least 1 year - Treated with pioglitazone at a stable dose of ≥30 mg/day with or without metformin for at least the previous 3 months - HbA1c measurement of ≥7.0% and ≤10.0% Exclusion criteria • use of oral or injectable glucose-lowering agents other than pioglitazone and metformin within 3 months prior to the time of screening • fasting plasma glucose at screening >250 mg/dl (13.9 mmol/l) • history of unexplained pancreatitis, chronic pancreatitis, pancreatectomy, stomach/gastric surgery or inflammatory bowel disease; end-stage renal disease and/or dialysis for patients treated only with pioglitazone and for patients treated with metformin in addition to pioglitazone • creatinine>1.4 mg/dl in women or>1.5 mg/dl in men • history of allergic reaction to anyclinically relevant • history of gastrointestinal disease, with prolonged nausea and vomiting during the previous 6 months. GLP-1RAs.
Patient characteristics	Gender = male (5): 53% (lixisenatide), 51% (placebo) Age = mean years: 56 (lixisenatide), 55.3 (placebo) BMI = mean kg/m^2: 33.7 (lixisenatide), 34.4 (placebo) Weight (kg) = 92.9 (lixisenatide), 96.7 (placebo) Risk of cardiovascular diseases (e.g. previous MI)
Intervention	Intervention: Lixisenatide 20ug/day (323 participants) Background therapy: pioglitazone with/without metformin
Comparison	Comparison: Placebo (161 participants) Background therapy: pioglitazone with/without metformin

Bibliographic reference	**Pinget M, Goldenberg R, Niemoeller E, Muehlen-Bartmer I, Guo H, and Aronson R. (2013). Efficacy and safety of lixisenatide once daily versus placebo in type 2 diabetes insufficiently controlled on pioglitazone (GetGoal-P). Diabetes, and Obesity & Metabolism, 15(11), pp.1000-7.**
Outcome measures	Mortality (death due to myocardial infarction)
Study dates	September 2008 and June 2011
Comments (Risk of bias)	

Bias	Authors judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Corresponding treatment numbers were allocated using an interactive voice response system according to a predefined randomisation list.
Allocation concealment (selection bias)	Low risk	Corresponding treatment numbers were allocated using an interactive voice response system according to a predefined randomisation list.
Blinding of participants and researchers (performance bias)	Low risk	Double-blinded.
Blinding of outcome assessment (detection bias)	Low risk	Investigational product was double-blinded.
Incomplete outcome data (attrition bias)	Low risk	Missing outcome data balanced in numbers across groups with similar reasons for missing outcome data across groups.
Selective reporting (reporting bias)	Low risk	The study protocol is not available but all outcomes specified are reported in the pre-specified way.

Bibliographic reference	**Pratley R, Nauck M, Bailey T, et al. (2011). One year of liraglutide treatment offers sustained and more effective glycaemic control and weight reduction compared with sitagliptin, both in combination with metformin, in patients with type 2 diabetes: a randomised, parallel-group, open-label trial. International Journal of Clinical Practice, 65(4), pp.397-407.** **Pratley R, Nauck M, Bailey T, et al. (2010). Liraglutide versus sitagliptin for patients with type 2 diabetes who did not have adequate glycaemic control with metformin: a 26-week, randomised, parallel-group, open-label trial. Lancet (London, and England), 375(9724), pp.1447-56.**
Study type	Randomised controlled trial
Participants	Inclusion criteria • Adults 18 to 80 years with T2D • HbA1c of 7.5 to 10% • BMI of 45 or lower • Had been treated with metformin for 3 months oor longer Exclusion criteria • Previous treatment with any antihyperglycaemic drug apart from metformin within 3 months of the trial • Recurrent major hypoglycaemia or hypoglycaemic unawareness • Contraindication to trial drugs • Impaired renal or hepatic function • Clinically significant cardiovascular disease • Cancer
Patient characteristics	Gender, male = 51.6% (liraglutide 1.2), 52.5% (liraglutide 1.8), 54.8% (sitagliptin) Age = 55.9 (liraglutide 1.2), 55 (liraglutide 1.8), 55 (sitagliptin) BMI = 32.6 (liraglutide 1.2), 33.1 (liraglutide 1.8), 32.6 (sitagliptin) Weight (kg) = not reported Risk of cardiovascular diseases (e.g. previous MI) = not reported
Intervention	Intervention: liraglutide 1.2 mg (n = 225) and 1.8 mg (n = 221) Background therapy: metformin
Comparison	Comparison: sitagliptin (n = 219)

Bibliographic reference	**Pratley R, Nauck M, Bailey T, et al. (2011). One year of liraglutide treatment offers sustained and more effective glycaemic control and weight reduction compared with sitagliptin, both in combination with metformin, in patients with type 2 diabetes: a randomised, parallel-group, open-label trial. International Journal of Clinical Practice, 65(4), pp.397-407.** **Pratley R, Nauck M, Bailey T, et al. (2010). Liraglutide versus sitagliptin for patients with type 2 diabetes who did not have adequate glycaemic control with metformin: a 26-week, randomised, parallel-group, open-label trial. Lancet (London, and England), 375(9724), pp.1447-56.**
	Background therapy: metformin
Outcome measures	CV mortality Myocardial infarction Heart failure Diabetic retinopathy
Study dates	September 2008 and June 2011
Comments (Risk of bias)	

Bias	Authors judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Computer generated, randomly assigned in a 1:1:1 ratio stratified by country.
Allocation concealment (selection bias)	Low risk	Consecutive allocation of the randomisation code to individual participants was concealed by use of a telephone based or web-based randomisation system.
Blinding of participants and researchers (performance bias)	High risk	Open-labelled.
Blinding of outcome assessment (detection bias)	Low risk	Data was masked from the statistician until database release.
Incomplete outcome data (attrition bias)	High risk	Higher number of patients in Liraglutide 1.2mg group withrew in randomised phase, but similar number in extension phase.

Bibliographic reference	**Pratley R, Nauck M, Bailey T, et al. (2011). One year of liraglutide treatment offers sustained and more effective glycaemic control and weight reduction compared with sitagliptin, both in combination with metformin, in patients with type 2 diabetes: a randomised, parallel-group, open-label trial. International Journal of Clinical Practice, 65(4), pp.397-407.** **Pratley R, Nauck M, Bailey T, et al. (2010). Liraglutide versus sitagliptin for patients with type 2 diabetes who did not have adequate glycaemic control with metformin: a 26-week, randomised, parallel-group, open-label trial. Lancet (London, and England), 375(9724), pp.1447-56.**

Selective reporting (reporting bias)	Low risk	The study protocol is available (NCT00700817) and the outcomes of interest are reported in the pre-specified way.

Bibliographic reference	**Riddle M, Aronson R, Home P, et al. (2013a) Adding once-daily lixisenatide for type 2 diabetes inadequately controlled by established basal insulin: a 24-week, randomized, placebo-controlled comparison (GetGoal-L). Diabetes Care; 36(9):2489-96.**
Study type	A randomised controlled trial to examine the efficacy and safety of adding once-daily lixisenatide to established basal insulin therapy (dosage maintained except for the avoidance of hypoglycaemia), alone or together with metformin, in people with long-duration type 2 diabetes and inadequate glycemic control. Follow-up 24 weeks.
Participants	Inclusion criteria • Adults with type 2 diabetes diagnosed ≥1 year at the time of screening • Use of a basal insulin regimen for ≥3months with a stable dose (±20%) ≥30 units/day for ≥2 months before screening • HbA1c = 7–10% • Candidates using metformin must have taken a stable dose of at least 1.5 g/day (South Korea, at least 1.0 g/day) for at least 3 months before screening Exclusion criteria • FPG >13.9 mmol/L (250 mg/dL) • BMI ≤20.0 kg/m^2 • Weight change >5.0 kg over the 3 months before screening

<table>
<tr><td>Bibliographic reference</td><td>Riddle M, Aronson R, Home P, et al. (2013a) Adding once-daily lixisenatide for type 2 diabetes inadequately controlled by established basal insulin: a 24-week, randomized, placebo-controlled comparison (GetGoal-L). Diabetes Care; 36(9):2489-96.</td></tr>
<tr><td></td><td>• History of unexplained pancreatitis, end-stage renal disease, or allergic reaction to any GLP-1RA in the past
• Pregnancy</td></tr>
<tr><td>Patient characteristics</td><td>Gender = male 45% (lixisenatide); 49% (placebo)
Age = mean (SD) 57 years (10) (lixisenatide); 57 years (10) (placebo)
BMI = mean (SD) 31.9 kg/m^2 (6.2) (lixisenatide); 32.6 kg/m^2 (6.3) (placebo)
Weight = mean (SD) 87.1 kg (20.0) (lixisenatide); 88.9 kg (20.8) (placebo)
Risk of cardiovascular diseases (e.g. previous MI) = not reported.</td></tr>
<tr><td>Intervention</td><td>Intervention: once-daily lixisenatide in a two-step dose-increase regimen from 10 µg up to 20 µg given subcutaneously within 1 h before the morning meal (328 participants)
Background therapy: If used at enrolment, metformin was continued at a stable dose throughout the study and basal insulin dosage was to remain relatively stable throughout the study.</td></tr>
<tr><td>Comparison</td><td>Comparison: once-daily placebo in a two-step dose-increase regimen from 10 µg up to 20 µg given subcutaneously within 1 h before the morning meal (167 participants)
Background therapy: If used at enrolment, metformin was continued at a stable dose throughout the study and basal insulin dosage was to remain relatively stable throughout the study.</td></tr>
<tr><td>Outcome measures</td><td>Sudden cardiac death</td></tr>
<tr><td>Study dates</td><td>July 2008 to February 2011.</td></tr>
<tr><td>Comments (Risk of bias)</td><td>
<table>
<tr><th>Bias</th><th>Authors judgment</th><th>Support for judgment</th></tr>
<tr><td>Random sequence generation (selection bias)</td><td>Low risk</td><td>Treatment numbers were allocated on day 1, using an interactive voice-response system, after completion of the baseline assessment.</td></tr>
<tr><td>Allocation concealment (selection bias)</td><td>Low risk</td><td>Eligible participants were centrally randomised.</td></tr>
<tr><td>Blinding of participants and researchers (performance bias)</td><td>Low risk</td><td>Lixisenatide or placebo was packaged into treatment kits and labelled with a number.</td></tr>
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Bibliographic reference	**Riddle M, Aronson R, Home P, et al. (2013a) Adding once-daily lixisenatide for type 2 diabetes inadequately controlled by established basal insulin: a 24-week, randomized, placebo-controlled comparison (GetGoal-L). Diabetes Care; 36(9):2489-96.**

		Investigators did not have access to the randomisation code.
Blinding of outcome assessment (detection bias)	Low risk	A cardiovascular event adjudication committee reviewed masked events.
Incomplete outcome data (attrition bias)	Low risk	Missing outcome data balanced in numbers across groups with similar reasons for missing outcome data across groups.
Selective reporting (reporting bias)	Low risk	The study protocol is available (NCT00975286) and the outcomes of interest are reported in the pre-specified way.

Bibliographic reference	**Riddle M, Forst T, Aronson R, et al. (2013b) Adding once-daily lixisenatide for type 2 diabetes inadequately controlled with newly initiated and continuously titrated basal insulin glargine: a 24-week, randomized, placebo-controlled study (GetGoal-Duo 1). Diabetes Care; 36(9):2497-503.**
Study type	Randomised controlled trial
Participants	Inclusion criteria - Adults with type 2 diabetes for at least 1year at the time of screening. - Use of metformin at a stable dose of at least 1.5 g/day for at least 3 months alone or in combination with a sulfonylurea or glinide or a thiazolidinedione (TZD), or a combination of these - HbA1c ≥7.0 and ≤10% (≥53 to ≤86 mmol/mol) - BMI >20 kg/m^2. Exclusion criteria - use of oral or injectable antihyperglycemic agents other than metformin, sulfonylureas, glinides, and TZDs within 3 months - weight-loss drugs if not at a stable dose for ≥3 months

<table>
<tr><td>Bibliographic reference</td><td>Riddle M, Forst T, Aronson R, et al. (2013b) Adding once-daily lixisenatide for type 2 diabetes inadequately controlled with newly initiated and continuously titrated basal insulin glargine: a 24-week, randomized, placebo-controlled study (GetGoal-Duo 1). Diabetes Care; 36(9):2497-503.</td></tr>
<tr><td></td><td>- history of hypoglycaemia unawareness,
- gastrointestinal disease associated with prolonged nausea and vomiting
- hypersensitivity to insulin glargine or allergic reaction to any GLP-1RAs.</td></tr>
<tr><td>Patient characteristics</td><td>Gender = male: 49% (lixisenatide), 51% (insulin)
Age = mean years: 56 (lixisenatide), 56 (insulin)
BMI = 31.7 (lixisenatide), 32 (insulin)
Weight (kg) = 86.8 (lixisenatide), 87.3 (insulin)
Risk of cardiovascular diseases (e.g. previous MI) = not reported</td></tr>
<tr><td>Intervention</td><td>Intervention: lixisenatide (10 ug for 1 week, 15 ug for 1 week, and then 20ug maintenance dosage if tolerated), with injections self- administered by participants up to 1 hour before breakfast. (223 participants)
Background therapy: Insulin glargine + metformin (+thiazolidinedione if previously used)</td></tr>
<tr><td>Comparison</td><td>Comparison: placebo (223 participants)
Background therapy: Insulin glargine + metformin (+thiazolidinedione if previously used)</td></tr>
<tr><td>Outcome measures</td><td>Myocardial infarction leading to death</td></tr>
<tr><td>Study dates</td><td>October 2009 to August 2011</td></tr>
<tr><td>Comments (Risk of bias)</td><td>
<table>
<tr><th>Bias</th><th>Authors judgment</th><th>Support for judgment</th></tr>
<tr><td>Random sequence generation (selection bias)</td><td>Low risk</td><td>Corresponding treatment numbers for each randomized participant were allocated using a centralized interactive voice response system.</td></tr>
<tr><td>Allocation concealment (selection bias)</td><td>Low risk</td><td>Corresponding treatment numbers for each randomized participant were allocated using a centralized interactive voice response system.</td></tr>
<tr><td>Blinding of participants and researchers (performance bias)</td><td>Low risk</td><td>Double-blinded.</td></tr>
</table>
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Bibliographic reference	**Riddle M, Forst T, Aronson R, et al. (2013b) Adding once-daily lixisenatide for type 2 diabetes inadequately controlled with newly initiated and continuously titrated basal insulin glargine: a 24-week, randomized, placebo-controlled study (GetGoal-Duo 1). Diabetes Care; 36(9):2497-503.**

Blinding of outcome assessment (detection bias)	Low risk	Investigators did not have access to the randomization code, the bioanalyst was blinded,
Incomplete outcome data (attrition bias)	Low risk	Missing outcome data balanced in numbers across groups with similar reasons for missing outcome data across groups.
Selective reporting (reporting bias)	Low risk	The study protocol is available (NCT00975286) and the outcomes of interest are reported in the pre-specified way.

Bibliographic reference	**Rosenstock J, Rodbard H, Bain S, et al. (2016a) Prandial Options to Advance Basal Insulin Glargine Therapy: Testing Lixisenatide Plus Basal Insulin Versus Insulin Glulisine Either as Basal-Plus or Basal-Bolus in Type 2 Diabetes: The GetGoal Duo-2 Trial. Diabetes Care; 39(8):1318-28.**
Study type	Randomised controlled trial
Participants	Inclusion criteria - Adults with type 2 diabetes for at least 1 year - BMI > 20 – 40 kg/m^2 - Stable dose of basal insulin (≥ 20 units/day) for at least 2 months before screening alone or combined with stable doses of oral antidiabetic Exclusion criteria - History of gastrointestinal disease - History of unexplained/chronic pancreatitis - Alanine/aspartate aminotransferase, amylase, or lipase levels more than three times the upper limit of normal or calcitonin levels > 20 pg/mL.

<table>
<tr><td>Bibliographic reference</td><td>Rosenstock J, Rodbard H, Bain S, et al. (2016a) Prandial Options to Advance Basal Insulin Glargine Therapy: Testing Lixisenatide Plus Basal Insulin Versus Insulin Glulisine Either as Basal-Plus or Basal-Bolus in Type 2 Diabetes: The GetGoal Duo-2 Trial. Diabetes Care; 39(8):1318-28.</td></tr>
<tr><td>Patient characteristics</td><td>Gender = Male: 46.3% (lixisenatide), 45.3% (insulin glulisine once daily), 44.3% (insulin glulisine 3 times daily)
Age = mean years: 59.8 (lixisenatide), 60.2 (insulin glulisine once daily), 59.4 (insulin glulisine 3 times daily)
BMI = 32.3 (lixisenatide), 31.9 (insulin glulisine once daily), 32.5 (insulin glulisine 3 times daily)
Risk of cardiovascular diseases (e.g. previous MI): not reported</td></tr>
<tr><td>Intervention</td><td>Intervention: Lixisenatide up to 20ug/day (297 participants)
Background therapy: stable dose of basal insulin (≥ 20 units/day) with or without metformin</td></tr>
<tr><td>Comparison</td><td>Comparison:
- Insulin glulisine once daily (298 participants)
- Insulin glulisine 3 times daily (295 participants)
Background therapy: stable dose of basal insulin (≥ 20 units/day) with or without metformin</td></tr>
<tr><td>Outcome measures</td><td>Mortality (death due to chronic heart failure)</td></tr>
<tr><td>Study dates</td><td>January 2013 – December 2014</td></tr>
<tr><td>Comments (Risk of bias)</td><td>
<table>
<tr><th>Bias</th><th>Authors judgment</th><th>Support for judgment</th></tr>
<tr><td>Random sequence generation (selection bias)</td><td>Low risk</td><td>Interactive voice or web system.</td></tr>
<tr><td>Allocation concealment (selection bias)</td><td>Unclear</td><td>Not reported.</td></tr>
<tr><td>Blinding of participants and researchers (performance bias)</td><td>High risk</td><td>Open-labelled.</td></tr>
<tr><td>Blinding of outcome assessment (detection bias)</td><td>Unclear</td><td>Not reported.</td></tr>
<tr><td>Incomplete outcome data (attrition bias)</td><td>Low risk</td><td>Missing outcome data balanced in numbers across groups with similar reasons for missing outcome data across groups.</td></tr>
<tr><td>Selective reporting (reporting bias)</td><td>Low risk</td><td>The study protocol is available (NCT01768559) and the</td></tr>
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Bibliographic reference	**Rosenstock J, Rodbard H, Bain S, et al. (2016a) Prandial Options to Advance Basal Insulin Glargine Therapy: Testing Lixisenatide Plus Basal Insulin Versus Insulin Glulisine Either as Basal-Plus or Basal-Bolus in Type 2 Diabetes: The GetGoal Duo-2 Trial. Diabetes Care; 39(8):1318-28.**
	outcomes of interest are reported in the pre-specified way.

Bibliographic reference	**Seino Y, Min KW, Niemoeller E, et al. (2012) Randomized, double-blind, placebo-controlled trial of the once-daily GLP-1 receptor agonist lixisenatide in Asian patients with type 2 diabetes insufficiently controlled on basal insulin with or without a sulfonylurea (GetGoal-L-Asia). Diabetes Obes Metab; 14(10):910-7.**
Study type	A randomised controlled trial to assess the efficacy and safety of once-daily lixisenatide versus placebo in Asian patients with type 2 diabetes insufficiently controlled on basal insulin ± sulfonylurea. Follow-up: 24 weeks
Participants	Inclusion criteria • Male and female participants aged 25 to 81 years with type 2 diabetes (≥1 year duration) currently on stable basal insulin therapy with or without a sulfonylurea and with HbA1c between 7 and 10% Exclusion criteria • Use of oral or injectable glucose-lowering agents other than sulfonylurea or basal insulin within 3 months prior to the time of screening • Fasting plasma glucose (FPG) at screening >250 mg/dl (13.9 mmol/l) • History of unexplained pancreatitis, chronic pancreatitis, pancreatectomy, stomach/gastric surgery or inflammatory bowel disease • History of metabolic acidosis, including diabetic ketoacidosis, within 1 year prior to screening • History within the previous 6 months of myocardial infarction, stroke or heart failure requiring hospitalization or drug or alcohol abuse • Uncontrolled/inadequately controlled hypertension at the time of screening • Amylase and/or lipase greater than three times or aspartate aminotransferase (AST), alanine aminotransferase (ALT) or alkaline phosphatase (ALP) greater than two times the upper limit of the normal laboratory range • End-stage renal disease and/or dialysis and clinically relevant history of gastrointestinal disease, with prolonged nausea and vomiting during the previous 6 months.
Patient characteristics	Gender = male 44.8% (lixisenatide); 51.0% (placebo) Age = mean (SD) 58.7 years (10.2) (lixisenatide); 58.0 years (10.1) (placebo)

<table>
<tr><td>Bibliographic reference</td><td>Seino Y, Min KW, Niemoeller E, et al. (2012) Randomized, double-blind, placebo-controlled trial of the once-daily GLP-1 receptor agonist lixisenatide in Asian patients with type 2 diabetes insufficiently controlled on basal insulin with or without a sulfonylurea (GetGoal-L-Asia). Diabetes Obes Metab; 14(10):910-7.</td></tr>
<tr><td></td><td>BMI = mean (SD) 25.4 kg/m^2 (3.7) (lixisenatide); 25.2 kg/m^2 (3.9) (placebo)
Weight = mean (SD) 65.93 kg (13.0)(lixisenatide); 65.6 kg (12.47) (placebo)
Risk of cardiovascular diseases (e.g. previous MI) = not reported</td></tr>
<tr><td>Intervention</td><td>Intervention: lixisenatide up to 20 µg administered subcutaneously once daily within 1 h before breakfast (154 participants)
Background therapy: established doses of basal insulin with or without sulfonylureas.</td></tr>
<tr><td>Comparison</td><td>Comparison: placebo administered subcutaneously once daily within 1 h before breakfast (157 participants)
Background therapy: established doses of basal insulin with or without sulfonylureas.</td></tr>
<tr><td>Outcome measures</td><td>Nonfatal ischemic stroke</td></tr>
<tr><td>Study dates</td><td>Not reported</td></tr>
<tr><td>Comments (Risk of bias)</td><td>
<table>
<tr><th>Bias</th><th>Authors judgment</th><th>Support for judgment</th></tr>
<tr><td>Random sequence generation (selection bias)</td><td>Low risk</td><td>Randomisation of subjects and allocation of medication was performed using an interactive voice response system.</td></tr>
<tr><td>Allocation concealment (selection bias)</td><td>Low risk</td><td>Randomisation of subjects and allocation of medication was performed using an interactive voice response system.</td></tr>
<tr><td>Blinding of participants and researchers (performance bias)</td><td>Low risk</td><td>The study was double-blind to assigned treatment, but not to treatment volume but outcomes of interest are not likely to be influenced by lack of blinding.</td></tr>
<tr><td>Blinding of outcome assessment (detection bias)</td><td>Low risk</td><td>Unclear if there was blinding of outcome assessment but cardiovascular and microvascular outcomes are not likely to be influenced by lack of blinding.</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Seino Y, Min KW, Niemoeller E, et al. (2012) Randomized, double-blind, placebo-controlled trial of the once-daily GLP-1 receptor agonist lixisenatide in Asian patients with type 2 diabetes insufficiently controlled on basal insulin with or without a sulfonylurea (GetGoal-L-Asia). Diabetes Obes Metab; 14(10):910-7.**

Incomplete outcome data (attrition bias)	Low risk	Missing outcome data balanced in numbers across groups with similar reasons for missing outcome data across groups.
Selective reporting (reporting bias)	Low risk	The study protocol is not available but all expected outcomes were reported.

Bibliographic reference	**Weinstock R, Guerci B, Umpierrez G, et al. (2015). Safety and efficacy of once-weekly dulaglutide versus sitagliptin after 2years in metformin-treated patients with type 2 diabetes (AWARD-5): a randomized, phase III study. Diabetes, and Obesity & Metabolism, 17(9), pp.849-58.**
Study type	A randomised controlled trial Follow-up: 104 weeks
Participants	Inclusion criteria • Aged 18 – 75 years with T2D • HbA1c of > 8% and ≤ 9.5% on diet and exercise alone or ≥ 7% and ≤9.5% on monotherapy or combination therapy (metformin lus another antihyperglycaemic) • BMI of 25-40 kg/m^2 Exclusion criteria • Not reported.
Patient characteristics	Gender = 47% were male Age = 54 years BMI = 31 kg/m^2 Weight = not reported Risk of cardiovascular diseases (e.g. previous MI) = not reported
Intervention	Intervention: Dulaglutide 1.5 mg n = 304 Background therapy: metformin

<table>
<tr><td>Bibliographic reference</td><td>Weinstock R, Guerci B, Umpierrez G, et al. (2015). Safety and efficacy of once-weekly dulaglutide versus sitagliptin after 2years in metformin-treated patients with type 2 diabetes (AWARD-5): a randomized, phase III study. Diabetes, and Obesity & Metabolism, 17(9), pp.849-58.</td></tr>
<tr><td>Comparison</td><td>Comparison: Sitagliptin 100 mg n = 315
Background therapy: metformin</td></tr>
<tr><td>Outcome measures</td><td>Cardiovascular mortality</td></tr>
<tr><td>Study dates</td><td>Not reported</td></tr>
<tr><td>Comments (Risk of bias)</td><td>
<table>
<tr><th>Bias</th><th>Authors judgment</th><th>Support for judgment</th></tr>
<tr><td>Random sequence generation (selection bias)</td><td>Low risk</td><td>Computer generated random sequence using an interactive voice response system.</td></tr>
<tr><td>Allocation concealment (selection bias)</td><td>Unclear risk</td><td>Not reported.</td></tr>
<tr><td>Blinding of participants and researchers (performance bias)</td><td>Low risk</td><td>Double-blinded.</td></tr>
<tr><td>Blinding of outcome assessment (detection bias)</td><td>Low risk</td><td>Cardiovascular events were adjudicated by an independent committee.</td></tr>
<tr><td>Incomplete outcome data (attrition bias)</td><td>Low risk</td><td>Missing outcome data balanced in numbers across groups with similar reasons for missing outcome data across groups.</td></tr>
<tr><td>Selective reporting (reporting bias)</td><td>Low risk</td><td>The study protocol is not available but all expected outcomes were reported.</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Yu Pan C, Han P, Liu X, et al. (2014). 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/Metabolism Research Reviews, 30(8), pp.726-35.**
Study type	A randomised controlled trial Follow-up: 24 week
Participants	Inclusion criteria • Male and female Asan (China, Hong Kong, Malaysia, and Thailand) participants with T2D diagnosed for at least 1 year and inadequately controlled on metformin wit or without sulphonylurea. • Stable dose of metformin between 1 and 1.5 mg/day • Stable sulphonylurea at maximum effective dose for 3 months prior to screening Exclusion criteria • History of hypoglycaemia unawareness • History of unexplained pancreatitis • Pancreactomy • Stomach/gastric surgery • Inflammatory bowel disease or patients considered by the investigator at high risk of acute pancreatitis • Personal/family history of medullary thyroid cancer • History of metabolic acidosis, including diabetic ketoacidosis within 1 year prior to screening • Renal impairment • History of gastrointestinal disease
Patient characteristics	Gender = male 55.5% (lixisenatide); 46.9% (placebo) Age = mean (SD) 54.5 years (10.2) (lixisenatide); 55.1 years (10.1) (placebo) BMI = mean (SD) 26.8 kg/m^2 (3.7) (lixisenatide); 27.1 kg/m^2 (3.9) (placebo) Weight = mean (SD) 73.2 kg (13.0)(lixisenatide); 72.7 kg (12.47) (placebo) Risk of cardiovascular diseases (e.g. previous MI) = not reported
Intervention	Intervention: Lixisenatide 20 ug n = 196 Background therapy: metformin with or without sulphonylurea
Comparison	Comparison: Placebo n = 194 Background therapy: metformin with or without sulphonylurea

Bibliographic reference	**Yu Pan C, Han P, Liu X, et al. (2014). 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/Metabolism Research Reviews, 30(8), pp.726-35.**
Outcome measures	Cardiovascular mortality
Study dates	Not reported

Comments (Risk of bias)

Bias	Authors judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Interactive voice response system/interactive web-based system.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of participants and researchers (performance bias)	Low risk	Double-blinded.
Blinding of outcome assessment (detection bias)	Unclear risk	Not reported.
Incomplete outcome data (attrition bias)	Low risk	Missing outcome data balanced in numbers across groups with similar reasons for missing outcome data across groups.
Selective reporting (reporting bias)	Low risk	The study protocol is not available but all expected outcomes were reported.

A number of studies did not report any relevant events taking place within the study, but did report that no cardiovascular deaths occurred in either arm of the trial. These studies cannot be included in the meta-analysis because it is not possible to calculate a relative risk when no events occur in either arm. A brief summary of these studies is reported below.

Study	Sample size	Intervention	Comparator	Background treatment
Ahren B, Dimas A, Miossec P, et al (2013) Efficacy and safety of lixisenatide once-daily morning or evening injections in type 2 diabetes inadequetly controlled on metformin (GetGoal-M). Diabetes Care; 36:2543-50	680	Lixisenatide once daily	Placebo once daily	Metformin
Davies M, Heller S, Sreenan S, et al (2013) Once-weekly exenatide versus once- or twice-daily insulin detemir. Diabetes care 36(5), 1368-76	216	Exenatide once weekly	insulin detemir	Metformin or a combination of metformin and a sulfonylurea
Ferdinand K, White W, Calhoun D, et al. (2014). Effects of the once-weekly glucagon-like peptide-1 receptor agonist dulaglutide on ambulatory blood pressure and heart rate in patients with type 2 diabetes mellitus. Hypertension, 64(4), pp.731-7.	755	Dulaglutide once weekly	Placebo	Baseline oral antihyperglycaemic
Grunberger G, Chang A, Garcia Soria G, et al (2012) Monotherapy with the once-weekly GLP-1 analogue dulaglutide for 12 weeks in patients with Type 2 diabetes: dose-dependent effects on glycaemic control in a randomized, double-blind, placebo-controlled study. Diabetic medicine; 29(10):1260-7	167	Dulaglutide once weekly	Placebo once weekly	None
Kadowaki T, Namba M, Iwamoto K, et al. (2010). Improved glycemic control and reduced body weight with exenatide twice daily: A 24-week, double-blind, randomized, placebo-controlled, parallel, phase 3 study in japanese patients with type 2 diabetes over 24 weeks. Journal of diabetes investigation, 2(3), pp.210-217. Kadowaki T, Namba M, Yamamura A, et al. (2009). Exenatide exhibits dose-dependent effects on glycemic control over 12 weeks in Japanese patients with suboptimally controlled type 2 diabetes. Endocrine Journal, 56(3), pp.415-24.	153	Exenatide twice daily	Placebo	Sulphonylurea, sulphonylurea with biguanide, sulphonylurea with thiazolidinedione
Kaku K, Rasmussen MF, Clauson P, et al (2010) Improved glycaemic control with minimal hypoglycaemia	264	Liraglutide once daily	Placebo once daily	Sulphonylurea

Study	Sample size	Intervention	Comparator	Background treatment
and no weight change with the once-daily human glucagon-like peptide-1 analogue liraglutide as add-on to sulphonylurea in Japanese patients with type 2 diabetes. Diabetes, Obesity and Metabolism; 12(4):341-7				
Kapitza C, Forst T, Coester HV, et al (2013) Pharmacodynamic characteristics of lixisenatide once daily versus liraglutide once daily in patients with type 2 diabetes insufficiently controlled on metformin. Diabetes, Obesity and Metabolism; 15:642–649	148	Lixisenatide once daily	Liraglutide once daily	Metformin
Miyagawa J, Odawara M, Takamura T, et al. (2015) Once-weekly glucagon-like peptide-1 receptor agonist dulaglutide is non-inferior to once-daily liraglutide and superior to placebo in Japanese patients with type 2 diabetes: a 26-week randomized phase III study. Diabetes, and Obesity & Metabolism 17(10), 974-83 Odawara M, Miyagawa J, Iwamoto N, et al. (2016). Once-weekly glucagon-like peptide-1 receptor agonist dulaglutide significantly decreases glycated haemoglobin compared with once-daily liraglutide in Japanese patients with type 2 diabetes: 52weeks of treatment in a randomized phase III study. Diabetes, and Obesity & Metabolism, 18(3), pp.249-57.	492	Dulaglutide once weekly Liraglutide once daily	Placebo	None or diet and exercise only
Marre M, Shaw J, Brändle M, et al (2009) Liraglutide, a once-daily human GLP-1 analogue, added to a sulphonylurea over 26 weeks produces greater improvements in glycaemic and weight control compared with adding rosiglitazone or placebo in subjects with Type 2 diabetes (LEAD-1 SU). Diabetic Medicine; 26:268-78	1,041	Liraglutide once daily	Placebo once daily	Glimepiride
Mathieu C, Rodbard HW, Cariou B, et al (2014) A comparison of adding liraglutide versus a single daily dose of insulin aspart to insulin degludec in subjects with	177	Liraglutide once daily	Insulin aspart	Insulin degludec and metformin

Study	Sample size	Intervention	Comparator	Background treatment
type 2 diabetes (BEGIN: VICTOZA ADD-ON). Diabetes, Obesity and Metabolism; 16:636–644				
Seino Y, Nakajima H, Miyahara H, et al. (2009). Safety, tolerability, pharmacokinetics and pharmacodynamics of albiglutide, a long-acting GLP-1-receptor agonist, in Japanese subjects with type 2 diabetes mellitus. Current Medical Research & Opinion, 25(12), pp.3049-57.	40	Abliglutide weekly and biweekly	Placebo	Diet or a signle oral antihyperglycaemic (other than thiazolidinedone)
Seino Y, Takami A, Boka G, et al. (2014). Pharmacodynamics of the glucagon-like peptide-1 receptor agonist lixisenatide in Japanese and Caucasian patients with type 2 diabetes mellitus poorly controlled on sulphonylureas with/without metformin. Diabetes, and Obesity and Metabolism, 16(8), pp.739-747.	120	Lixisenatide once or twice daily	Placebo	Sulphonylureas with or without metformin
Zang L, Liu Y, Geng J, et al (2016) Efficacy and safety of liraglutide versus sitagliptin, both in combination with metformin, in Chinese patients with type 2 diabetes: a 26-week, open-label, randomized, active comparator clinical trial. Diabetes, Obesity and Metabolism 18:803-11	368	Liraglutide once daily	Sitagliptin once daily	Metformin
Zinman B, Gerich J, Buse JB, et al (2009) Efficacy and Safety of the Human Glucagon-Like Peptide-1 Analog Liraglutide in Combination With Metformin and Thiazolidinedione in Patients With Type 2 Diabetes (LEAD-4 Met+TZD). Diabetes Care 32:1224-30	533	Liraglutide once daily	Placebo once daily	Metformin and rosiglitazone
Yu Pan, C., Han, P., Liu, X. et al (2014) 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/metabolism research and reviews, 30(8), pp.726-735.	390	Lixisenatide once daily	Placebo once daily	Metformin with or without sulphylurea

One study did not report any relevant events taking place within the study, but reported that no renal failure events occurred in either arm of the trial. This study cannot be included in the meta-analysis because it is not possible to calculate a relative risk when no events occur in either arm. A brief summary of this study is reported below.

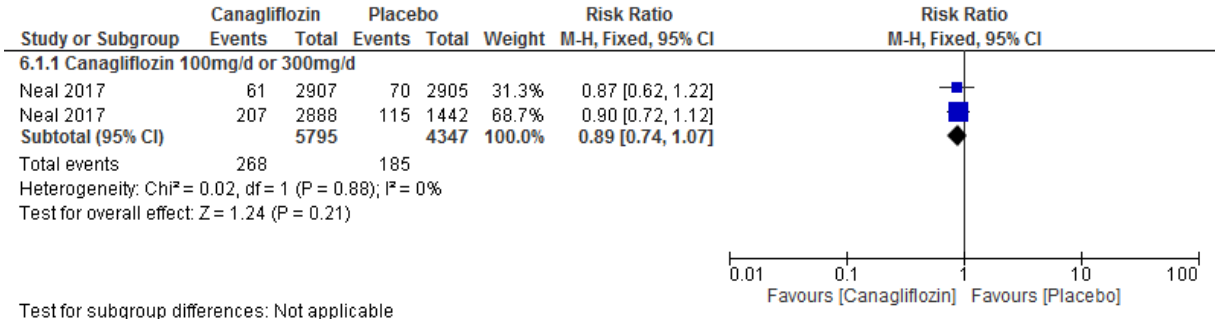
Study	Sample size	Intervention	Comparator	Background treatment
Gadde K, Vetter M, Iqbal N, et al (2017). Efficacy and safety of autoinjected exenatide once-weekly suspension versus sitagliptin or placebo with metformin in patients with type 2 diabetes: the DURATION-NEO-2 randomized clinical study. Diabetes, Obesity and Metabolism.	365	Exenatide once weekly	Sitagliptin once daily or placebo	Metformin

Appendix E – Forest plots

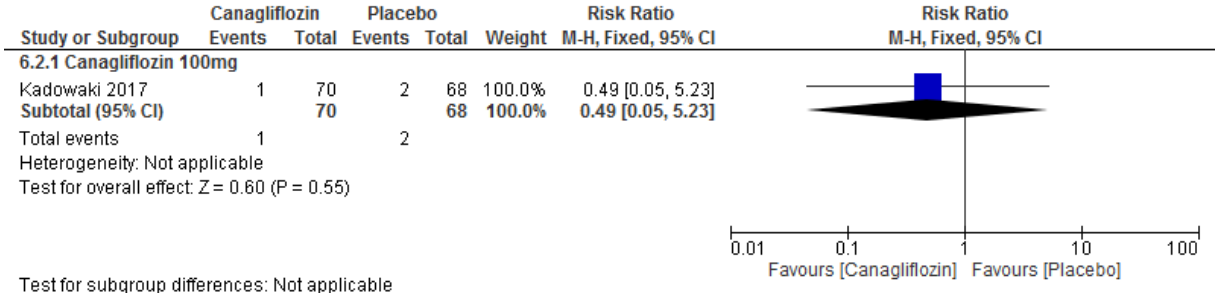
SGLT-2 inhibitors

Canagliflozin vs placebo

CV mortality

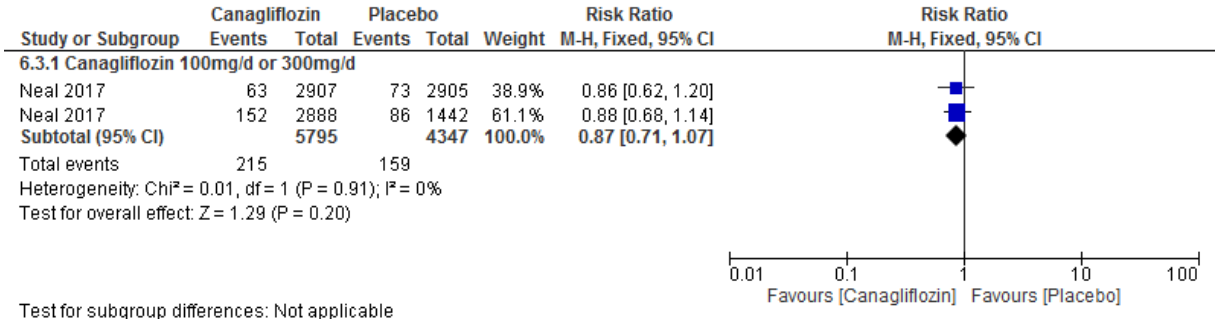


Cardiovascular-related events

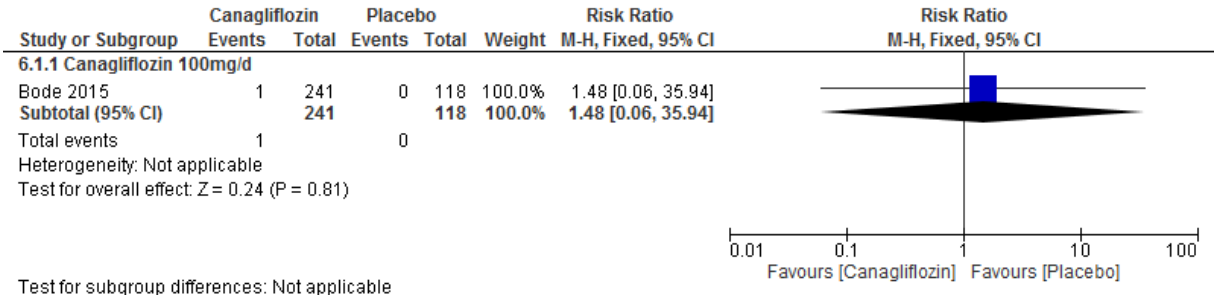


Kadowaki 2017 was not included in the GRADE table because cardiovascular-related events were only reported as adverse events.

Non-fatal MI

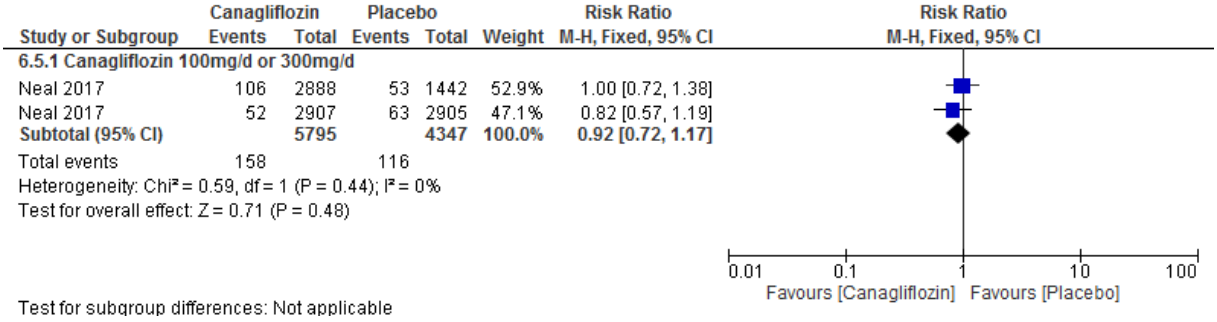


Fatal stroke

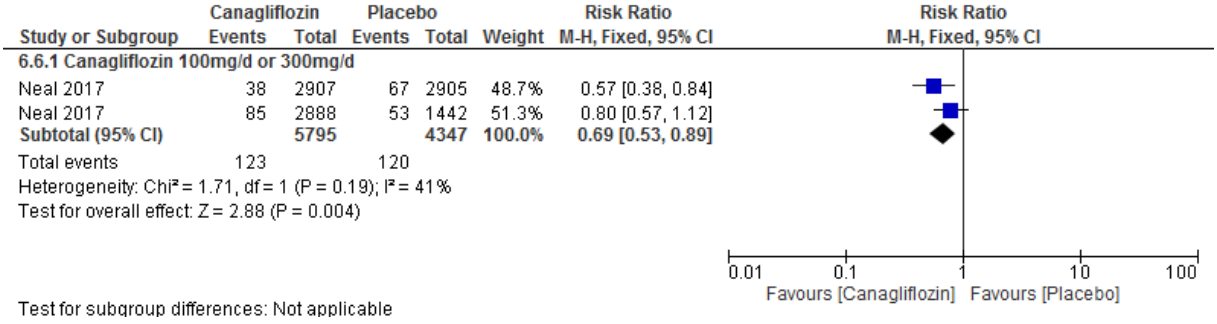


Bode 2015 was not included in the GRADE table because fatal stroke was only reported as an adverse event.

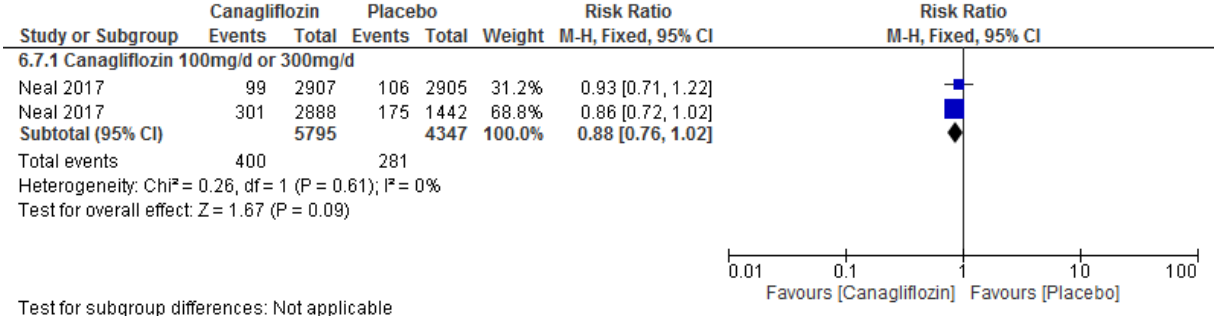
Non-fatal stroke



Hospitalisations for heart failure

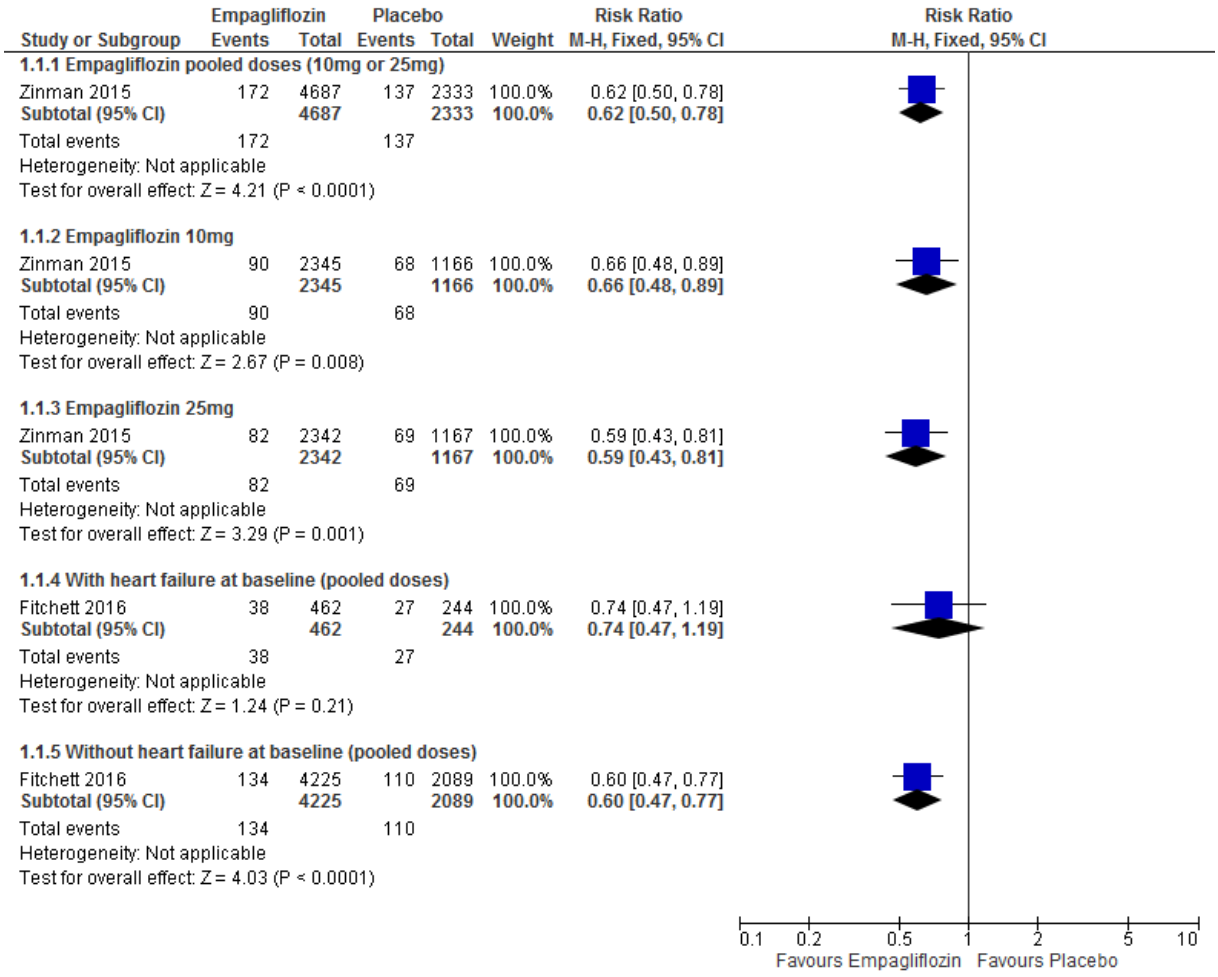


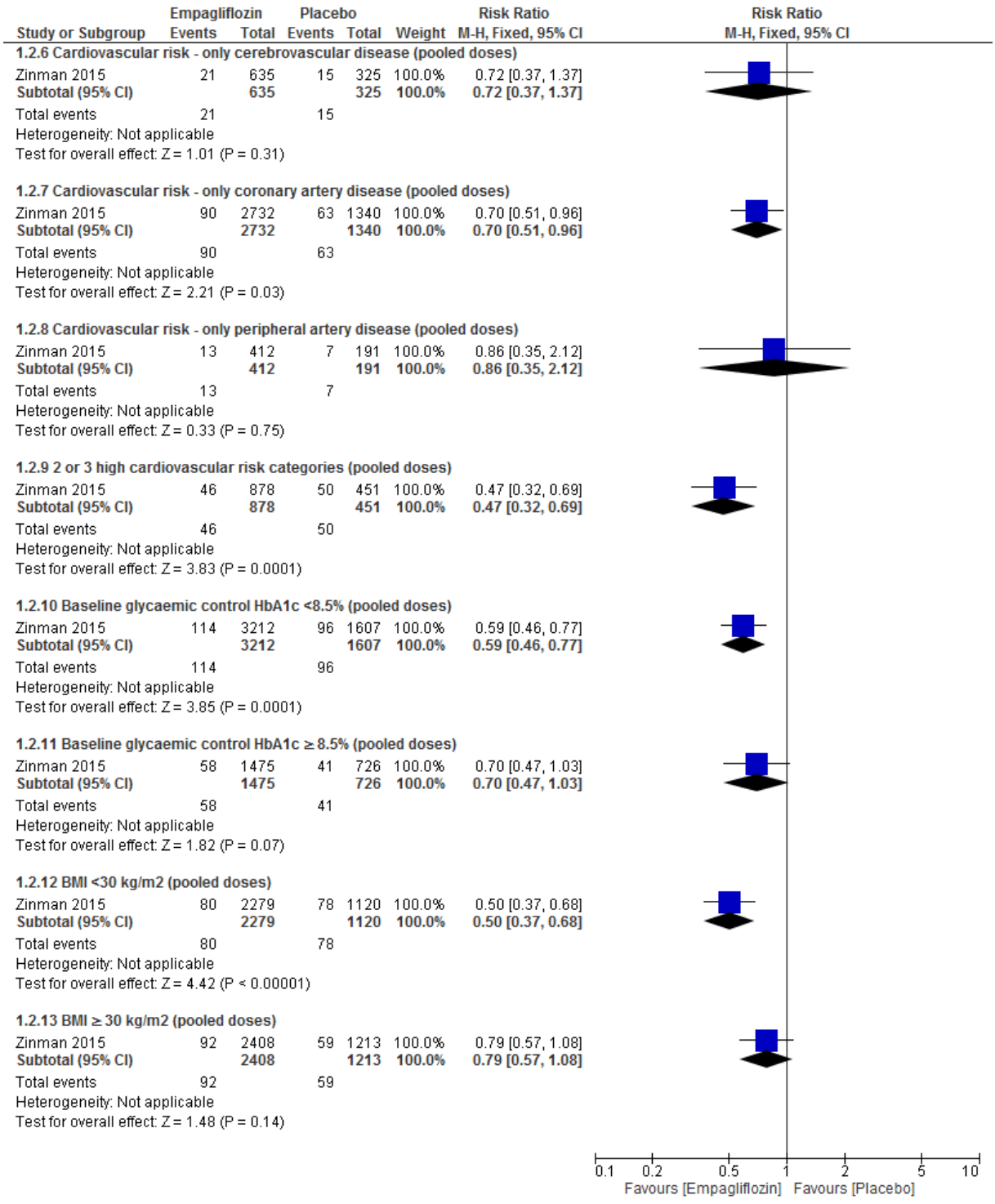
All-cause mortality

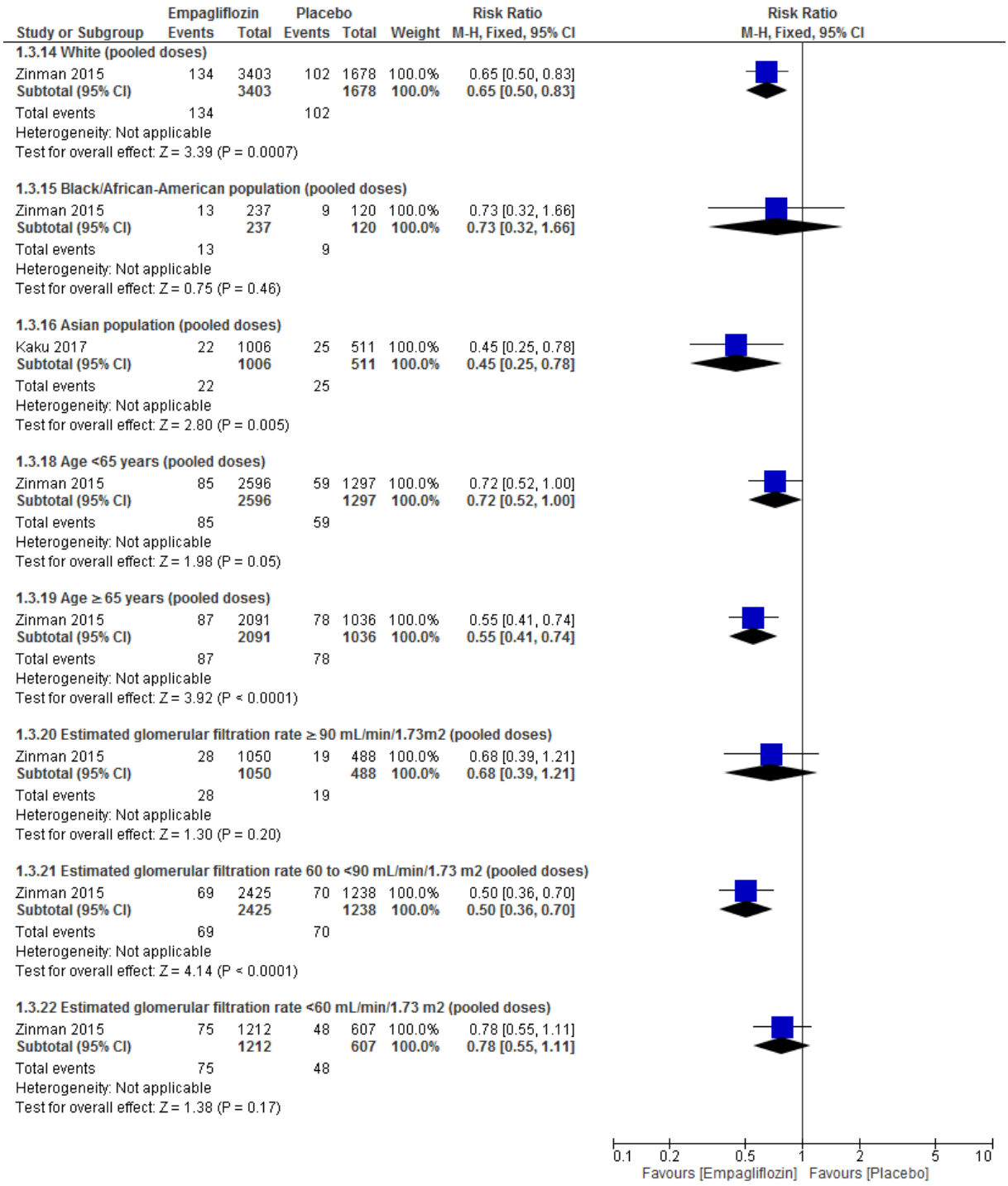


Empagliflozin vs placebo

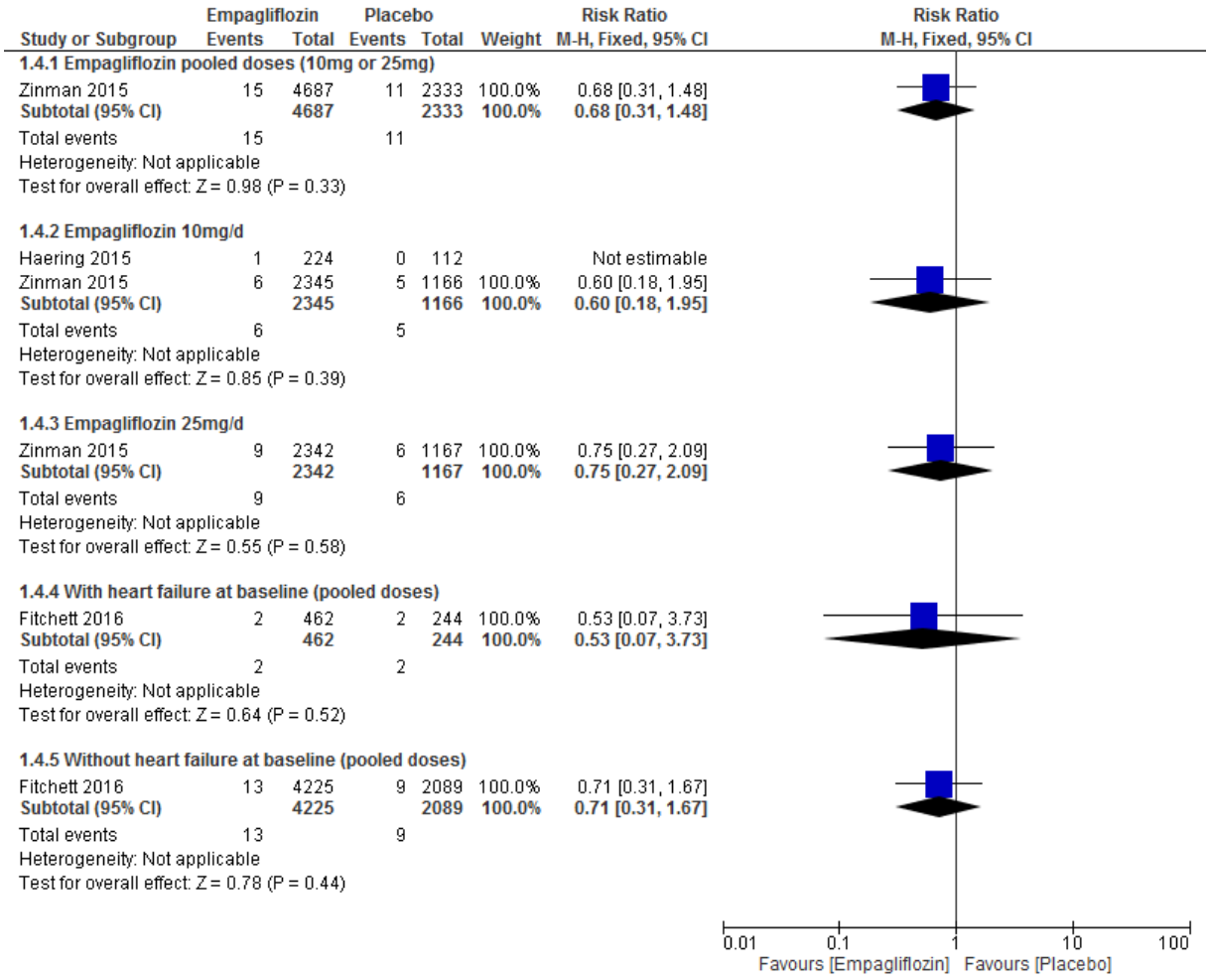
CV mortality




Empagliflozin
Placebo
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
1.2.6 Cardiovascular risk - only cerebrovascular disease (pooled doses)
Zinman 2015 21 635 15 325 100.0% 0.72 [0.37, 1.37]
Subtotal (95% CI) 635 325 100.0% 0.72 [0.37, 1.37]
Total events 21 15
Heterogeneity: Not applicable
Test for overall effect: Z = 1.01 (P = 0.31)
1.2.7 Cardiovascular risk - only coronary artery disease (pooled doses)
Zinman 2015 90 2732 63 1340 100.0% 0.70 [0.51, 0.96]
Subtotal (95% CI) 2732 1340 100.0% 0.70 [0.51, 0.96]
Total events 90 63
Heterogeneity: Not applicable
Test for overall effect: Z = 2.21 (P = 0.03)
1.2.8 Cardiovascular risk - only peripheral artery disease (pooled doses)
Zinman 2015 13 412 7 191 100.0% 0.86 [0.35, 2.12]
Subtotal (95% CI) 412 191 100.0% 0.86 [0.35, 2.12]
Total events 13 7
Heterogeneity: Not applicable
Test for overall effect: Z = 0.33 (P = 0.75)
1.2.9 2 or 3 high cardiovascular risk categories (pooled doses)
Zinman 2015 46 878 50 451 100.0% 0.47 [0.32, 0.69]
Subtotal (95% CI) 878 451 100.0% 0.47 [0.32, 0.69]
Total events 46 50
Heterogeneity: Not applicable
Test for overall effect: Z = 3.83 (P = 0.0001)
1.2.10 Baseline glycaemic control HbA1c <8.5% (pooled doses)
Zinman 2015 114 3212 96 1607 100.0% 0.59 [0.46, 0.77]
Subtotal (95% CI) 3212 1607 100.0% 0.59 [0.46, 0.77]
Total events 114 96
Heterogeneity: Not applicable
Test for overall effect: Z = 3.85 (P = 0.0001)
1.2.11 Baseline glycaemic control HbA1c ≥ 8.5% (pooled doses)
Zinman 2015 58 1475 41 726 100.0% 0.70 [0.47, 1.03]
Subtotal (95% CI) 1475 726 100.0% 0.70 [0.47, 1.03]
Total events 58 41
Heterogeneity: Not applicable
Test for overall effect: Z = 1.82 (P = 0.07)
1.2.12 BMI <30 kg/m2 (pooled doses)
Zinman 2015 80 2279 78 1120 100.0% 0.50 [0.37, 0.68]
Subtotal (95% CI) 2279 1120 100.0% 0.50 [0.37, 0.68]
Total events 80 78
Heterogeneity: Not applicable
Test for overall effect: Z = 4.42 (P < 0.00001)
1.2.13 BMI ≥ 30 kg/m2 (pooled doses)
Zinman 2015 92 2408 59 1213 100.0% 0.79 [0.57, 1.08]
Subtotal (95% CI) 2408 1213 100.0% 0.79 [0.57, 1.08]
Total events 92 59
Heterogeneity: Not applicable
Test for overall effect: Z = 1.48 (P = 0.14)
0.1 0.2 0.5 1 2 5 10
Favours [Empagliflozin] Favours [Placebo]

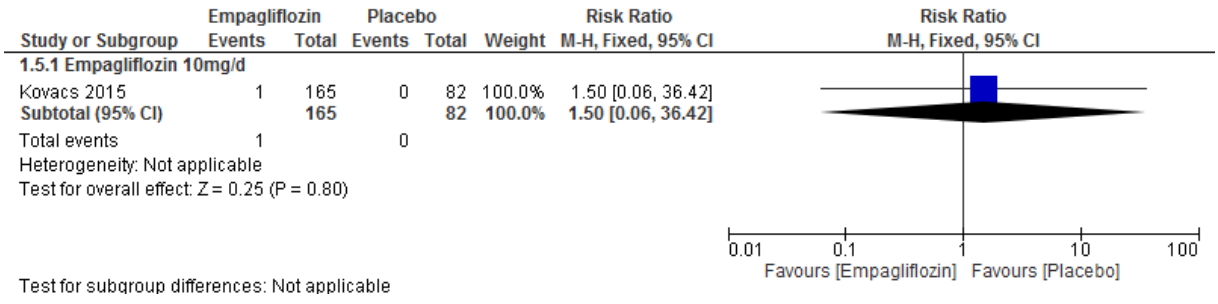

Empagliflozin
Placebo
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
1.3.14 White (pooled doses)
Zinman 2015 134 3403 102 1678 100.0% 0.65 [0.50, 0.83]
Subtotal (95% CI) 3403 1678 100.0% 0.65 [0.50, 0.83]
Total events 134 102
Heterogeneity: Not applicable
Test for overall effect: Z = 3.39 (P = 0.0007)
1.3.15 Black/African-American population (pooled doses)
Zinman 2015 13 237 9 120 100.0% 0.73 [0.32, 1.66]
Subtotal (95% CI) 237 120 100.0% 0.73 [0.32, 1.66]
Total events 13 9
Heterogeneity: Not applicable
Test for overall effect: Z = 0.75 (P = 0.46)
1.3.16 Asian population (pooled doses)
Kaku 2017 22 1006 25 511 100.0% 0.45 [0.25, 0.78]
Subtotal (95% CI) 1006 511 100.0% 0.45 [0.25, 0.78]
Total events 22 25
Heterogeneity: Not applicable
Test for overall effect: Z = 2.80 (P = 0.005)
1.3.18 Age <65 years (pooled doses)
Zinman 2015 85 2596 59 1297 100.0% 0.72 [0.52, 1.00]
Subtotal (95% CI) 2596 1297 100.0% 0.72 [0.52, 1.00]
Total events 85 59
Heterogeneity: Not applicable
Test for overall effect: Z = 1.98 (P = 0.05)
1.3.19 Age ≥ 65 years (pooled doses)
Zinman 2015 87 2091 78 1036 100.0% 0.55 [0.41, 0.74]
Subtotal (95% CI) 2091 1036 100.0% 0.55 [0.41, 0.74]
Total events 87 78
Heterogeneity: Not applicable
Test for overall effect: Z = 3.92 (P < 0.0001)
1.3.20 Estimated glomerular filtration rate ≥ 90 mL/min/1.73m2 (pooled doses)
Zinman 2015 28 1050 19 488 100.0% 0.68 [0.39, 1.21]
Subtotal (95% CI) 1050 488 100.0% 0.68 [0.39, 1.21]
Total events 28 19
Heterogeneity: Not applicable
Test for overall effect: Z = 1.30 (P = 0.20)
1.3.21 Estimated glomerular filtration rate 60 to <90 mL/min/1.73 m2 (pooled doses)
Zinman 2015 69 2425 70 1238 100.0% 0.50 [0.36, 0.70]
Subtotal (95% CI) 2425 1238 100.0% 0.50 [0.36, 0.70]
Total events 69 70
Heterogeneity: Not applicable
Test for overall effect: Z = 4.14 (P < 0.0001)
1.3.22 Estimated glomerular filtration rate <60 mL/min/1.73 m2 (pooled doses)
Zinman 2015 75 1212 48 607 100.0% 0.78 [0.55, 1.11]
Subtotal (95% CI) 1212 607 100.0% 0.78 [0.55, 1.11]
Total events 75 48
Heterogeneity: Not applicable
Test for overall effect: Z = 1.38 (P = 0.17)
0.1 0.2 0.5 1 2 5 10
Favours [Empagliflozin] Favours [Placebo]

Fatal acute MI



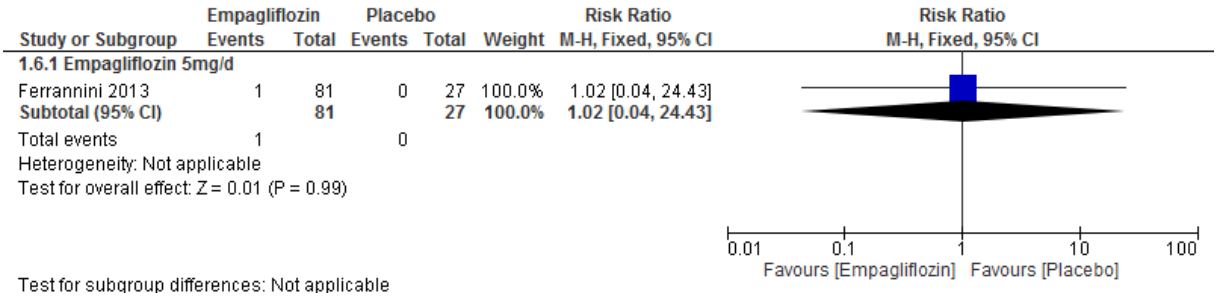
Haering 2015 was not included in the GRADE table because fatal acute MI was only reported as an adverse event.

Fatal MI



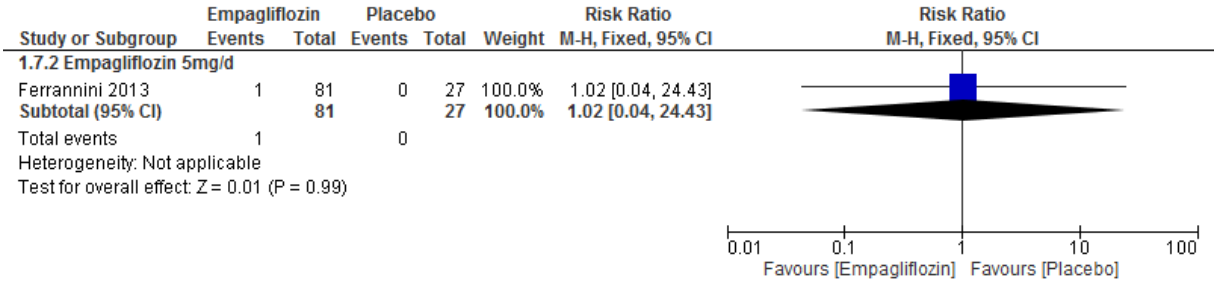
Kovacs 2015 was not included in the GRADE table because fatal MI was only reported as an adverse event.

Non-fatal acute MI



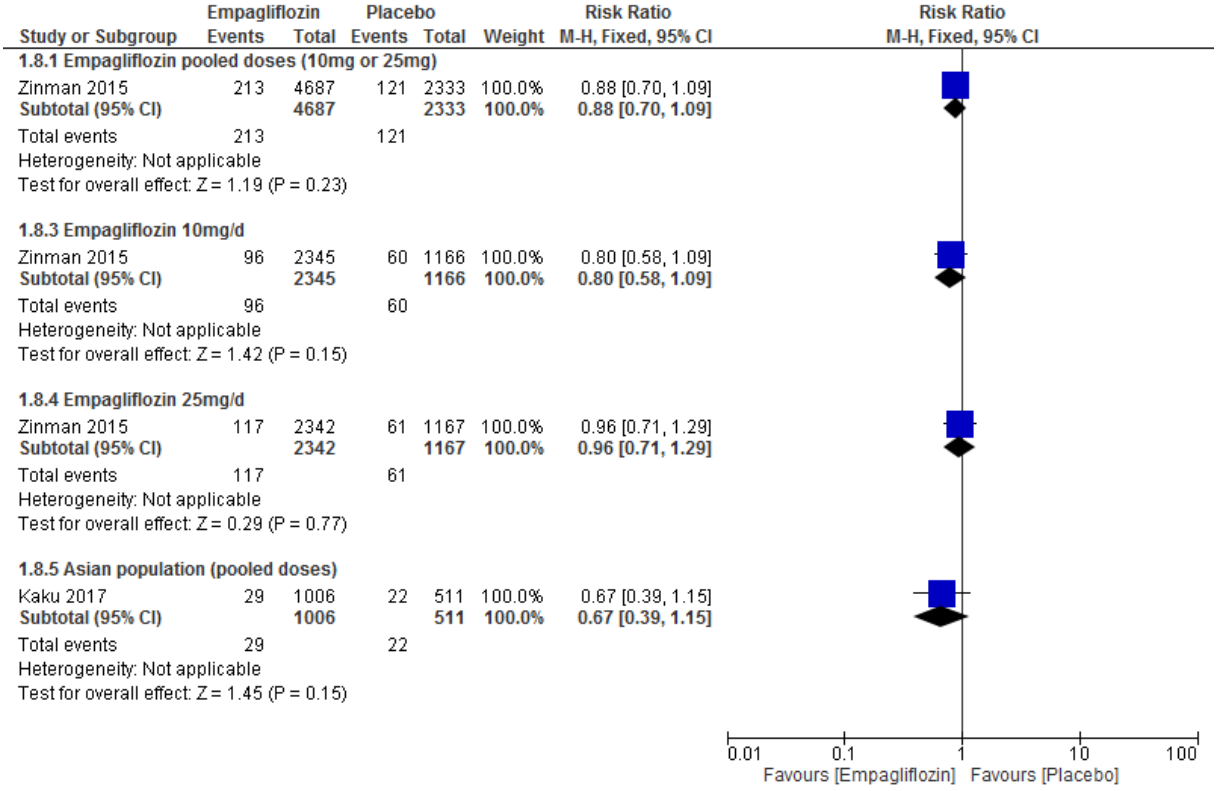
Ferrannini 2013 was not included in the GRADE table because non-fatal acute MI was only reported as an adverse event.

Non-fatal MI

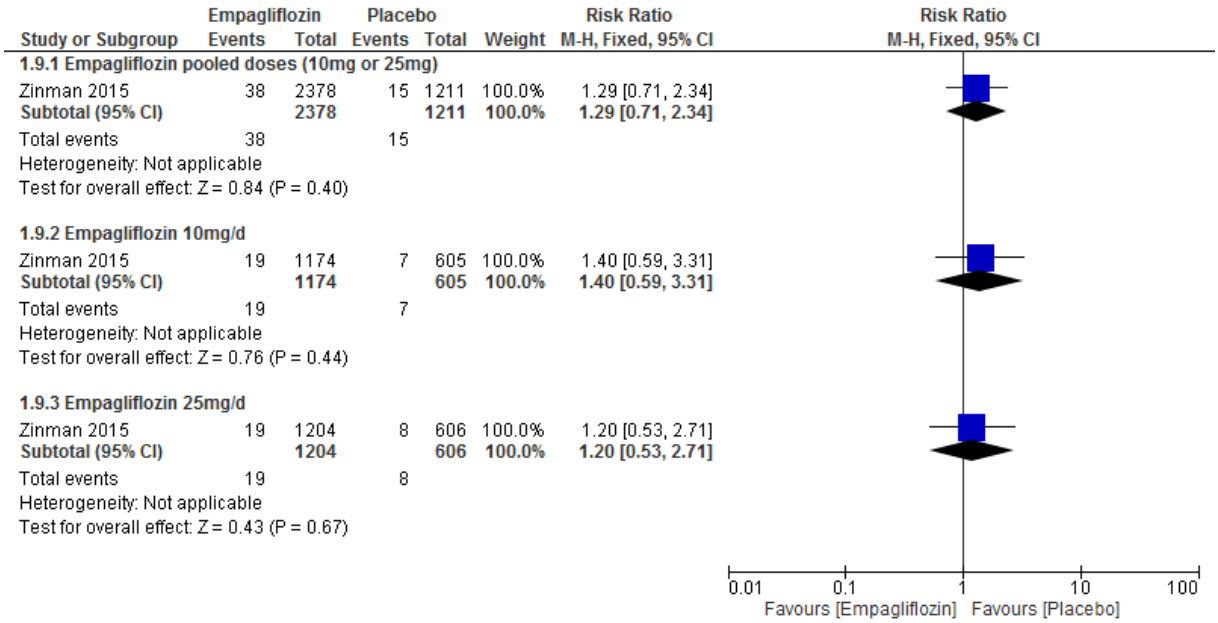


Ferrannini 2013 was not included in the GRADE table because non-fatal MI was only reported as an adverse event.

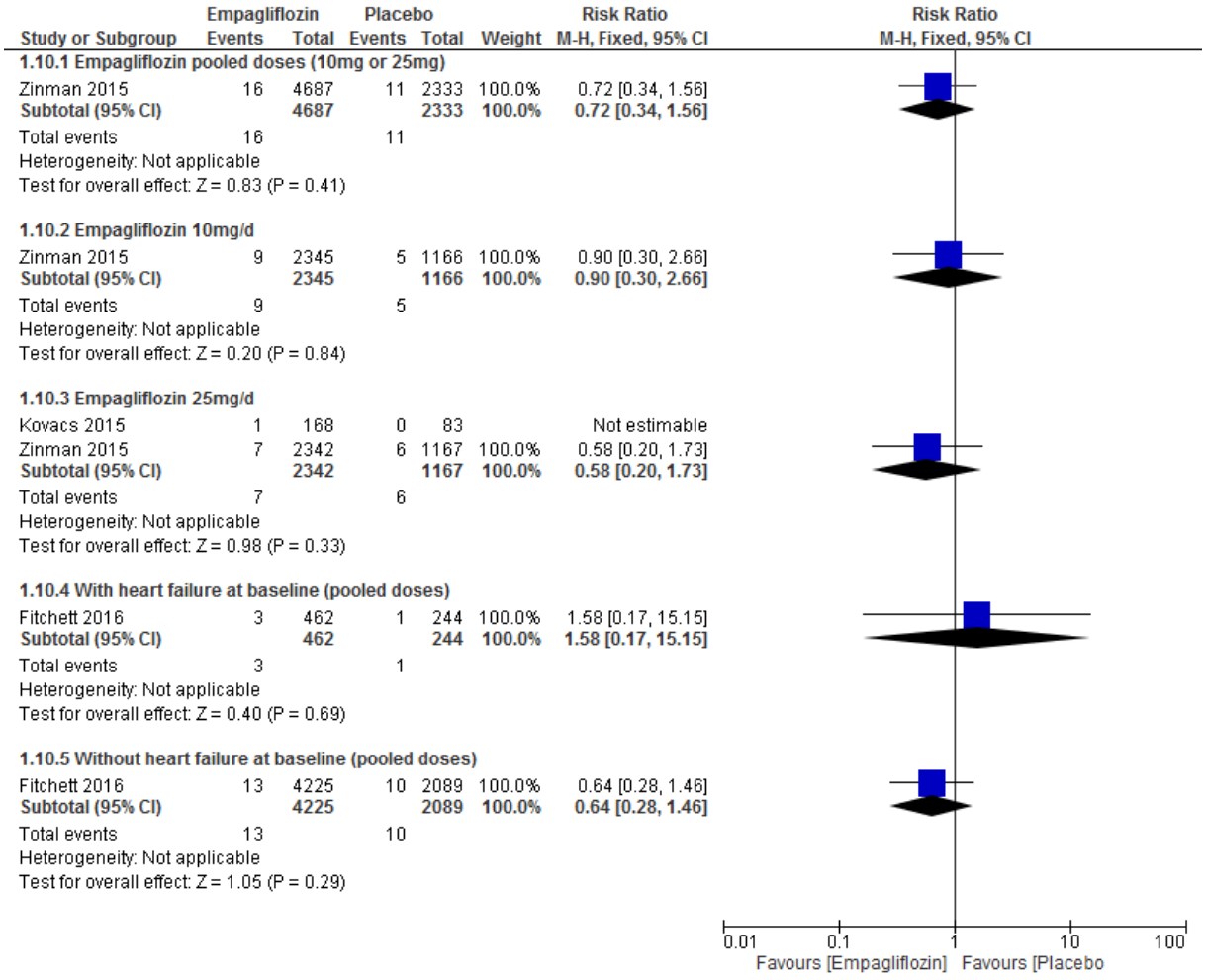
Non-fatal MI excluding silent MI



Non-fatal silent MI

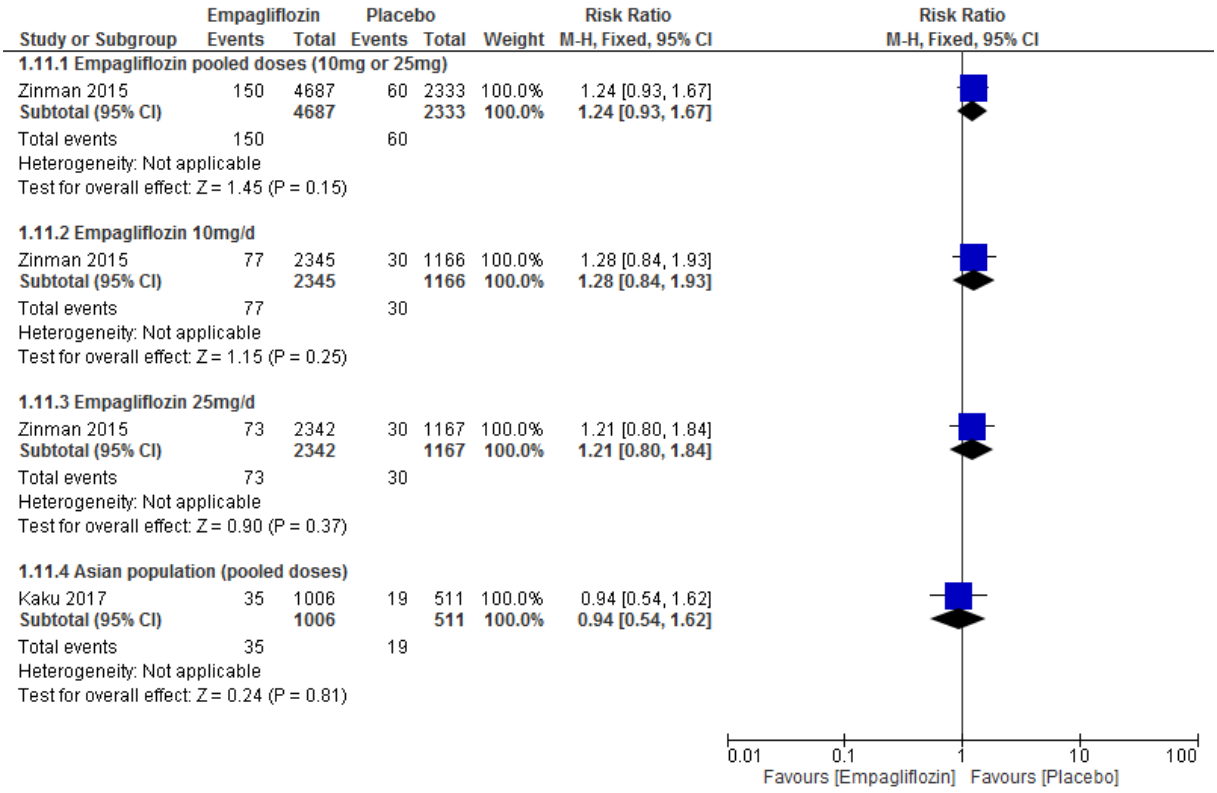


Fatal stroke

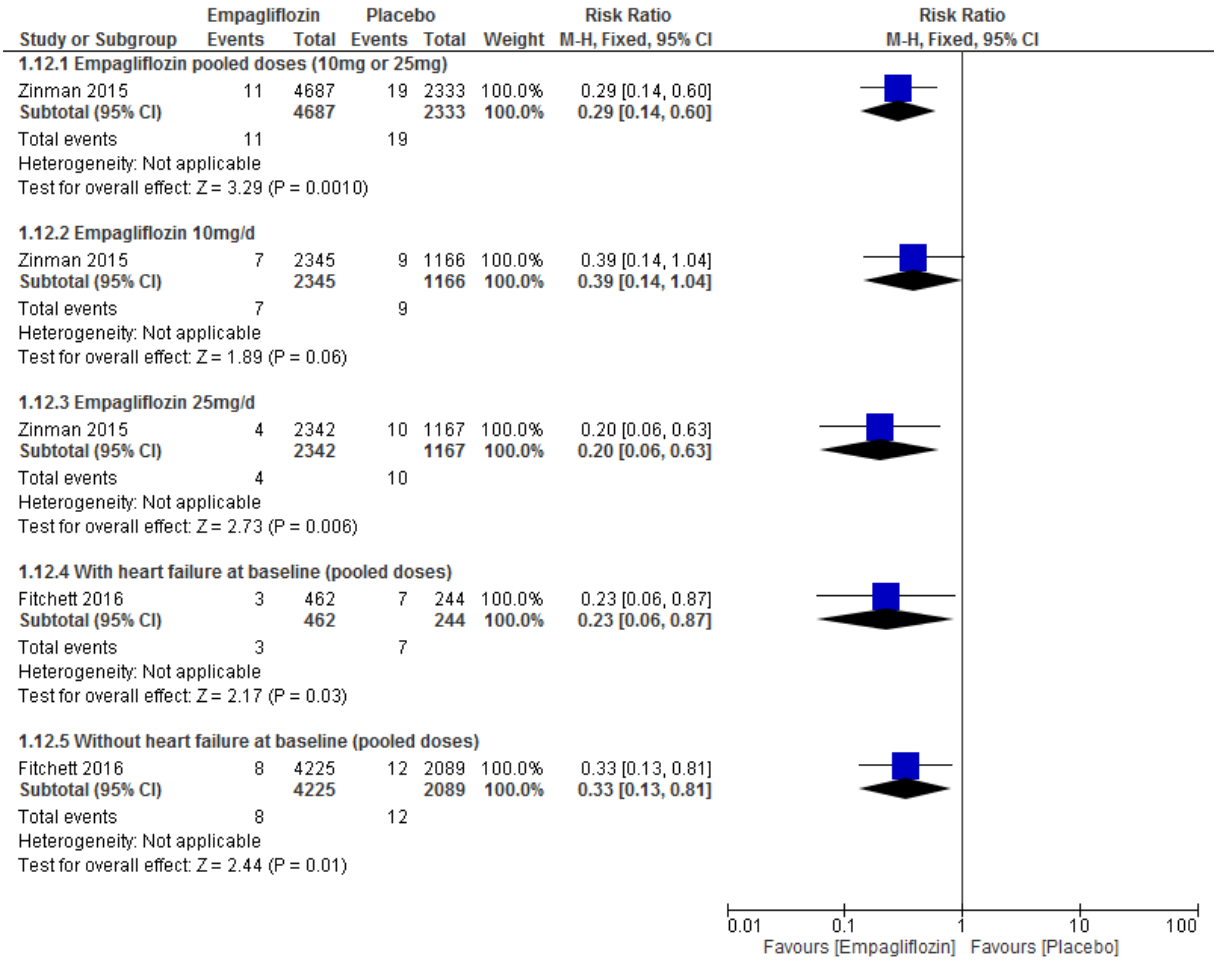


Kovacs 2015 was not included in the GRADE table because fatal stroke was only reported as an adverse event.

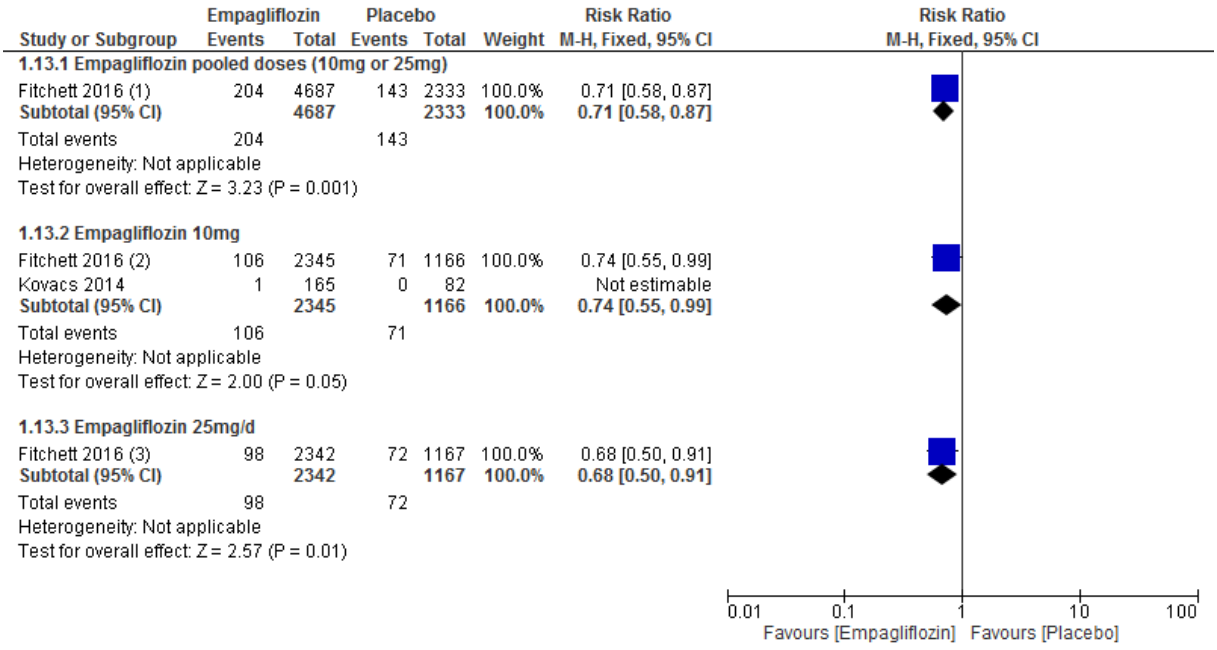
Non-fatal stroke



Fatal heart failure



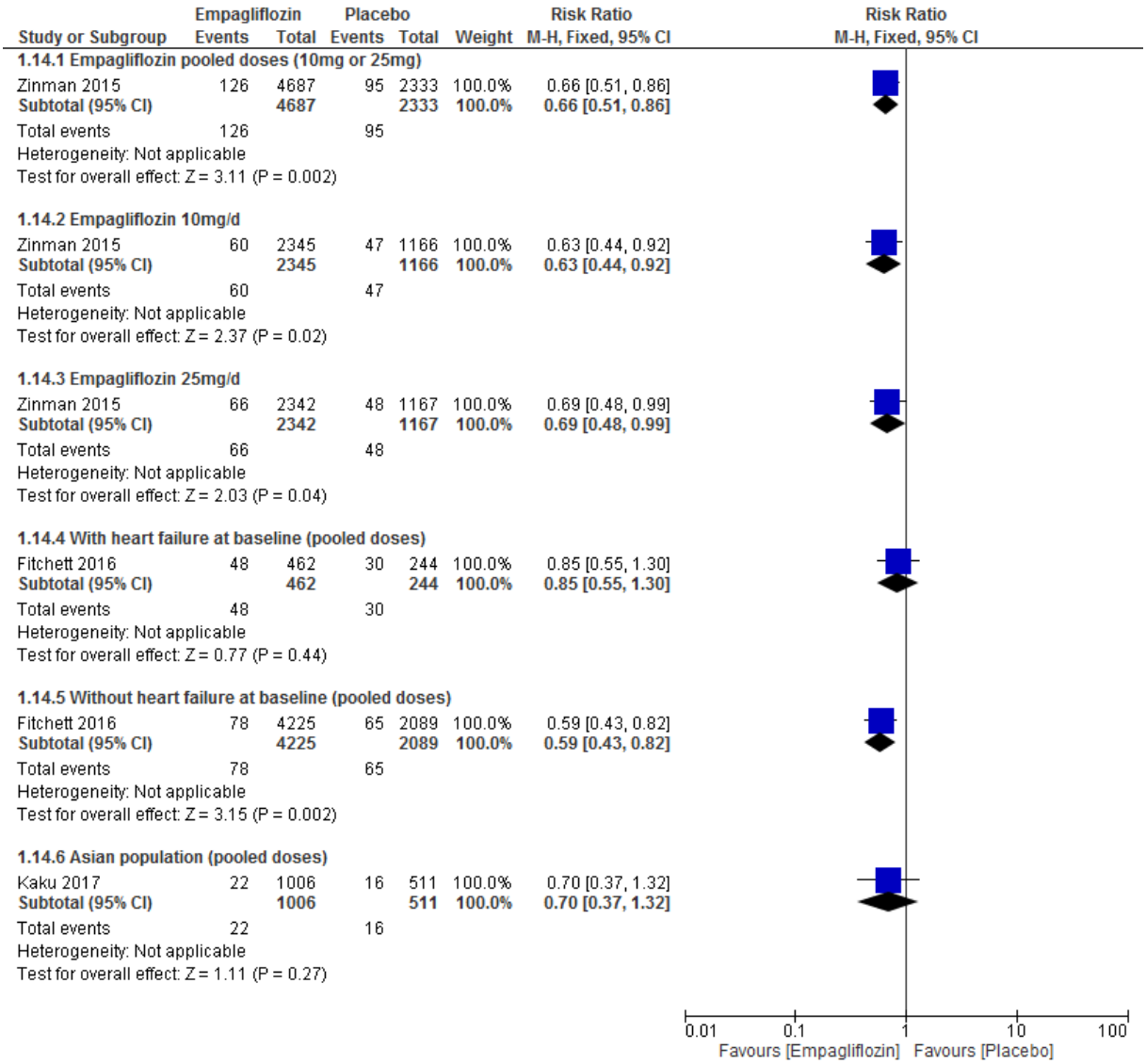
Non-fatal heart failure



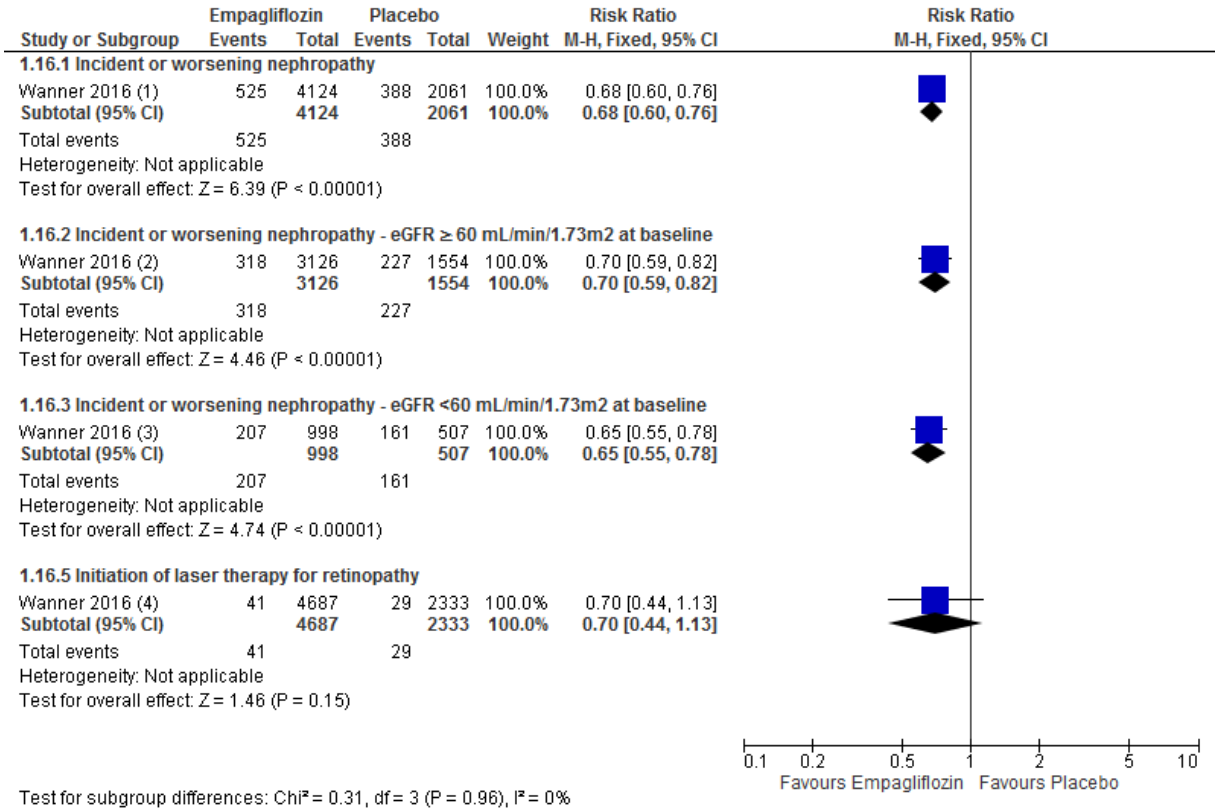
Footnotes
(1) Investigator-reported heart failure
(2) Investigator-reported heart failure
(3) Investigator-reported heart failure

Kovacs 2014 was not included in the GRADE table because fatal stroke was only reported as an adverse event.

Hospitalisation for heart failure



Microvascular outcomes (empagliflozin pooled doses [10mg/d or 25mg/d])

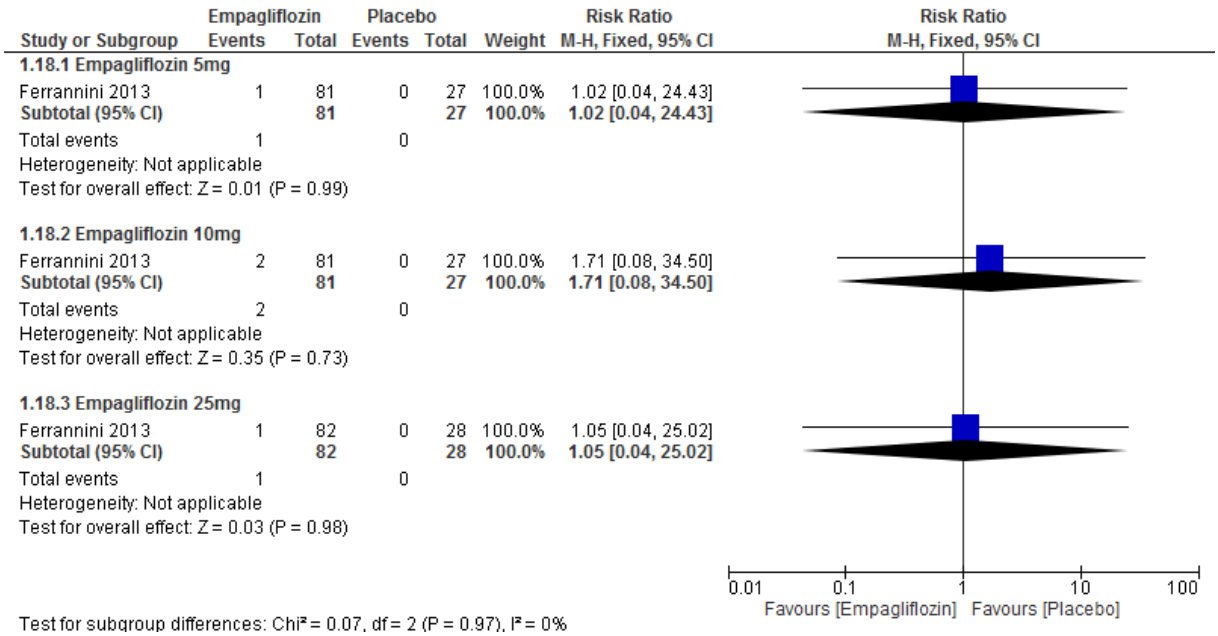


Test for subgroup differences: Chi² = 0.31, df = 3 (P = 0.96), I² = 0%

Footnotes

(1) Participants who received at least one dose of either empagliflozin or placebo.
(2) Participants with prevalent kidney disease treated with ≥1 dose of study drug.
(3) Participants with prevalent kidney disease treated with ≥1 dose of study drug.
(4) Participants treated with ≥1 dose of study drug.

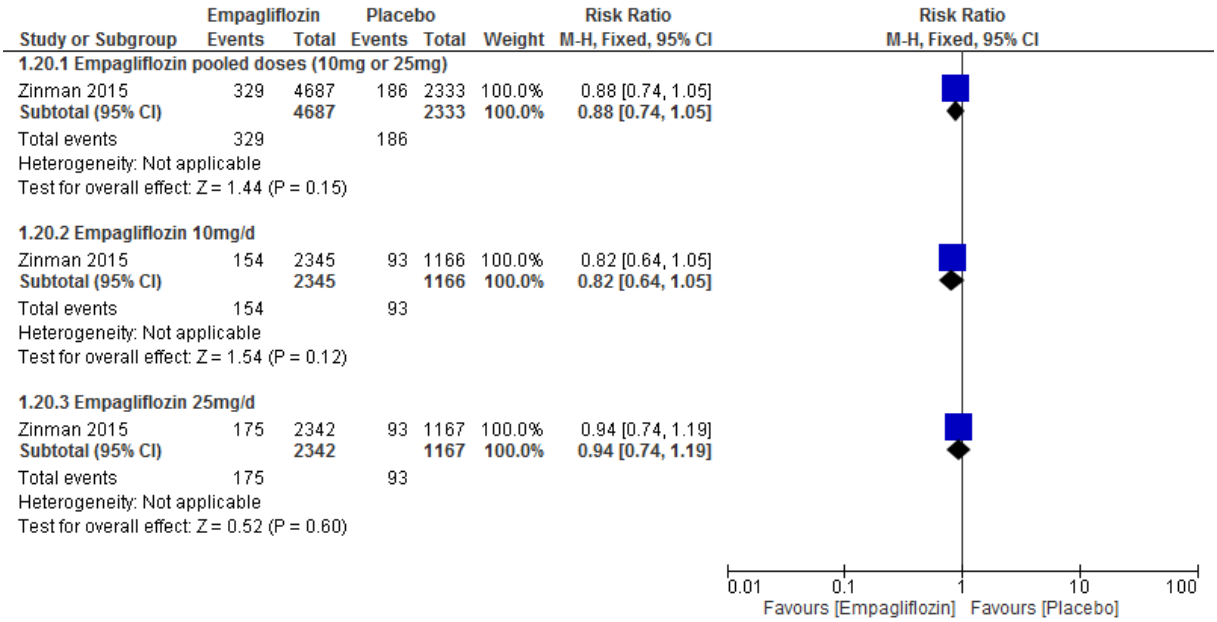
Diabetic nephropathy



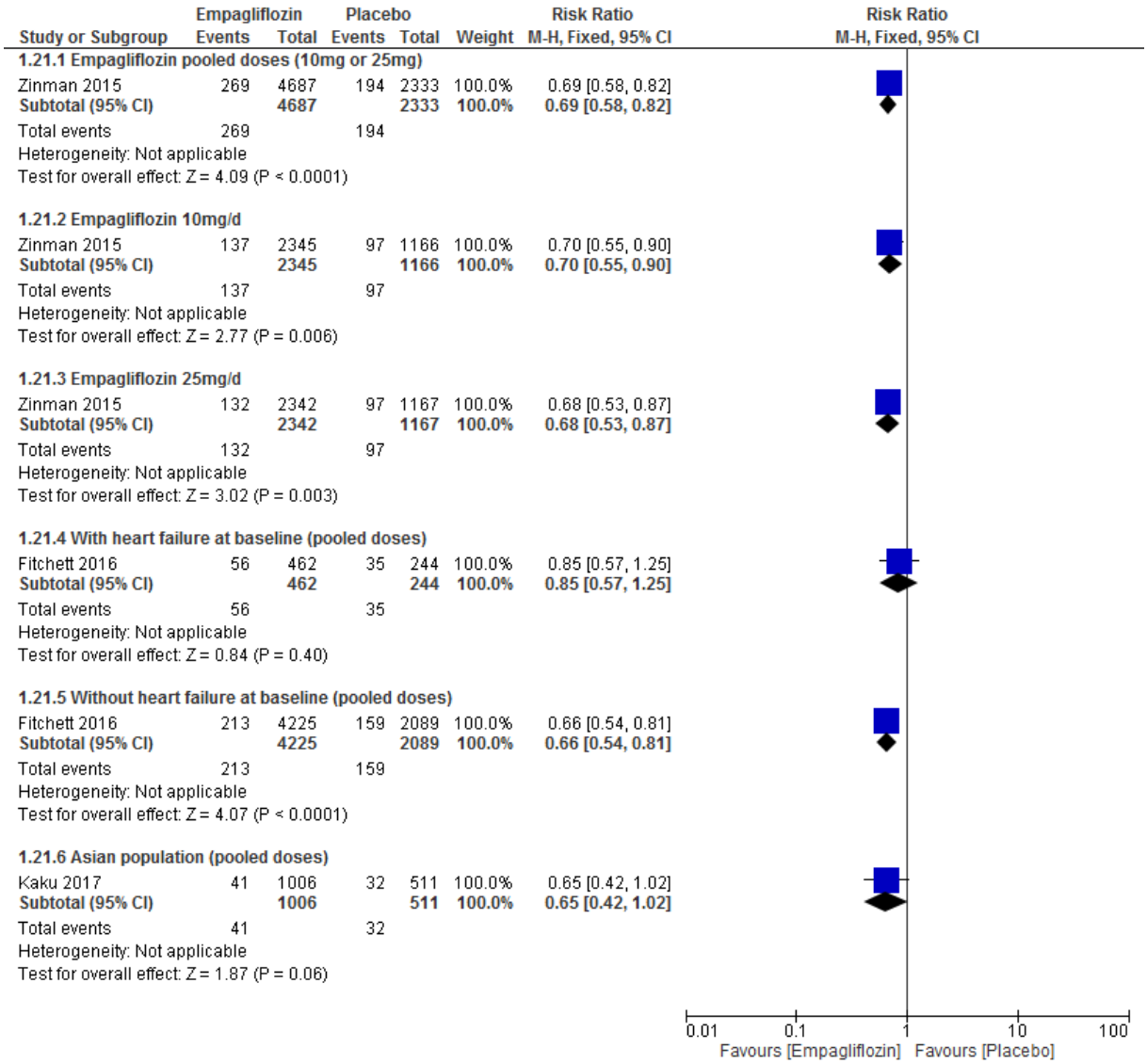
Test for subgroup differences: Chi² = 0.07, df = 2 (P = 0.97), I² = 0%

Ferrannini 2013 was not included in the GRADE table because diabetic nephropathy was only reported as an adverse event.

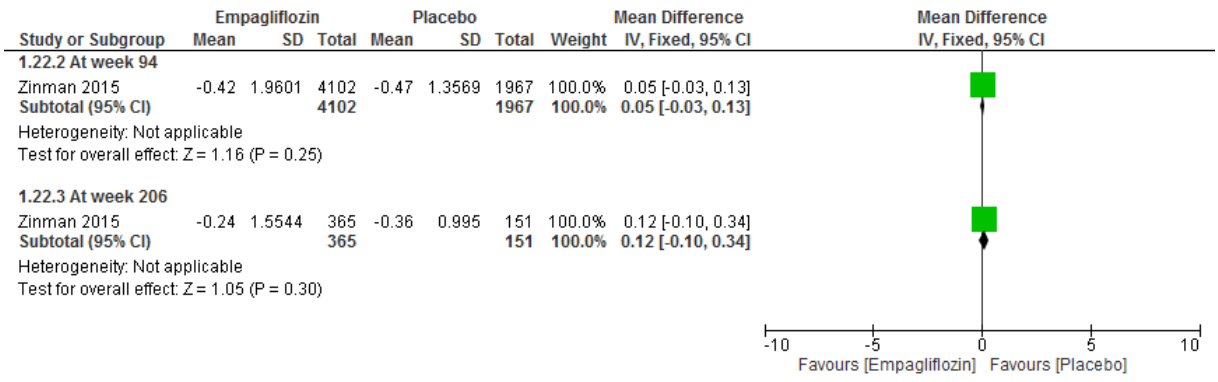
Coronary revascularisation procedure



All-cause mortality

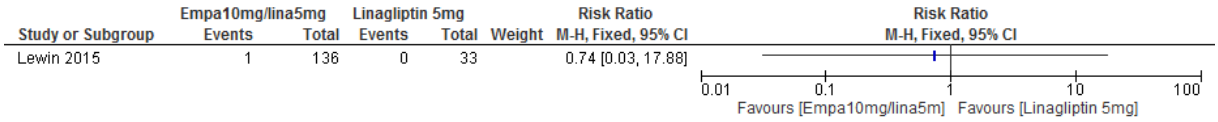


Adjusted mean differences in HbA1c (empagliflozin pooled doses [10mg/d or 25mg/d])



Empagliflozin 10mg/d plus linagliptin 5mg/d vs linagliptin 5mg/d

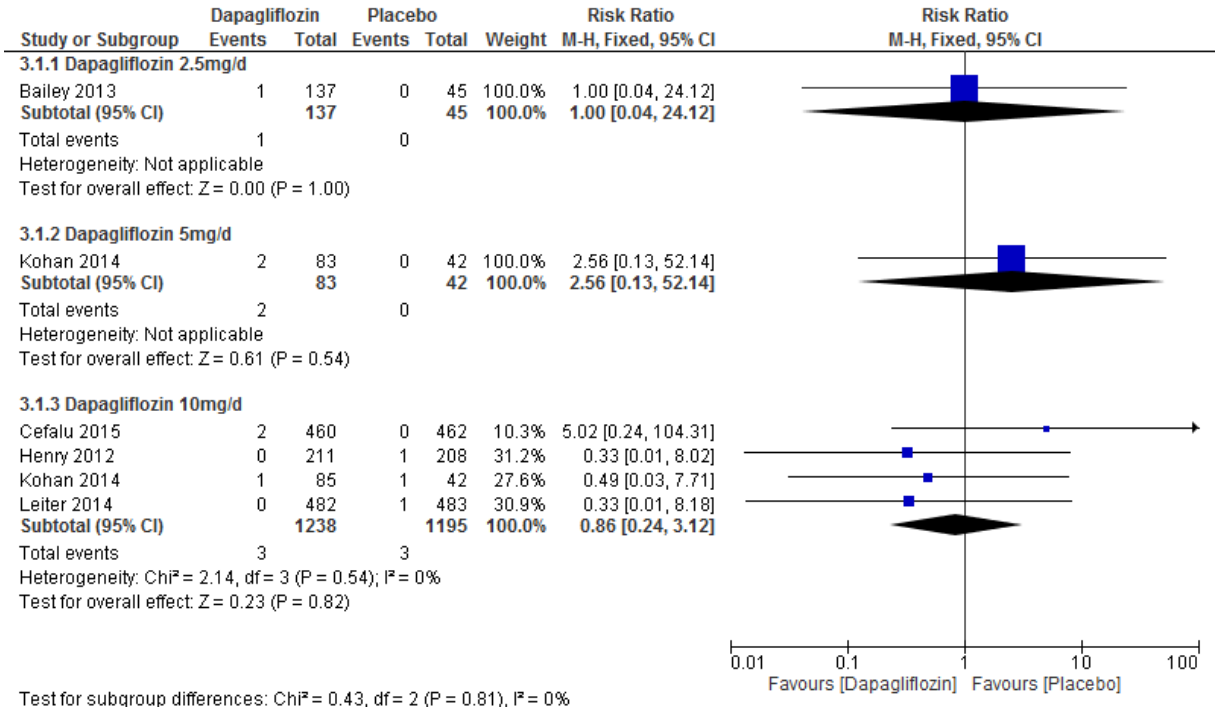
Fatal haemorrhagic stroke



Lewin 2015 was not included in the GRADE table because fatal haemorrhagic stroke was only reported as an adverse event.

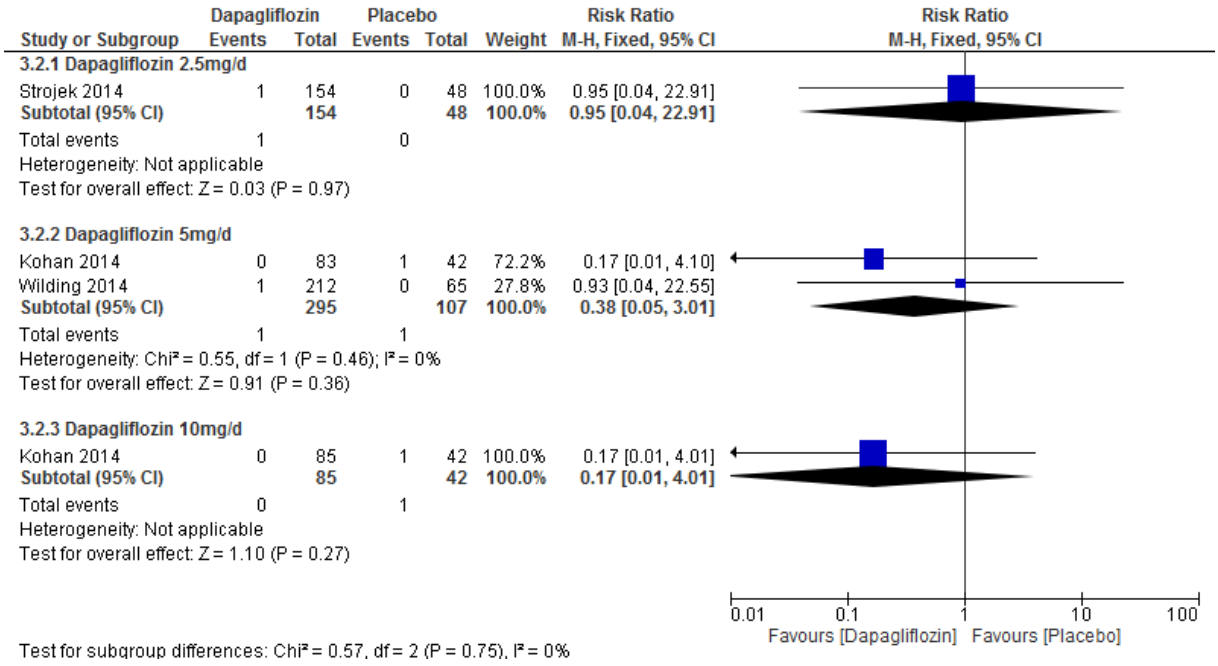
Dapagliflozin vs placebo

Fatal MI



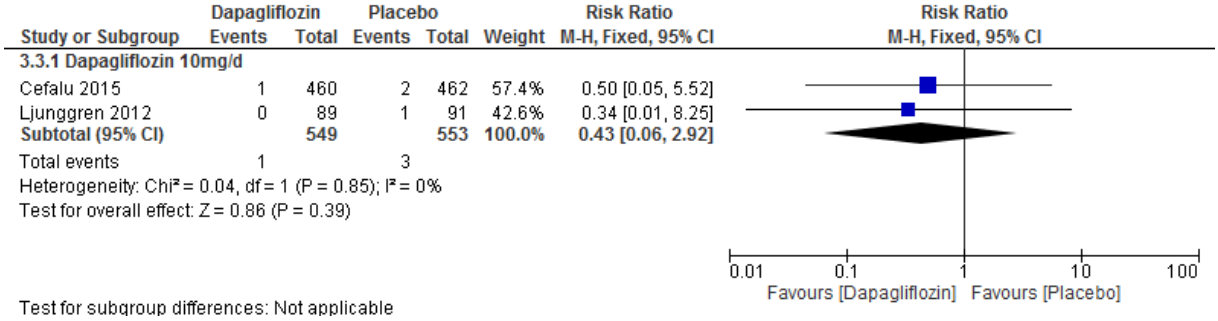
Bailey 2013, Kohan 2014, Cefalu 2015, Henry 2012, and Leiter 2014 were not included in the GRADE table because fatal MI was only reported as an adverse event.

Fatal acute MI



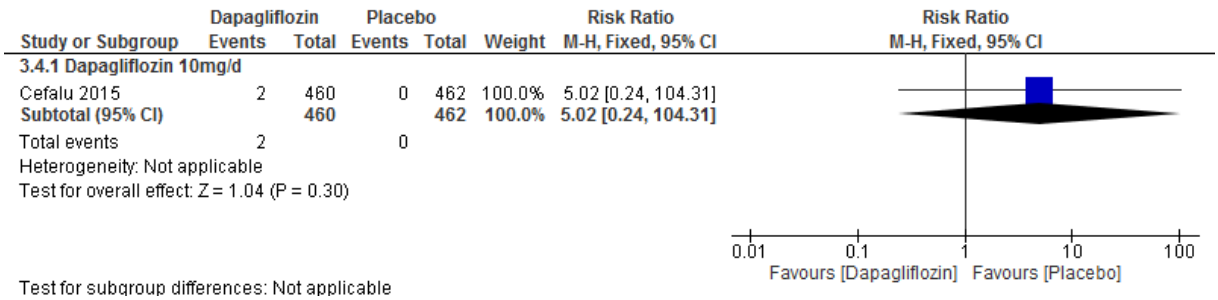
Strojek 2014, Kohan 2014, and Wilding 2014 were not included in the GRADE table because fatal acute MI was only reported as an adverse event.

Non-fatal acute MI



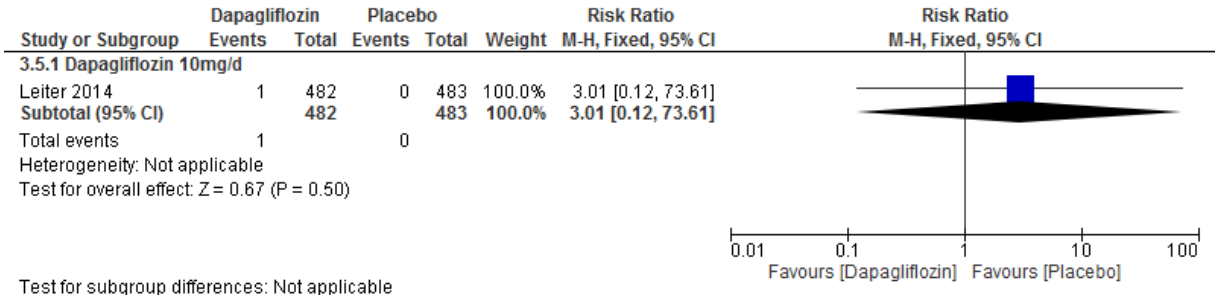
Cefalu 2015 and Ljunggren 2012 were not included in the GRADE table because non-fatal acute MI was only reported as an adverse event.

Non-fatal MI



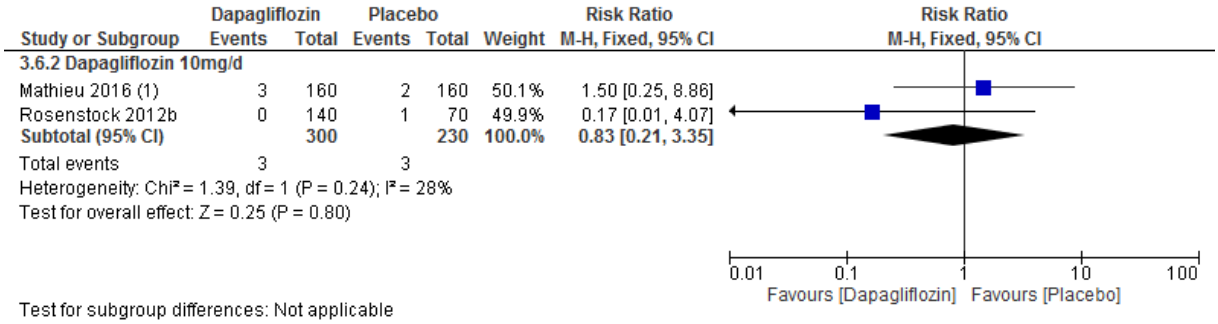
Cefalu 2015 was not included in the GRADE table because non-fatal MI was only reported as an adverse event.

Fatal heart failure



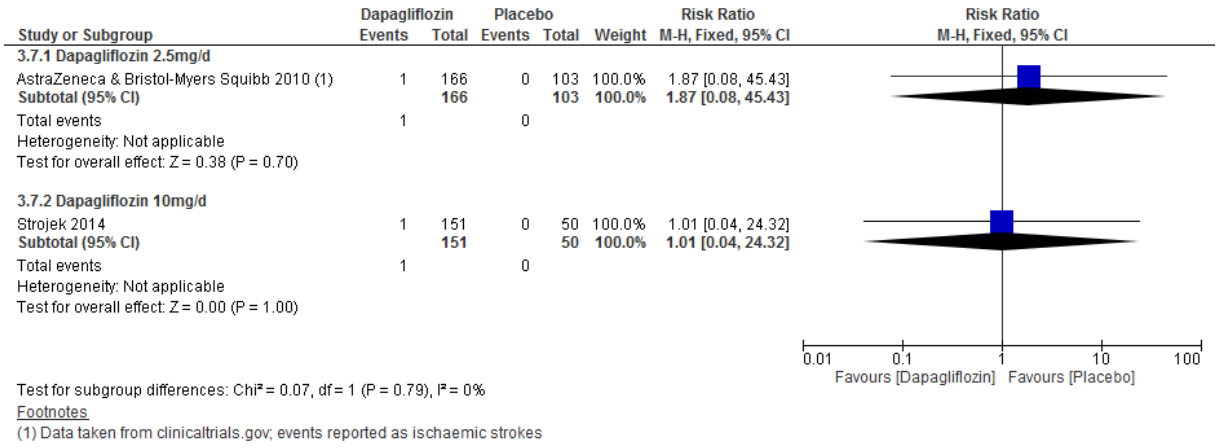
Leiter 2014 was not included in the GRADE table because fatal heart failure was only reported as an adverse event.

Non-fatal heart failure



Mathieu 2016 and Rosenstock 2012b were not included in the GRADE table because non-fatal heart failure was only reported as an adverse event.

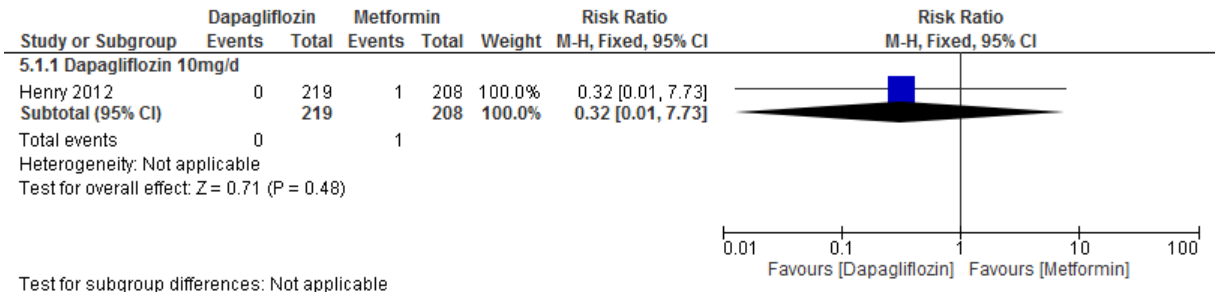
Non-fatal stroke



AstraZeneca & Bristol-Myers Squibb 2010 and Strojeck 2014 were not included in the GRADE table because non-fatal stroke was only reported as an adverse event.

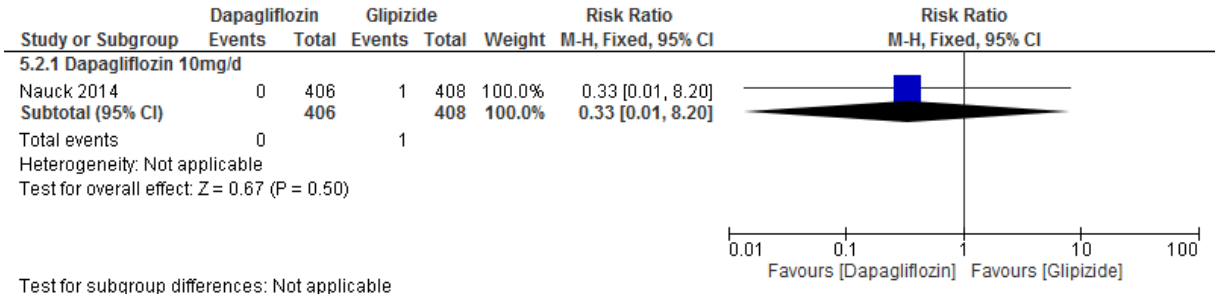
Dapagliflozin vs active control

Fatal MI



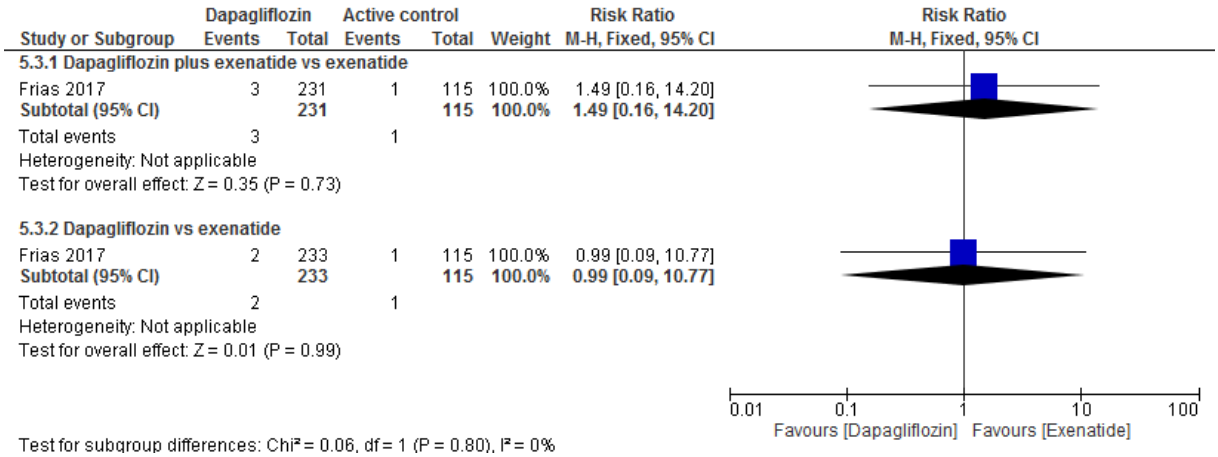
Henry 2012 was not included in the GRADE table because fatal MI was only reported as an adverse event.

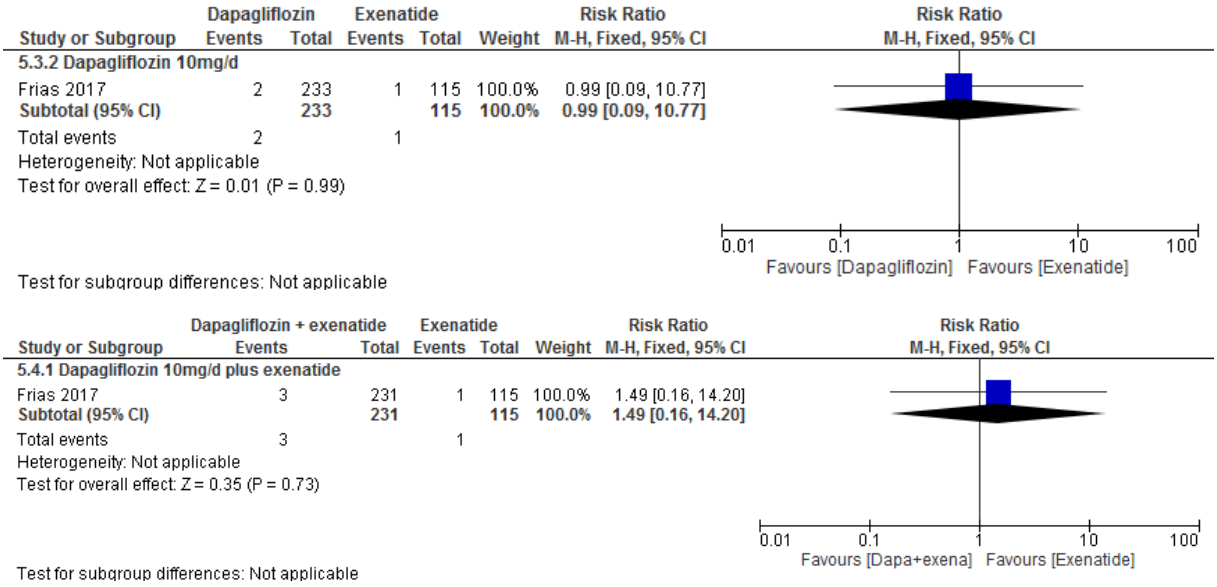
Fatal acute MI



Nauck 2014 was not included in the GRADE table because fatal acute MI was only reported as an adverse event.

Cardiovascular events

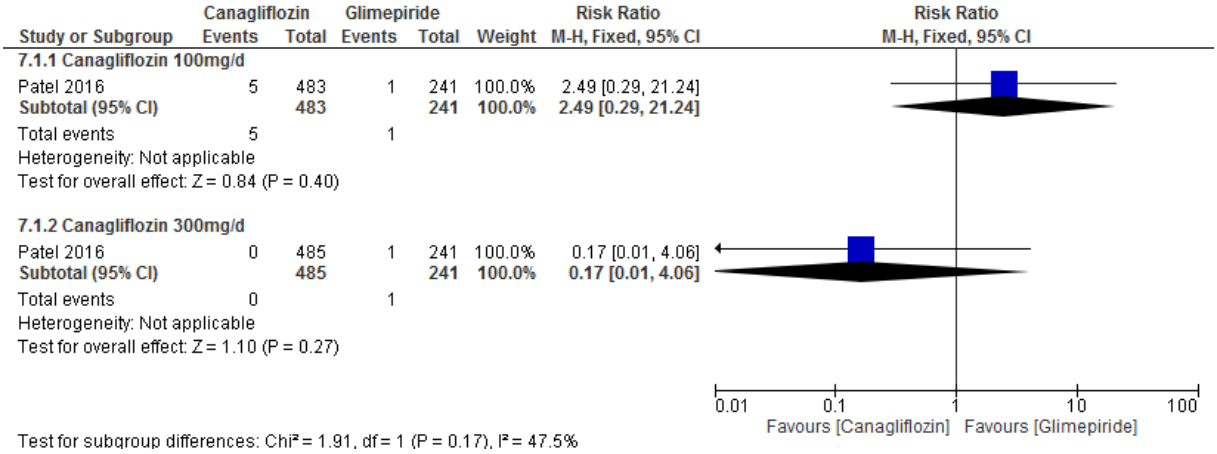




Frias 2017 was not included in the GRADE table because cardiovascular outcomes were only reported as adverse events.

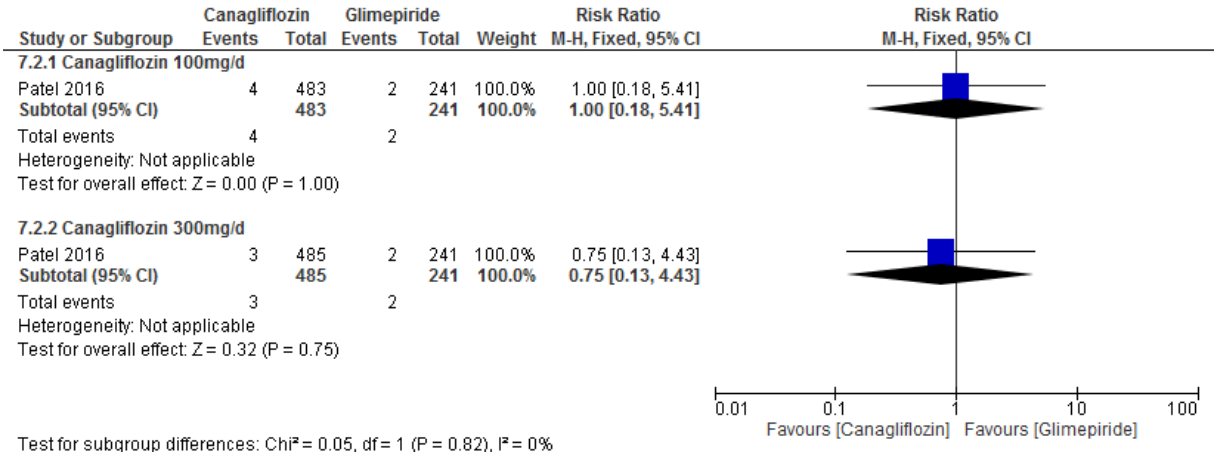
Canagliflozin vs glimepiride

Cardiovascular mortality



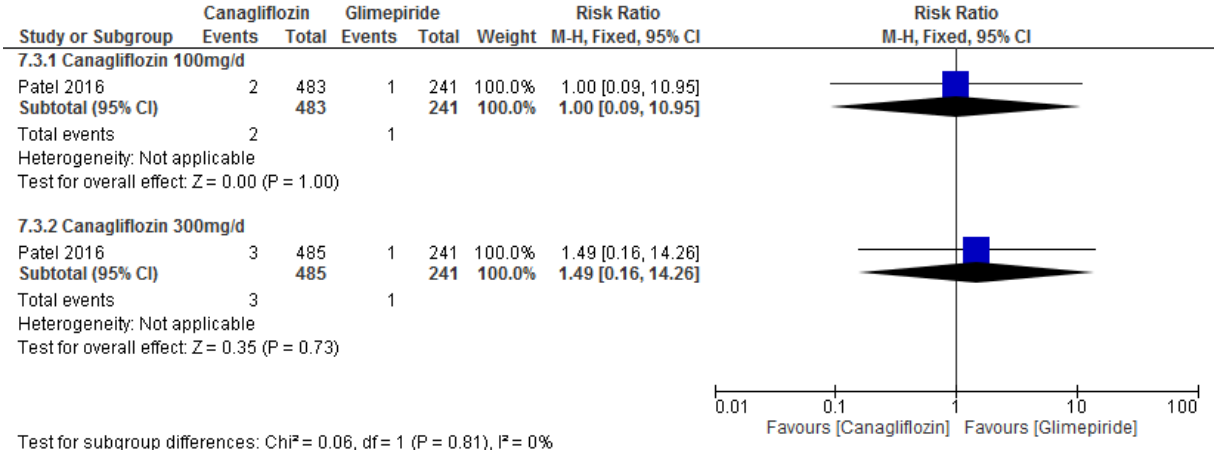
Patel 2016 was not included in the GRADE table because cardiovascular mortality was only reported as an adverse event.

Non-fatal MI



Patel 2016 was not included in the GRADE table because non-fatal MI was only reported as an adverse event.

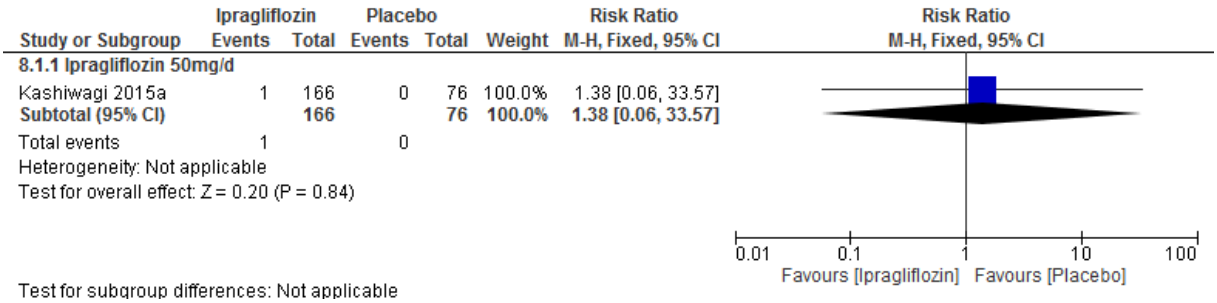
Non-fatal stroke



Patel 2016 was not included in the GRADE table because non-fatal stroke was only reported as an adverse event.

Ipragliflozin vs placebo

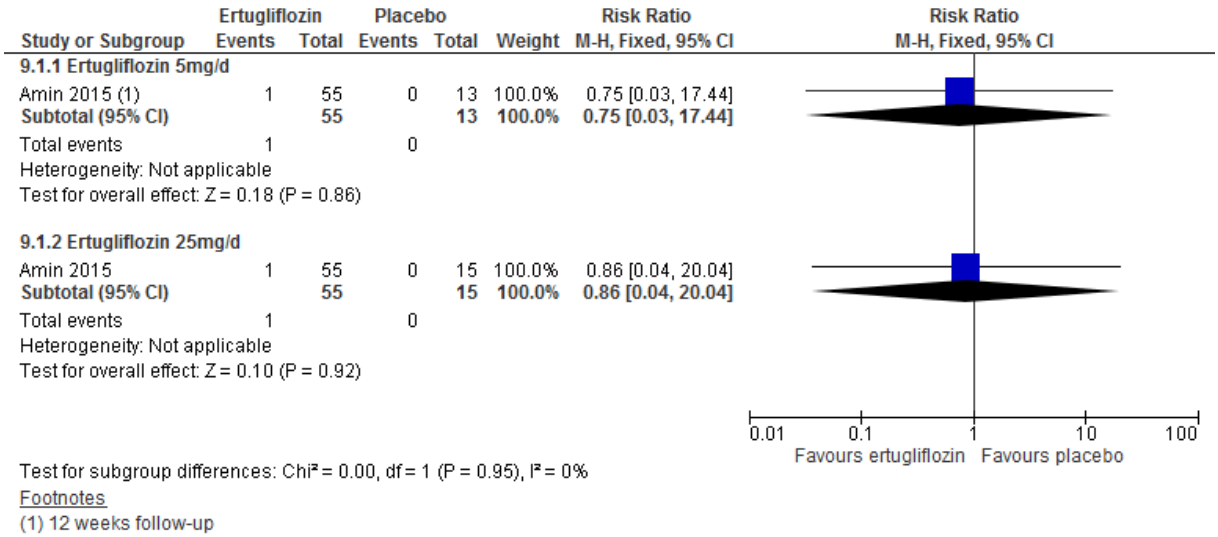
Proliferative rethinopathy



Kashiwagi 2015a was not included in the GRADE table because proliferative retinopathy was only reported as an adverse event.

Ertugliflozin vs placebo

Non-fatal acute MI

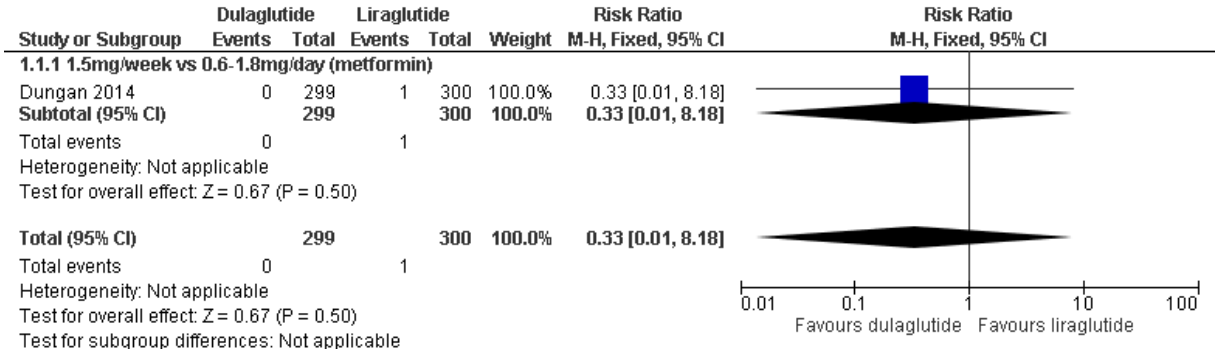


Amin 2015 was not included in the GRADE table because non-fatal acute MI was only reported as an adverse event.

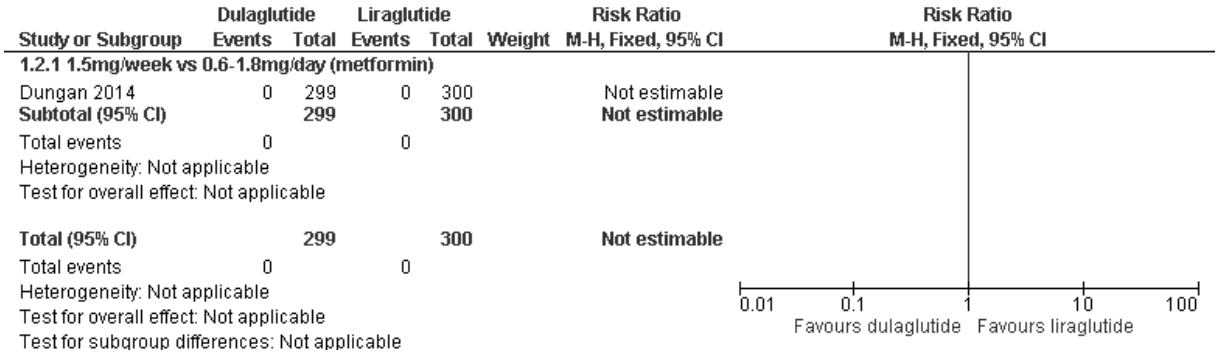
GLP-1 mimetics

Dulaglutide vs liraglutide

MI

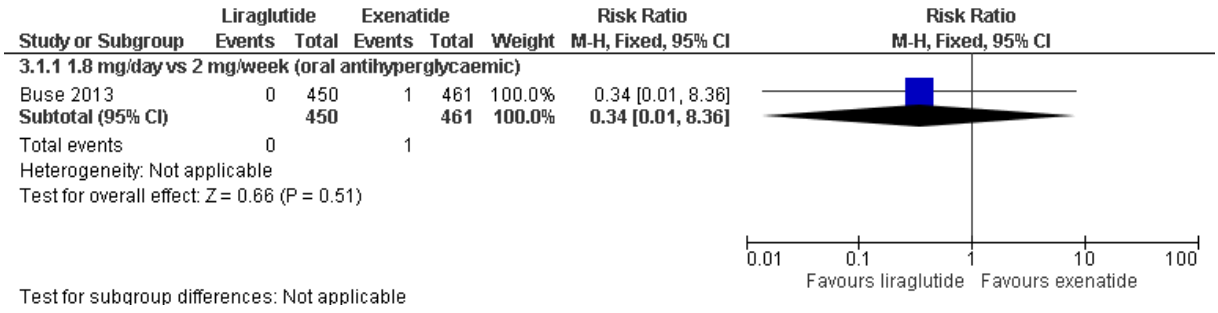


CV mortality

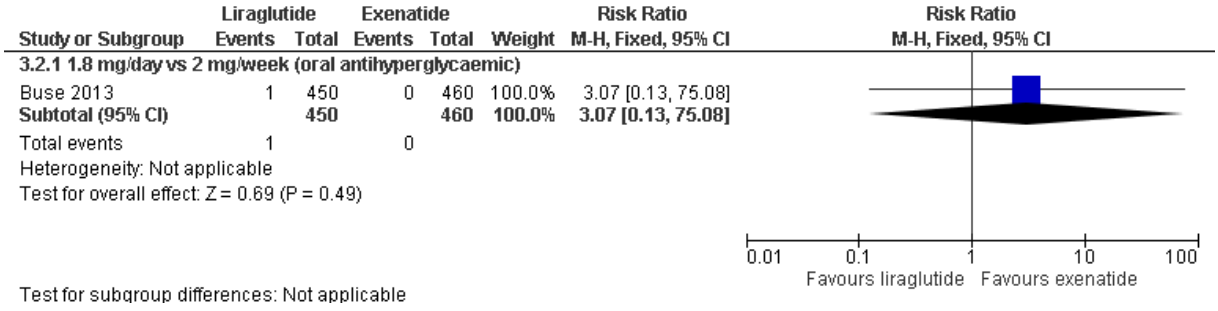


Liraglutide vs exenatide

MI

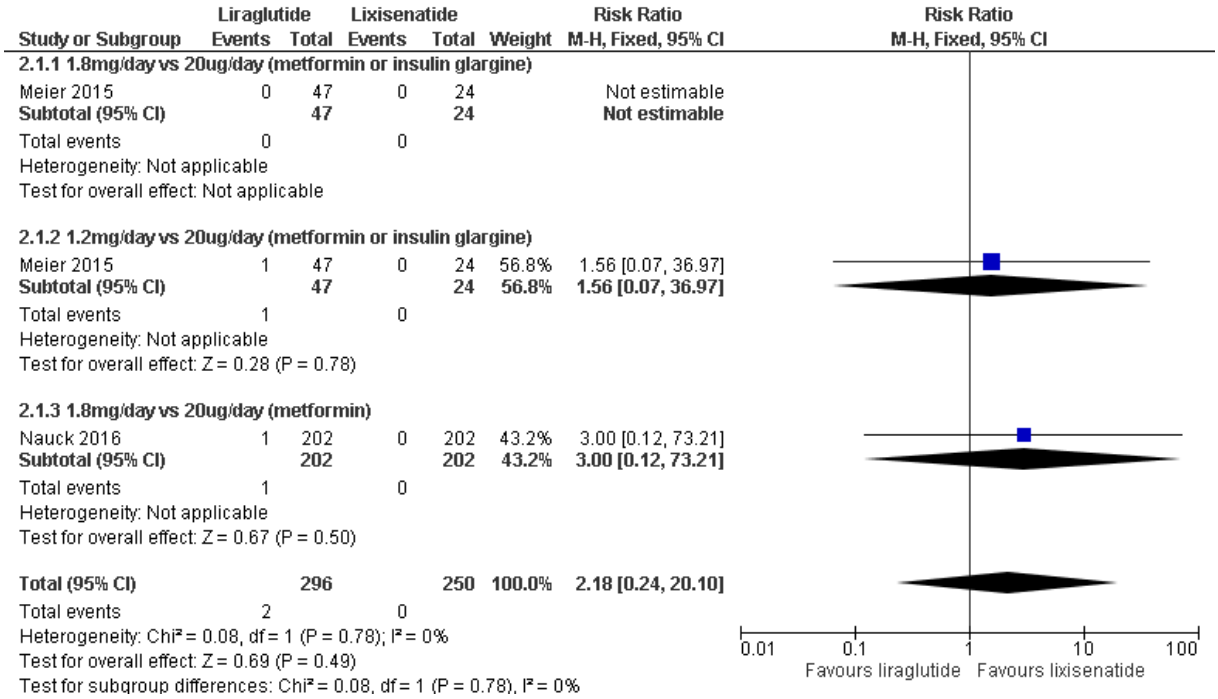


Brain stem infarction

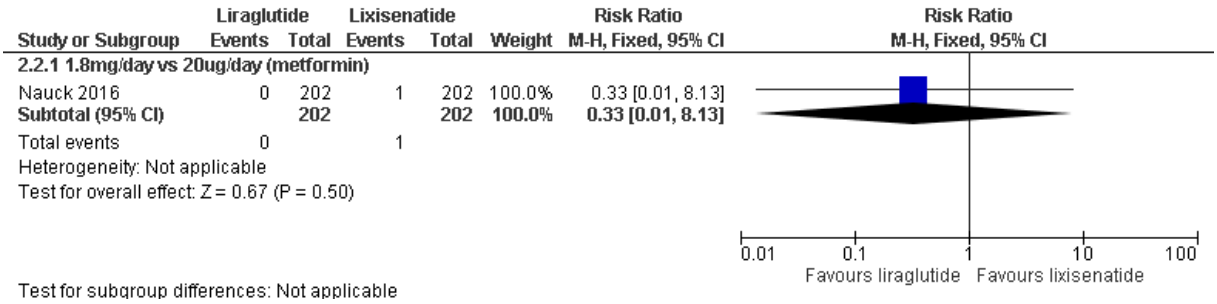


Liraglutide vs lixisenatide

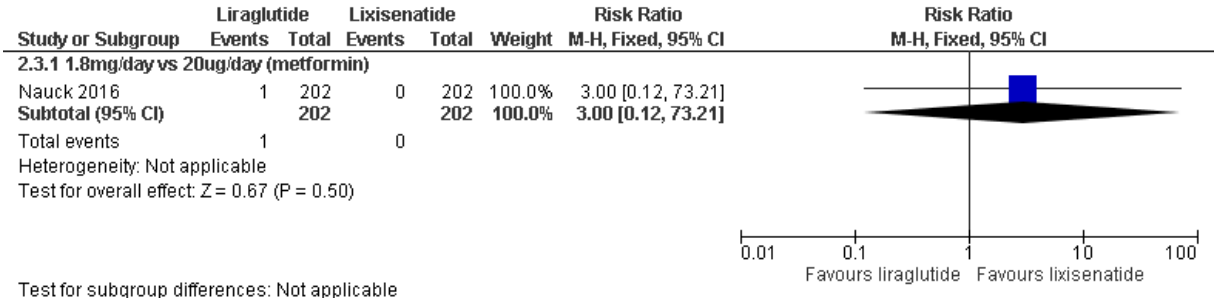
MI



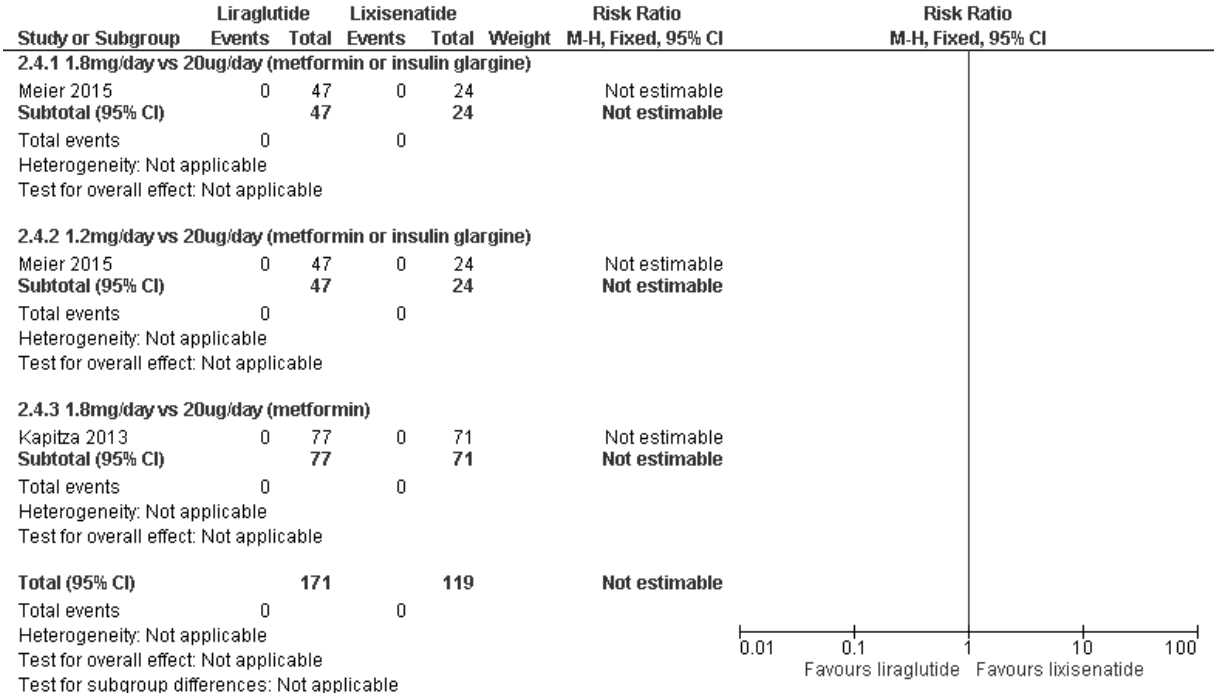
Cardiac failure



Ischaemic stroke



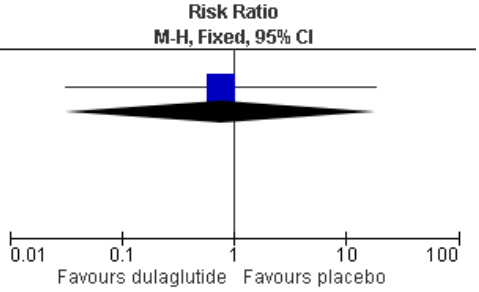
CV mortality



Dulaglutide vs placebo

Cerebrovascular accident

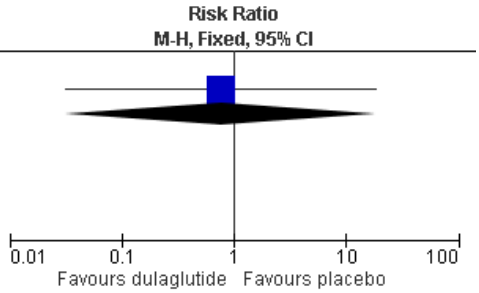
Study or Subgroup	Dulaglutide Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
14.1.2 1.5mg once weekly (glimepride)						
Dungan 2016	1	239	0	60	100.0%	0.76 [0.03, 18.49]
Subtotal (95% CI)		**239**		**60**	**100.0%**	**0.76 [0.03, 18.49]**
Total events	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.17 (P = 0.87)						



Test for subgroup differences: Not applicable

Hospitalisation for cardiac failure

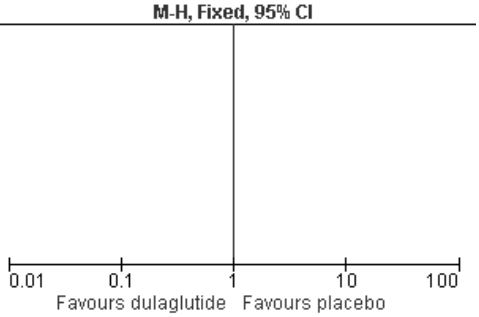
Study or Subgroup	Dulaglutide Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
14.2.1 1.5mg once weekly (glimepride)						
Dungan 2016	1	239	0	60	100.0%	0.76 [0.03, 18.49]
Subtotal (95% CI)		**239**		**60**	**100.0%**	**0.76 [0.03, 18.49]**
Total events	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.17 (P = 0.87)						



Test for subgroup differences: Not applicable

CV mortality

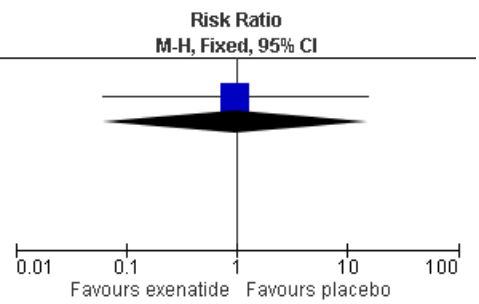
Study or Subgroup	Dulaglutide Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
14.3.1 0.1-1.5mg/day						
Grunberger 2012	0	132	0	32		Not estimable
Subtotal (95% CI)		**132**		**32**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**132**		**32**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						



Exenatide vs placebo

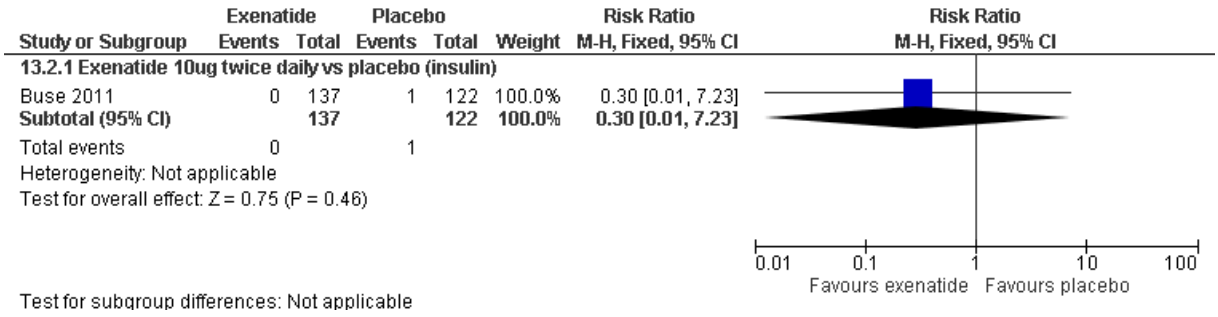
Myocardial infarction

Study or Subgroup	Exenatide Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
13.1.1 Exenatide 10ug twice daily vs placebo (sulphonylurea)						
Buse 2004	1	129	1	123	100.0%	0.95 [0.06, 15.08]
Subtotal (95% CI)		**129**		**123**	**100.0%**	**0.95 [0.06, 15.08]**
Total events	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.03 (P = 0.97)						



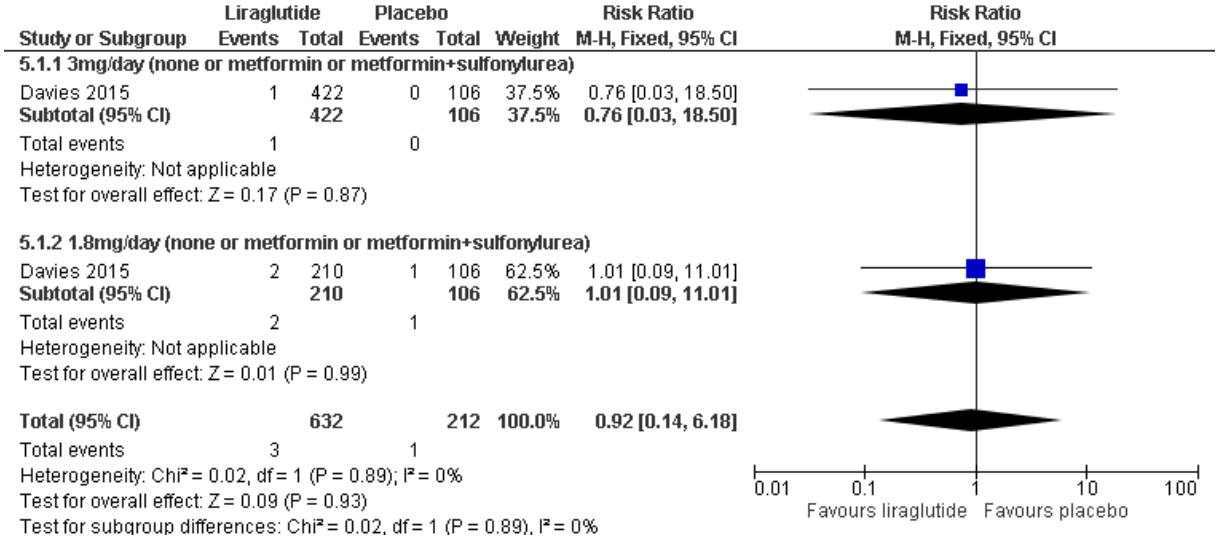
Test for subgroup differences: Not applicable

Myocardial infarction mortality

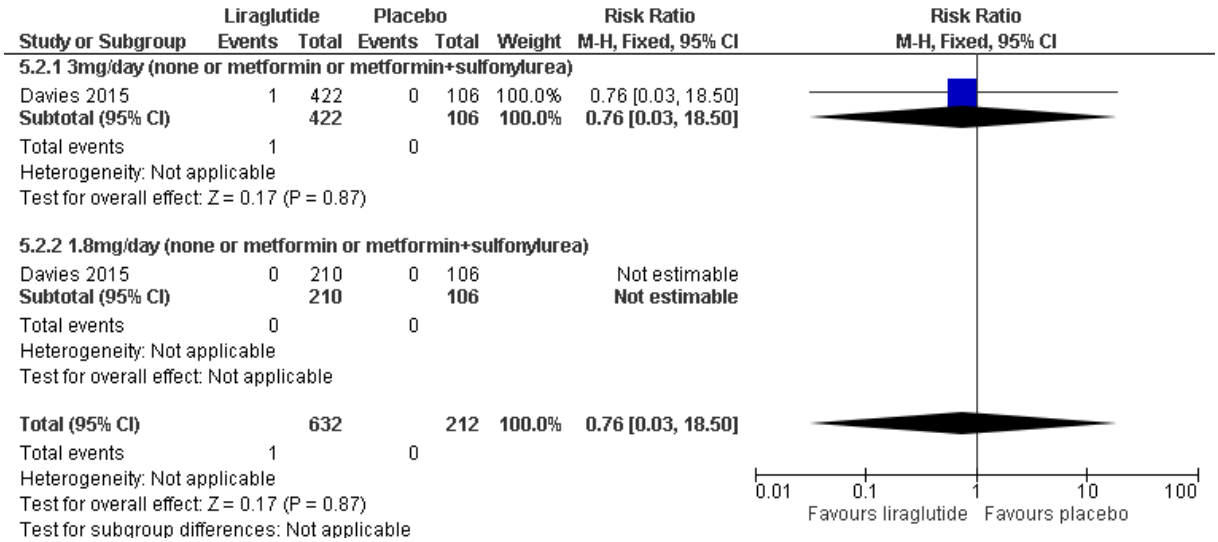


Liraglutide vs placebo

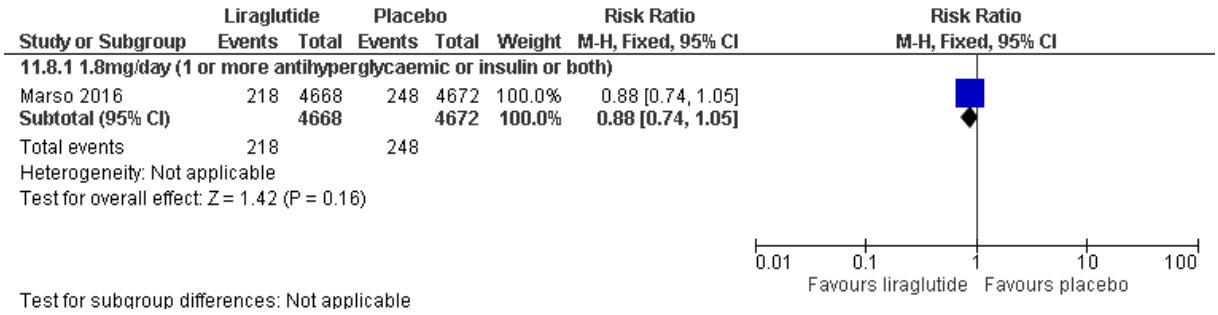
Cerebrovascular event



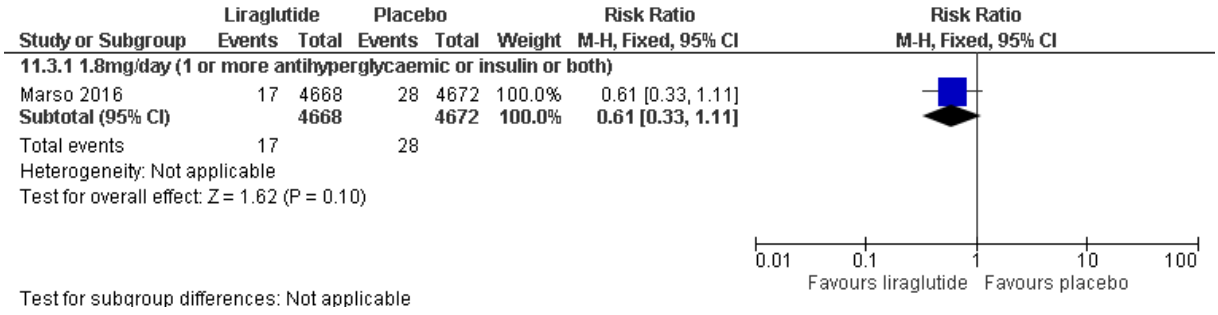
Heart failure



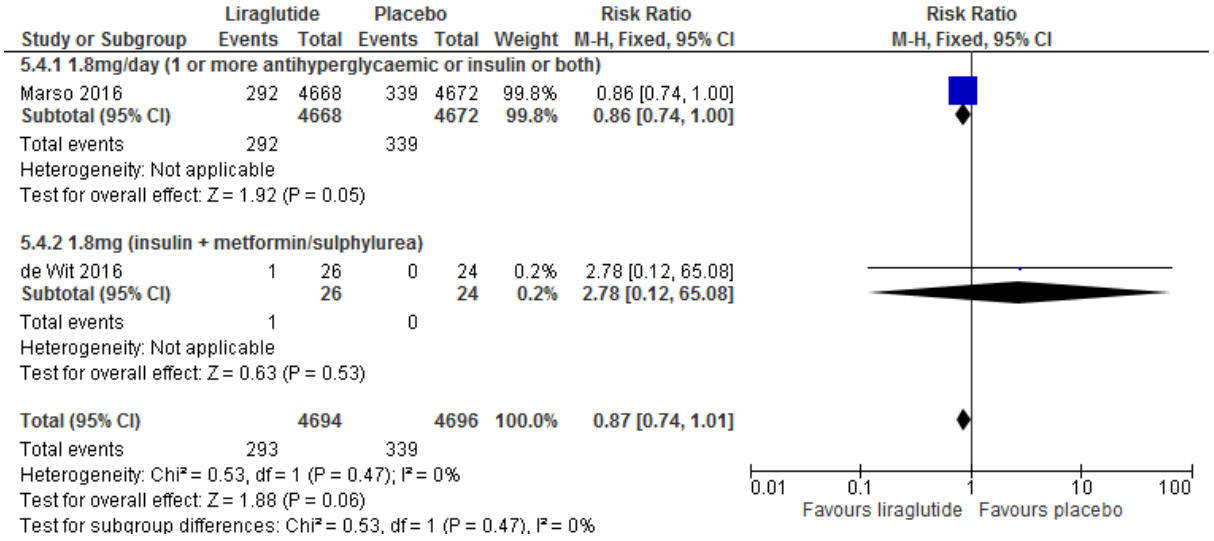
Hospitalisation for heart failure



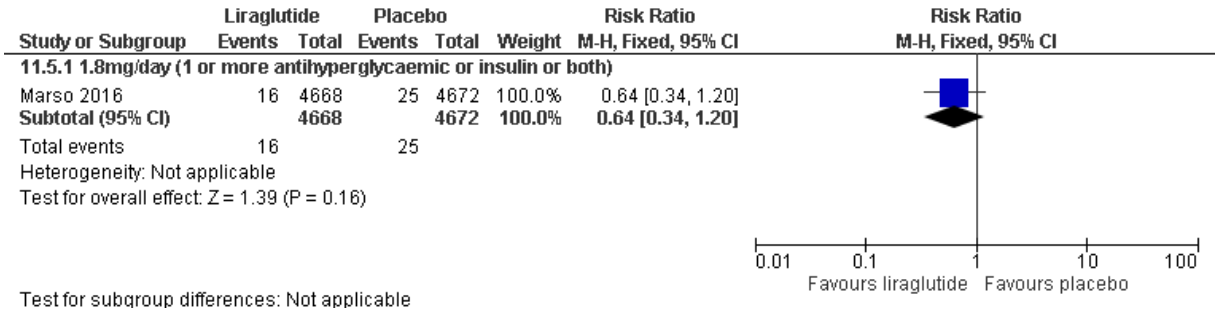
MI mortality



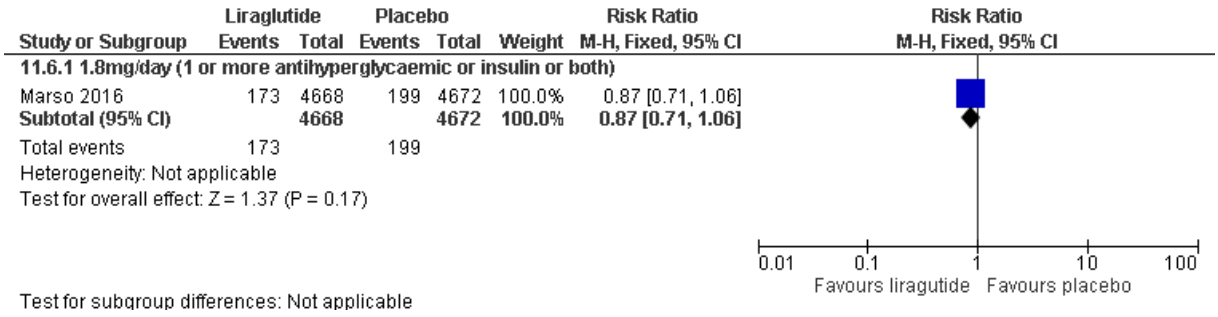
MI



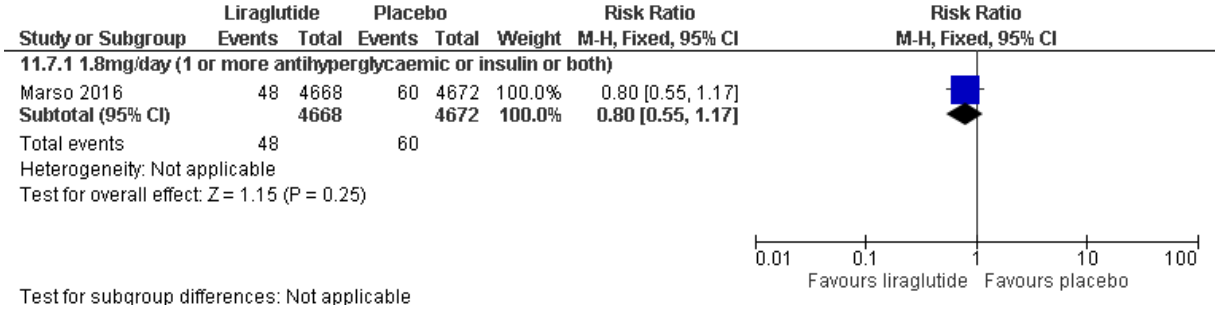
Stroke mortality



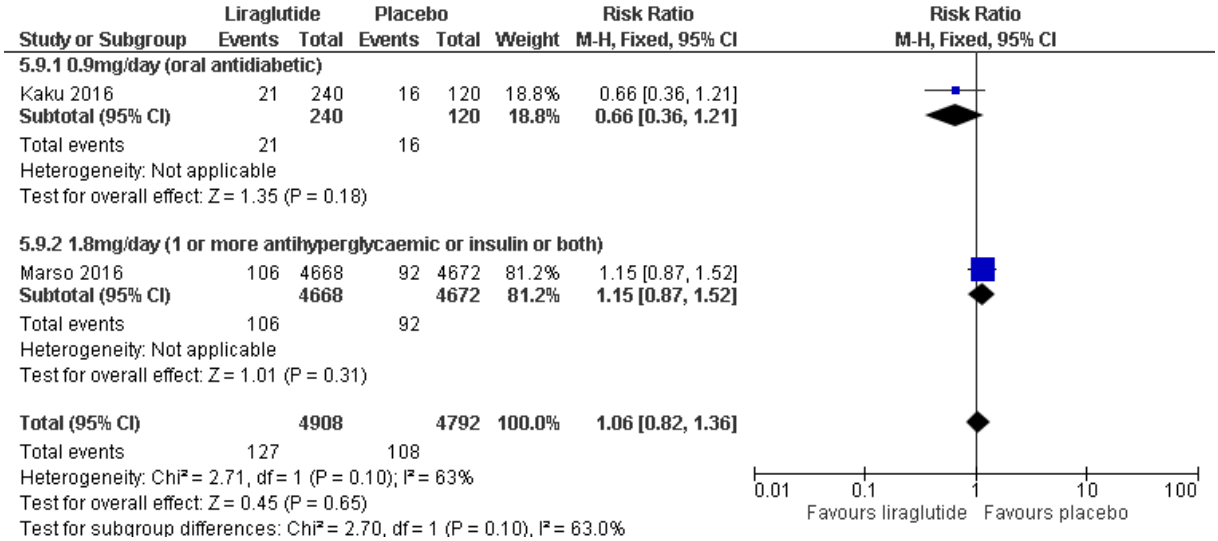
Stroke



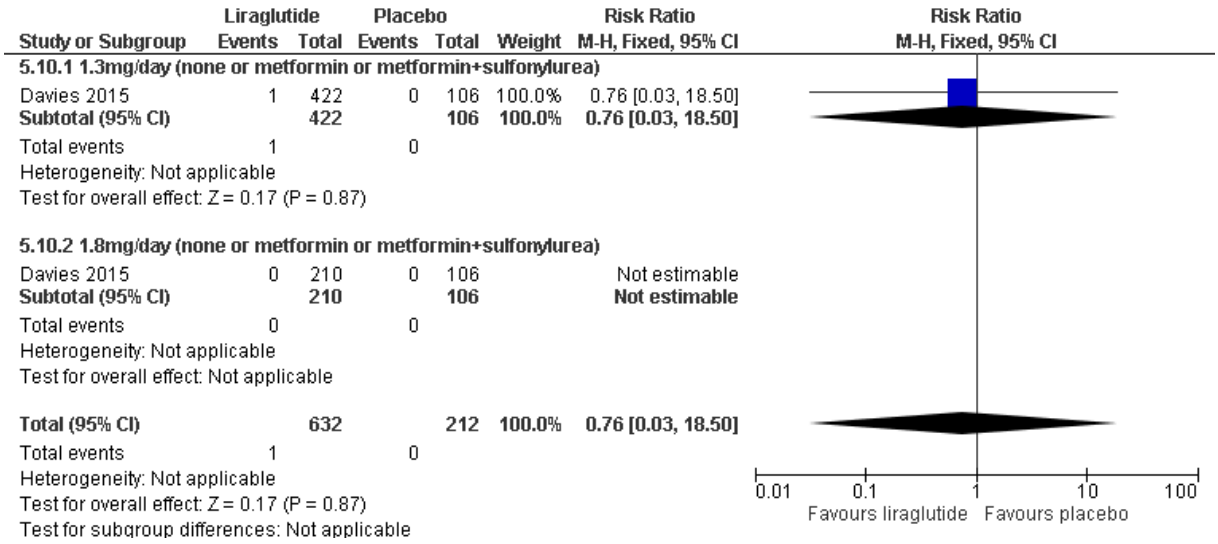
Transient ischaemic attack



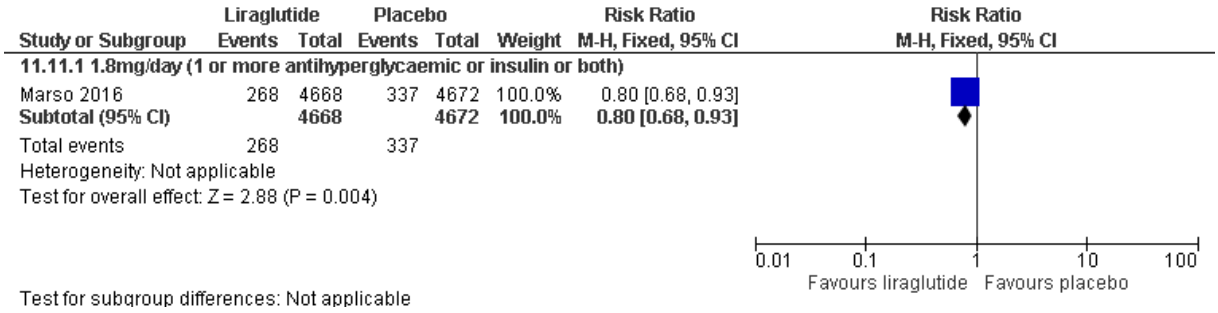
Diabetic retinopathy



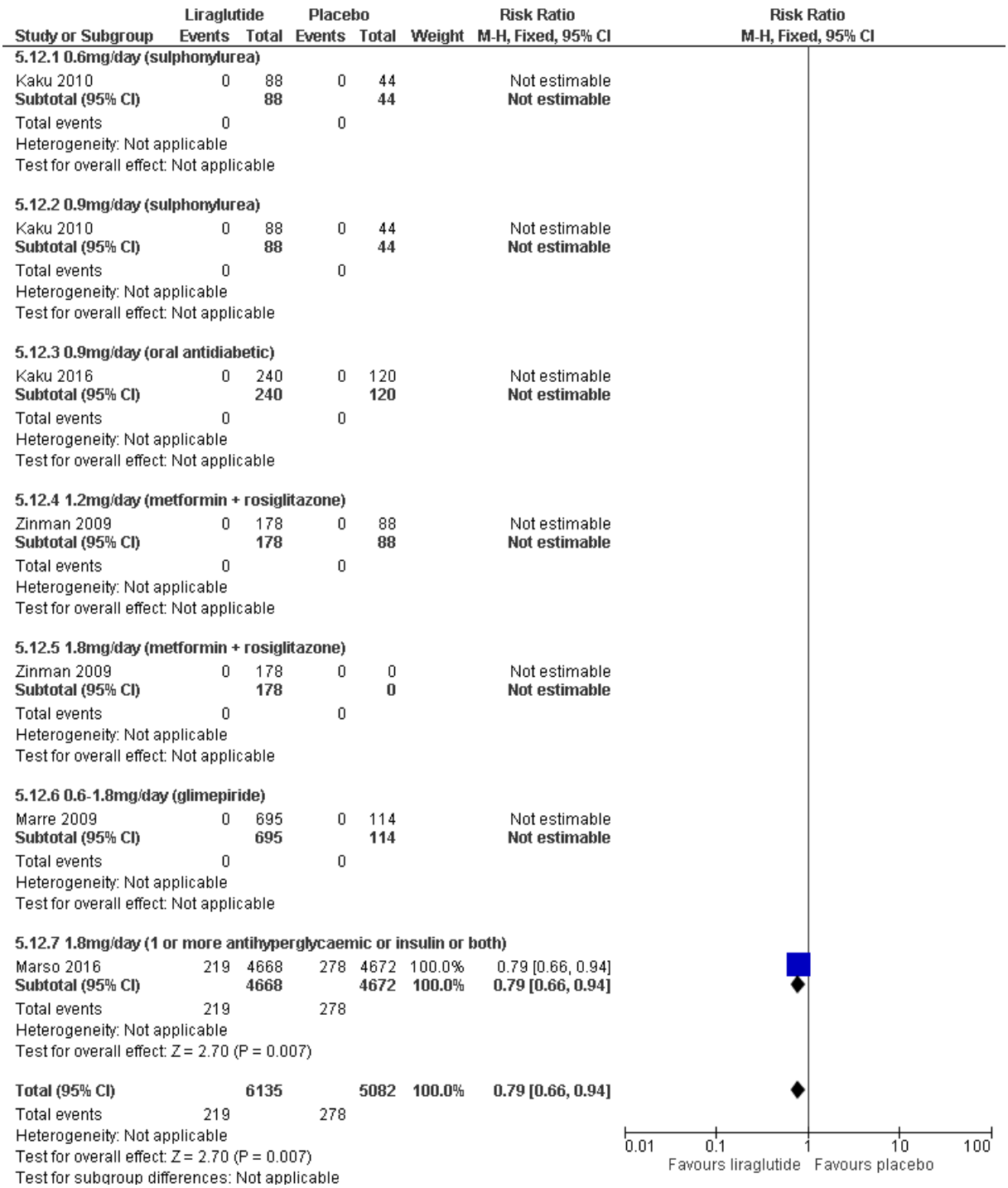
Renal failure



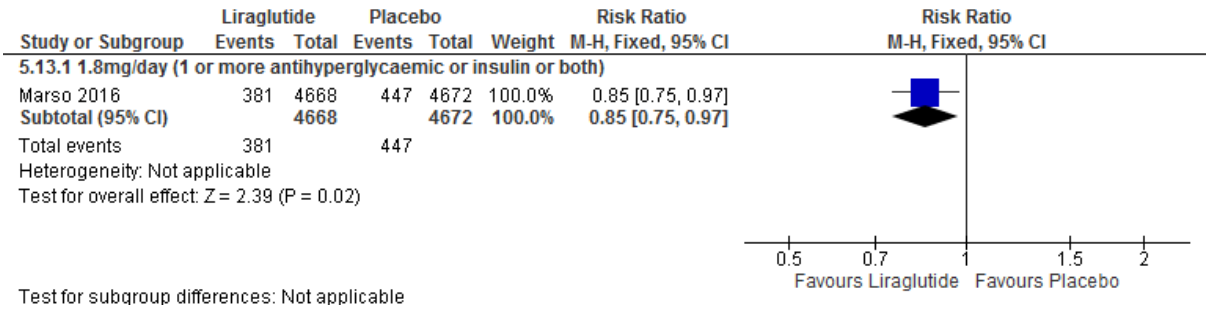
Nephropathy



CV mortality

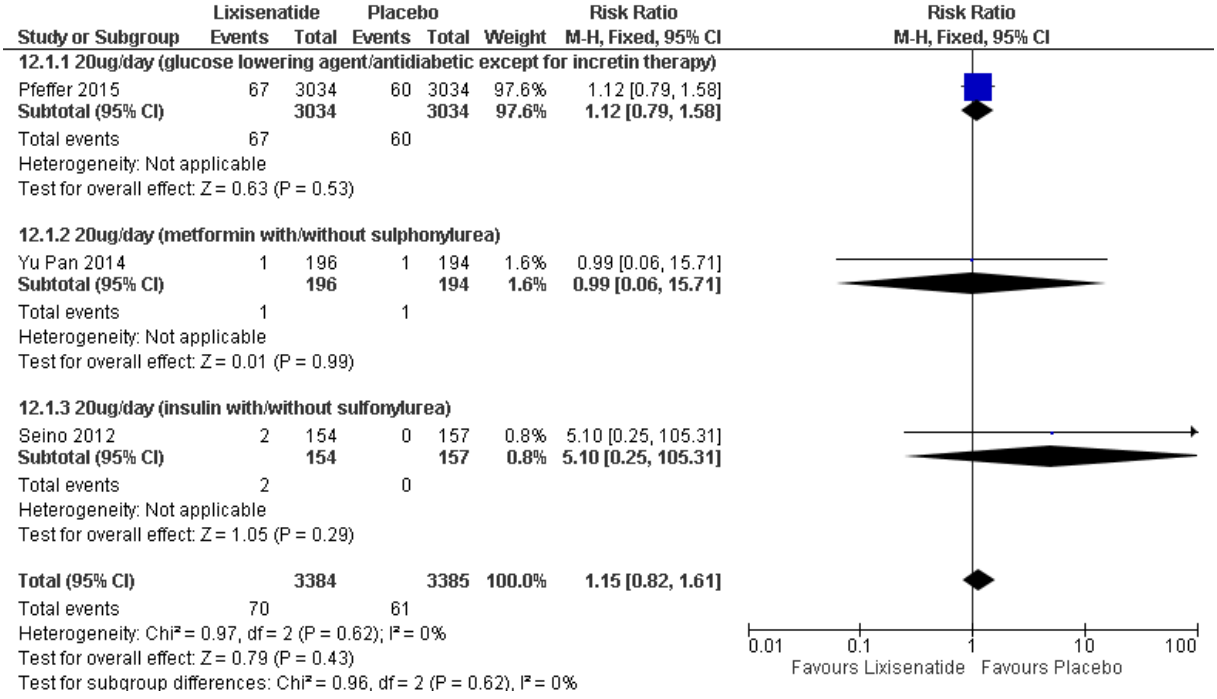


All-cause mortality

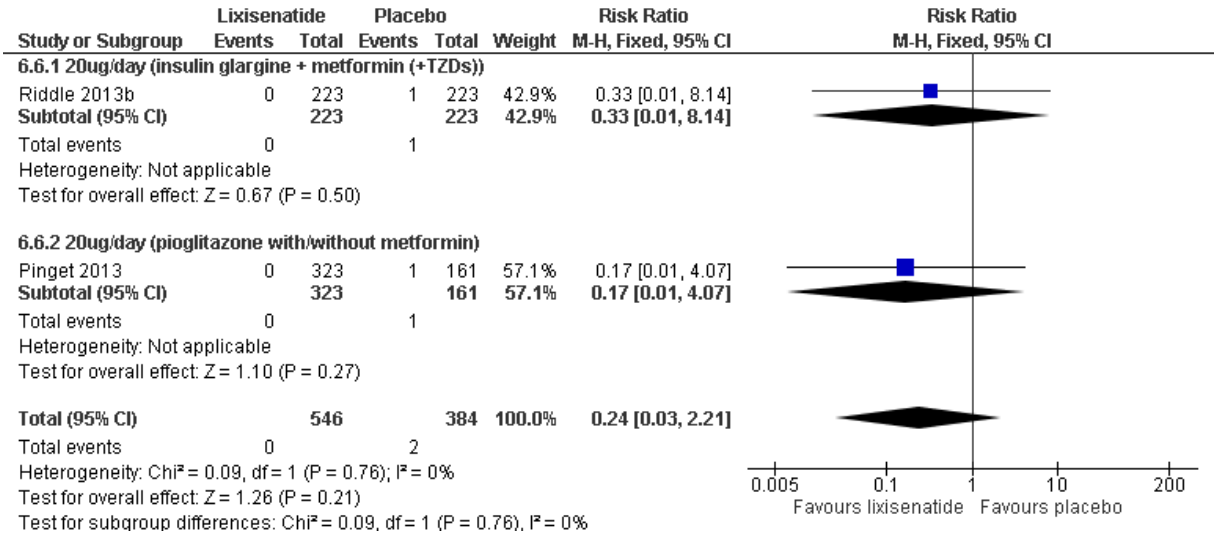


Lixisenatide vs placebo

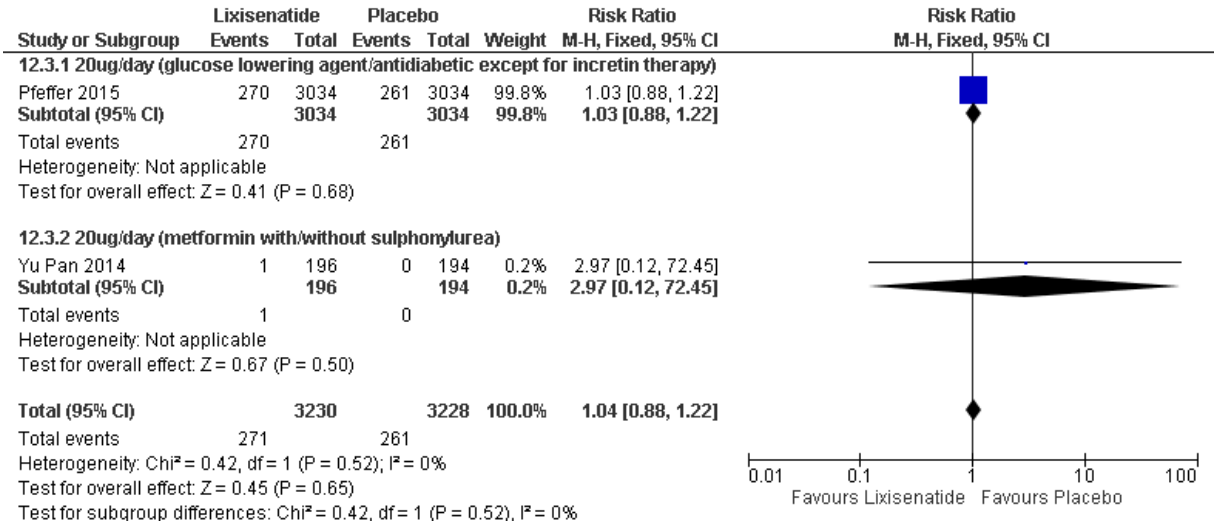
Stroke



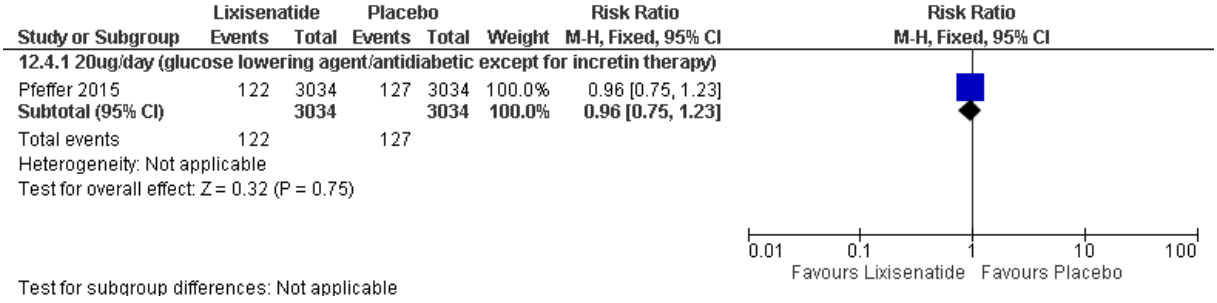
MI mortality



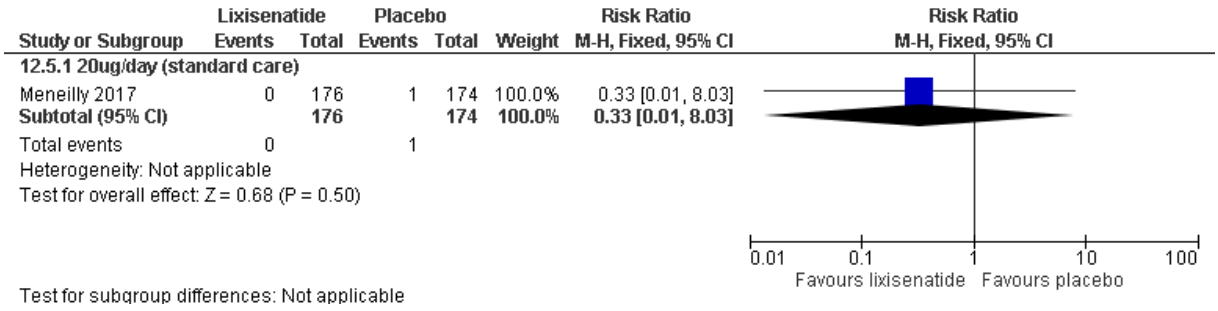
MI



Hospitalisation for heart failure

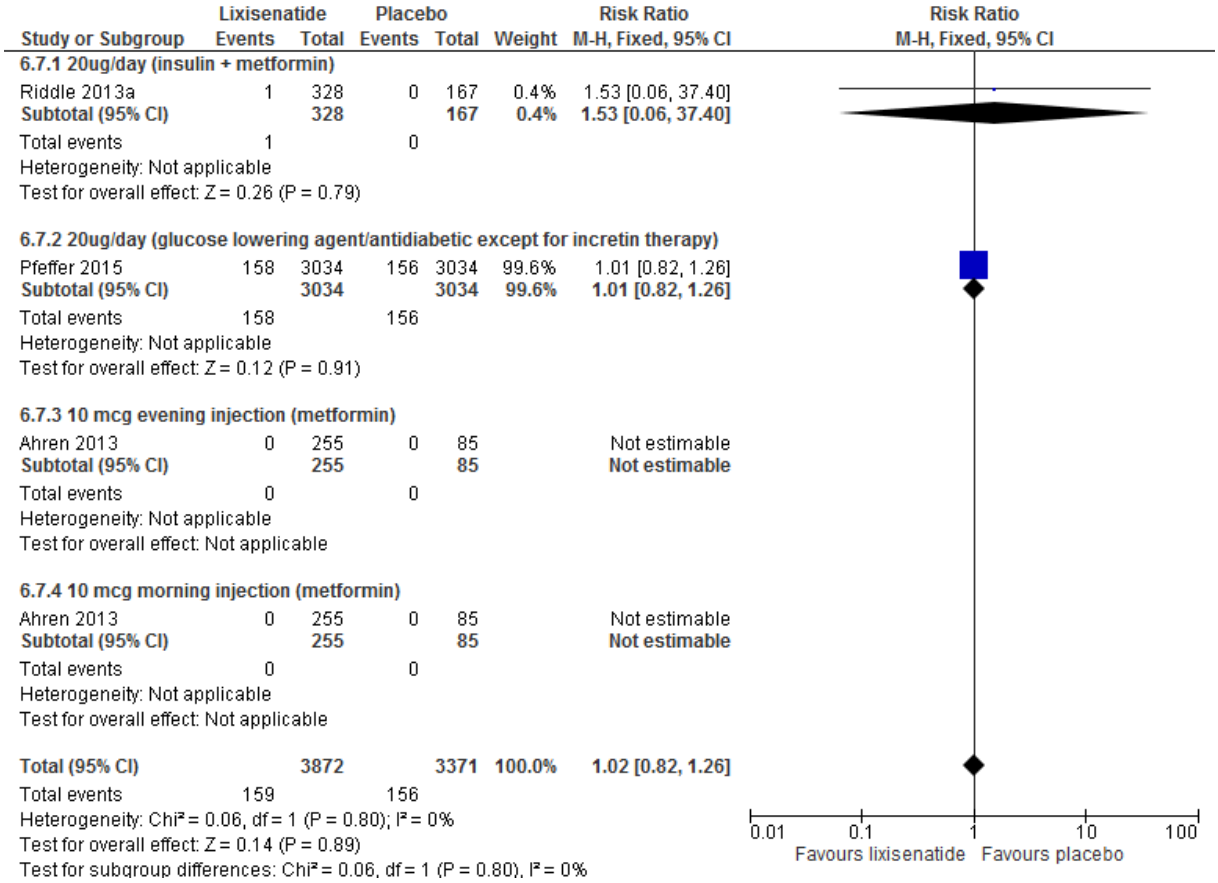


Aortic aneurysm mortality

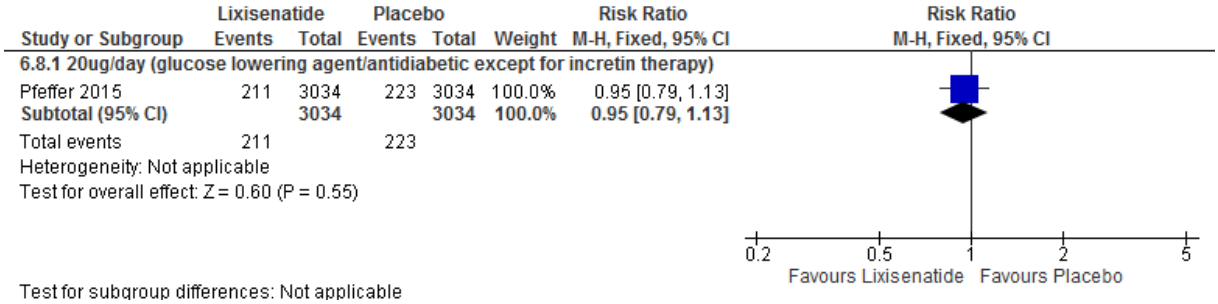


Test for subgroup differences: Not applicable

CV mortality



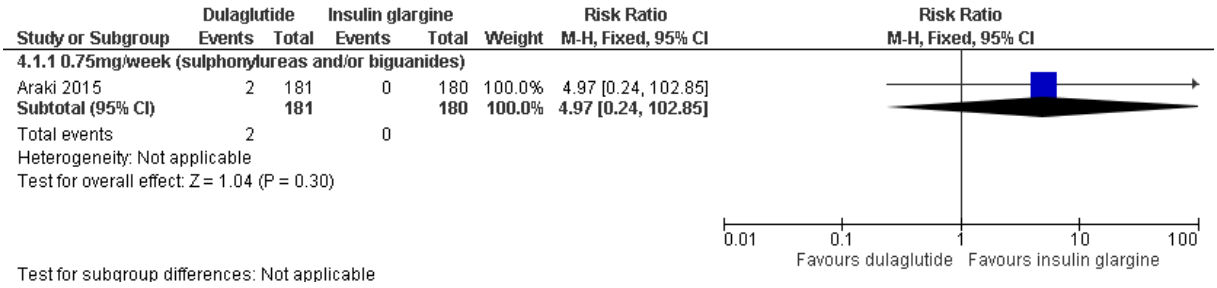
All-cause mortality



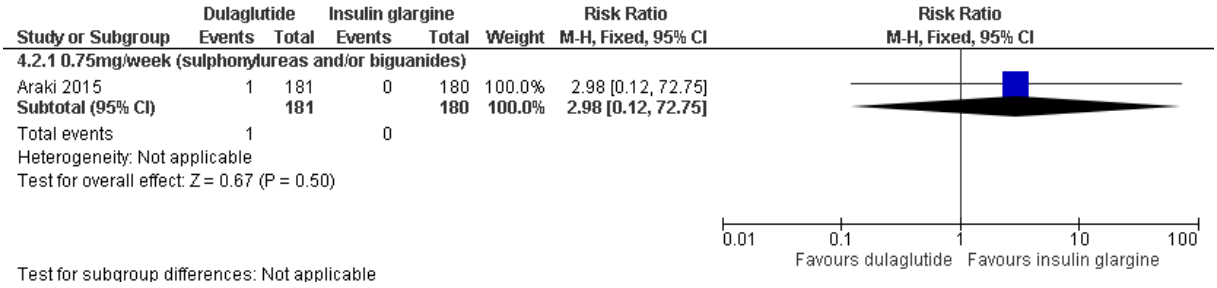
Test for subgroup differences: Not applicable

Dulaglutide vs insulin glargine

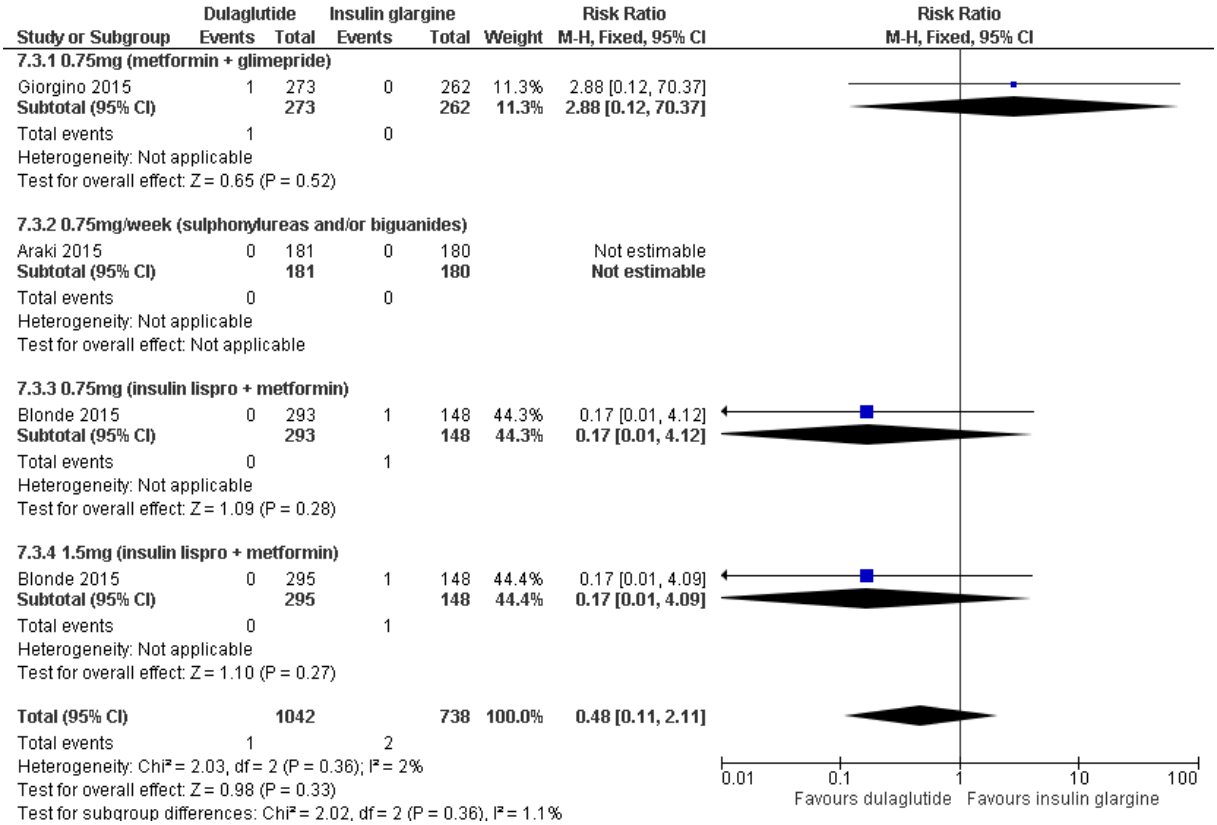
Cerebral infarction



MI

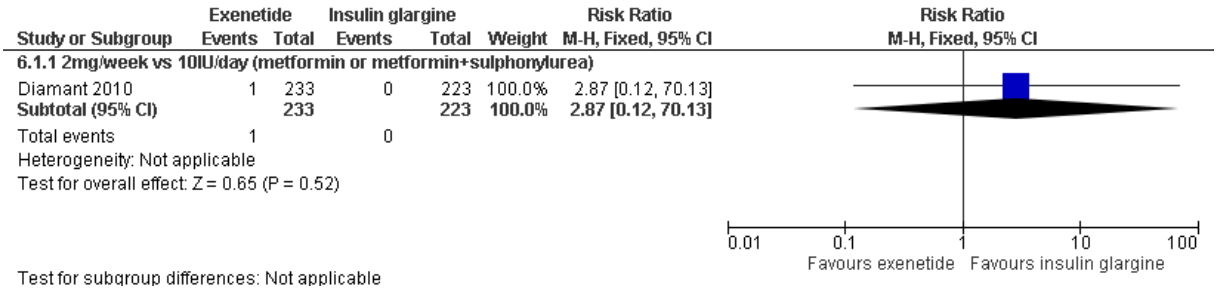


CV mortality

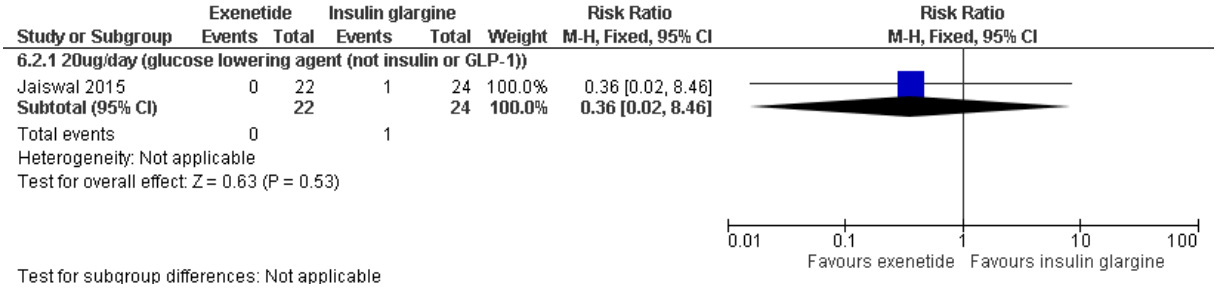


Exenatide vs insulin glargine

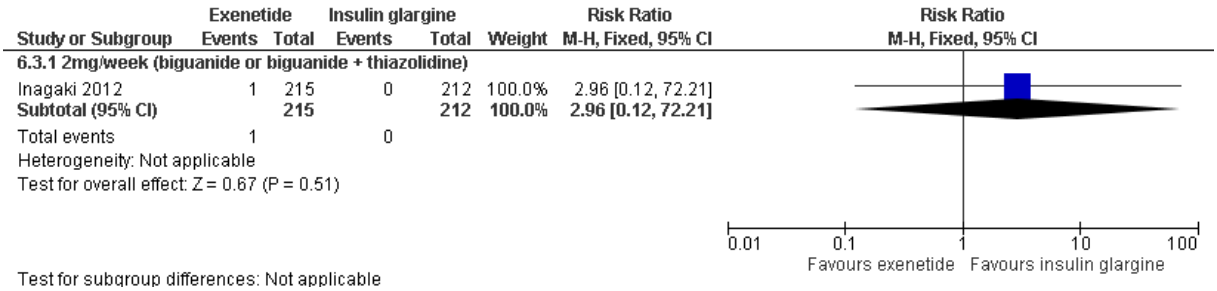
Cerebrovascular accident



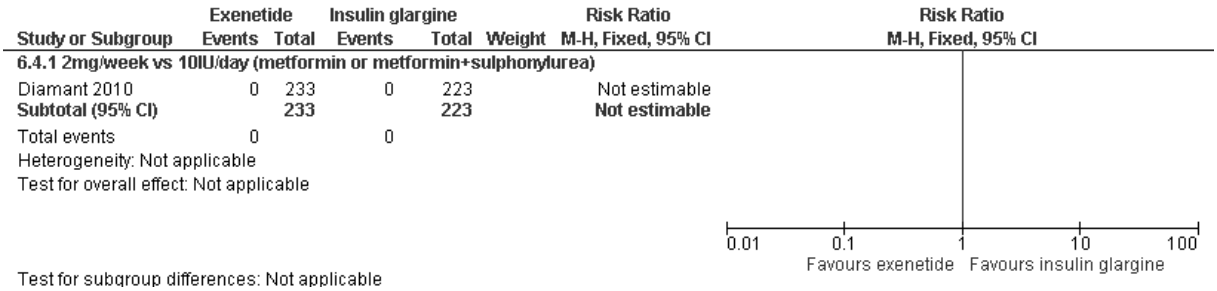
Toe amputation



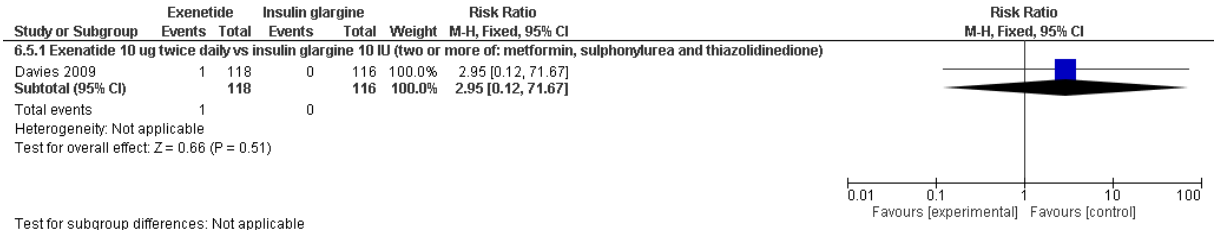
Heart failure mortality



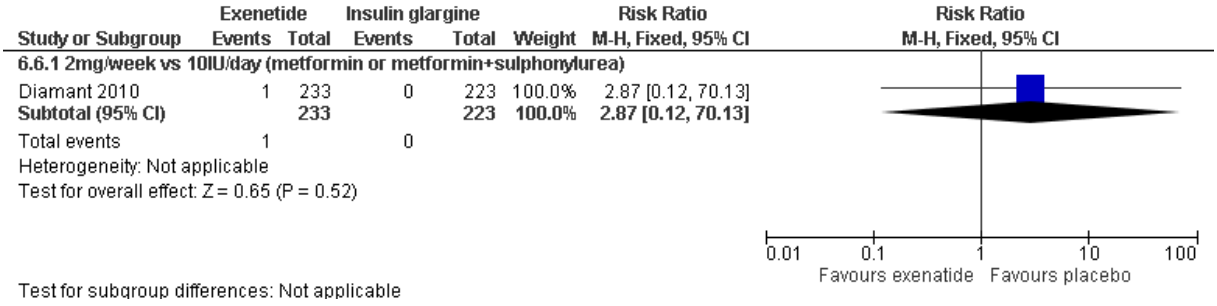
CV mortality



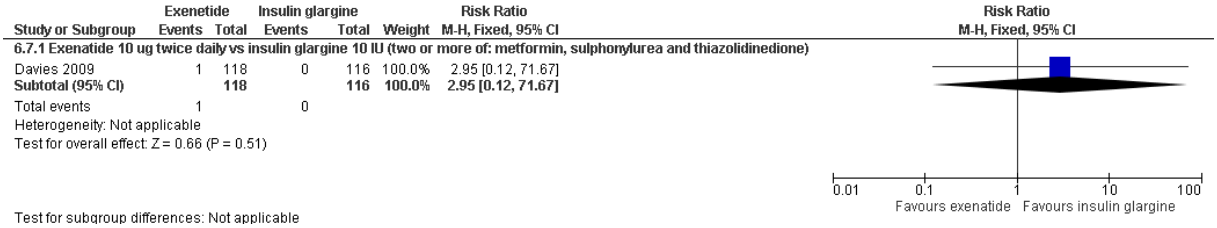
Acute myocardial infarction



Myocardial infarction

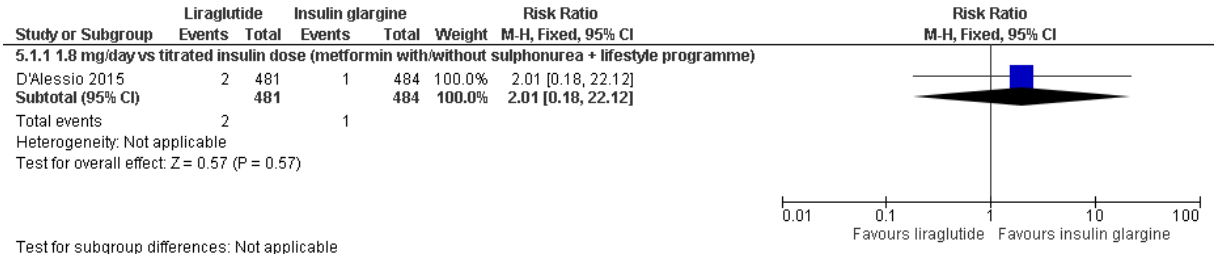


Acute renal failure

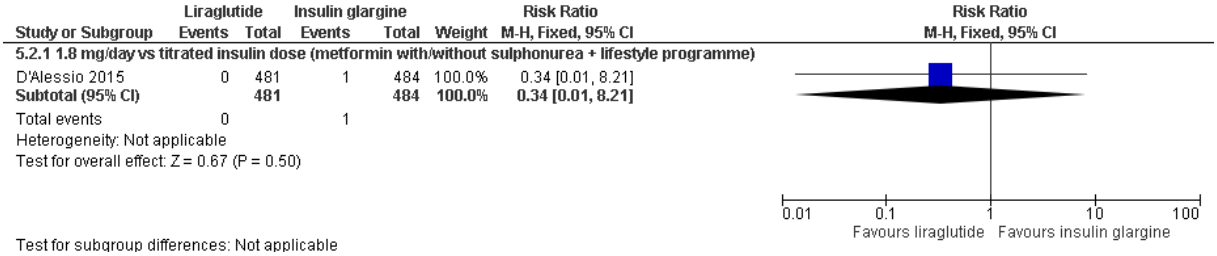


Liraglutide vs insulin glargine

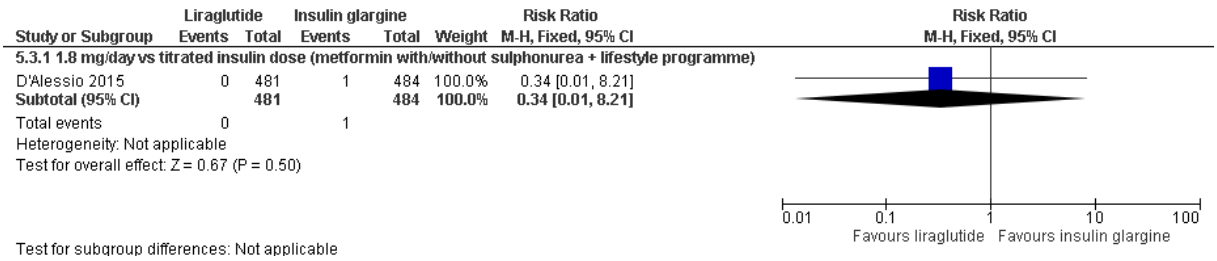
Cerebrovascular accident



Ischaemic stroke

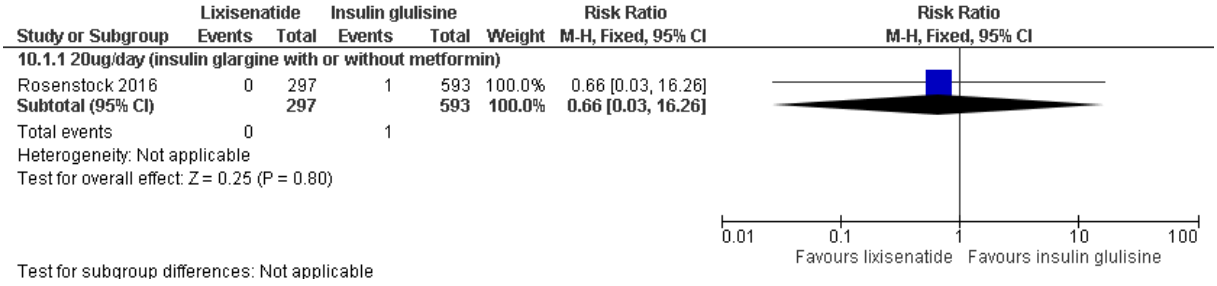


Chronic cardiac failure



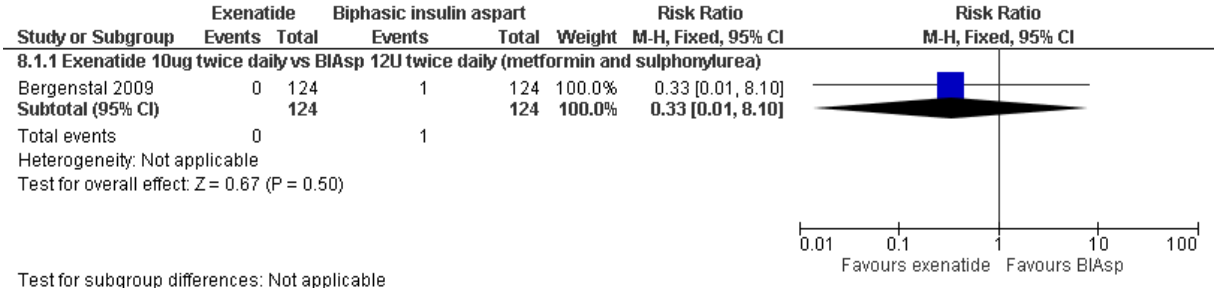
Lixisenatide vs insulin glulisine

Chronic heart failure mortality



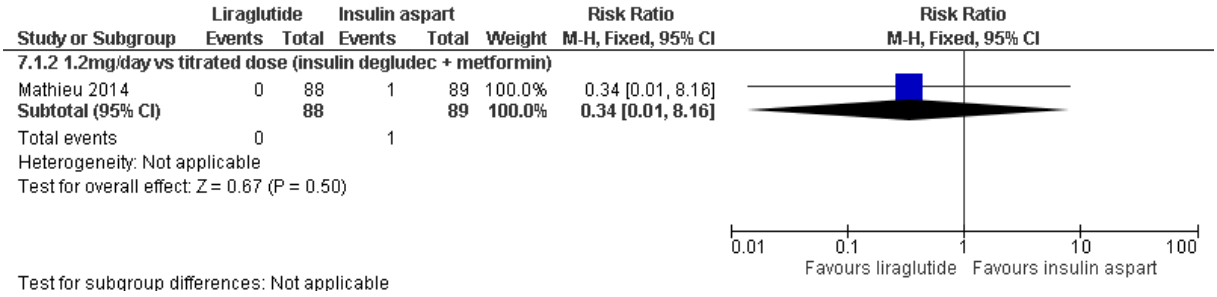
Exenatide vs biphasic insulin aspart

Cardiovascular mortality

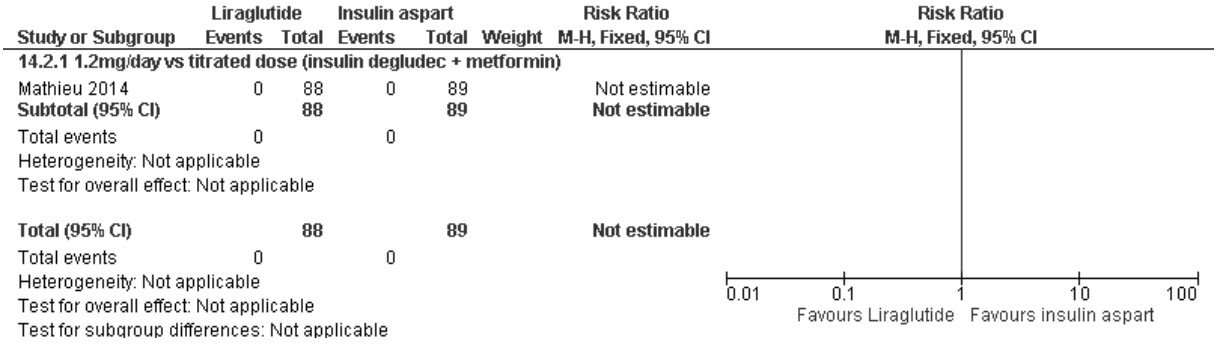


Liraglutide vs insulin aspart

Stroke

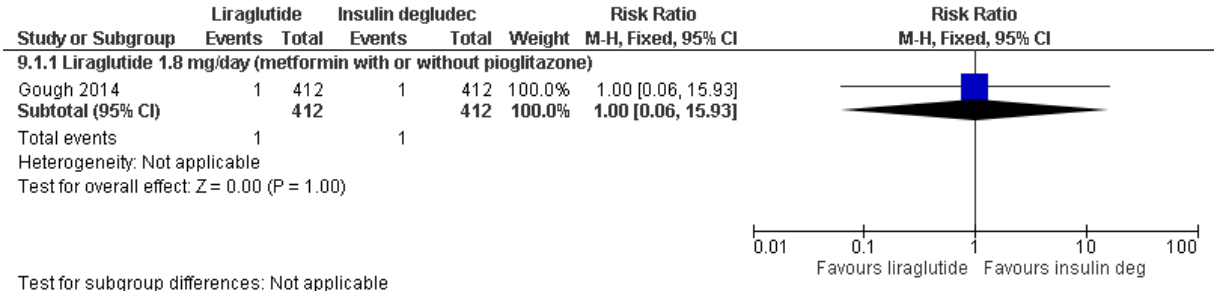


CV mortality



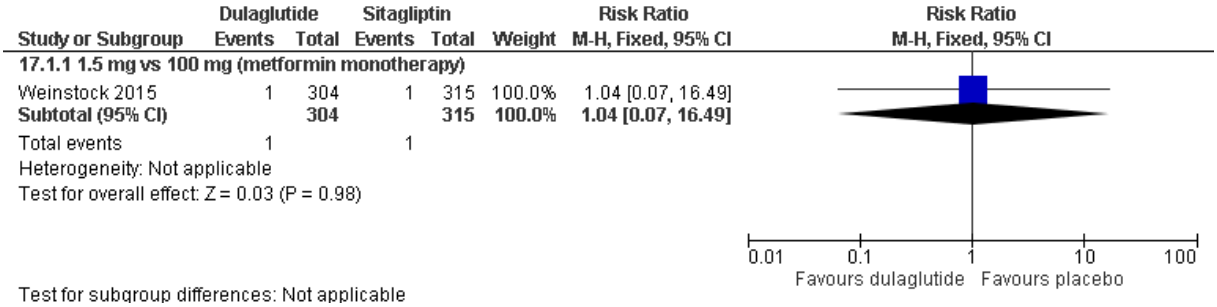
Liraglutide vs insulin degludec

Myocardial infarction



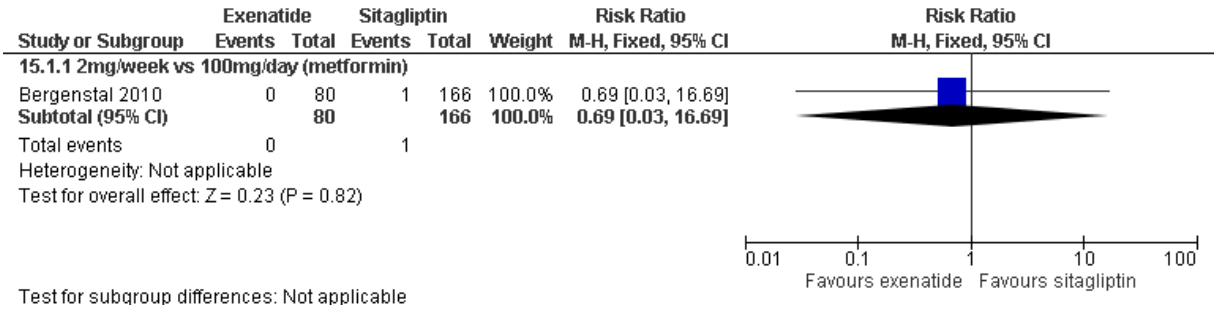
Dulaglutide vs sitagliptin

Cardiovascular mortality

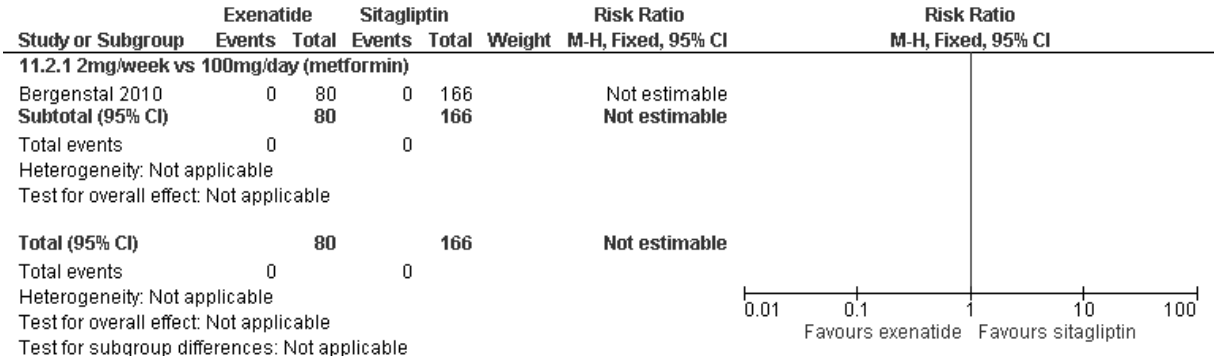


Exenatide vs sitagliptin

Cerebrovascular accident

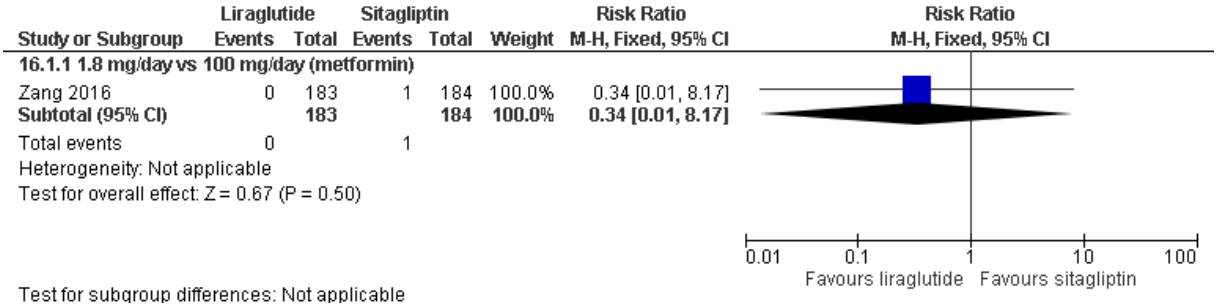


Acute renal failure

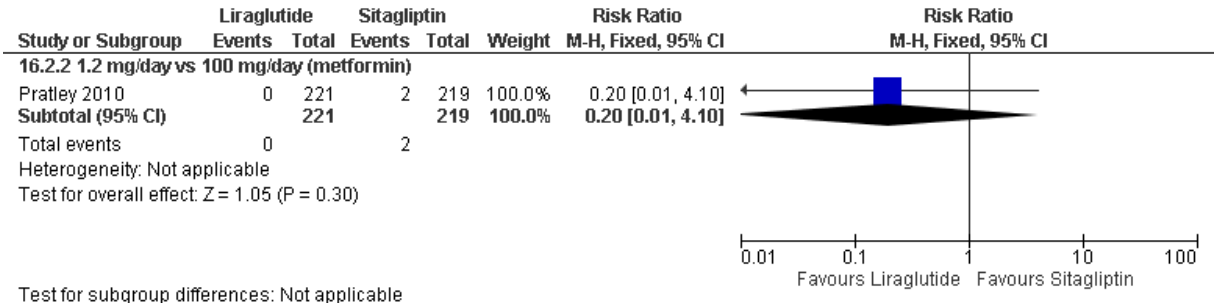


Liraglutide vs sitagliptin

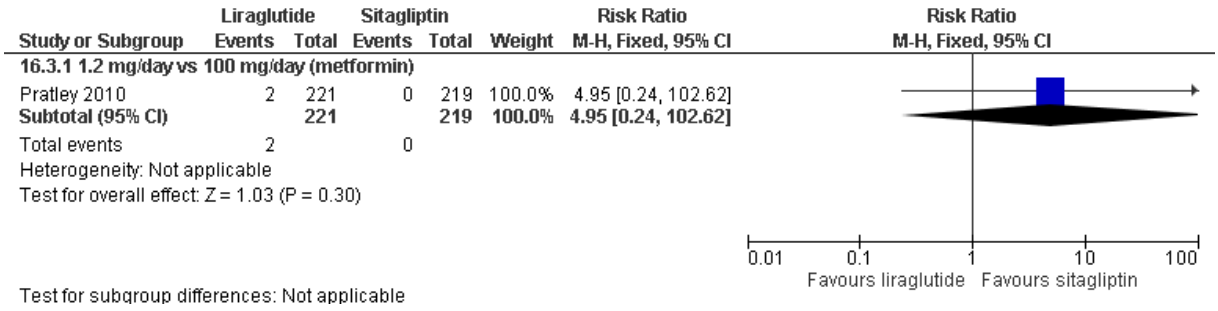
Cerebral infarction



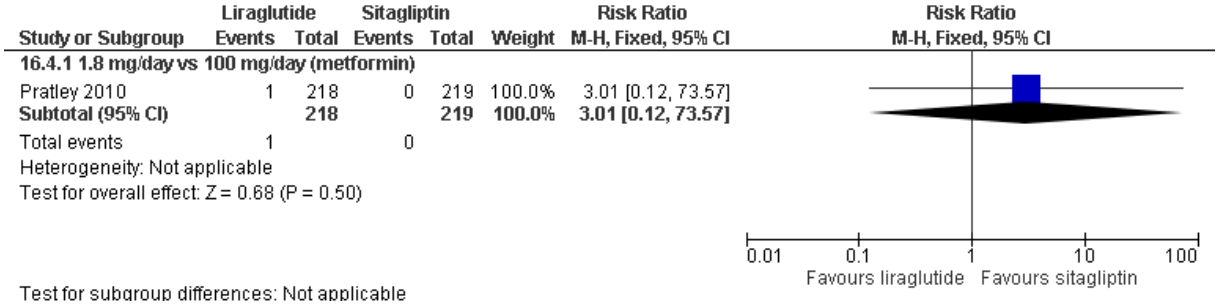
CV mortality



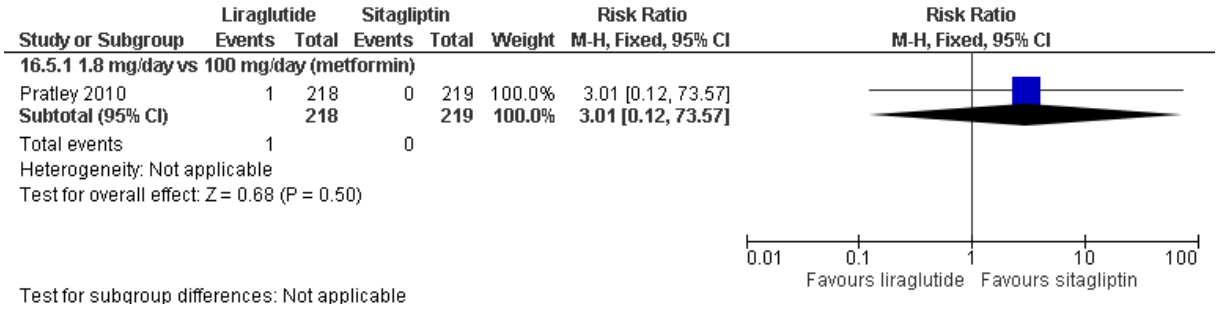
Myocardial infarction



Heart failure

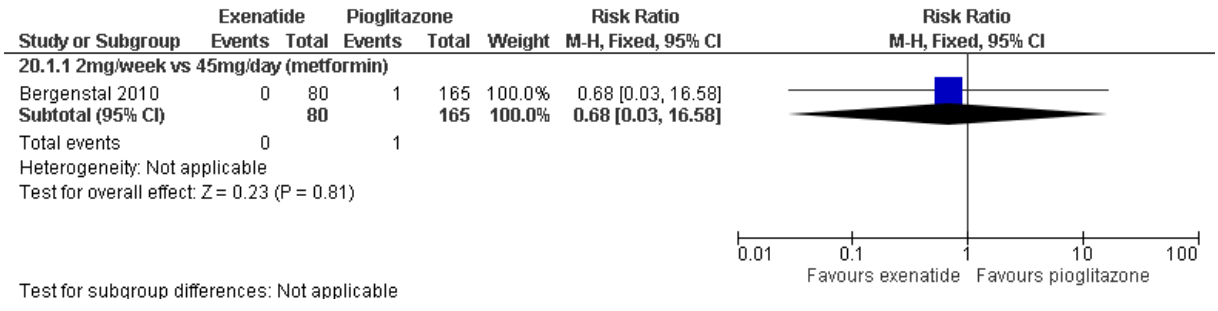


Diabetic retinopathy

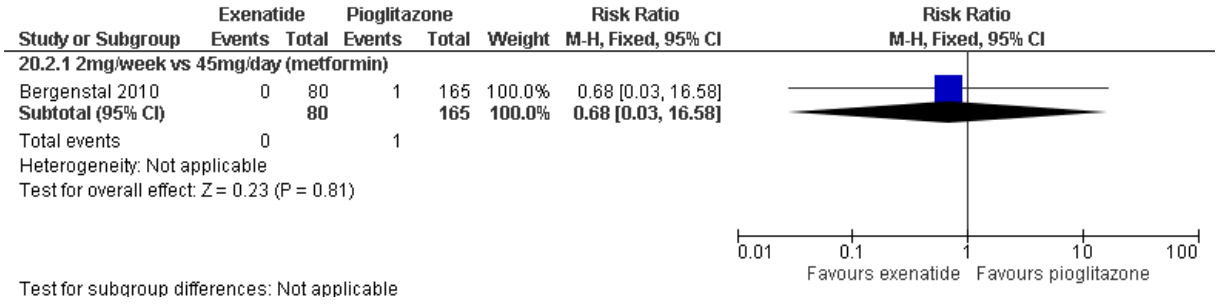


Exenatide vs pioglitazone

Cerebrovascular accident

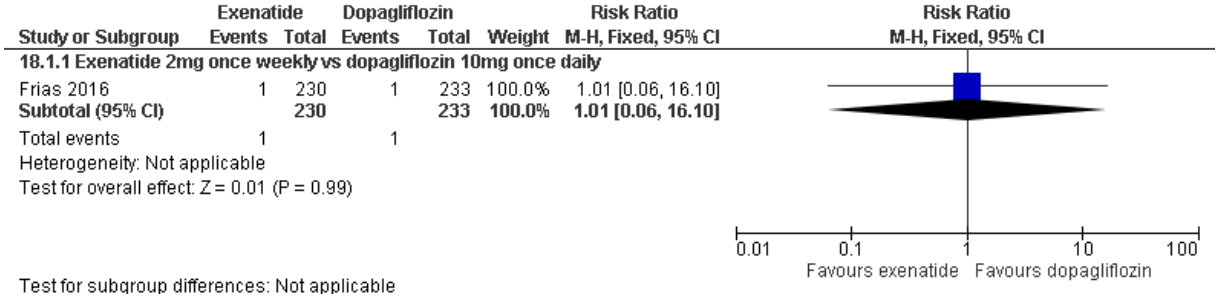


Acute renal failure

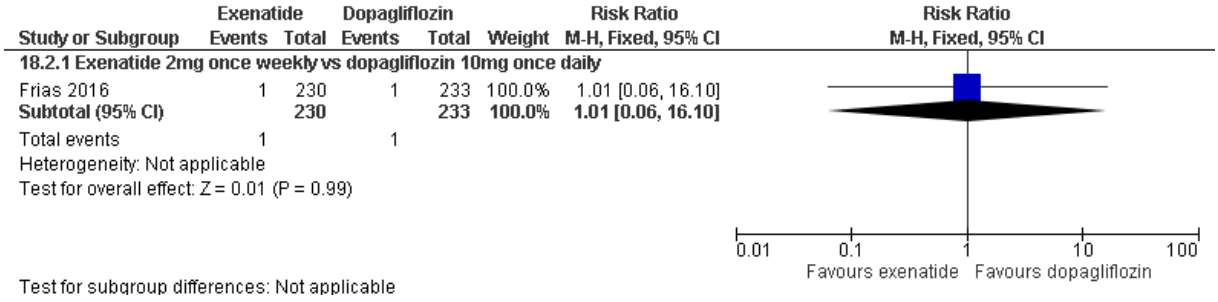


Exenatide vs dopaglilflozin

Cardiovascular mortality

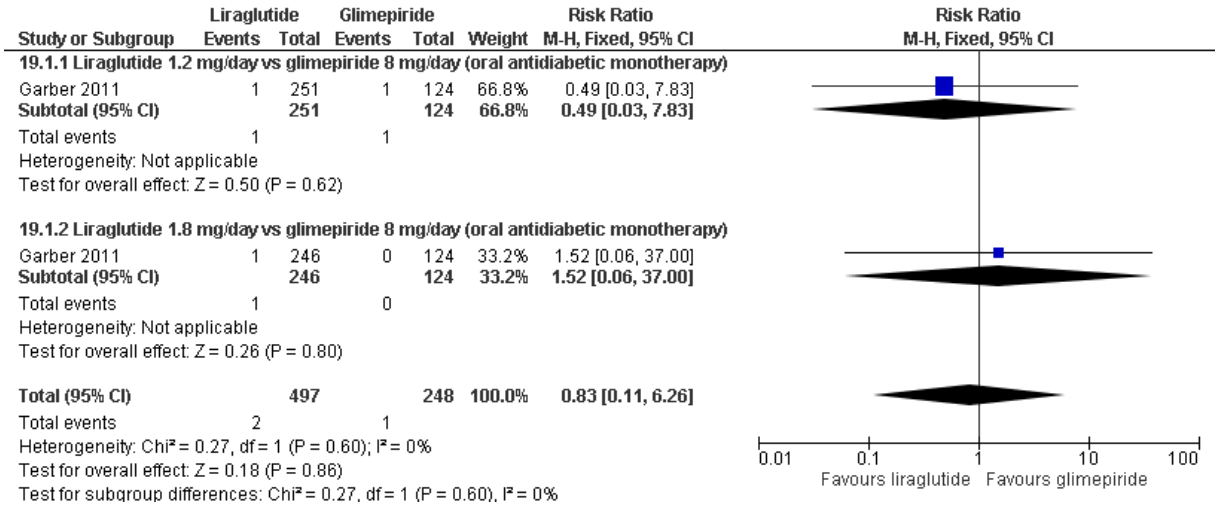


Renal failure



Liraglutide vs glimepiride

Myocaridal infarction



Appendix F – GRADE tables

SGLT-2 inhibitors

Canagliflozin (100mg/d or 300mg/d) versus placebo

Quality assessment						No of patients		Summary of results	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Canagliflozin	Placebo	Effect estimate Risk Ratio (95% CI) Hazard Ratio (95% CI)	
Cardiovascular mortality									
1 (Neal 2017)	RCT	Not serious	Not serious	N/A[1]	Serious[2]	268/5,795	185/4,347	RR 0.89 (0.74, 1.07) HR 0.87 (0.72, 1.06)	MODERATE
Non-fatal myocardial infarction									
1 (Neal 2017)	RCT	Not serious	Not serious	N/A[1]	Serious[2]	215/5,795	159/4,347	RR 0.87 (0.71, 1.07) HR 0.85 (0.69, 1.05)	MODERATE
Non-fatal stroke									
1 (Neal 2017)	RCT	Not serious	Not serious	N/A[1]	Very serious[3]	158/5,795	116/4,347	RR 0.92 (0.72, 1.17) HR 0.90 (0.71, 1.15)	LOW
Hospitalisation for heart failure									
1 (Neal 2017)	RCT	Not serious	Serious[4]	N/A[1]	Not serious	123/5,795	120/4,347	RR 0.69 (0.53, 0.89) HR 0.67 (0.52, 0.87)	MODERATE
Lower limb amputation – all amputations									
1 (Neal 2017)	RCT	Not serious	Not serious	N/A[1]	Not serious	6.30[5]	3.37[5]	HR 1.97 (1.41, 2.75)	HIGH
Lower limb amputation – with history of amputation									
1 (Neal 2017)	RCT	Not serious	Not serious	N/A[1]	Not serious	96.30[6]	59.16[6]	HR 2.15 (1.11, 4.19)	HIGH
Lower limb amputation – without history of amputation									
1 (Neal 2017)	RCT	Not serious	Not serious	N/A[1]	Not serious	4.68[6]	2.48[6]	HR 1.88 (1.27, 2.78)	HIGH
All-cause mortality									
1 (Neal 2017)	RCT	Not serious	Not serious	N/A[1]	Serious[2]	400/5,795	281/4,347	RR 0.88 (0.76, 1.02)	MODERATE

Quality assessment						No of patients		Summary of results	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Canagliflozin	Placebo	Effect estimate Risk Ratio (95% CI) Hazard Ratio (95% CI)	
								HR 0.87 (0.74, 1.01)	

[1]Inconsistency not applicable as outcome is from one study.
[2]Evidence was downgraded by one as 95% CI crossed 1 MID.
[3]Evidence was downgraded by two as 95% CI crossed 2 MIDs.
[4]Evidence was downgraded by one as overall rates for heart failure were not reported.
[5]Event rate of lower-limp amputations per 1000 patient-years.
[6]Absolute risk of lower limb amputation per 1000 person-years.

Empagliflozin versus placebo – cardiovascular mortality

Quality assessment						No of patients		Summary of results	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Empagliflozin	Placebo	Effect estimate Risk Ratio (95% CI) Hazard Ratio (95% CI)	
Empagliflozin pooled doses (10mg/d and 25mg/d)									
1 (Zinman 2015)	RCT	Not serious	Not serious	N/A[1]	Not serious	172/4,687	137/2,333	RR 0.62 (0.50, 0.78) HR 0.62 (0.49, 0.77)	HIGH
Empagliflozin 10mg/d									
1 (Zinman 2015)	RCT	Not serious	Not serious	N/A[1]	Not serious	90/2,345	137/2,333	RR 0.66 (0.48, 0.89) HR 0.65 (0.50, 0.85)	HIGH
Empagliflozin 25mg/d									
1 (Zinman 2015)	RCT	Not serious	Not serious	N/A[1]	Not serious	82/2,342	137/2,333	RR 0.59 (0.43, 0.81) HR 0.59 (0.45, 0.77)	HIGH
With heart failure at baseline (pooled doses)									
1 (Zinman 2015)[2]	RCT	Not serious	Not serious	N/A[1]	Serious[3]	38/462	27/244	RR 0.74 (0.47, 1.19) HR 0.71 (0.43, 1.16)	MODERATE
Without heart failure at baseline (pooled doses)									
1 (Zinman 2015)[2]	RCT	Not serious	Not serious	N/A[1]	Not serious	134/4,225	110/2,089	RR 0.60 (0.47, 0.77) HR 0.60 (0.47, 0.77)	HIGH

Quality assessment						No of patients		Summary of results	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Empagliflozin	Placebo	Effect estimate Risk Ratio (95% CI) Hazard Ratio (95% CI)	
Cardiovascular risk - only cerebrovascular disease at baseline (pooled doses)									
1 (Zinman 2015)	RCT	Not serious	Not serious	N/A[1]	Serious[3]	21/635	15/325	RR 0.72 (0.37, 1.37) HR 0.72 (0.37, 1.39)	MODERATE
Cardiovascular risk - only coronary artery disease at baseline (pooled doses)									
1 (Zinman 2015)	RCT	Not serious	Not serious	N/A[1]	Not serious	90/2,732	63/1,340	RR 0.70 (0.51, 0.96) HR 0.69 (0.50, 0.95)	HIGH
Cardiovascular risk - only peripheral artery disease at baseline (pooled doses)									
1 (Zinman 2015)	RCT	Not serious	Not serious	N/A[1]	Serious[3]	13/412	7/191	RR 0.86 (0.35, 2.12) HR 0.85 (0.34, 2.13)	MODERATE
2 or 3 high cardiovascular risk categories at baseline (pooled doses)									
1 (Zinman 2015)	RCT	Not serious	Not serious	N/A[1]	Not serious	46/878	50/451	RR 0.47 (0.32, 0.69) HR 0.47 (0.31, 0.70)	HIGH
Baseline glycaemic control HbA1c <8.5% (pooled doses)									
1 (Zinman 2015)	RCT	Not serious	Not serious	N/A[1]	Not serious	114/3,212	96/1,607	RR 0.59 (0.46, 0.77) HR 0.59 (0.45, 0.77)	HIGH
Baseline glycaemic control HbA1c ≥8.5% (pooled doses)									
1 (Zinman 2015)	RCT	Not serious	Not serious	N/A[1]	Serious[3]	58/1,475	41/726	RR 0.70 (0.47, 1.03) HR 0.69 (0.46, 1.03)	MODERATE
BMI <30 kg/m^2 at baseline (pooled doses)									
1 (Zinman 2015)	RCT	Not serious	Not serious	N/A[1]	Not serious	80/2,279	78/1,120	RR 0.50 (0.37, 0.68) HR 0.50 (0.37, 0.68)	HIGH
BMI ≥30 kg/m^2 at baseline (pooled doses)									
1 (Zinman 2015)	RCT	Not serious	Not serious	N/A[1]	Serious[3]	92/2,408	59/1,213	RR 0.79 (0.57, 1.08) HR 0.78 (0.56, 1.08)	MODERATE
White population (pooled doses)									
1 (Zinman 2015)	RCT	Not serious	Not serious	N/A[1]	Not serious	134/3,403	102/1,678	RR 0.65 (0.50, 0.83) HR 0.64 (0.50, 0.83)	HIGH

Quality assessment						No of patients		Summary of results	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Empagliflozin	Placebo	Effect estimate Risk Ratio (95% CI) Hazard Ratio (95% CI)	
Black/African-American population (pooled doses)									
1 (Zinman 2015)	RCT	Not serious	Not serious	N/A[1]	Serious[3]	13/237	9/120	RR 0.73 (0.32, 1.66) HR 0.77 (0.33, 1.79)	MODERATE
Asian population (pooled doses)									
1 (Zinman 2015)	RCT	Not serious	Not serious	N/A[1]	Not serious	22/1,006	25/511	RR 0.45 (0.25, 0.78) HR 0.44 (0.25, 0.78)	HIGH
Age <65 years at baseline (pooled doses)									
1 (Zinman 2015)	RCT	Not serious	Not serious	N/A[1]	Serious[3]	85/2,596	59/1,297	RR 0.72 (0.52, 1.00) HR 0.72 (0.52, 1.01)	MODERATE
Age ≥65 years at baseline (pooled doses)									
1 (Zinman 2015)	RCT	Not serious	Not serious	N/A[1]	Not serious	87/2,091	78/1,036	RR 0.55 (0.41, 0.74) HR 0.54 (0.40, 0.73)	HIGH
eGFR ≥90 mL/min/1.73 m^2 at baseline (pooled doses)									
1 (Zinman 2015)	RCT	Not serious	Not serious	N/A[1]	Serious[3]	28/1,050	19/488	RR 0.68 (0.39, 1.21) HR 0.70 (0.39, 1.25)	MODERATE
eGFR 60 to <90 mL/min/1.73 m^2 at baseline (pooled doses)									
1 (Zinman 2015)	RCT	Not serious	Not serious	N/A[1]	Not serious	69/2,425	70/1,238	RR 0.50 (0.36, 0.70) HR 0.49 (0.35, 0.68)	HIGH
eGFR <60 mL/min/1.73 m^2 at baseline (pooled doses)									
1 (Zinman 2015)	RCT	Not serious	Not serious	N/A[1]	Serious[3]	75/1,212	48/607	RR 0.78 (0.55, 1.11) HR 0.78 (0.54, 1.12)	MODERATE

[1]Inconsistency not applicable as outcome is from one study.
[2]Results reported by Fitchett 2016.
[3]Evidence was downgraded by one as effect estimate is not significant (crosses line of no effect).

Empagliflozin versus placebo – fatal acute myocardial infarction

Quality assessment						No of patients		Summary of results	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Empagliflozin	Placebo	Effect estimate Risk Ratio (95% CI)	
Empagliflozin pooled doses (10mg/d and 25mg/d)									
1 (Zinman 2015)	RCT	Not serious	Not serious	N/A[1]	Serious[2]	15/4,687	11/2,333	RR 0.68 (0.31, 1.48)	MODERATE
Empagliflozin 10mg/d									
1 (Zinman 2015)	RCT	Not serious	Not serious	N/A[1]	Serious[2]	6/2,345	5/1,166	RR 0.60 (0.18, 1.95)	MODERATE
Empagliflozin 25mg/d									
1 (Zinman 2015)	RCT	Not serious	Not serious	N/A[1]	Serious[2]	9/2,342	6/1,167	RR 0.75 (0.27, 2.09)	MODERATE
With heart failure at baseline (pooled doses)									
1 (Zinman 2015)[3]	RCT	Not serious	Not serious	N/A[1]	Serious[2]	2/462	2/244	RR 0.53 (0.07, 3.73)	MODERATE
Without heart failure at baseline (pooled doses)									
1 (Zinman 2015)[3]	RCT	Not serious	Not serious	N/A[1]	Serious[2]	13/4,225	9/2,089	RR 0.71 (0.31, 1.67)	MODERATE

[1]Inconsistency not applicable as outcome is from one study.
[2]Results reported by Fitchett 2016.
[3]Evidence was downgraded by one as effect estimate is not significant (crosses line of no effect).

Empagliflozin versus placebo – non-fatal myocardial infarction excluding silent myocardial infarction

Quality assessment						No of patients		Summary of results	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Empagliflozin	Placebo	Effect estimate Risk Ratio (95% CI) Hazard Ratio (95% CI)	
Empagliflozin pooled doses (10mg/d and 25mg/d)									
1 (Zinman 2015)	RCT	Not serious	Not serious	N/A[1]	Serious[2]	213/4,687	121/2,333	RR 0.88 (0.70, 1.09) HR 0.87 (0.70, 1.09)	MODERATE
Empagliflozin 10mg/d									
1 (Zinman 2015)	RCT	Not serious	Not serious	N/A[1]	Serious[2]	96/2,345	121/2,333	RR 0.80 (0.58, 1.09) HR 0.79 (0.60, 1.03)	MODERATE
Empagliflozin 25mg/d									
1 (Zinman 2015)	RCT	Not serious	Not serious	N/A[1]	Very serious[3]	117/2,342	121/2,333	RR 0.96 (0.71, 1.29)	LOW

Quality assessment						No of patients		Summary of results	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Empagliflozin	Placebo	Effect estimate Risk Ratio (95% CI) Hazard Ratio (95% CI)	
								HR 0.95 (0.74, 1.23)	
Asian population (pooled doses)									
1 (Zinman 2015)[4]	RCT	Not serious	Not serious	N/A[1]	Very serious[3]	29/1,006	22/511	RR 0.67 (0.39, 1.15) HR 0.65 (0.37, 1.13)	LOW

[1]Inconsistency not applicable as outcome is from one study.
[2]Evidence was downgraded by one as 95% CI crossed 1 MID.
[3]Evidence was downgraded by two as 95% CI crossed 2 MID.
[4]Results reported by Kaku 2017.

Empagliflozin versus placebo – non-fatal silent myocardial infarction

Quality assessment						No of patients		Summary of results	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Empagliflozin	Placebo	Effect estimate Risk Ratio (95% CI) Hazard Ratio (95% CI)	
Empagliflozin pooled doses (10mg/d and 25mg/d)									
1 (Zinman 2015)	RCT	Not serious	Not serious	N/A[1]	Very serious[2]	38/2,378	15/1,211	RR 1.26 (0.70, 2.29) HR 1.28 (0.70, 2.33)	LOW
Empagliflozin 10mg/d									
1 (Zinman 2015)	RCT	Not serious	Not serious	N/A[1]	Very serious[2]	19/1,174	15/1,211	RR 1.35 (0.57, 3.20) HR 1.32 (0.67, 2.60)	LOW
Empagliflozin 25mg/d									
1 (Zinman 2015)	RCT	Not serious	Not serious	N/A[1]	Very serious[2]	19/1,204	15/1,211	RR 1.18 (0.52, 2.70) HR 1.24 (0.63, 2.45)	LOW

[1]Inconsistency not applicable as outcome is from one study.
[2]Evidence was downgraded by two as 95% CI crossed 2 MID.

Empagliflozin versus placebo – fatal stroke

Quality assessment						No of patients		Summary of results	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Empagliflozin	Placebo	Effect estimate Risk Ratio (95% CI)	
Empagliflozin pooled doses (10mg/d and 25mg/d)									
1 (Zinman 2015)	RCT	Not serious	Not serious	N/A[1]	Serious[2]	16/4,687	11/2,333	RR 0.72 (0.34, 1.56)	MODERATE
Empagliflozin 10mg/d									
1 (Zinman 2015)	RCT	Not serious	Not serious	N/A[1]	Serious[2]	9/2,345	5/1,166	RR 0.90 (0.30, 2.66)	MODERATE
Empagliflozin 25mg/d									
1 (Zinman 2015)	RCT	Not serious	Not serious	N/A[1]	Serious[2]	7/2,342	6/1,167	RR 0.58 (0.20, 1.73)	MODERATE
With heart failure at baseline (pooled doses)									
1 (Zinman 2015)[3]	RCT	Not serious	Not serious	N/A[1]	Serious[2]	3/462	1/244	RR 1.58 (0.17, 15.15)	MODERATE
Without heart failure at baseline (pooled doses)									
1 (Zinman 2015)[3]	RCT	Not serious	Not serious	N/A[1]	Serious[2]	13/4,225	10/2,089	RR 0.64 (0.28, 1.46)	MODERATE

[1]Inconsistency not applicable as outcome is from one study.
[2]Evidence was downgraded by one as effect estimate is not significant (crosses line of no effect).
[3]Results reported by Fitchett 2016.

Empagliflozin versus placebo – non-fatal stroke

Quality assessment						No of patients		Summary of results	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Empagliflozin	Placebo	Effect estimate Risk Ratio (95% CI) Hazard Ratio (95% CI)	
Empagliflozin pooled doses (10mg/d and 25mg/d)									
1 (Zinman 2015)	RCT	Not serious	Not serious	N/A[1]	Serious[2]	150/4,687	60/2333	RR 1.24 (0.93, 1.67) HR 1.24 (0.92, 1.67)	MODERATE
Empagliflozin 10mg/d									
1 (Zinman 2015)	RCT	Not serious	Not serious	N/A[1]	Very serious[3]	77/2,345	60/2,333	RR 1.28 (0.84, 1.93) HR 1.27 (0.91, 1.79)	LOW
Empagliflozin 25mg/d									
1 (Zinman 2015)	RCT	Not serious	Not serious	N/A[1]	Very serious[3]	73/2,342	60/2,333	RR 1.21 (0.80, 1.84)	LOW

Quality assessment						No of patients		Summary of results	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Empagliflozin	Placebo	Effect estimate Risk Ratio (95% CI) Hazard Ratio (95% CI)	
								HR 1.20 (0.85, 1.69)	
Asian population (pooled doses)									
1 (Zinman 2015)[4]	RCT	Not serious	Not serious	N/A[1]	Very serious[3]	35/1,006	19/511	RR 0.94 (0.54, 1.62) HR 0.92 (0.53, 1.62)	LOW

[1]Inconsistency not applicable as outcome is from one study.
[2]Evidence was downgraded by one as 95% CI crossed 1 MID.
[3]Evidence was downgraded by two as 95% CI crossed 2 MID.
[4]Results reported by Kaku 2017.

Empagliflozin versus placebo – fatal heart failure

Quality assessment						No of patients		Summary of results	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Empagliflozin	Placebo	Effect estimate Risk Ratio (95% CI)	
Empagliflozin pooled doses (10mg/d and 25mg/d)									
1 (Zinman 2015)	RCT	Not serious	Not serious	N/A[1]	Not serious	11/4,687	19/2,333	RR 0.29 (0.14, 0.60)	HIGH
Empagliflozin 10mg/d									
1 (Zinman 2015)	RCT	Not serious	Not serious	N/A[1]	Serious[2]	7/2,345	9/1,166	RR 0.39 (0.14, 1.04)	MODERATE
Empagliflozin 25mg/d									
1 (Zinman 2015)	RCT	Not serious	Not serious	N/A[1]	Not serious	4/2,342	10/1,167	RR 0.20 (0.06, 0.63)	HIGH
With heart failure at baseline (pooled doses)									
1 (Zinman 2015)[3]	RCT	Not serious	Not serious	N/A[1]	Not serious	3/462	7/244	RR 0.23 (0.06, 0.87)	HIGH
Without heart failure at baseline (pooled doses)									
1 (Zinman 2015)[3]	RCT	Not serious	Not serious	N/A[1]	Not serious	8/4,225	12/2,089	RR 0.33 (0.13, 0.81)	HIGH

[1]Inconsistency not applicable as outcome is from one study.
[3]Evidence was downgraded by one as effect estimate is not significant (crosses line of no effect).
[2]Results reported by Fitchett 2016.

Empagliflozin versus placebo – investigator-reported non-fatal heart failure

Quality assessment						No of patients		Summary of results	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Empagliflozin	Placebo	Effect estimate Risk Ratio (95% CI) Hazard Ratio (95% CI)	
Empagliflozin pooled doses (10mg/d and 25mg/d)									
1 (Zinman 2015)[1]	RCT	Not serious	Not serious	N/A[1]	Not serious	204/4,687	143/2,333	RR 0.71 (0.58, 0.87) HR 0.70 (0.56, 0.87)	HIGH
Empagliflozin 10mg/d									
1 (Zinman 2015)[1]	RCT	Not serious	Not serious	N/A[1]	Serious[2]	106/2,345	143/2,333	RR 0.74 (0.55, 0.99) HR 0.73 (0.57, 0.94)	MODERATE
Empagliflozin 25mg/d									
1 (Zinman 2015)[1]	RCT	Not serious	Not serious	N/A[1]	Serious[2]	98/2,342	143/2,333	RR 0.68 (0.50, 0.91) HR 0.67 (0.52, 0.86)	MODERATE

[1]Results reported by Fitchett 2016.
[2]Inconsistency not applicable as outcome is from one study.
[3]Evidence was downgraded by one as 95% CI crossed 1 MID.

Empagliflozin versus placebo – hospitalisation for heart failure

Quality assessment						No of patients		Summary of results	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Empagliflozin	Placebo	Effect estimate Risk Ratio (95% CI) Hazard Ratio (95% CI)	
Empagliflozin pooled doses (10mg/d and 25mg/d)									
1 (Zinman 2015)	RCT	Not serious	Not serious	N/A[1]	Not serious	126/4,687	95/2,333	RR 0.66 (0.51, 0.86) HR 0.65 (0.50, 0.85)	HIGH
Empagliflozin 10mg/d									
1 (Zinman 2015)	RCT	Not serious	Not serious	N/A[1]	Serious[2]	60/2,345	95/2,333	RR 0.63 (0.44, 0.92) HR 0.62 (0.45, 0.86)	MODERATE
Empagliflozin 25mg/d									
1 (Zinman 2015)	RCT	Not serious	Not serious	N/A[1]	Serious[2]	66/2,342	95/2,333	RR 0.69 (0.48, 0.99) HR 0.68 (0.50, 0.93)	MODERATE

Quality assessment						No of patients		Summary of results	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Empagliflozin	Placebo	Effect estimate Risk Ratio (95% CI) Hazard Ratio (95% CI)	
With heart failure at baseline (pooled doses)									
1 (Zinman 2015)[3]	RCT	Not serious	Not serious	N/A[1]	Very serious[4]	48/462	30/244	RR 0.85 (0.55, 1.30) HR 0.75 (0.48, 1.19)	LOW
Without heart failure at baseline (pooled doses)									
1 (Zinman 2015)[3]	RCT	Not serious	Not serious	N/A[1]	Not serious	78/4,225	65/2,089	RR 0.59 (0.43, 0.82) HR 0.59 (0.43, 0.82)	HIGH
Asian population (pooled doses)									
1 (Zinman 2015)[5]	RCT	Not serious	Not serious	N/A[1]	Very serious[4]	22/1,006	16/511	RR 0.70 (0.37, 1.32) HR 0.70 (0.37, 1.33)	LOW

[1]Inconsistency not applicable as outcome is from one study.
[2]Evidence was downgraded by one as 95% CI crossed 1 MID.
[3]Results reported by Fitchett 2016.
[4]Evidence was downgraded by two as 95% CI crossed 2 MID.
[5]Results reported by Kaku 2017.

Empagliflozin pooled doses (10mg/d and 25mg/d) versus placebo – microvascular outcomes

Quality assessment						No of patients		Summary of results	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Empagliflozin	Placebo	Effect estimate Risk Ratio (95% CI) Hazard Ratio (95% CI)	
Incident or worsening nephropathy[1]									
1 (Zinman 2015)[2]	RCT	Not serious	Not serious	N/A[3]	Not serious	525/4,124	388/2,061	RR 0.68 (0.60, 0.76) HR 0.61 (0.53, 0.70)	HIGH
Incident or worsening nephropathy[4] – eGFR ≥60 mL/min/1.73m^2 and/or macroalbuminuria (urine albumin-to-creatinine ratio >300 mg/g) at baseline									
1 (Zinman 2015)[2]	RCT	Not serious	Not serious	N/A[3]	Not serious	318/3,126	227/1,554	RR 0.70 (0.59, 0.82)	HIGH
Incident or worsening nephropathy[4] – eGFR <60 mL/min/1.73m^2 and/or macroalbuminuria (urine albumin-to-creatinine ratio >300 mg/g) at baseline									
1 (Zinman 2015)[2]	RCT	Not serious	Not serious	N/A[3]	Not serious	207/998	161/507	RR 0.65 (0.55, 0.78) HR 0.58 (0.47, 0.71)	HIGH

Quality assessment						No of patients		Summary of results	Quality
No of studies	**Design**	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Empagliflozin**	**Placebo**	**Effect estimate Risk Ratio (95% CI) Hazard Ratio (95% CI)**	
Initiation of laser therapy for retinopathy[5]									
1 (Zinman 2015)[2]	RCT	Not serious	Not serious	N/A[3]	Very serious[6]	41/4,687	29/2,333	RR 0.70 (0.44, 1.13) HR 0.69 (0.43, 1.12)	LOW

[1]Participants who received at least one dose of either empagliflozin or placebo.
[2]Results reported by Wanner 2016.
[3]Inconsistency not applicable as outcome is from one study.
[4]Participants with prevalent kidney disease treated with ≥1 dose of study drug.
[5]Participants treated with ≥1 dose of study drug.
[6]Evidence was downgraded by two as 95% CI crossed 2 MID.
eGFR: estimated glomerular filtration rate

Empagliflozin versus placebo – coronary revascularisation procedure

Quality assessment						No of patients		Summary of results	Quality
No of studies	**Design**	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Empagliflozin**	**Placebo**	**Effect estimate Risk Ratio (95% CI) Hazard Ratio (95% CI)**	
Empagliflozin pooled doses (10mg/d and 25mg/d)									
1 (Zinman 2015)	RCT	Not serious	Not serious	N/A[1]	Serious[2]	329/4,687	186/2,333	RR 0.88 (0.74, 1.05) HR 0.86 (0.72, 1.04)	MODERATE
Empagliflozin 10mg/d									
1 (Zinman 2015)	RCT	Not serious	Not serious	N/A[1]	Serious[2]	154/2,345	186/2,333	RR 0.82 (0.64, 1.05) HR 0.81 (0.65, 1.00)	MODERATE
Empagliflozin 25mg/d									
1 (Zinman 2015)	RCT	Not serious	Not serious	N/A[1]	Very serious[3]	175/2,342	186/2,333	RR 0.94 (0.74, 1.19) HR 0.92 (0.75, 1.13)	LOW

[1]Inconsistency not applicable as outcome is from one study.
[2]Evidence was downgraded by one as 95% CI crossed 1 MID.
[3]Evidence was downgraded by two as 95% CI crossed 2 MID.

Empagliflozin versus placebo – all-cause mortality

Quality assessment						No of patients		Summary of results	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Empagliflozin	Placebo	Effect estimate Risk Ratio (95% CI) Hazard Ratio (95% CI)	
Empagliflozin pooled doses (10mg/d and 25mg/d)									
1 (Zinman 2015)	RCT	Not serious	Not serious	N/A[1]	Not serious	269/4,687	194/2,333	RR 0.69 (0.58, 0.82) HR 0.68 (0.57, 0.82)	HIGH
Empagliflozin 10mg/d									
1 (Zinman 2015)	RCT	Not serious	Not serious	N/A[1]	Not serious	137/2,345	194/2,333	RR 0.70 (0.55, 0.90) HR 0.70 (0.56, 0.87)	HIGH
Empagliflozin 25mg/d									
1 (Zinman 2015)	RCT	Not serious	Not serious	N/A[1]	Not serious	132/2,342	194/2,333	RR 0.68 (0.53, 0.87) HR 0.67 (0.54, 0.83)	HIGH
With heart failure at baseline (pooled doses)									
1 (Zinman 2015)[2]	RCT	Not serious	Not serious	N/A[1]	Serious[3]	56/462	35/244	RR 0.85 (0.57, 1.25) HR 0.79 (0.52, 1.20)	MODERATE
Without heart failure at baseline (pooled doses)									
1 (Zinman 2015)[2]	RCT	Not serious	Not serious	N/A[1]	Not serious	213/4,225	159/2,089	RR 0.66 (0.54, 0.81) HR 0.66 (0.51, 0.81)	HIGH
Asian population (pooled doses)									
1 (Zinman 2015)[4]	RCT	Not serious	Not serious	N/A[1]	Serious[3]	41/1,006	32/511	RR 0.65 (0.42, 1.02) HR 0.64 (0.40, 1.01)	MODERATE

[1]Inconsistency not applicable as outcome is from one study.
[2]Results reported by Fitchett 2016.
[3]Evidence was downgraded by one as effect estimate is not significant (crosses line of no effect).
[4]Results reported by Kaku 2017.

GLP-1 mimetics

Liraglutide 1.8mg/day versus placebo

Quality assessment						No of patients		Summary of results	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Liraglutide	Placebo	Effect estimate Risk Ratio (95% CI)	
Myocardial infarction									
1 (Marso 2016)	RCT	No serious	No serious	N/A[1]	serious [2]	292/4668	339/4672	0.86 (0.74, 1.00)	MODERATE
Myocardial infarction mortality									
1 (Marso 2016)	RCT	No serious	No serious	N/A[1]	serious[3]	17/4668	28/4672	0.61 (0.33, 1.11)	MODERATE
Stroke									
1 (Marso 2016)	RCT	No serious	No serious	N/A[1]	Serious[2]	175/4668	202/4672	0.87 (0.71, 1.06)	MODERATE
Stroke mortality									
1 (Marso 2016)	RCT	No serious	No serious	N/A[1]	Serious[3]	16/4668	25/4672	0.64 (0.34, 1.20)	MODERATE
Transient ischaemic attack									
1 (Marso 2016)	RCT	No serious	No serious	N/A[1]	Very serious[4]	48/4668	60/4672	0.80 (0.55, 1.17)	LOW
Diabetic retinopathy									
1 (Marso 2016)	RCT	No serious	No serious	N/A[1]	Very serious[4]	106/4668	92/4672	1.15 (0.87, 1.52)	LOW
Nephropathy									
1 (Marso 2016)	RCT	No serious	No serious	N/A[1]	Serious[2]	268/4668	337/4672	0.80 (0.68, 0.93)	MODERATE
Cardiovascular mortality									
1 (Marso 2016)	RCT	No serious	No serious	N/A[1]	No serious	219/4668	278/4672	0.79 (0.66, 0.94)	HIGH
All-cause mortality									
1 (Marso 2016)	RCT	No serious	No serious	N/A[1]	No serious	381/4668	447/4672	0.85 (0.75, 0.97)	HIGH

1 Inconsistency not applicable as outcome is from one study.
2 Evidence was downgraded by one as 95% CI crossed 1 MID.
3 Evidence was downgraded by one as effect estimate is not significant (crosses line of no effect).
4 Evidence was downgraded by one as 95% CI crossed 2 MIDs.

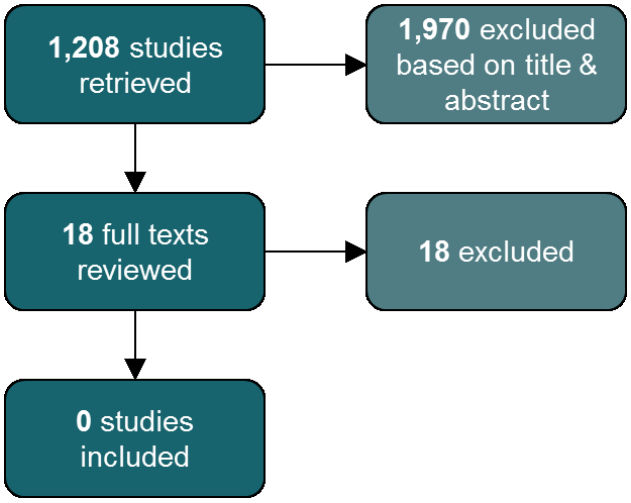
Lixisenatide up to 20 µg vs placebo

Quality assessment						No of patients		Summary of results	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Lixisenatide	Placebo	Effect estimate Risk Ratio (95% CI)	
Myocardial infarction									
1 (Pfeffer 2015)	RCT	No serious	No serious	N/A[1]	Very serious[2]	270/3034	261/3034	1.03 (0.88, 1.22)	LOW
Stroke									
1 (Pfeffer 2015)	RCT	No serious	No serious	N/A[1]	Very serious[2]	67/3034	60/3034	1.12 (0.79, 1.58)	LOW
Hospitalisation for heart failure									
1 (Pfeffer 2015)	RCT	No serious	Serious[3]	N/A[1]	Very serious[2]	122/3034	127/3034	0.96 (0.75, 1.23)	VERY LOW
Cardiovascular mortality									
1 (Pfeffer 2015)	RCT	No serious	No serious	N/A[1]	Serious[4]	158/3034	156/3034	1.01 (0.82, 1.26)	MODERATE
All-cause mortality									
1 (Pfeffer 2015)	RCT	No serious	No serious	N/A[1]	Serious[4]	221/3034	223/3034	0.95 (0.79, 1.13)	MODERATE

1 Inconsistency not applicable as outcome is from one study.
2 Evidence was downgraded by one as 95% CI crossed 2 MIDs.
3 Evidence was downgraded by one as outcome is indirect for 'heart failure' which was not reported in the study.
4 Evidence was downgraded by one as effect estimate is not significant (crosses line of no effect).

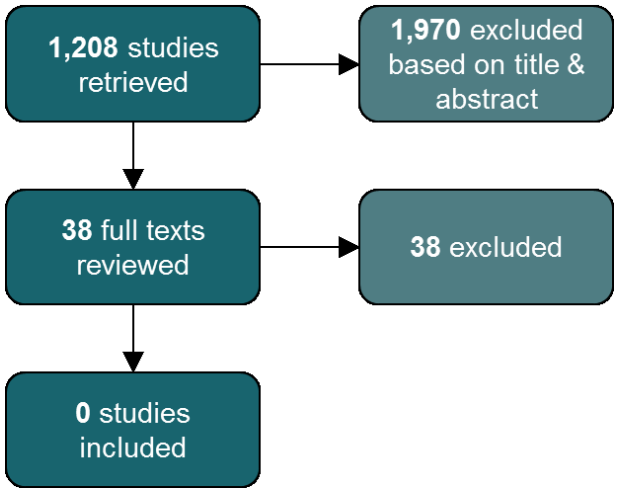
Appendix G – Economic evidence study selection

SGLT-2 inhibitors

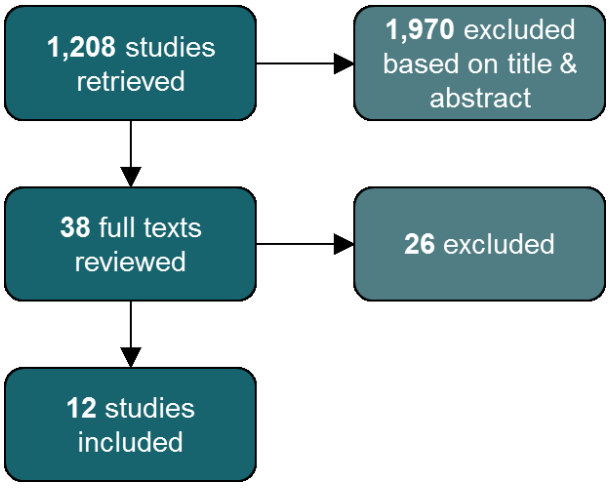


GLP-1 mimetics

In adults with Type 2 diabetes, what is the clinical effectiveness of GLP1 mimetics on cardiovascular outcomes?



In adults with Type 2 diabetes, what are the differences between a). The assumptions used in the HE model that informed NG28 and b). The empirical evidence from RCTs?


1,208 studies retrieved
1,970 excluded based on title & abstract
38 full texts reviewed
26 excluded
12 studies included

Appendix H – Economic evidence tables

GLP-1 mimetics

Study	1. Applicability 2. Limitations	Comparison(s)	Setting	Duration Discount rate(s)	Relative effects parameters [1]	Results / conclusion	ICER sensitivity to SBP and lipids
Beaudet et al. (2011)	1. Directly applicable 2. Potentially serious [a,b]	Exenatide once weekly vs. insulin glargine	UK, NHS	50 years 3.5% (costs, QALYs)	BMI, HbA1c, hypoglycaemic events, **lipids**, **SBP**.	Exenatide ICER: £10,597	SBP: negligible effect on ICER Lipids: negligible effect on ICER
(a) Baseline and relative effects data informed by 1 study. *(b) Potential conflict of interest.*							
Bruhn et al. (2016)	1. Partially applicable [c,d] 2. Potentially serious [e]	Albiglutide vs. 1. insulin lispro (both + insulin glargine) 2. insulin glargine 3. sitagliptin	US, payer	50 years Discount rates not clear.	BMI, HbA1c, hypoglycaemic events, **lipids**, **SBP**.	Albiglutide ICER: 1. $43,541 2. $79,166 3. $22,094	SBP: minor (ICERs: 1. $51,027 2. $152,400 3. $23,797) Lipids: minor (ICERs: 1. $47,057 2. $85,851 3. $22,646)
(c) US study. *(d) Base case discount rates unclear (>0%, <6%).* *(e) Potential conflict of interest.*							
Fonseca et al. (2013)	1. Partially applicable [f,g] 2. Potentially serious [h,i]	Exenatide once weekly (o.w) vs. 1. exenatide twice daily (b.i.d) 2. insulin glargine	Spain, health service	35 years 3.0% (costs, QALYs)	BMI, HbA1c, hypoglycaemic events, **lipids**, **SBP**.	Exenatide o.w dominates b.i.d. ICER vs. insulin glargine: €12,084	SBP: minor (ICER vs. insulin: €9,679 to €14,357).
(f) Spanish study. *(g) 3% discount rates.* *(h) Baseline and relative effects data informed by 1 study for comparison with insulin glargine.* *(i) Potential conflict of interest.*							

Gao et al. (2012)	1. Partially applicable [j,k] 2. Potentially serious [l]	Glimepride vs. 1. liraglutide 1.8 mg 2. liraglutide 1.2 mg 3. liraglutide 0.6 mg	China, health care system	30 years 3.0% (costs, QALYs)	Body weight, **cholesterol**, HbA1c, **SBP**.	Liraglutide 1.8 mg ICER >3x GDP per capita vs. glimepride.	SBP: incremental QALYs sensitive (+0.168 to +0.060).
(j) Chinese study. *(k) 3% discount rates.* *(l) Baseline and relative effects data informed by 1 study.*							
Hunt et al. (2017a)	1. Directly applicable 2. Potentially serious [m,n,o]	1. Exenatide b.i.d 2. Liraglutide 1.2 mg 3. Lixisenatide 20 µg	UK, NHS	50 years 3.5% (costs, QALYs)	BMI, HbA1c, **SBP**.	Liraglutide dominates	SBP: negligible
(m) Unit costs of treatment not reported. *(n) No probabilistic sensitivity analysis.* *(o) Potential conflict of interest.*							
Hunt et al. (2017b)	1. Directly applicable 2. Potentially serious [p,q,r]	Liraglutide 1.8 mg vs. lixisenatide 20 µg (both + metformin)	UK, NHS	Lifetime 3.5% (costs, QALYs)	BMI, HbA1c, hypoglycaemic events, **lipids**, **SBP**.	Liraglutide ICER: £8,901	SBP: negligible Lipids: minor (ICER: £11,679)
(p) Baseline and relative effects data informed by 1 clinical study. *(q) Unit costs not reported.* *(r) Potential conflict of interest.*							
Minshall et al. (2008)	1. Partially applicable [s,t,u] 2. Potentially serious [v,w]	Exentide b.i.d vs. no further treatment	US, payer	30 years 3.0% (costs, QALYs)	BMI, HbA1c, **lipids**, **SBP**.	Exenatide ICER: $36,133	SBP: minor Lipids: minor (ICER: $41,738)
(s) US study. *(t) 3% discount rates.* *(u) Comparator is placebo.* *(v) Baseline and relative effects data informed by 1 study.* *(w) Potential conflict of interest.*							

Perez et al. (2015)	1. Partially applicable [x,y] 2. Potentially serious [z,aa,bb]	Liraglutide 1.8 mg vs. sitagliptin 100 mg (both + metformin)	Spain, health service	Lifetime 3.0% (costs, QALYs)	BMI, HbA1c, hypoglycaemic events, **lipids**, **SBP**.	Liraglutide ICER: €10,436	SBP: negligible Lipids: minor (ICER: €12,119)
(x) Spanish study. *(y) 3% discount rates.* *(z) Baseline and relative effects data informed by 1 study.* *(aa) No probabilistic sensitivity analysis.* *(bb) Potential conflict of interest.*							
Ray et al. (2007)	1. Directly applicable 2. Very serious [cc,dd,ee]	Exenatide b.i.d vs. insulin glargine o.d (both + metformin + sulfonylurea)	UK, NHS	Lifetime 3.5% (costs, QALYs)	BMI, HbA1c, hypoglycaemic events, **lipids**, **SBP**.	Exenatide ICER: £22,420 (price equal to insulin glargine).	SBP: minor (ICER: £26,144) Lipids: minor (ICER: £23,996)
(cc) Baseline and relative effects data informed by 1 study. *(dd) No unit price for exenatide at the time of publication.* *(ee) Potential conflict of interest.*							
Roussel et al. (2015)	1. Partially applicable [ff,gg] 2. Potentially serious [hh,ii]	Liraglutide 1.2 mg vs. 1. sitagliptin 2. glimepride (all + metformin)	France, payer	Lifetime 3.0% (costs, QALYs)	BMI, HbA1c, hypoglycaemic events, **lipids**, **SBP**.	Albiglutide ICER: 1. €10,275 2. €20,709	SBP: minor (ICERs: 1. €10,113 2. €25,834) Lipids: minor (ICERs: 1. €10,511 2. €26,634)
(ff) French study. *(gg) 3% discount rates.* *(hh) Baseline and relative effects data for each comparison informed by 1 study.* *(ii) Potential conflict of interest.*							
Tzanetakos et al. (2014)	1. Partially applicable [jj] 2. Potentially serious [kk,ll]	1. Liraglutide 1.2 mg vs. sitagliptin 2. Liraglutide 1.8 mg vs. exenatide b.i.d (all + metformin or glimepride or both)	Greece, payer	Lifetime 3.5% (costs, QALYs)	BMI, HbA1c, hypoglycaemic events, **lipids**, **SBP**.	Liraglutide ICER: 1. €15,101 2. €6,818	SBP: minor (ICERs: 1. €14,086 to €16,246 2. €5,380 to €7,327) Lipids: minor (ICERs: 1. €12,693 to €16,577 2. €5,373 to €9,400)
(jj) Greek study.							

(kk) Baseline and relative effects data for each comparison informed by 1 study. *(ll) Potential conflict of interest.*							
Valentine et al. (2011)	1. Partially applicable [mm,nn] 2. Potentially serious [oo,pp,qq,rr]	Liraglutide 1.8 mg vs. exenatide b.i.d (both + metformin or sulfonylurea or both)	6 W/N European countries, payer	40 years 1.5% to 4.0% across settings	BMI, HbA1c, hypoglycaemic events, **lipids**, **SBP**.	Liraglutide ICERs between €6,902 and €13,546 across settings	SBP and lipids together: minor (ICER: base case €6,902 increases to €11,707)
(mm) Various non-UK settings. *(nn) Various discount rates.* *(oo) Baseline and relative effects data informed by 1 study.* *(pp) Unit costs of treatment not reported.* *(qq) One-way sensitivity analysis only reported for Swiss results.* *(rr) Potential conflict of interest.*							
1. Bold type indicates relative effect parameters used to distinguish between treatments in predicting future cardiovascular event risks that were not used in NG28. For this purpose, BMI and body weight were assumed to be correlated sufficiently to be considered equivalent parameters.							
GDP, gross domestic product; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SBP, systolic blood pressures.							

Appendix I – Health economic analysis

GLP-1 mimetics

Economic (cost–utility) modelling was not conducted for this topic. However, 2 exploratory analyses were conducted to explore the clinical assumptions used in the NG28 model.

First, we re-simulated the original model over a relatively short-term duration. This would be useful for the committee in assessing the face validity of the predicted event rates over a short time frame, whereas the NG28 analysis was over a lifetime horizon. This analysis would also allow the committee to understand which intermediate measures of treatment effect are the most influential within the NG28 model in determining the incidence of CV events and mortality.

Secondly, we sought to estimate how well the NG28 model predicts CV outcomes reported in the recent LEADER and ELIXA trials of GLP-1 mimetics. It was felt that doing so would help the committee determine the suitability of the NG28 model in predicting CV outcomes associated with GLP-1 mimetics in the high risk popuations of LEADER and ELIXA.

Correlation between effects and CV outcomes

For the first exploratory analysis described above, we re-simulated the original model over a relatively short-term (5-year) duration. The NG28 model treatment effects were informed by a series of network meta-analyses undertaken by the NICE development team for the guideline. The resulting relative effects were fed into a validated existing model that predicts the long-term rate of various CV events (UKPDS Outcomes Model 1 [OM1]), based on a person's characteristics in a number of risk factors. The treatment effects evaluated were:

- Change in HbA1c a 1 year
- Change in weight a 1 year
- Rate of hypoglycaemic events
- Treatment discontinuation due to adverse events (intolerance)

Of these, changes in HbA1c and weight were used by the UKPDS OM1 in predicting differences in CV event rates between interventions. Relative treatment effects on other characteristics included in the UKPDS risk equations, such as SBP, cholesterol and blood lipids, were not modelled, as treatments targeting those risk factors were considered elsewhere in NG28.

CV event rates for the lifetime NG28 model duration were reported in the appendices for NG28. We re-simulated the base case model to extract 5-year CV event rates following the first treatment intensification, to facilitate comparison with clinical evidence. First intensification was selected as this is the stage in the treatment pathway at which GLP-1 mimetics were included in the model as relevant potential options for treatment. A 5-year duration was chosen to mitigate for treatment dropouts occurring within 1 year of treatment initiation, and the 1-year lagged effect of changes in HbA1c on CV event risk, which might lead to uninformative short-term correlations between treatment effects and outcomes. 5-year CV event rates predicted by the NG28 model are presented in Table 1. The correlation coefficients between these 5-year event rates and absolute treatment effects used in the model are presented in Table 2.

Table 1: 5-year cardiovascular event rates predicted by the NG28 base case economic model

5-year event rate	CV event						
First intensification therapy	Amputation	Blindness	Renal failure	CHF	IHD	MI	Stroke
Exenatide-Metformin	0.39%	2.21%	0.29%	3.76%	2.88%	8.53%	3.82%
Linagliptin-Metformin	0.39%	2.20%	0.29%	3.75%	2.87%	8.49%	3.80%
Liraglutide-Metformin	0.38%	2.16%	0.29%	3.71%	2.84%	8.41%	3.76%
Metformin-Pioglitazone	0.38%	2.17%	0.29%	3.72%	2.85%	8.44%	3.78%
Metformin-Sitagliptin	0.40%	2.21%	0.29%	3.77%	2.88%	8.53%	3.82%
Metformin-Sulfonylurea	0.39%	2.17%	0.29%	3.73%	2.86%	8.46%	3.78%
Metformin-Vildagliptin	0.39%	2.19%	0.29%	3.74%	2.86%	8.47%	3.79%

Key: CHF, congestive heart failure; CV, cardiovascular; IHD, ischaemic heart disease; MI, myocardial infarction.

Table 2: Correlation between 5-year cardiovascular event rates and absolute treatment effects used in the NG28 base case economic model

Correlation	Treatment effect			
CV event	HbA1c change (at 1 year)	Weight change (at 1 year)	Dropout rate	Hypoglycaemic event rate
Amputation	0.990	-0.202	-0.452	-0.114
Blindness	0.983	-0.297	-0.406	-0.273
Renal failure	-0.182	-0.633	0.474	-0.534
CHF	0.997	-0.257	-0.410	-0.138
IHD	0.995	-0.134	-0.498	-0.100
MI	0.996	-0.255	-0.401	-0.111
Stroke	0.995	-0.252	-0.427	-0.212
Life years	-0.989	0.229	0.412	0.056

Key: CHF, congestive heart failure; CV, cardiovascular; IHD, ischaemic heart disease; MI, myocardial infarction.

These results show 5-year CV event rates predicted by the NG28 model are much more strongly associated with HbA1c treatment effects than differences in weight change, treatment discontinuation and hypoglycaemic event rates. Reduction in HbA1c is almost perfectly correlated with survival, though HbA1c change is positively correlated with the incidence of most CV event rates, potentially due to living for longer to experience such events. Weight change and the incidence of hypoglycaemic events exhibit particularly weak correlations with CV event rates. The incidence of 5-year renal failure, which exhibits very little correlation with HbA1c treatment effects. This is likely to be because HbA1c is not used directly in the UKPDS OM1 risk equation for renal failure, but only indirectly through its effect on the risk of blindness (Clarke et al. 2004). The overall picture suggests that the NG28 model is highly dependent on relative effects in HbA1c.

UKPDS OM1

As noted above, the NG28 model utilised the UKPDS OM1 (published in 2004) to translate changes in risk factors to CV event rates, then ultimately to costs and QALYs. It is noted in the guideline that an updated version of the UKPDS risk model (OM2, described by Hayes et

al. 2013) was being developed while the guideline was itself in development, but that an executable version of OM2 would not be available in time to be used in the NG28 model.

An executable version of UKPDS OM2 has now been made available. The updated model utilises longer-term data to inform its CV event risk equations and is broader in scope, using additional risk factors (such as estimated GFR and white blood cell count) and predicting additional event risks (such as secondary MI and stroke). OM2 has been shown to predict significantly fewer CV events than OM1 (Hayes et al. 2013). However, it is not clear what the effect of using OM2 would have on the cost–utility results of the NG28 model.

LEADER and ELIXA trials in UKPDS OM1

In the second modelling analysis, considered useful by the guideline committee, we sought to estimate how well the NG28 model predicts CV outcomes reported in 2 recent GLP-1 mimetic trials, LEADER and ELIXA. The LEADER and ELIXA study populations are characterised a more prominent history of cardiac complications than earlier trials included in the original model, and LEADER predicts a statistically significant benefit in CV events avoided for liraglutide compared with placebo. The committee felt that exploring whether the UKPDS prediction equations predict these would provide useful information as to whether there is some other mechanism by which GLP-1 mimetics avoid CV events, one not captured through changes to the intermediate outcomes used in the UKPDS OM1 (and therefore the original NG28 model, and most existing diabetes models).

To perform this analysis, we first used the NG28 model to construct a cohort of 5000 patients, simulated to match given baseline characteristics on average. These characteristics were obtained from the LEADER and ELIXA trials where reported (Table 3 and Table 4). Where the NG28 model required the log-transformation of a variable, and the trial only reported that characteristic on the natural scale, the standard deviation of the log-transformed variable was estimated using the methods suggested by Quan and Zhang (2003). Where the trials did not report characteristics that were required by the UKPDS OM1, characteristics from the THIN database – used by the original NG28 model – were applied. The trial populations most closely matched the THIN data for patients at their second treatment intensification, therefore this stage in the clinical pathway was used. Details of the original model are available in Appendix F of the original guideline (Type 2 diabetes in adults: management; NICE, 2015).

Table 3: LEADER data applied in the UKPDS model (OM1)

LEADER trial	Placebo	Liraglutide
Characteristic	**Mean (SD)**	**Mean (SD)**
Age at baseline (years)	64.4 (7.2)	64.2 (7.2)
Gender, male (%)	64.0	64.5
HbA1c (%) • Year 1 • Year 2 • Year 3 • Year 4	8.7 (1.5) 8.0 7.9 7.9 8.0	8.7 (1.6) 7.3 7.4 7.55 7.65
Height (cm)	168 [a]	168 [a]
History of HF (%)	17.8	17.9
History of IHD (%)	26.3	26.6
History of MI (%)	30.0	31.4
History of RF (%)	24.0	25.4

History of stroke (%)	16.6	15.6
SBP (mmHg) • Year 1 • Year 2 • Year 3 • Year 4	135.9 (17.7) 136.0 135.75 135.5 136.0	135.9 (17.8) 134.0 134.5 134.5 135.0
Weight (kg) [b]	91.6 (20.8)	91.9 (21.2)
Notes: (a) Height estimated using reported weight and BMI (placebo: 32.5; liraglutide: 32.5). (b) Change in weight during follow-up was presented, however the UKPDS model does not facilitate manually inputting weight over time.		
Key: HF, heart failure; IHD, ischaemic heart disease; MI, myocardial infarction; RF, renal failure; SBP, systolic blood pressure; SD, standard deviation.		

Table 4: ELIXA data applied in the UKPDS model (OM1)

ELIXA trial	Placebo	Lixisenatide
Characteristic	**Mean (SD)**	**Mean (SD)**
Age at baseline (years)	60.6 (9.6)	59.9 (9.7)
Age at diagnosis (years)	51.2 [a]	50.7 [a]
Cholesterol: HDL (mg/dL)	42.9	43.0
Cholesterol: total (mg/dL)	153.3 (45.1)	153.7 (44.1)
Ethnicity (%) [b]	W: 84.5 AI: 12.1 AC: 3.4	W: 82.8 AI: 13.3 AC: 3.9
Gender, male (%)	69.1	69.6
HbA1c (%) • Year 1 • Year 2 • Year 3	7.6 (1.3) 7.525 7.6 7.55	7.7 (1.3) 7.325 7.45 7.45
Height (cm)	168 [c]	168 [c]
History of HF (%)	22.3	22.5
History of MI (%)	100	100
History of MI, days since event	72.2 (43.9)	71.8 (43.4)
History of stroke (%)	6.2	4.7
SBP (mmHg) • Year 1 • Year 2 • Year 3	130 (17) 130.5 132.5 131.5	129 (17) 131.75 130.75 132.25
Smoking status (%) [d]	Y: 11.7 F: 37.1 N: 51.2	Y: 11.7 F: 37.1 N: 51.2
Weight (kg) [e]	85.1 (19.6)	84.6 (19.2)
Notes: (a) Age at diagnosis estimated using reported time since diagnosis (placebo: 9.4 (8.3) years; lixisenatide: 9.2 (8.2) years). (b) Reported 'other' ethnicity group included in 'white' group. (c) Height estimated using reported weight and BMI (placebo: 30.2; lixisenatide: 30.1). (d) Only current smokers reported; former and non-smokers estimated based on proportion of former and non-smokers in THIN dataset (original NG28 model). (e) Change in weight during follow-up was presented, however the UKPDS model does not facilitate manually inputting weight over time.		

Key: AC (ethnicity), Afro-Caribbean; F (smoking status), former smoker; AI (ethnicity), Asian-Indian; HDL, high-density lipoprotein; HF, heart failure; IHD, ischaemic heart disease; MI, myocardial infarction; N (smoking status): non-smoker; RF, renal failure; SBP, systolic blood pressure; SD, standard deviation; W (ethnicity), white or 'other'; Y (smoking status): smoker.

For each trial arm, once the sample of 5000 baseline patients had been generated, their data were stored in the UKPDS model. The UKPDS model allows the user to manually specify values of certain intermediate risk factors each year after baseline; if no such data are specified, it predicts them using its own equations (Clarke et al. 2004). Of the risk factors that can be specified over time, both trials presented HbA1c and SBP, LEADER up to 3 years and ELIXA up to 4 years. These data were presented graphically; we estimated the values based from the trial publication figures, and applied the estimated values for each year in the UKPDS OM1. As a result, both the baseline cohort and projection of key intermediate characteristics matched the LEADER and ELIXA studies as closely as possible. Like the NG28 model, we assumed that changes in these intermediate variables over time were applied equally to each of the 5000 simulated patients.

The UKPDS model was then run for the number of whole years that best matched the relevant trial – 5 years for LEADER, 4 years for ELIXA. The model was run 4 times for each of the 2 trials: once replicating the NG28 model assumption of only applying HbA1c treatment effects over time, and once allowing the change in SBP over time to vary as well, both for the placebo and intervention arms. The number of CV events predicted by the UKPDS model could then be compared with the trial CV events data directly, as well as incremental differences in CV events (intervention compared with placebo).

Results for the LEADER trial are presented in Table 5, and for the ELIXA trial in Table 6. In the LEADER analysis, applying only HbA1c effects, the UKPDS model predicts significantly more MI and all cause mortality events over 5 years than the observed trial data. The model underpredicts the incidence of heart failure, though the RCT reported on "heart failure leading to hospitalisation", meaning this is likely to be an imperfect comparison. The incidence of stroke is fairly well predicted by the model. When SBP effects were also applied, all event rates fell by small amounts. In terms of the relative event rates on the placebo and liraglutide arms, model results favoured liraglutide, which is consistent with the trial results. However, the magnitude of benefit in favour of liraglutide was higher in the trial than predicted by the UKPDS model for all events with data.

In the ELIXA analysis, applying only HbA1c effects, the UKPDS model predictions for any cause mortality are notably closer to the observed trial data than the LEADER analysis. However, here the model predicts notably fewer MI events over 4 years than the trial data, and predicts a benefit in MI events avoided for lixisenatide that was not observed in ELIXA. The underprediction of MI events may explain why predicted overall mortality is closer to the observed values here than in the LEADER analysis. When SBP effects were applied alongside HbA1c effects, all total event rates fell but the differences between lixisenatide and placebo event rates remained stable. These differences all suggest that lixisenatide may provide benefit in terms of reducing the incidence of CV events, which was not observed in the trial for all events.

Table 5: Comparison of UKPDS Outcomes Model 1 and LEADER trial outcomes

CV event	Predicted 5-year event rate						Observed RCT event rate [a]		
	HbA1c effects only			HbA1c and SBP effects					
	Placebo	Liraglutide	Difference	Placebo	Liraglutide	Difference	Placebo	Liraglutide	Difference
Myocardial infarction	13.24%	12.64%	-0.59%	13.06%	12.42%	-0.64%	9.06%	7.69%	-1.37%
Heart failure [b]	2.93%	2.75%	-0.18%	2.88%	2.67%	-0.21%	6.76%	5.82%	-0.94%

Stroke	5.29%	5.22%	-0.07%	5.23%	5.07%	-0.15%	5.35%	4.88%	-0.47%
Any cause mortality	20.33%	19.85%	-0.48%	20.23%	19.77%	-0.46%	11.75%	9.97%	-1.78%

*Note: (a) Estimated 5-year cumulative incidence based on reported event rates per 100 person-years (=1-exp(-incidence per person per year*5)*
(b) RCT reports heart failure leading to hospitalisation.

Key: CV, cardiovascular; IHD, ischaemic heart disease; RCT, randomised controlled trial.

Table 6: Comparison of UKPDS Outcomes Model 1 and ELIXA trial outcomes

CV event	Predicted 4-year event rate						Observed RCT event rate [a]		
	HbA1c effects only			HbA1c and SBP effects					
	Placebo	Lixisenatide	Difference	Placebo	Lixisenatide	Difference	Placebo	Lixisenatide	Difference
Myocardial infarction	8.39%	7.65%	-0.74%	8.17%	7.47%	-0.70%	15.13%	15.46%	+0.34%
Heart failure [b]	1.80%	1.67%	-0.13%	1.73%	1.62%	-0.12%	7.32%	6.95%	-0.37%
Stroke	2.57%	2.33%	-0.24%	2.47%	2.29%	-0.18%	3.54%	3.92%	+0.39%
Any cause mortality	10.16%	9.17%	-0.99%	10.02%	9.07%	-0.95%	12.37%	11.66%	-0.70%

*Note: Estimated 4-year cumulative incidence based on reported event rates per 100 person-years (=1-exp(-incidence per person per year*4)*
(b) RCT reports heart failure leading to hospitalisation.

Key: CV, cardiovascular; IHD, ischaemic heart disease; RCT, randomised controlled trial.

This exploratory analysis suggests that where notable differences in observed CV event rates exist (LEADER), the UKPDS OM1 predicts the direction of benefit but may underpredict the magnitude of benefit. Where no significant differences in CV events exist (ELIXA), the direction of benefit predicted by the model may contradict the trial evidence. Compared with the LEADER trial outcomes, the UKPDS model overpredicted the incidence of MI and mortality. These results held whether the UKPDS model used only HbA1c treatment effects or both HbA1c and SBP effects.

This analysis therefore suggests that the UKPDS OM1, using HbA1c with or without SBP as intermediate outcomes, may inaccurately predict CV and mortality outcomes and underestimate the potential benefits of liraglutide in populations with high risk of CV events. It may also overestimate the benefit of lixisenatide in some outcomes, most notably the incidence of MI. This is potentially because the UKPDS dataset, with which the model was developed, did not include people with a recently history of CV events, and was therefore a lower risk population than the LEADER and ELIXA trials. The resulting equations may therefore be poorly suited to predicting the outcomes of high CV risk patients, particularly in terms of mortality. Importantly, however, this exploratory undertaking was limited by an imperfect matching of LEADER and ELIXA participant characteristics due to the trials not reporting all inputs required by the UKPDS model. Where such baseline data were not reported, the original data from the THIN database were applied. In populations with a history of CV events or pre-existing CV complications, as per LEADER and ELIXA, it is likely that some of those missing characteristics would also be significantly different to people in the THIN dataset. Furthermore, the correlation between different patient characteristics might differ in the LEADER and ELIXA populations compared with the THIN dataset. In our analysis, a cohort of 5000 patients was generated based on the specified baseline characteristics, with the correlation between different characteristics from the NG28 model (based on the THIN dataset) used to generate each patient. This is a simplifying assumption, if having a history of CV events or pre-existing CV complications changes how different characteristics are related to one-another.

SGLT-2 inhibitors

CANVAS and EMPA-REG trials in UKPDS OM1

The same exploratory analysis of the UKPDS model, described above, was also conducted for the 2 recent SGLT-2 inhibitor trials, CANVAS and EMPA-REG. The CANVAS and EMPA-REG study populations are also characterised by a high CV risk.

The NG28 model was used to construct a cohort of 5000 patients, simulated to match the CANVAS and EMPA-REG baseline characteristics as closely as possible. The characteristics obtained from the trials, where reported, are shown in Table 7 and Table 8, following the same methods detailed in the GLP-1 mimetics analysis above. For the EMPA-REG study, the pooled empagliflozin 10 mg and 25 mg data were used as only pooled CV outcomes were reported. Details of the original model are available in Appendix F of the original guideline (Type 2 diabetes in adults: management; NICE, 2015).

Table 7: CANVAS data applied in the UKPDS model (OM1)

CANVAS trial	Placebo	Canagliflozin
Characteristic	**Mean (SD)**	**Mean (SD)**
Age at baseline (years)	63.4 (8.2)	63.2 (8.3)
Age at diagnosis (years)	49.7 [a]	49.7 [a]
Cholesterol: HDL (mmol/L)	1.2 (0.3)	1.2 (0.3)
Cholesterol: total (mmol/L)	4.4 (1.2)	4.4 (1.1)
Ethnicity (%) [b]	W: 84.7 AI: 11.7 AC: 3.7	W: 83.6 AI: 13.4 AC: 3.0
Gender, male (%)	63.3%	64.9%
HbA1c (%) • Year 1 • Year 2 • Year 3 • Year 4 • Year 5 • Year 6	8.2 (0.9) 8.16 8.13 8.12 8.20 8.27 8.33	8.2 (0.9) 7.56 7.71 7.80 7.95 8.06 8.12
History of amputation (%)	2.3	2.3
History of HF (%)	15.1	13.9
History of IHD (%) [c]	46.0	44.7
History of MI (%) [c]	12.1	11.8
History of stroke (%) [c]	8.6	8.3
SBP (mmHg) • Year 1 • Year 2 • Year 3 • Year 4 • Year 5 • Year 6	136.9 (15.8) 135.4 135.2 135.3 135.2 135.8 135.8	136.4 (15.8) 130.8 131.1 131.6 131.9 132.2 132.1
Smoking status (%) [d]	Y: 18.1 F: 34.4 N: 47.5	Y: 17.6 F: 34.6 N: 47.8

Notes: (a) Age at diagnosis estimated using reported time since diagnosis (placebo: 13.7 (7.8) years; canagliflozin: 13.5 (7.7) years).

(b) Reported 'other' ethnicity group included in 'white' group.

(c) Trial reports history of CVD. Assumed to consist of either IHD, MI or stroke, distributed proportionately to their prevalence in the THIN dataset (IHD: 9.7%, MI: 2.5%, stroke: 1.8%).

(d) Trial reports number of current smokers. Former and non-smokers estimated as proportionate to the THIN dataset (50.2% non-smokers, 36.4% former smokers).

Key: AC (ethnicity), Afro-Caribbean; F (smoking status), former smoker; AI (ethnicity), Asian-Indian; CVD, cardiovascular disease; HDL, high-density lipoprotein; HF, heart failure; IHD, ischaemic heart disease; MI, myocardial infarction; N (smoking status): non-smoker; RF, renal failure; SBP, systolic blood pressure; SD, standard deviation; W (ethnicity), white or 'other'; Y (smoking status): smoker.

Table 8: EMPA-REG data applied in the UKPDS model (OM1)

EMPA-REG trial	Placebo	Empaglifozin (pooled)
Characteristic	**Mean (SD)**	**Mean (SD)**
Age at baseline (years)	63.2 (8.8)	63.1 (8.6)
Cholesterol: HDL [b] (mg/dL)	44.0 (11.3)	44.6 (11.9)
Cholesterol: total (mg/dL)	161.9 (43.1)	163.5 (44.2)
Ethnicity (%) [a]	W: 73.0 AI: 21.9 AC: 5.1	W: 73.5 AI: 21.5 AC: 5.1
Gender, male (%)	72.0	71.2
HbA1c (%) • Year 1 • Year 2 • Year 3 • Year 4	8.08 (0.84) 7.975 7.975 8.10 8.15	8.07 (0.85) 7.475 7.56 7.70 7.86
Height (cm)	168 [c]	168 [c]
History of HF (%)	10.5	9.9
History of IHD (%)	10.2	10.6
History of MI (%)	46.4	46.7
History of stroke (%)	23.7	23.1
SBP (mmHg) • Year 1 • Year 2 • Year 3 • Year 4	135.8 (17.2) 135.0 135.0 135.0 136.4	135.3 (16.9) 131.6 132.0 132.0 134.0
Weight (kg) [b]	86.6 (19.1)	86.2 (18.9)

Notes: (a) Change in HDL and weight during follow-up were presented, however the UKPDS model does not facilitate manually inputting weight over time.

(b) Reported 'other' ethnicity group included in 'white' group.

(c) Height estimated using reported weight and BMI (placebo: 30.7; empagliflozin: 30.6).

Key: HF, heart failure; IHD, ischaemic heart disease; MI, myocardial infarction; SBP, systolic blood pressure; SD, standard deviation.

For each trial arm, once the sample of 5000 baseline patients had been generated, their data were stored in the UKPDS model. The UKPDS model allows the user to manually specify values of certain intermediate risk factors each year after baseline; if no such data are specified, it predicts them using its own equations (Clarke et al. 2004). Of the risk factors that can be specified over time, both trials presented HbA1c and SBP, CANVAS up to 6 years and EMPA-REG up to 4 years. These data were extracted from the trial publication figures.

As a result, both the baseline cohort and projection of key intermediate characteristics matched the trials as closely as possible. Like the NG28 model, we assumed that changes in these intermediate variables over time were applied equally to each of the 5000 simulated patients.

The UKPDS model was then run for the number of whole years that best matched the relevant trial – 7 years for CANVAS, 5 years for EMPA-REG. The model was run 4 times for each of the 2 trials: once replicating the NG28 model assumption of only applying HbA1c treatment effects over time, and once allowing the change in SBP over time to vary as well, both for the placebo and intervention arms. The number of CV events predicted by the UKPDS model could then be compared with the trial CV events data directly, as well as incremental differences in CV events (intervention compared with placebo).

Results for the CANVAS trial are presented in Table 5, and for the EMPA-REG trial in Table 6. In the CANVAS analysis, applying only HbA1c effects, the UKPDS significantly overpredicts the incidence of MI and all cause mortality events over 7 years compared with the trial data. It predicts slightly more stroke events, and fewer heart failure events. These results are similar to the LEADER analysis in the GLP1 mimetics section above. When SBP effects were applied alongside HbA1c effects, all event rates fell by small amounts. The model overpredicted the benefit of canagliflozin over placebo in terms of MI and death, but these may be a result of the very high predicted absolute event rates. Canagliflozin's benefit in reducing heart failure events is notably underestimated.

In the EMPA-REG analysis, applying only HbA1c effects, the UKPDS model predictions for MI events are much closer to the observed trial values, but the benefit of empagliflozin over placebo is not captured. The benefits of empagliflozin in reducing MI, heart failure and mortality move closer to the observed values when SBP effects are also applied, but remain far from the true values. The observed higher stroke rate in the trial was not reflected in the model predictions when HbA1c alone or HbA1c and SBP effects were included. In both cases, overall mortality was significantly overpredicted.

Table 9: Comparison of UKPDS Outcomes Model 1 and CANVAS trial outcomes

CV event	Predicted 7-year event rate						Observed RCT event rate [a]		
	HbA1c effects only			HbA1c and SBP effects			Placebo	Canagliflozin	Diff.
	Placebo	Canagliflozin	Difference	Placebo	Canagliflozin	Difference			
Myocardial infarction	25.67%	23.84%	-1.83%	25.00%	22.81%	-2.19%	8.57%	7.80%	-0.77%
Heart failure [a]	2.18%	2.17%	-0.01%	2.10%	2.03%	-0.07%	5.91%	3.78%	-2.13%
Stroke	8.22%	7.71%	-0.51%	7.64%	6.76%	-0.88%	6.50%	5.38%	-1.12%
Any cause mortality	31.37%	29.82%	-1.55%	30.95%	29.07%	-1.88%	12.76%	11.41%	-1.35%

*Notes: (a) Estimated 7-year cumulative incidence based on reported event rates per 1,000 person-years (=1-exp(-incidence per person per year*7)*

(b) RCT reports heart failure leading to hospitalisation.

Key: CV, cardiovascular; IHD, ischaemic heart disease; RCT, randomised controlled trial.

Table 10: Comparison of UKPDS Outcomes Model 1 and EMPA-REG trial outcomes

CV event	Predicted 5-year event rate						Observed RCT event rate [a]		
	HbA1c effects only			HbA1c and SBP effects			Placebo	Empagli-flozin	Diff.
	Placebo	Empagliflozin	Diff.	Placebo	Empagliflozin	Diff.			
Myocardial infarction	5.74%	5.75%	+0.01%	5.64%	5.55%	-0.08%	5.29%	4.46%	-0.82%
Heart failure [b]	2.94%	2.67%	-0.27%	2.87%	2.56%	-0.32%	4.01%	2.66%	-1.35%

Stroke	3.58%	3.30%	-0.28%	3.50%	3.03%	-0.46%	2.92%	3.45%	+0.53%
Any cause mortality	17.90%	17.05%	-0.85%	17.83%	16.85%	-0.98%	8.04%	5.61%	-2.43%

Note: (a) Estimated 5-year cumulative incidence based on reported persons experiencing event.
(b) RCT reports heart failure leading to hospitalisation.

Key: CV, cardiovascular; IHD, ischaemic heart disease; RCT, randomised controlled trial.

Like the equivalent GLP1 mimetics analysis described earlier, this analysis suggests that UKPDS OM1 may be poorly suited to predicting CV outcomes and all-cause mortality in populations with high CV risk, and that the relative outcomes associated with SGLT-2 inhibitors might not be accurately captured. These results held whether the UKPDS model used only HbA1c treatment effects or both HbA1c and SBP effects. However, our exploratory analysis is associated with the same limitations described above for the GLP1 mimetics analysis.

Appendix J – Excluded studies

Clinical studies

SGLT-2 inhibitors

Short Title	Title	Reason for exclusion
Anderson (2017)	Empagliflozin: Role in Treatment Options for Patients with Type 2 Diabetes Mellitus	Inappropriate study design
Araki (2015)	Long-term treatment with empagliflozin as add-on to oral antidiabetes therapy in Japanese patients with type 2 diabetes mellitus	All groups received same SGLT-2 inhibitor
Bailey (2012)	Dapagliflozin monotherapy in drug-naïve patients with diabetes: a randomized-controlled trial of low-dose range	Duplicate publication
Bailey (2014)	Attainment of diabetes-related quality measures with canagliflozin versus sitagliptin	No relevant outcomes reported
Barnett (2015)	Consistent weight changes irrespective of baseline HbA1c with the combination of empagliflozin/linagliptin (EMPA/LINA) in subjects with type 2 diabetes (T2DM)	Conference abstract
Bilezikian (2016)	Evaluation of Bone Mineral Density and Bone Biomarkers in Patients With Type 2 Diabetes Treated With Canagliflozin	No relevant outcomes reported
Brice (2015)	Analysis of empagliflozin vs glimepiride by Quality and Outcomes Framework targets: Post hoc analysis of a head-to-head study	Conference abstract
Canagliflozin for the... (2013)	Canagliflozin for the treatment of type 2 diabetes	Inappropriate study design
Canagliflozin for type... (2011)	Canagliflozin for type 2 diabetes mellitus	Inappropriate study design
Cefalu (2013)	Efficacy and safety of canagliflozin versus glimepiride in patients with type 2 diabetes inadequately controlled with metformin (CANTATA-SU): 52 week results from a randomised, double-blind, phase 3 non-inferiority trial	No relevant outcomes reported
Chilton (2015)	Effects of empagliflozin on blood pressure and markers of arterial stiffness and vascular resistance in patients with type 2 diabetes	Inappropriate study design
Chirila (2016)	Treatment satisfaction in type 2 diabetes patients taking empagliflozin compared with patients taking glimepiride	No relevant outcomes reported

Short Title	Title	Reason for exclusion
Daniele (2017)	Dapagliflozin enhances fat oxidation and ketone production in patients with type 2 diabetes	No relevant outcomes reported
Davies (2015)	Incidence of genital mycotic infections decreases over time in older patients with type 2 diabetes mellitus treated with canagliflozin	Conference abstract
Devineni (2013)	Pharmacokinetics and pharmacodynamics of canagliflozin, a sodium glucose co-transporter 2 inhibitor, in subjects with type 2 diabetes mellitus	No relevant outcomes reported
Dobbins (2012)	Remogliflozin etabonate, a selective inhibitor of the sodium-dependent transporter 2 reduces serum glucose in type 2 diabetes mellitus patients	No relevant outcomes reported
Empagliflozin and progression... (2016)	Empagliflozin and progression of kidney disease in type 2 diabetes	Duplicate publication
Ferrannini (2013)	Renal glucose handling: impact of chronic kidney disease and sodium-glucose cotransporter 2 inhibition in patients with type 2 diabetes	No relevant outcomes reported
Ferrannini (2013)	Long-term safety and efficacy of empagliflozin, sitagliptin, and metformin: an active-controlled, parallel-group, randomized, 78-week open-label extension study in patients with type 2 diabetes	No relevant outcomes reported
Fitchett (2017)	Effect of empagliflozin on mortality and causes of death in patients with type 2 diabetes at high cardiovascular risk	Conference abstract
Fonseca (2013)	Active- and placebo-controlled dose-finding study to assess the efficacy, safety, and tolerability of multiple doses of ipragliflozin in patients with type 2 diabetes mellitus	No relevant outcomes reported
Forst (2016)	Effects on alpha- and beta-cell function of sequentially adding empagliflozin and linagliptin to therapy in people with type 2 diabetes previously receiving metformin: An exploratory mechanistic study	No relevant outcomes reported
Fulcher (2016)	Efficacy and safety of canagliflozin when used in conjunction with incretin-mimetic therapy in patients with type 2 diabetes	No relevant outcomes reported
Grandy (2014)	Health-related quality of life (EQ-5D) among type 2 diabetes mellitus patients treated with dapagliflozin over 2 years	No relevant outcomes reported

Short Title	Title	Reason for exclusion
Grandy (2014)	Changes in weight loss-related quality of life among type 2 diabetes mellitus patients treated with dapagliflozin	No relevant outcomes reported
Grandy (2016)	Patient-reported outcomes among patients with type 2 diabetes mellitus treated with dapagliflozin in a triple-therapy regimen for 52 weeks	No relevant outcomes reported
Gu (2016)	Cost-Effectiveness of Dapagliflozin versus Acarbose as a Monotherapy in Type 2 Diabetes in China	Inappropriate study design
Hansen (2014)	Postprandial dynamics of plasma glucose, insulin, and glucagon in patients with type 2 diabetes treated with saxagliptin plus dapagliflozin add-on to metformin therapy	No relevant outcomes reported
Hayashi (2017)	Dapagliflozin decreases small dense low-density lipoprotein-cholesterol and increases high-density lipoprotein 2-cholesterol in patients with type 2 diabetes: comparison with sitagliptin	No relevant outcomes reported
Heise (2013)	Safety, tolerability, pharmacokinetics and pharmacodynamics following 4 weeks' treatment with empagliflozin once daily in patients with type 2 diabetes	No relevant outcomes reported
Heise (2015)	Assessing pharmacokinetic interactions between the sodium glucose cotransporter 2 inhibitor empagliflozin and hydrochlorothiazide or torasemide in patients with type 2 diabetes mellitus: a randomized, open-label, crossover study	No relevant outcomes reported
Heise (2016)	Pharmacodynamic Effects of Single and Multiple Doses of Empagliflozin in Patients With Type 2 Diabetes	All groups received same SGLT-2 inhibitor
Heise (2016)	Acute Pharmacodynamic Effects of Empagliflozin With and Without Diuretic Agents in Patients With Type 2 Diabetes Mellitus	All groups received same SGLT-2 inhibitor
Heise (2017)	Pharmacodynamic Effects of Single and Multiple Doses of Empagliflozin in Patients With Type 2 Diabetes	Duplicate publication
Hussey (2013)	Safety, pharmacokinetics and pharmacodynamics of remogliflozin etabonate, a novel SGLT2 inhibitor, and metformin when co-administered in subjects with type 2 diabetes mellitus	No relevant outcomes reported
Iijima (2015)	Pharmacokinetics, Pharmacodynamics, and Safety of	No relevant outcomes reported

Short Title	Title	Reason for exclusion
	Canagliflozin in Japanese Patients with Type 2 Diabetes Mellitus	
Inagaki (2014)	Efficacy and safety of canagliflozin monotherapy in Japanese patients with type 2 diabetes inadequately controlled with diet and exercise: a 24-week, randomized, double-blind, placebo-controlled, Phase III study	No relevant outcomes reported
Inagaki (2015)	Efficacy and safety of canagliflozin alone or as add-on to other oral antihyperglycemic drugs in Japanese patients with type 2 diabetes: A 52-week open-label study	All groups received same SGLT-2 inhibitor
Inagaki (2015)	Safety and efficacy of canagliflozin in Japanese patients with type 2 diabetes mellitus: post hoc subgroup analyses according to body mass index in a 52-week open-label study	No relevant outcomes reported
Inagaki (2015)	Effects of Baseline Blood Pressure and Low-Density Lipoprotein Cholesterol on Safety and Efficacy of Canagliflozin in Japanese Patients with Type 2 Diabetes Mellitus	All groups received same SGLT-2 inhibitor
Iwasaki (2016)	Baseline low-density lipoprotein cholesterol predicts the hemoglobin A1c-lowering effect of dapagliflozin in Japanese patients with type 2 diabetes mellitus	No relevant outcomes reported
Jinnouchi (2016)	Impact of Reduced Renal Function on the Glucose-Lowering Effects of Luseogliflozin, a Selective SGLT2 Inhibitor, Assessed by Continuous Glucose Monitoring in Japanese Patients with Type 2 Diabetes Mellitus	No relevant outcomes reported
Kaku (2014)	Efficacy and safety of dapagliflozin monotherapy in Japanese patients with type 2 diabetes inadequately controlled by diet and exercise	No relevant outcomes reported
Kashiwagi (2015)	Efficacy and safety of ipragliflozin as an add-on to pioglitazone in Japanese patients with inadequately controlled type 2 diabetes: a randomized, double-blind, placebo-controlled study (the SPOTLIGHT study)	No relevant outcomes reported
Kashiwagi (2015)	Ipragliflozin improves glycemic control in Japanese patients with type 2 diabetes mellitus: the BRIGHTEN study: BRIGHTEN: double-blind randomized study of ipragliflozin to show its efficacy as monotherapy in T2DM patients	No relevant outcomes reported

Short Title	Title	Reason for exclusion
Kashiwagi (2015)	Long-term safety, tolerability and efficacy of ipragliflozin in Japanese patients with type 2 diabetes mellitus: -IGNITE study-. [Japanese]	Not English
Kasichayanula (2013)	The influence of kidney function on dapagliflozin exposure, metabolism and pharmacodynamics in healthy subjects and in patients with type 2 diabetes mellitus	No relevant outcomes reported
Lavalle-Gonzalez (2013)	Efficacy and safety of canagliflozin compared with placebo and sitagliptin in patients with type 2 diabetes on background metformin monotherapy: a randomised trial	No relevant outcomes reported
Leiter (2016)	Simultaneous Reduction in Both HbA1c and Body Weight with Canagliflozin Versus Glimepiride in Patients with Type 2 Diabetes on Metformin	No relevant outcomes reported
Li (2016)	Influence of Dapagliflozin on Glycemic Variations in Patients with Newly Diagnosed Type 2 Diabetes Mellitus	No relevant outcomes reported
Mancia (2016)	Impact of Empagliflozin on Blood Pressure in Patients With Type 2 Diabetes Mellitus and Hypertension by Background Antihypertensive Medication	No relevant outcomes reported
Matthaei (2015)	Randomized, Double-Blind Trial of Triple Therapy With Saxagliptin Add-on to Dapagliflozin Plus Metformin in Patients With Type 2 Diabetes	All groups received same SGLT-2 inhibitor
Matthaei (2016)	One-year efficacy and safety of saxagliptin add-on in patients receiving dapagliflozin and metformin	All groups received same SGLT-2 inhibitor
Merovci (2014)	Dapagliflozin improves muscle insulin sensitivity but enhances endogenous glucose production	No relevant outcomes reported
Merovci (2015)	Dapagliflozin lowers plasma glucose concentration and improves beta-cell function	No relevant outcomes reported
Merovci (2016)	Effect of Dapagliflozin With and Without Acipimox on Insulin Sensitivity and Insulin Secretion in T2DM Males	No relevant outcomes reported
Monami (2017)	Effects of SGLT-2 inhibitors on mortality and cardiovascular events: a comprehensive meta-analysis of randomized controlled trials	Inappropriate study design
Muscelli (2016)	Metabolic consequences of acute and chronic empagliflozin administration in treatment-naive and	No relevant outcomes reported

Short Title	Title	Reason for exclusion
	metformin pretreated patients with type 2 diabetes	
Nct (2013)	A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study to Evaluate the Blood Pressure Reduction With Ambulatory Blood Pressure Monitoring (ABPM), Safety, and Tolerability of Canagliflozin in the Treatment of Subjects With Hypertension and Type 2 Diabetes Mellitus	No relevant outcomes reported
Neal (2015)	Efficacy and safety of canagliflozin, an inhibitor of sodium-glucose cotransporter 2, when used in conjunction with insulin therapy in patients with type 2 diabetes	No relevant outcomes reported
Neeland (2016)	Empagliflozin reduces body weight and indices of adipose distribution in patients with type 2 diabetes mellitus	No relevant outcomes reported
Neeland (2016)	Empagliflozin reduces body weight and indices of adipose distribution in patients with type 2 diabetes mellitus	Duplicate publication
Neslusan (2015)	Cost-Effectiveness of Canagliflozin versus Sitagliptin as Add-on to Metformin in Patients with Type 2 Diabetes Mellitus in Mexico	Health economics outcomes
Nicolle (2012)	Effect of canagliflozin, a sodium glucose co-transporter 2 (SGLT2) inhibitor, on bacteriuria and urinary tract infection in subjects with type 2 diabetes enrolled in a 12-week, phase 2 study	No relevant outcomes reported
Nishimura (2015)	Effect of empagliflozin monotherapy on postprandial glucose and 24-hour glucose variability in Japanese patients with type 2 diabetes mellitus: a randomized, double-blind, placebo-controlled, 4-week study	No relevant outcomes reported
Nishimura (2016)	Sodium-glucose cotransporter 2 inhibitor luseogliflozin improves glycaemic control, assessed by continuous glucose monitoring, even on a low-carbohydrate diet	No relevant outcomes reported
Nyirjesy (2012)	Evaluation of vulvovaginal symptoms and Candida colonization in women with type 2 diabetes mellitus treated with canagliflozin, a sodium glucose co-transporter 2 inhibitor	No relevant outcomes reported
Okajima (2016)	Preventive effect of ipragliflozin on nocturnal hypoglycemia in patients with type 2 diabetes treated with basal-bolus insulin therapy: An open-	No relevant outcomes reported

Short Title	Title	Reason for exclusion
	label, single-center, parallel, randomized control study	
Prato (2017)	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	Duplicate publication
Qiu (2014)	Efficacy and safety of twice-daily treatment with canagliflozin, a sodium glucose co-transporter 2 inhibitor, added on to metformin monotherapy in patients with type 2 diabetes mellitus	No relevant outcomes reported
Rosenstock (2012)	Dose-ranging effects of canagliflozin, a sodium-glucose cotransporter 2 inhibitor, as add-on to metformin in subjects with type 2 diabetes	No relevant outcomes reported
Rosenstock (2015)	Impact of empagliflozin added on to basal insulin in type 2 diabetes inadequately controlled on basal insulin: A 78-week randomized, double-blind, placebo-controlled trial	No relevant outcomes reported
Rosenstock (2015)	Greater dose-ranging effects on A1C levels than on glucosuria with LX4211, a dual inhibitor of SGLT1 and SGLT2, in patients with type 2 diabetes on metformin monotherapy	Dual SGLT1 and SGLT2 inhibitor
Rosenstock (2016)	Initial Combination Therapy With Canagliflozin Plus Metformin Versus Each Component as Monotherapy for Drug-Naive Type 2 Diabetes	No relevant outcomes reported
Samukawa (2016)	Substantial Effects of Luseogliflozin Revealed by Analyzing Responses to Postprandial Hyperglycemia: Post Hoc Subanalyses of a Randomized Controlled Study	No relevant outcomes reported
Sarashina (2014)	Effect of renal impairment on the pharmacokinetics, pharmacodynamics, and safety of empagliflozin, a sodium glucose cotransporter 2 inhibitor, in Japanese patients with type 2 diabetes mellitus	No relevant outcomes reported
Sasaki (2015)	Pharmacokinetics, Pharmacodynamics, and Safety of Luseogliflozin in Japanese Patients with Type 2 Diabetes Mellitus: A Randomized, Single-blind, Placebo-controlled Trial	No relevant outcomes reported
Seino (2014)	Dose-finding study of luseogliflozin in Japanese patients with type 2 diabetes mellitus: a 12-week, randomized, double-blind, placebo-controlled, phase II study	No relevant outcomes reported

Short Title	Title	Reason for exclusion
Seino (2015)	Fifty-two-week long-term clinical study of luseogliflozin as monotherapy in Japanese patients with type 2 diabetes mellitus inadequately controlled with diet and exercise	Inappropriate study design
Seman (2010)	Safety and tolerability of bi 10773, a sodium-glucose co-transporter (SGLT-2) inhibitor, following 8-days treatment in patients with type 2 diabetes	Conference abstract
Stein (2015)	A greater proportion of people with Type 2 diabetes, inadequately controlled on metformin, reach the composite target of HbA1c <7.5% (59mmol/mol) and >3% body weight reduction when treated with either canagliflozin 100mg or 300mg compared with sitagliptin 100mg at 52 weeks	Conference abstract
Sykes (2015)	Randomized trial showing efficacy and safety of twice-daily remogliflozin etabonate for the treatment of type 2 diabetes	No relevant outcomes reported
Sykes (2015)	Randomized efficacy and safety trial of once-daily remogliflozin etabonate for the treatment of type 2 diabetes	No relevant outcomes reported
Tinahones (2017)	Linagliptin as add-on to empagliflozin and metformin in patients with type 2 diabetes: Two 24-week randomized, double-blind, double-dummy, parallel-group trials	No relevant outcomes reported
van Haalen (2014)	Cost effectiveness of adding dapagliflozin to insulin for the treatment of type 2 diabetes mellitus in the Netherlands	Health economics outcomes
Veltkamp (2012)	Combination treatment with ipragliflozin and metformin: a randomized, double-blind, placebo-controlled study in patients with type 2 diabetes mellitus	No relevant outcomes reported
Wan (2016)	Switching from sulphonylurea to a sodium-glucose cotransporter2 inhibitor in the fasting month of Ramadan is associated with a reduction in hypoglycaemia	No relevant outcomes reported
Wang (2016)	Sodium-glucose co-transporter-2 inhibitors suppress atrial natriuretic peptide secretion in patients with newly diagnosed Type 2 diabetes	No relevant outcomes reported
Wilding (2010)	Sustained effectiveness of dapagliflozin over 48 weeks in patients with type 2 diabetes poorly controlled with insulin	Conference abstract

Short Title	Title	Reason for exclusion
Wilding (2013)	Efficacy and safety of ipragliflozin in patients with type 2 diabetes inadequately controlled on metformin: a dose-finding study	No relevant outcomes reported
Yabe (2016)	SGLT2 inhibitor use and dietary carbohydrate intake in Japanese individuals with type 2 diabetes: a randomized, open-label, 3-arm parallel comparative exploratory study	All groups received same SGLT-2 inhibitor
Yale (2013)	Efficacy and safety of canagliflozin in subjects with type 2 diabetes and chronic kidney disease	No relevant outcomes reported
Yale (2014)	Efficacy and safety of canagliflozin over 52 weeks in patients with type 2 diabetes mellitus and chronic kidney disease	No relevant outcomes reported
Yong (2016)	Pharmacokinetics and Pharmacodynamics of Henagliflozin, a Sodium Glucose Co-Transporter 2 Inhibitor, in Chinese Patients with Type 2 Diabetes Mellitus	No relevant outcomes reported
Zambrowicz (2012)	LX4211, a dual SGLT1/SGLT2 inhibitor, improved glycemic control in patients with type 2 diabetes in a randomized, placebo-controlled trial	Dual SGLT1 and SGLT2 inhibitor
Zambrowicz (2015)	LX4211 therapy reduces postprandial glucose levels in patients with type 2 diabetes mellitus and renal impairment despite low urinary glucose excretion	Dual SGLT1 and SGLT2 inhibitor
Zhao (2015)	Pharmacokinetic and Pharmacodynamic Properties and Tolerability of Single- and multiple-dose Once-daily Empagliflozin, a Sodium Glucose Cotransporter 2 Inhibitor, in Chinese Patients With Type 2 Diabetes Mellitus	No relevant outcomes reported
Zinman (2014)	Baseline characteristics of participants enrolled in the empagliflozin cardiovascular outcome trial (EMPA-REG OUTCOMETM) in patients with type 2 diabetes	Conference abstract

GLP-1 mimetics

Short Title	Title	Reason for exclusion
Abd (2017)	A meta-analysis comparing clinical effects of short- or long-acting GLP-1 receptor agonists versus insulin treatment from head-to-head studies in type 2 diabetic patients	Outcomes in protocol not included in analysis; studies included were reviewed for outcomes.
Abdul-Ghani (2015)	Initial combination therapy with metformin, pioglitazone and exenatide is more	No outcomes from protocol reported.

Short Title	Title	Reason for exclusion
	effective than sequential add-on therapy in subjects with new-onset diabetes. Results from the Efficacy and Durability of Initial Combination Therapy for Type 2 Diabetes (EDICT): a randomized trial	
Ahmann (2015)	Efficacy and safety of liraglutide versus placebo added to basal insulin analogues (with or without metformin) in patients with type 2 diabetes: A randomized, placebo-controlled trial	No outcomes from protocol reported.
Ahren (2014)	HARMONY 3: 104-week randomized, double-blind, placebo- and active-controlled trial assessing the efficacy and safety of albiglutide compared with placebo, sitagliptin, and glimepiride in patients with type 2 diabetes taking metformin	No outcomes from protocol reported.
Ahren (2016)	Postprandial Glucagon Reductions Correlate to Reductions in Postprandial Glucose and Glycated Hemoglobin with Lixisenatide Treatment in Type 2 Diabetes Mellitus: A Post Hoc Analysis	Post-hoc analysis.
Alvarez-Villalobos (2016)	Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes	Editor's comment.
Apovian (2010)	Effects of exenatide combined with lifestyle modification in patients with type 2 diabetes	No outcomes from protocol reported.
Ard (2017)	Efficacy and safety of liraglutide 3.0 mg for weight management are similar across races: subgroup analysis across the SCALE and phase II randomized trials	No outcomes from protocol reported.
Arturi (2016)	Liraglutide improves cardiac function in patients with type 2 diabetes and chronic heart failure	No outcomes from protocol reported.
Bailey (2016)	Switching from sitagliptin to liraglutide in subjects with type 2 diabetes: Analysis of composite endpoints from the LIRA-SWITCH randomised trial	No outcomes from protocol reported.
Bailey (2017)	Efficacy and safety of switching from sitagliptin to liraglutide in subjects with type 2 diabetes (LIRA-SWITCH): a randomized, double-blind, double-dummy, active-controlled 26-week trial	No outcomes from protocol reported.
Bain (2015)	A randomised, placebo-controlled trial of liraglutide as adjunct to basal insulin analogues in subjects with Type 2 diabetes (LIRA-ADD2BASAL)	No outcomes from protocol reported.
Barnett (2007)	Tolerability and efficacy of exenatide and titrated insulin glargine in adult patients with type 2 diabetes previously uncontrolled with metformin or a sulfonylurea: a multinational, randomized, open-label, two-period, crossover noninferiority trial	No outcomes from protocol reported.

Short Title	Title	Reason for exclusion
Berg (2011)	Effects of exenatide twice daily versus sitagliptin on 24-h glucose, glucoregulatory and hormonal measures: a randomized, double-blind, crossover study	No outcomes from protocol reported.
Best (2012)	The effects of exenatide bid on metabolic control, medication use and hospitalization in patients with type 2 diabetes mellitus in clinical practice: a systematic review	Inappropriate study design
Bode (2011)	Comparison of the efficacy and tolerability profile of liraglutide, a once-daily human GLP-1 analog, in patients with type 2 diabetes >65 and <65 years of age: a pooled analysis from phase III studies	No outcomes from protocol reported.
Bode (2014)	Effect of liraglutide 3.0/1.8 mg on body weight and cardiometabolic risk factors in overweight/obese adults with type 2 diabetes: SCALE diabetes randomised, double-blind, 56-week trial	No outcomes from protocol reported.
Bolli (2014)	Efficacy and safety of lixisenatide once daily vs. placebo in people with Type 2 diabetes insufficiently controlled on metformin (GetGoal-F1)	No outcomes from protocol reported.
Brath (2013)	Therapeutic efficacy of lixisenatide added to basal insulin is greater when FPG is well controlled	No outcomes from protocol reported.
Broglio (2017)	Beneficial effect of lixisenatide after 76 weeks of treatment in patients with type 2 diabetes mellitus: A meta-analysis from the GetGoal programme	Outcomes in protocol not included in analysis; studies included were reviewed for outcomes.
Brunt (2015)	Change in patient-reported outcomes (PROs) and the relationship with clinical parameters in patients with Type 2 diabetes receiving once weekly dulaglutide or insulin glargine in the Assessment of Weekly Administration of Dulaglutide in Diabetes (AWARD-2 and-4) studies	No outcomes from protocol reported.
Bunck (2010)	Exenatide affects circulating cardiovascular risk biomarkers independently of changes in body composition	No outcomes from protocol reported.
Bunck (2010)	One-year treatment with exenatide vs. insulin glargine: effects on postprandial glycemia, lipid profiles, and oxidative stress	No outcomes from protocol reported.
Bunck (2010)	Three-year exenatide therapy, followed by a 4-week off-drug period, had a sustainable effect on beta-cell disposition index in metformin treated patients with type 2 diabetes	No outcomes from protocol reported.

Short Title	Title	Reason for exclusion
Bunck (2011)	Effects of exenatide on measures of beta-cell function after 3 years in metformin-treated patients with type 2 diabetes	Inappropriate study design
Bunck (2011)	Effects of exenatide on measures of ?-cell function after 3 years in metformin-treated patients with type 2 diabetes	No outcomes from protocol reported.
Buse (2009)	Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6)	Indirect outcome.
Buse (2009)	Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6)	No outcomes from protocol reported.
Buse (2010)	Switching to once-daily liraglutide from twice-daily exenatide further improves glycemic control in patients with type 2 diabetes using oral agents	Inappropriate study design
Buse (2011)	Liraglutide treatment is associated with a low frequency and magnitude of antibody formation with no apparent impact on glycemic response or increased frequency of adverse events: results from the Liraglutide Effect and Action in Diabetes (LEAD) trials	No outcomes from protocol reported.
Buse (2011)	Weight change in placebo-and exenatide (BID)-treated subjects with type 2 diabetes on insulin glargine: Effects of sex, diabetes duration, baseline A1C, and insulin dose	Inappropriate study design
Buse (2014)	Addition of exenatide BID to insulin glargine: a post-hoc analysis of the effect on glycemia and weight across a range of insulin titration	No outcomes from protocol reported.
Carr (2014)	Harmony 2 year 3 Results: Albiglutide monotherapy in drug naive patients with type 2 diabetes mellitus	No outcomes from protocol reported.
Chalasani (2010)	Effect of once weekly exenatide on ALT and cardiometabolic risk factors in adults with type 2 diabetes	No outcomes from protocol reported.
Chaudhuri (2012)	Exenatide exerts a potent antiinflammatory effect	No outcomes from protocol reported.
Chavez (2010)	Effect of pioglitazone, exenatide, and combined pioglitazone plus exenatide therapy on beta cell function in type 2 diabetes mellitus	No outcomes from protocol reported.
Darpo (2014)	Albiglutide Does Not Prolong QTc Interval in Healthy Subjects: A Thorough ECG Study	No outcomes from protocol reported.
Davies (2014)	Liraglutide 3.0 mg for weight management in obese/overweight adults with type 2 diabetes: SCALE diabetes 56-week	No outcomes from protocol reported.

Short Title	Title	Reason for exclusion
	randomised, double-blind, placebo-controlled trial	
Davies (2015)	Efficacy of Liraglutide for Weight Loss Among Patients With Type 2 Diabetes: The SCALE Diabetes Randomized Clinical Trial	Duplicate article
Davis (2007)	Exploring the substitution of exenatide for insulin in patients with type 2 diabetes treated with insulin in combination with oral antidiabetes agents	No outcomes from protocol reported.
de Wit (2014)	Liraglutide reverses pronounced insulin-associated weight gain, improves glycaemic control and decreases insulin dose in patients with type 2 diabetes: a 26 week, randomised clinical trial (ELEGANT)	No outcomes from protocol reported.
DeFronzo (2005)	Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes	No outcomes from protocol reported.
DeFronzo (2008)	Effects of exenatide versus sitagliptin on postprandial glucose, insulin and glucagon secretion, gastric emptying, and caloric intake: a randomized, cross-over study	No outcomes from protocol reported.
DeFronzo (2010)	Effects of exenatide plus rosiglitazone on beta-cell function and insulin sensitivity in subjects with type 2 diabetes on metformin	No outcomes from protocol reported.
Derosa (2010)	Exenatide versus glibenclamide in patients with diabetes	No outcomes from protocol reported.
Derosa (2010)	Exenatide versus glibenclamide in patients with diabetes	No outcomes from protocol reported.
Derosa (2011)	Exenatide or glimepiride added to metformin on metabolic control and on insulin resistance in type 2 diabetic patients	No outcomes from protocol reported.
Derosa (2012)	Exenatide plus metformin compared with metformin alone on ?-cell function in patients with Type 2 diabetes	No outcomes from protocol reported.
Derosa (2013)	Variation in inflammatory markers and glycemic parameters after 12 months of exenatide plus metformin treatment compared with metformin alone: a randomized placebo-controlled trial	No outcomes from protocol reported.
DeVries (2012)	Sequential intensification of metformin treatment in type 2 diabetes with liraglutide followed by randomized addition of basal insulin prompted by A1C targets	No outcomes from protocol reported.
Diamant (2011)	DURATION-3: Changes in cardiovascular risk factors observed in patients with type	No outcomes from protocol reported.

Short Title	Title	Reason for exclusion
	2 diabetes after 84-week therapy with exenatide once weekly or insulin glargine	
Diamant (2013)	Impact on cardiovascular risk factors of exenatide BID vs insulin lispro TID added to titrated insulin glargine QD in metformin-treated type 2 diabetes mellitus patients: The 4B trial	No outcomes from protocol reported.
Diamant (2014)	Exenatide once weekly versus insulin glargine for type 2 diabetes (DURATION-3): 3-year results of an open-label randomised trial.[Erratum appears in Lancet Diabetes Endocrinol. 2014 Jun;2(6):e13]	Duplicate article
Ding (2016)	Effect of glucagon-like peptide-1 on major cardiovascular outcomes in patients with type 2 diabetes mellitus: A meta-analysis of randomized controlled trials	Systematic review or meta-analysis: relevant papers included were reviewed.
Distiller (2014)	A 24-week, prospective, randomized, open-label, treat-to-target pilot study of obese type 2 diabetes patients with severe insulin resistance to assess the addition of exenatide on the efficacy of U-500 regular insulin plus metformin	No outcomes from protocol reported.
Drucker (2008)	Exenatide once weekly versus twice daily for the treatment of type 2 diabetes: a randomised, open-label, non-inferiority study	Intervention not included
Esposito (2011)	GLP-1 receptor agonists and HBA1c target of <7% in type 2 diabetes: meta-analysis of randomized controlled trials	No outcomes from protocol reported.
Faber (2014)	Glucagon-like peptide-1 analogue liraglutide does not improve microvascular myocardial function in patients with type 2 diabetes-a randomized, single-blinded cross over trial	No outcomes from protocol reported.
Fan (2013)	Exenatide improves type 2 diabetes concomitant with non-alcoholic fatty liver disease	Inappropriate study design
Feinglos (2005)	Effects of liraglutide (NN2211), a long-acting GLP-1 analogue, on glycaemic control and bodyweight in subjects with Type 2 diabetes	No outcomes from protocol reported.
Ferdinand (2016)	Cardiovascular safety for once-weekly dulaglutide in type 2 diabetes: a pre-specified meta-analysis of prospectively adjudicated cardiovascular events	Systematic review or meta-analysis: relevant papers included were reviewed.
Fineman (2004)	Effectiveness of progressive dose-escalation of exenatide (exendin-4) in reducing dose-limiting side effects in subjects with type 2 diabetes	No outcomes from protocol reported.
Fisher (2015)	Cardiovascular safety of albiglutide in the Harmony programme: A meta-analysis	Systematic review or meta-analysis: relevant papers included were reviewed.

Short Title	Title	Reason for exclusion
Fonseca (2012)	Efficacy and safety of the once-daily GLP-1 receptor agonist lixisenatide in monotherapy: a randomized, double-blind, placebo-controlled trial in patients with type 2 diabetes (GetGoal-Mono)	No outcomes from protocol reported.
Fournier (2014)	Indirect comparison of lixisenatide versus neutral protamine Hagedorn insulin as add-on to metformin and sulphonylurea in patients with type 2 diabetes mellitus	No outcomes from protocol reported.
Frandsen (2016)	Liraglutide as adjunct to insulin treatment in type 1 diabetes does not interfere with glycaemic recovery or gastric emptying rate during hypoglycaemia: a randomised, placebo-controlled, double-blind, parallel-group study	No outcomes from protocol reported.
Gallwitz (2010)	Adding liraglutide to oral antidiabetic drug therapy: onset of treatment effects over time	No outcomes from protocol reported.
Gallwitz (2011)	Exenatide twice daily versus premixed insulin aspart 70/30 in metformin-treated patients with type 2 diabetes: a randomized 26-week study on glycemic control and hypoglycemia	No outcomes from protocol reported.
Gallwitz (2012)	Exenatide twice daily versus glimepiride for prevention of glycaemic deterioration in patients with type 2 diabetes with metformin failure (EUREXA): an open-label, randomised controlled trial	No outcomes from protocol reported.
Gao (2009)	Efficacy and safety of exenatide in patients of Asian descent with type 2 diabetes inadequately controlled with metformin or metformin and a sulphonylurea	No outcomes from protocol reported.
Garber (2009)	Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): a randomised, 52-week, phase III, double-blind, parallel-treatment trial	No outcomes from protocol reported.
Gilbert (2016)	Comparison of the Long-Term Effects of Liraglutide and Glimepiride Monotherapy on Bone Mineral Density in Patients with Type 2 Diabetes	No outcomes from protocol reported.
Gill (2010)	Effect of exenatide on heart rate and blood pressure in subjects with type 2 diabetes mellitus: a double-blind, placebo-controlled, randomized pilot study	No outcomes from protocol reported.
Guerci (2013)	Safety and efficacy of dulaglutide versus sitagliptin after 104 weeks in type 2 diabetes (award-5)	No outcomes from protocol reported.
Gurkan (2014)	Evaluation of exenatide versus insulin glargine for the impact on endothelial functions and cardiovascular risk markers	No outcomes from protocol reported.
Hanefeld (2014)	Lixisenatide treatment for older patients with type 2 diabetes mellitus uncontrolled	No outcomes from protocol reported.

Short Title	Title	Reason for exclusion
	on oral antidiabetics: meta-analysis of five randomized controlled trials (Provisional abstract)	
Harder (2004)	The effect of liraglutide, a long-acting glucagon-like peptide 1 derivative, on glycemic control, body composition, and 24-h energy expenditure in patients with type 2 diabetes	No outcomes from protocol reported.
Heine (2005)	Exenatide versus insulin glargine in patients with suboptimally controlled type 2 diabetes: A randomized trial	No outcomes from protocol reported.
Home (2015)	Efficacy and tolerability of albiglutide versus placebo or pioglitazone over 1year in people with type 2 diabetes currently taking metformin and glimepiride: HARMONY 5	No outcomes from protocol reported.
Horowitz (2012)	Effect of the once-daily human GLP-1 analogue liraglutide on appetite, energy intake, energy expenditure and gastric emptying in type 2 diabetes	No outcomes from protocol reported.
Htike (2016)	Efficacy and safety of glucagon-like peptide-1 receptor agonists in type 2 diabetes: A systematic review and mixed-treatment comparison analysis	No outcomes from protocol reported.
Idorn (2014)	Safety and efficacy of liraglutide in patients with type 2 diabetes and end-stage renal disease: An investigator-initiated, randomised, placebocontrolled trial	No outcomes from protocol reported.
Irie (2008)	Tolerability, pharmacokinetics and pharmacodynamics of the once-daily human GLP-1 analog liraglutide in Japanese healthy subjects: a randomized, double-blind, placebo-controlled dose-escalation study	No outcomes from protocol reported.
Jaiswal (2015)	Effects of exenatide on measures of diabetic neuropathy in subjects with type 2 diabetes: results from an 18-month proof-of-concept open-label randomized study	No outcomes from protocol reported.
Jendle (2014)	Better glycaemic control and less weight gain with once weekly dulaglutide vs bedtime insulin glargine, both combined with thrice daily lispro, in type 2 diabetes (AWARD-4)	No outcomes from protocol reported.
Kaku (2010)	Improved glycaemic control with minimal hypoglycaemia and no weight change with the once-daily human glucagon-like peptide-1 analogue liraglutide as add-on to sulphonylurea in Japanese patients with type 2 diabetes	Dosage not licensed for long term use in the UK.
Kaku (2016)	Liraglutide is effective and well tolerated in combination with an oral antidiabetic drug in Japanese patients with type 2	Dosage not licensed in the UK.

Short Title	Title	Reason for exclusion
	diabetes: A randomized, 52-week, open-label, parallel-group trial.[Erratum appears in J Diabetes Investig. 2016 Mar;7(2):279; PMID: 27042283]	
Katout (2014)	Effect of GLP-1 mimetics on blood pressure and relationship to weight loss and glycemia lowering: results of a systematic meta-analysis and meta-regression	No outcomes from protocol reported.
Ke (2015)	The effect of liraglutide as subsequent treatment after short-term intensive insulin therapy on glucose control and beta-cell function in newly diagnosed type 2 diabetic patients	No outcomes from protocol reported.
Kendall (2005)	Effects of exenatide (exendin-4) on glycemic control over 30 weeks in patients with type 2 diabetes treated with metformin and a sulfonylurea	No outcomes from protocol reported.
Kim (2007)	Effects of once-weekly dosing of a long-acting release formulation of exenatide on glucose control and body weight in subjects with type 2 diabetes	No outcomes from protocol reported.
Kim (2016)	Cardiovascular effect of incretin-based therapy in patients with type 2 diabetes mellitus: Systematic review and meta-Analysis	No outcomes from protocol reported.
Klein (2014)	Liraglutide's safety, tolerability, pharmacokinetics, and pharmacodynamics in pediatric type 2 diabetes: a randomized, double-blind, placebo-controlled trial	Population not included.
Klonoff (2008)	Exenatide effects on diabetes, obesity, cardiovascular risk factors and hepatic biomarkers in patients with type 2 diabetes treated for at least 3 years	No outcomes from protocol reported.
Kulve (2015)	Liraglutide decreases food related CNS activation after short-term, but not after longer-term treatment in patients with diabetes	No outcomes from protocol reported.
Lane (2014)	The effect of addition of liraglutide to high-dose intensive insulin therapy: a randomized prospective trial	No outcomes from protocol reported.
Leiter (2014)	Efficacy and safety of the once-weekly GLP-1 receptor agonist albiglutide versus sitagliptin in patients with type 2 diabetes and renal impairment: a randomized phase III study	Indirect population
Li (2012)	Efficacy and safety comparison between liraglutide as add-on therapy to insulin and insulin dose-increase in Chinese subjects with poorly controlled type 2 diabetes and abdominal obesity	No outcomes from protocol reported.
Li (2015)	Effect of exenatide, insulin and pioglitazone on bone metabolism in	No outcomes from protocol reported.

Short Title	Title	Reason for exclusion
	patients with newly diagnosed type 2 diabetes	
Li (2015)	Effect of exenatide, insulin, and pioglitazone on body weight and body fat distribution in newly diagnosed T2DM	No outcomes from protocol reported.
Lind (2015)	Liraglutide in people treated for type 2 diabetes with multiple daily insulin injections: randomised clinical trial (MDI Liraglutide trial)	Duplicate article
Lingvay (2016)	Effect of insulin glargine up-titration vs insulin degludec/liraglutide on glycated hemoglobin levels in patients with uncontrolled type 2 diabetes: The DUAL v randomized clinical trial	Differences between intervention and comparison background treatments.
Linjawi (2017)	The Efficacy of IDegLira (Insulin Degludec/Liraglutide Combination) in Adults with Type 2 Diabetes Inadequately Controlled with a GLP-1 Receptor Agonist and Oral Therapy: DUAL III Randomized Clinical Trial	Inappropriate comparison.
Linnebjerg (2006)	Exenatide: effect of injection time on postprandial glucose in patients with Type 2 diabetes	No outcomes from protocol reported.
Liraglutide and cardiovascular... (2016)	Liraglutide and cardiovascular outcomes in type 2 diabetes	Editor's comment.
Madsbad (2004)	Improved glycemic control with no weight increase in patients with type 2 diabetes after once-daily treatment with the long-acting glucagon-like peptide 1 analog liraglutide (NN2211): a 12-week, double-blind, randomized, controlled trial	No outcomes from protocol reported.
Madsbad (2016)	Review of head-to-head comparisons of glucagon-like peptide-1 receptor agonists	No outcomes from protocol reported.
Malloy (2009)	Pharmacology and tolerability of a single dose of exenatide in adolescent patients with type 2 diabetes mellitus being treated with metformin: a randomized, placebo-controlled, single-blind, dose-escalation, crossover study	No outcomes from protocol reported.
Margulies (2016)	Effects of liraglutide on clinical stability among patients with advanced heart failure and reduced ejection fraction: A randomized clinical trial	Indirect population
Mathieu (2013)	Addition of liraglutide vs addition of a single dose of insulin aspart to insulin degludec plus metformin in patients with type 2 diabetes	No outcomes from protocol reported.
Mathieu (2013)	Comparison of addition of liraglutide to insulin degludec plus metformin vs. addition of a single dose of rapid-acting insulin analog to largest meal in type 2 diabetes	No outcomes from protocol reported.

Short Title	Title	Reason for exclusion
Matthaei (2012)	Patients with type 2 diabetes initiating exenatide twice daily or insulin in clinical practice: CHOICE study	Inappropriate study design
Matyjaszek-Matuszek (2013)	Exenatide twice daily versus insulin glargine for the treatment of type 2 diabetes in Poland - subgroup data from a randomised multinational trial GWAA	No outcomes from protocol reported.
Meneilly (2003)	Effects of 3 months of continuous subcutaneous administration of glucagon-like peptide 1 in elderly patients with type 2 diabetes	Intervention unclear, only 'GLP-1' reported.
Moretto (2008)	Efficacy and tolerability of exenatide monotherapy over 24 weeks in antidiabetic drug-naive patients with type 2 diabetes: a randomized, double-blind, placebo-controlled, parallel-group study.[Erratum appears in Clin Ther. 2008 Oct;30(10):1937]	Intervention (exenatide or lixisenatide) not administered with another antihyperglycaemic.
Mosenzon (2015)	Efficacy and safety of liraglutide 3.0 Mg and 1.8 Mg in weight loss responders vs non-responders in overweight/obese adults with type 2 diabetes (T2D): A subgroup analysis of the scale diabetes trial	No outcomes from protocol reported.
Nandy (2014)	The effect of liraglutide on endothelial function in patients with type 2 diabetes	No outcomes from protocol reported.
Nathanson (2012)	Effects of intravenous exenatide in type 2 diabetic patients with congestive heart failure: a double-blind, randomised controlled clinical trial of efficacy and safety	No outcomes from protocol reported.
Nauck (2006)	Five weeks of treatment with the GLP-1 analogue liraglutide improves glycaemic control and lowers body weight in subjects with type 2 diabetes	No outcomes from protocol reported.
Nauck (2009)	Adding liraglutide to oral antidiabetic drug monotherapy: efficacy and weight benefits	No outcomes from protocol reported.
Nauck (2009)	Efficacy and safety comparison of liraglutide, glimepiride, and placebo, all in combination with metformin, in type 2 diabetes	No outcomes from protocol reported.
Nauck (2013)	Efficacy and safety of dulaglutide vs. Sitagliptin after 52 weeks in type 2 diabetes (AWARD-5)	No outcomes from protocol reported.
Nauck (2015)	Erratum: Efficacy and Safety of Dulaglutide Versus Sitagliptin After 52 Weeks in Type 2 Diabetes in a Randomized Controlled Trial (AWARD-5) (Diabetes Care (2014) 37 (2149-2158))	Erratum to previous study.
Nauck (2016)	Efficacy and safety of once-weekly GLP-1 receptor agonist albiglutide (HARMONY 2): 52 week primary endpoint results from a randomised, placebo-controlled trial in	No outcomes from protocol reported.

Short Title	Title	Reason for exclusion
	patients with type 2 diabetes mellitus inadequately controlled with diet and exercise	
Nelson (2007)	The incretin mimetic exenatide as a monotherapy in patients with type 2 diabetes	Intervention (exenatide or lixisenatide) not administered with another antihyperglycaemic.
Neumiller (2009)	Liraglutide: a once-daily incretin mimetic for the treatment of type 2 diabetes mellitus	No outcomes from protocol reported.
Ojo (2016)	The use of exenatide in managing markers of cardiovascular risk in patients with type 2 diabetes: A systematic review	No outcomes from protocol reported.
Poon (2005)	Exenatide improves glycemic control and reduces body weight in subjects with type 2 diabetes: a dose-ranging study	No outcomes from protocol reported.
Pozzilli (2016)	Improved glycaemic control and weight loss with once weekly dulaglutide versus placebo, both added to titrated daily insulin glargine in type 2 diabetes patients (AWARD-9)	No outcomes from protocol reported.
Pratley (2012)	Efficacy and safety of once-weekly (QW) albiglutide vs. once-daily (QD) liraglutide in type 2 diabetes (T2D) inadequately controlled on oral agents: Harmony 7 trial	No outcomes from protocol reported.
Pratley (2014)	Once-weekly albiglutide versus once-daily liraglutide in patients with type 2 diabetes inadequately controlled on oral drugs (HARMONY 7): a randomised, open-label, multicentre, non-inferiority phase 3 study	No outcomes from protocol reported.
Probstfield (2016)	Glucose variability in a 26-week randomized comparison of mealtime treatment with rapid-acting insulin versus glp-1 agonist in participants with type 2 diabetes at high cardiovascular risk	No outcomes from protocol reported.
Quan (2016)	Gender-related different effects of a combined therapy of Exenatide and Metformin on overweight or obesity patients with type 2 diabetes mellitus	No outcomes from protocol reported.
Rappaport (2013)	A randomised trial comparing the addition of liraglutide to high dose intensive insulin therapy vs insulin up-titration in type 2 diabetes	No outcomes from protocol reported.
Ratner (2010)	Dose-dependent effects of the once-daily GLP-1 receptor agonist lixisenatide in patients with Type 2 diabetes inadequately controlled with metformin: a randomized, double-blind, placebo-controlled trial	No outcomes from protocol reported.
Reaney (2014)	Patient-reported outcomes (PRO) from a 104 week, phase 3, randomised, placebo-controlled study comparing once weekly dulaglutide to sitagliptin and placebo in	No outcomes from protocol reported.

Short Title	Title	Reason for exclusion
	metformin-treated patients with Type 2 diabetes; the Assessment of Weekly Administration of Dulaglutide in Diabetes (AWARD-5) trial	
Rendell (2014)	Harmony 2 year 3 results: Albiglutide monotherapy in drug-naive patients with T2DM	No outcomes from protocol reported.
Retnakaran (2014)	Liraglutide and the preservation of pancreatic beta-cell function in early type 2 diabetes: the LIBRA trial	No outcomes from protocol reported.
Reusch (2013)	HARMONY 1 results at week 52 primary endpoint: Once-weekly albiglutide vs placebo in patients with type 2 diabetes mellitus not controlled on pioglitazone +/- metformin	No outcomes from protocol reported.
Reusch (2014)	Efficacy and safety of once-weekly glucagon-like peptide 1 receptor agonist albiglutide (HARMONY 1 trial): 52-week primary endpoint results from a randomized, double-blind, placebo-controlled trial in patients with type 2 diabetes mellitus not controlled on pioglitazone, with or without metformin	No outcomes from protocol reported.
Rosenstock (2009)	Potential of albiglutide, a long-acting GLP-1 receptor agonist, in type 2 diabetes: a randomized controlled trial exploring weekly, biweekly, and monthly dosing	No outcomes from protocol reported.
Rosenstock (2013)	One-year sustained glycemic control and weight reduction in type 2 diabetes after addition of liraglutide to metformin followed by insulin detemir according to HbA1c target	No outcomes from protocol reported.
Rosenstock (2013)	Efficacy and safety of lixisenatide once daily versus exenatide twice daily in type 2 diabetes inadequately controlled on metformin: a 24-week, randomized, open-label, active-controlled study (GetGoal-X)	No outcomes from protocol reported.
Rosenstock (2014)	Advancing basal insulin replacement in type 2 diabetes inadequately controlled with insulin glargine plus oral agents: a comparison of adding albiglutide, a weekly GLP-1 receptor agonist, versus thrice-daily prandial insulin lispro	No outcomes from protocol reported.
Rosenstock (2016)	Clinical impact of LixiLan, a fixed-ratio combination of insulin glargine plus lixisenatide in type 2 diabetes inadequately controlled on oral agents: LixiLan-O trial	No outcomes from protocol reported.
Russell-Jones (2009)	Liraglutide vs insulin glargine and placebo in combination with metformin and sulfonylurea therapy in type 2 diabetes mellitus (LEAD-5 met+SU): a randomised controlled trial	No outcomes from protocol reported.

Short Title	Title	Reason for exclusion
Russell-Jones (2012)	Efficacy and safety of exenatide once weekly versus metformin, pioglitazone, and sitagliptin used as monotherapy in drug-naive patients with type 2 diabetes (DURATION-4): a 26-week double-blind study	No outcomes from protocol reported.
Schernthaner (2017)	Treatment escalation options for patients with type 2 diabetes after failure of exenatide twice daily or glimepiride added to metformin: results from the prospective European Exenatide (EUREXA) study	Inappropriate study design
Seino (2011)	Glucagon-like peptide-1 analog liraglutide in combination with sulfonylurea safely improves blood glucose measures vs sulfonylurea monotherapy in japanese patients with type 2 diabetes: Results of a 52-week, randomized, multicenter trial	Dosage not licensed for long term use in the UK.
Seino (2012)	Randomized, double-blind, placebo-controlled trial of the once-daily GLP-1 receptor agonist lixisenatide in Asian patients with type 2 diabetes insufficiently controlled on basal insulin with or without a sulfonylurea (GetGoal-L-Asia)	No outcomes from protocol reported.
Seino (2012)	The once-daily human glucagon-like peptide-1 analog, liraglutide, improves beta-cell function in Japanese patients with type 2 diabetes	No outcomes from protocol reported.
Seino (2015)	Long-term safety of once-daily lixisenatide in Japanese patients with type 2 diabetes mellitus: GetGoal-Mono-Japan	Intervention (exenatide or lixisenatide) not administered with another antihyperglycaemic.
Seino (2015)	Efficacy and Safety of Lixisenatide in Japanese Patients with Type 2 Diabetes Insufficiently Controlled with Basal Insulin+/-Sulfonylurea: A Subanalysis of the GetGoal-L-Asia Study	No outcomes from protocol reported.
Seino (2016)	Combination therapy with liraglutide and insulin in Japanese patients with type 2 diabetes: A 36-week, randomized, double-blind, parallel-group trial	Dosage not licensed in the UK.
Seino (2017)	Safety, tolerability, and efficacy of lixisenatide as monotherapy in Japanese patients with type 2 diabetes mellitus: An open-label, multicenter study	Inappropriate study design
Shao (2014)	Benefits of exenatide on obesity and non-alcoholic fatty liver disease with elevated liver enzymes in patients with type 2 diabetes	No outcomes from protocol reported.
Shyangdan (2010)	Glucagon-like peptide analogues for type 2 diabetes mellitus: Systematic review and meta-analysis	Systematic review or meta-analysis: relevant papers included were reviewed.
Shyangdan (2011)	Glucagon-like peptide analogues for type 2 diabetes mellitus	Systematic review or meta-analysis: relevant papers included were reviewed.

Short Title	Title	Reason for exclusion
Simo (2015)	Long-term changes in cardiovascular risk markers during administration of exenatide twice daily or glimepiride: results from the European exenatide study	No outcomes from protocol reported.
Singh (2017)	Glucagon-like peptide-1 receptor agonists compared with basal insulins for the treatment of type 2 diabetes mellitus: a systematic review and meta-analysis	Systematic review or meta-analysis: relevant papers included were reviewed.
Skrivanek (2013)	Dose-finding results in an adaptive trial of dulaglutide combined with metformin in type 2 diabetes (AWARD-5)	No outcomes from protocol reported.
Skrivanek (2014)	Dose-finding results in an adaptive, seamless, randomized trial of once-weekly dulaglutide combined with metformin in type 2 diabetes patients (AWARD-5)	No outcomes from protocol reported.
Smits (2016)	GLP-1-Based Therapies Have No Microvascular Effects in Type 2 Diabetes Mellitus: An Acute and 12-Week Randomized, Double-Blind, Placebo-Controlled Trial	No outcomes from protocol reported.
Smits (2016)	Pancreatic Effects of Liraglutide or Sitagliptin in Overweight Patients With Type 2 Diabetes: A 12-Week Randomized, Placebo-Controlled Trial	No outcomes from protocol reported.
Smits (2016)	Twelve week liraglutide or sitagliptin does not affect hepatic fat in type 2 diabetes: a randomised placebo-controlled trial	No outcomes from protocol reported.
Strand (2015)	The relationship of recurrent hypoglycemia with glycemic control and insulin change in patients treated with insulin glargine and exenatide twice daily vs. Insulin lispro or placebo	No outcomes from protocol reported.
Su (2014)	Effects of exenatide on glycemic control over 52 weeks in patients with type 2 diabetes. [Chinese]	Not English
Sun (2015)	Effect of glucagon-like peptide-1 receptor agonists on lipid profiles among type 2 diabetes: a systematic review and network meta-analysis	No outcomes from protocol reported.
Suzuki (2014)	Greater efficacy and improved endothelial dysfunction in untreated type 2 diabetes with liraglutide versus sitagliptin	No outcomes from protocol reported.
Takeshita (2015)	Vildagliptin vs liraglutide as a second-line therapy switched from sitagliptin-based regimens in patients with type 2 diabetes: A randomized, parallel-group study	No outcomes from protocol reported.
Tardif (2016)	Effects of lixisenatide on natriuretic peptides in patients with diabetes and acute coronary syndrome	No outcomes from protocol reported.
Terauchi (2014)	Monotherapy with the once weekly GLP-1 receptor agonist dulaglutide for 12 weeks	No outcomes from protocol reported.

Short Title	Title	Reason for exclusion
	in Japanese patients with type 2 diabetes: dose-dependent effects on glycaemic control in a randomised, double-blind, placebo-controlled study	
Tofe (2014)	Efficacy and safety of once weekly dulaglutide versus once daily liraglutide in type 2 diabetes (AWARD6)	No outcomes from protocol reported.
Trautmann (2013)	Exenatide once weekly: Sustained glycemic and weight control through 3 years compared with insulin glargine	No outcomes from protocol reported.
Tripathy (2015)	Effect of pioglitazone, exenatide and combination of pioglitazone and exenatide on plasma alpha-hydroxybutyrate in type 2 diabetes	No outcomes from protocol reported.
Trujillo (2014)	Albiglutide: a new GLP-1 receptor agonist for the treatment of type 2 diabetes	No outcomes from protocol reported.
Twigg (2016)	Once-daily liraglutide (1.2 mg) compared with twice-daily exenatide (10 mug) in the treatment of type 2 diabetes patients: An indirect treatment comparison meta-analysis	No outcomes from protocol reported.
Umpierrez (2013)	Efficacy and safety of dulaglutide vs. Metformin in type 2 diabetes (AWARD-3)	No outcomes from protocol reported.
Vanderheiden (2016)	Mechanisms of action of liraglutide in patients with type 2 diabetes treated with high-dose insulin	No outcomes from protocol reported.
Vanderheiden (2016)	Effect of adding liraglutide vs placebo to a high-dose Insulin regimen in patients with type 2 diabetes a randomized clinical trial	No outcomes from protocol reported.
Van Raalt (2016)	Exenatide improves β-cell function up to 3 years of treatment in patients with type 2 diabetes: a randomised controlled trial	No outcomes from protocol reported.
Vilsbøll (2008)	Liraglutide, a once-daily human GLP-1 analogue, improves pancreatic B-cell function and arginine-stimulated insulin secretion during hyperglycaemia in patients with Type 2 diabetes mellitus	No outcomes from protocol reported.
Violante (2012)	A randomized non-inferiority study comparing the addition of exenatide twice daily to sitagliptin or switching from sitagliptin to exenatide twice daily in patients with type 2 diabetes experiencing inadequate glycaemic control on metformin and sitagliptin	No outcomes from protocol reported.
von Scholten (2017)	The effect of liraglutide on renal function: A randomized clinical trial	No outcomes from protocol reported.
von Scholten (2017)	Liraglutide effects on cardiovascular risk biomarkers in patients with type 2 diabetes and albuminuria: A sub-analysis of a randomised, placebo-controlled, double-blind, cross-over trial	No outcomes from protocol reported.Indirect population
Weissman (2014)	HARMONY 4: randomised clinical trial comparing once-weekly albiglutide and	No outcomes from protocol reported.

Short Title	Title	Reason for exclusion
	insulin glargine in patients with type 2 diabetes inadequately controlled with metformin with or without sulfonylurea	
Wu (2010)	The effect of exenatide on inflammation and oxidative stress in type 2 diabetes mellitus	No outcomes from protocol reported.
Wu (2011)	Effect of exenatide on inflammatory and oxidative stress markers in patients with type 2 diabetes mellitus	No outcomes from protocol reported.
Wu (2014)	The cardiovascular effects of glucagon-like peptide-1 receptor agonists: a trial sequential analysis of randomized controlled trials	Systematic review or meta-analysis: relevant papers included were reviewed.
Wysham (2011)	DURATION-2: efficacy and safety of switching from maximum daily sitagliptin or pioglitazone to once-weekly exenatide	No outcomes from protocol reported.
Wysham (2015)	Five-year efficacy and safety data of exenatide once weekly: long-term results from the DURATION-1 randomized clinical trial	Post-hoc analysis.
Wysham (2016)	Baseline factors associated with glycaemic response to treatment with once-weekly dulaglutide in patients with type 2 diabetes	No outcomes from protocol reported.
Xu (2012)	Comparison of 24-week treatment with exenatide, insulin and pioglitazone in newly diagnosed and drug-naive T2DM	No outcomes from protocol reported.
Xue (2016)	Efficacy and safety of once-weekly glucagon-like peptide-1 receptor agonists compared with exenatide and liraglutide in type 2 diabetes: a systemic review of randomised controlled trials	No outcomes from protocol reported.
Yan (2015)	[The efficacy and safety of human glucagon-like peptide-1 analogue liraglutide in newly diagnosed type 2 diabetes with glycosylated hemoglobin A1c > 9]	Not English
Yang (2010)	Liraglutide vs glimepiride, both added to metformin, in an Asian population with T2D: Efficacy and safety findings from China, South Korea and India	Not English
Yang (2010)	Liraglutide provides similar glycemic control with reduced systolic blood pressure and body weight compared to glimepiride when added to metformin in chinese subjects with T2D	Not English
Yokoyama (2014)	Liraglutide Versus Sitagliptin in a 24-week, Multicenter, Open-label, Randomized, Parallel-group Study in Japanese Type 2 Diabetes Mellitus Patients Responding Inadequately to a Sulfonylurea and/or One or Two Other Oral Antidiabetic Drugs (JDDM 33)	No outcomes from protocol reported.

Short Title	Title	Reason for exclusion
Yuan (2012)	Efficacy and tolerability of exenatide monotherapy in obese patients with newly diagnosed type 2 diabetes: a randomized, 26 weeks metformin-controlled, parallel-group study	Not English
Zaccardi (2016)	Benefits and Harms of Once-Weekly Glucagon-like Peptide-1 Receptor Agonist Treatments: A Systematic Review and Network Meta-analysis	Systematic review or meta-analysis: relevant papers included were reviewed.
Zhang (2012)	Exenatide reduces urinary transforming growth factor-beta1 and type IV collagen excretion in patients with type 2 diabetes and microalbuminuria	No outcomes from protocol reported.
Zhang (2016)	Efficacy and safety of dulaglutide in patients with type 2 diabetes: a meta-analysis and systematic review	No outcomes from protocol reported.
Zinman (2007)	The effect of adding exenatide to a thiazolidinedione in suboptimally controlled type 2 diabetes: a randomized trial.[Erratum appears in Ann Intern Med. 2007 Jun 19;146(12):896], [Summary for patients in Ann Intern Med. 2007 Apr 3;146(7):I18; PMID: 17404346]	No outcomes from protocol reported.

Economic studies

SGLT-2 inhibitors

Excluded study	Reason for exclusion (2b)
Charokopou et al. (2015). Cost-effectiveness of dapagliflozin versus DPP-4 inhibitors as an add-on to Metformin in the Treatment of Type 2 Diabetes Mellitus from a UK Healthcare System Perspective. *BMC Health Serv Res;* 15: 496.	Economic analysis not informed by relative effects on cardiovascular events. Instead, relative effects on intermediate outcomes used (e.g. through validated risk models).
Charokopou et al. (2015). The cost-effectiveness of dapagliflozin versus sulfonylurea as an add-on to metformin in the treatment of Type 2 diabetes mellitus. *Diabetic Medicine;* 32(7): 890-8.	
Gu et al. (2016). Cost-Effectiveness of Dapagliflozin versus Acarbose as a Monotherapy in Type 2 Diabetes in China. *PLoS ONE;* 11(2): e0165629.	
McEwan et al. (2015). Refitting of the UKPDS 68 risk equations to contemporary routine clinical practice data in the UK. *Pharmacoeconomics;* 33(2): 149-61.	
McEwan et al. (2015). Estimating Cost-Effectiveness in Type 2 Diabetes: The Impact of Treatment Guidelines and Therapy Duration. *Med Decis Mak;* 35(5)5: 660-70.	
Neslusan et al. (2015). Cost-Effectiveness of Canagliflozin versus Sitagliptin as Add-on to Metformin in Patients with Type 2 Diabetes Mellitus in Mexico. *Value Health: Regional Issues;* 8: 8-19.	
Sabapathy et al. (2016). Cost-effectiveness of Canagliflozin versus Sitagliptin When Added to Metformin and Sulfonylurea in Type 2 Diabetes in Canada. *J Pop Therap Clin Pharmacol;* 23(2): e151-68.	

Shao et al. (2017). Cost-effectiveness analysis of dapagliflozin versus glimepiride as monotherapy in a Chinese population with type 2 diabetes mellitus. *Curr Med Res Op;* 33(2): 359-69.	
Van Haalen et al. (2014). Cost effectiveness of adding dapagliflozin to insulin for the treatment of type 2 diabetes mellitus in the Netherlands. *Clin Drug Invest;* 34(2): 135-46.	
Ektare et al. (2014). Cost efficiency of canagliflozin versus sitagliptin for type 2 diabetes mellitus. *Am J Managed Care;* 20 (10S): S204-15.	Not a cost–utility analysis.
Grandy et al. (2014). Health-related quality of life (EQ-5D) among type 2 diabetes mellitus patients treated with dapagliflozin over 2 years. *Int J Clin Practice;* 68(4): 486-94.	
Grandy et al. (2016). Patient-reported outcomes among patients with type 2 diabetes mellitus treated with dapagliflozin in a triple-therapy regimen for 52 weeks. *Diab, Obes & Metab;* 18(3): 306-9.	
Hirshberg & Katz (2013). Cardiovascular outcome studies with novel antidiabetes agents: Scientific and operational considerations. *Diab Care;* 36(2S): S253-8.	
Lafeuille et al. (2015). Economic simulation of canagliflozin and sitagliptin treatment outcomes in patients with type 2 diabetes mellitus with inadequate glycemic control. *J Med Econ;* 18(2): 113-25.	
Liebl et al. (2015). Health economic evaluation of type 2 diabetes mellitus: A clinical practice focused review. *Clin Med Ins: Endocrin Diab;* 8: 13-9.	
Naci et al. (2015). Preventing cardiovascular events with empagliflozin: at what cost? *Lancet Diab Endocrin;* 3(12): 931.	
Ravasio et al. (2016). Economic evaluation of canagliflozin versus glimepiride and sitagliptin in dual therapy with metformin for the treatment of type 2 diabetes in Italy. *Glob Reg Health Technol Assess;* 3(2): 92-101.	
Johnston et al. (2017). Canagliflozin, dapagliflozin and empagliflozin monotherapy for treating type 2 diabetes: systematic review and economic evaluation. *Health Technol Asses;* 21(2): 1-218.	Systematic review, no additional relevant studies identified.

GLP-1 mimetics

Excluded study	Reason for exclusion (2b)
Note: None of the studies listed below, nor those included in the evidence table for review question 2(b) (Appendix H) were included for review question 2(a). All were excluded because their economic analyses were not informed by relative effects on cardiovascular events. Instead, all use the same broad approach as the NG28 model, of using relative effects on intermediate outcomes to predict differences in future risk of cardiovascular events (e.g. through validated risk models).	
Mezquita-Raya et al. (2013). Incretin Therapy for Type 2 Diabetes in Spain: A Cost-Effectiveness Analysis of Liraglutide Versus Sitagliptin. *Diabetes Ther;* 4: 414-30.	Duplicate of Perez et al. (2015).
Mezquita-Raya et al. (2017). Liraglutide Versus Lixisenatide: Long-Term Cost-Effectiveness of GLP-1 Receptor Agonist Therapy for the Treatment of Type 2 Diabetes in Spain. *Diabetes Ther;* 8: 401-15.	Direct adaptation of Hunt et al. (2017a).
Samishkyn et al. (2012a). Long-term cost-utility analysis of exenatide once weekly versus insulin glargine for the treatment of type 2 diabetes patients in the US. *J Med Econ;* 15(S2): 6-13.	Direct adaptation of Beaudet et al. (2012).
Gaebler et al. (2012). Health and economic outcomes for exenatide once weekly, insulin, and pioglitazone therapies in the treatment of type 2 diabetes: a simulation analysis. *Vasc Health Risk Manag;* 8: 255-64.	Sensitivity analysis on relative effect parameters that differ to

Gordon et al. (2016). The cost-effectiveness of exenatide twice daily (BID) vs insulin lispro three times daily (TID) as add-on therapy to titrated insulin glargine in patients with type 2 diabetes. *J Med Econ;* 19(12): 1167-74.	the NG28 model were not reported.
Woehl et al. (2008). Evaluation of the cost effectiveness of exenatide versus insulin glargine in patients with sub-optimally controlled Type 2 diabetes in the United Kingdom. *Cardiovascular Diabetology;* 7: 24.	
Brändle et al. (2009). Exenatide versus insulin glargine: a cost-effectiveness evaluation in patients with Type 2 diabetes in Switzerland. *Int J Clin Pharmacology Ther;* 47(8): 501-15.	
Lee et al. (2010). Results of a Model Analysis of the Cost-Effectiveness of Liraglutide Versus Exenatide Added to Metformin, Glimepiride, or Both for the Treatment of Type 2 Diabetes in the United States. *Clinical Therapeutics;* 32(10): 1756-67.	
Ericsson et al. (2017). Cost Effectiveness of Insulin Degludec Plus Liraglutide (IDegLira) in a Fixed Combination for Uncontrolled Type 2 Diabetes Mellitus in Sweden. *Appl Health Econ Health Policyt;* 15: 237-48.	
Watkins et al. (2006). Application of economic analyses in U.S. managed care formulary decisions: a private payer's experience. *J Manag Care Pharm;* 12(9): 726-35.	
Mittendorf et al. (2009). Evaluation of exenatide vs. insulin glargine in type 2 diabetes: cost-effectiveness analysis in the German setting. *Diabetes, Obesity and Metabolism;* 11: 1068-79.	
Steen Carlsson et al. (2014). Cost-effectiveness of add-on treatments to metformin in a Swedish setting: liraglutide vs sulphonylurea or sitagplitin. *J Med Econ;* 17(9): 685-669.	
Davies (2010). Compared with glyburide, sitagliptin associated with incremental cost-effectiveness ratio of $169 572 per QALY and exenatide with $278 935 per QALY as second-line treatment in adult diabetics in the USA. *Evidence-Based Medicine*; 15:40-41.	
Davies et al. (2012). Cost–utility analysis of liraglutide compared with sulphonylurea or sitagliptin, all as add-on to metformin monotherapy in Type 2 diabetes mellitus. *Diabet Med;* 29(3): 313-20.	
Davies et al. (2016). Cost effectiveness of IDegLira vs. alternative basal insulin intensification therapies in patients with Type 2 Diabetes Mellitus uncontrolled on basal insulin in a UK setting. *PharmacoEconomics;* 34: 953-66.	
Guillermin et al. (2012). Long-term cost-consequence analysis of exenatide once weekly vs sitagliptin or pioglitazone for the treatment of type 2 diabetes patients in the United States. *J Med Econ;* 15(4): 654-63.	
Samishkyn et al. (2012b). Long-term clinical and economic outcomes associated with liraglutide versus sitagliptin therapy when added to metformin in the treatment of type 2 diabetes: a CORE Diabetes Model analysis. *J Med Econ;* 15(S2); 28-37.	
Dilla et al. (2017). The cost-effectiveness of dulaglutide versus liraglutide for the treatment of type 2 diabetes mellitus in Spain in patients with BMI ≥30 kg/m^2. *J Med Econ;* 20(5): 443-52.	
Chuang et al. (2016). Cost-effectiveness analysis of exenatide once-weekly versus dulaglutide, liraglutide, and lixisenatide for the treatment of type 2 diabetes mellitus: an analysis from the UK perspective. *J Med Econ;* 19(12): 1127-34.	Same relative effect parameters as NG28 model.

Huetson et al. (2015). Cost-effectiveness of once daily GLP-1 receptor agonist lixisenatide compared to bolus insulin both in combination with basal insulin for the treatment of patients with type 2 diabetes in Norway. *J Med Econ;* 18(8): 573-85.	
Kiadaliri et al. (2014). Cost–Utility Analysis of Glucagon-Like Peptide-1 Agonists Compared with Dipeptidyl Peptidase-4 Inhibitors or Neutral Protamine Hagedorn Basal Insulin as Add-On to Metformin in Type 2 Diabetes in Sweden. *Diabetes Ther;* 5: 591-607.	
Shaya et al. (2007). Clinical and economic evaluation of exenatide for formulary decisions. *J Med Econ;* 10: 529-37.	
Zhang et al. (2016). Long-Term Effectiveness and Cost-Effectiveness of Metformin Combined with Liraglutide or Exenatide for Type 2 DiabetesMellitus Based on the CORE Diabetes Model Study. *PLOS One;* 11(6): e0156393.	
Deshpande et al. (2011). Cost and effectiveness of exenatide combined with insulin, compared to exenatide combined with oral hypoglycaemic agents. *Practical Diabetes;* 28(9): 390-3.	Not a cost–utility analysis.
Edwards et al. (2006). Cost-effectiveness of intermediate or long-acting insulin versus exenatide in type 2 diabetes mellitus patients not optimally controlled on dual oral diabetes medications. *Pharmacy Practice;* 4(3): 129-33.	
Langer et al. (2013). Evaluating the short-term cost-effectiveness of liraglutide versus sitagliptin in patients with type 2 diabetes failing metformin monotherapy in the United States. *J Manag Care Pharm;* 19(3): 237-46.	

Appendix K – Cardiovascular definitions from CANVAS and CANVAS-R trial

The following definitions were taken from the supplementary appendix of Neal B, Perkovic V, Mahaffey KW, et al. (2017) Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. The New England Journal of Medicine 1-14.

A. Death

All deaths will be reviewed by the adjudicators. Because the main role is to identify cardiovascular deaths, the approach used will be to present all deaths as potential cardiovascular deaths and ask the committee to confirm or refute that the cause was cardiovascular. Because there is often confusion in reporting cause of death, the study will seek a proximate cause and underlying cause(s) of death in every case (although it is understood that it may not be possible to assign both for all deaths). The question about cardiovascular cause will be applied jointly to the proximate and underlying causes. The reason for assigning a death as cardiovascular or noncardiovascular, and the reasoning behind the adjudicator's assignment of the cause of death, will be documented.

The determination of the specific cause of cardiovascular death is complicated by the fact that the interest is particularly in one underlying cause of death (acute myocardial infarction [MI] and several modes of death (arrhythmia and heart failure/low output). It is noted that heart attack–related deaths are manifested as sudden death or heart failure, so these events need to be carefully defined.

Definition of cardiovascular death

Cardiovascular death includes death resulting from an acute MI, sudden cardiac death, death due to heart failure, death due to stroke, and death due to other cardiovascular causes, as follows:

1. **Death Due to Acute MI** refers to a death by any mechanism (arrhythmia, heart failure [HF], low output) within 30 days after a MI related to the immediate consequences of the myocardial infarction, such as progressive congestive heart failure (CHF), inadequate cardiac output, or recalcitrant arrhythmia. If these events occur after a "break" (e.g., a CHF- and arrhythmia-free period of at least a week), they should be designated by the immediate cause, even though the MI may have increased the risk of that event (e.g., late arrhythmic death becomes more likely after an acute MI). The acute MI should be verified to the extent possible by the diagnostic criteria outlined for acute MI or by autopsy findings showing recent MI or recent coronary thrombus. Sudden cardiac death, if accompanied by symptoms suggestive of myocardial ischemia, new ST elevation, new left bundle branch block (LBBB), or evidence of fresh thrombus by coronary angiography and/or at autopsy should be considered death resulting from an acute MI, even if death occurs before blood samples or 12-lead electrocardiogram (ECG) could be obtained, or at a time before the appearance of cardiac biomarkers in the blood. Death resulting from a procedure to treat a MI (percutaneous coronary intervention [PCI], coronary artery bypass graft surgery [CABG]), or to treat a complication resulting from MI, should also be considered death due to acute MI.
   Death resulting from a procedure to treat myocardial ischemia (angina) or death due to a MI that occurs as a direct consequence of a cardiovascular investigation/procedure/operation should be considered as a death due to other cardiovascular causes.

2. Sudden Cardiac Death refers to a death that occurs unexpectedly, not following an acute MI, and includes the following deaths:
   a. Death witnessed and instantaneous without new or worsening symptoms
   b. Death witnessed within 60 minutes of the onset of new or worsening cardiac symptoms, unless the symptoms suggest acute MI
   c. Death witnessed and attributed to an identified arrhythmia (e.g., captured on an ECG recording, witnessed on a monitor, or unwitnessed but found on implantable cardioverter-defibrillator review)
   d. Death after unsuccessful resuscitation from cardiac arrest
   e. Death after successful resuscitation from cardiac arrest and without identification of a noncardiac etiology (postcardiac arrest syndrome)
   f. Unwitnessed death without other cause of death (information regarding the patient's clinical status preceding death should be provided, if available)

General considerations

- A subject seen alive and clinically stable 12-24 hours prior to being found dead without any evidence or information of a specific cause of death should be classified as "sudden cardiac death." Typical scenarios include:
  - Subject well the previous day but found dead in bed the next day
  - Subject found dead at home on the couch with the television on
- Deaths for which there is no information beyond "Patient found dead at home" may be classified as "death due to other cardiovascular causes" or in some trials, "undetermined cause of death." Please see Definition of Undetermined Cause of Death, for full details.

3. **Death Due to HF or Cardiogenic Shock** refers to a death occurring in the context of clinically worsening symptoms and/or signs of heart failure without evidence of another cause of death and not following an acute MI. Note that deaths due to HF can have various etiologies, including one or more acute MIs (late effect), ischemic or nonischemic cardiomyopathy, or valve disease.

Death due to HF or Cardiogenic Shock should include sudden death occurring during an admission for worsening heart failure as well as death from progressive HF or cardiogenic shock following implantation of a mechanical-assist device.

New or worsening signs and/or symptoms of CHF include any of the following:

a. New or increasing symptoms and/or signs of HF requiring the initiation of, or an increase in, treatment directed at HF or occurring in a patient already receiving maximal therapy for HF

b. HF symptoms or signs requiring continuous intravenous therapy or chronic oxygen administration for hypoxia due to pulmonary edema

c. Confinement to bed predominantly due to HF symptoms

d. Pulmonary edema sufficient to cause tachypnea and distress **not** occurring in the context of an acute MI, worsening renal function, or as the consequence of an arrhythmia occurring in the absence of worsening heart failure

e. Cardiogenic shock not occurring in the context of an acute MI or as the consequence of an arrhythmia occurring in the absence of worsening HF

Cardiogenic shock is defined as systolic blood pressure (SBP) <90 mmHg for greater than 1 hour, not responsive to fluid resuscitation and/or heart rate correction, and felt to be secondary to cardiac dysfunction and associated with at least one of the following signs of hypoperfusion:

- Cool, clammy skin or
- Oliguria (urine output <30 ml/hour) or
- Altered sensorium or
- Cardiac index <2.2 l/min/m2

Cardiogenic shock can also be defined if SBP <90 mmHg and increases to ≥90 mmHg in less than 1 hour with positive inotropic or vasopressor agents alone and/or with mechanical support.

General Considerations

HF may have a number of underlying causes, including acute or chronic ischemia, structural heart disease (e.g., hypertrophic cardiomyopathy), and valvular heart disease. Where treatments are likely to have specific effects, and it is likely to be possible to distinguish between the various causes, then it may be reasonable to separate out the relevant treatment effects. For example, obesity drugs such as fenfluramine (pondimin) and dexfenfluramine (redux) were found to be associated with the development of valvular heart disease and pulmonary hypertension. In other cases, the aggregation implied by the definition above may be more appropriate.

4. **Death Due to Stroke** refers to death occurring up to 30 days after a stroke that is either due to the stroke or caused by a complication of the stroke.
5. **Death Due to Other Cardiovascular Causes** refers to a cardiovascular death not included in the above categories (e.g., dysrhythmia unrelated to sudden cardiac death, pulmonary embolism, cardiovascular intervention [other than one related to an acute MI], aortic aneurysm rupture, or peripheral arterial disease). Mortal complications of cardiac surgery or nonsurgical revascularization should be classified as cardiovascular deaths.

Definition of Noncardiovascular Death

Noncardiovascular death is defined as any death that is not thought to be due to a cardiovascular cause. Detailed recommendations on the classification of noncardiovascular causes of death are beyond the scope of this document. The level of detail needed and the optimum classification will depend on the nature of the study population and the anticipated number and type of noncardiovascular deaths. Any specific anticipated safety concern should be included as a separate cause of death. The following is a suggested list of noncardiovascular* causes of death:

1. **Nonmalignant Causes**
   - Pulmonary
   - Renal
   - Gastrointestinal
   - Hepatobiliary
   - Pancreatic
   - Infection (includes sepsis)
   - Noninfectious (e.g., systemic inflammatory response syndrome [SIRS])
   - Hemorrhage, not intracranial
   - Noncardiovascular system organ failure (e.g., hepatic failure)
   - Noncardiovascular surgery
   - Other noncardiovascular, specify:
   - Accidental/Trauma
   - Suicide
   - Drug overdose

* Death due to a gastrointestinal bleed should **not** be considered a cardiovascular death.

2. Malignant Causes

Malignancy should be coded as the cause of death if:

- Death results directly from the cancer; or
- Death results from a complication of the cancer (e.g., infection, complication of surgery/chemotherapy/radiotherapy); or
- Death results from withdrawal of other therapies because of concerns relating to the poor prognosis associated with the cancer.

Cancer deaths may arise from cancers that were present prior to randomization or which developed subsequently. It may be helpful to distinguish these 2 scenarios (i.e., worsening of prior malignancy, new malignancy).

Suggested categorization includes common organ systems, hematologic, or unknown.

Definition of Undetermined Cause of Death

Undetermined Cause of Death refers to a death not attributable to one of the above categories of cardiovascular death or to a noncardiovascular cause. Inability to classify the cause of death may be due to lack of information (e.g., the only available information is “patient died”) or when there is insufficient supporting information or detail to assign the cause of death. In general, the use of this category of death should be discouraged and should apply to a minimal number of patients in well-run clinical trials.

A common analytic approach for cause of death analyses is to assume that all undetermined cases are included in the cardiovascular category (e.g., presumed cardiovascular death,

specifically “death due to other cardiovascular causes”). Nevertheless, the appropriate classification and analysis of undetermined causes of death depends on the population, the intervention under investigation, and the disease process.

B. Myocardial Infarction

A nonfatal MI is an event that meets the definition below and does not result in death within 30 days from onset.

1. General Considerations

The term MI should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia.

In general, the diagnosis of MI requires the combination of:

- Evidence of myocardial necrosis (either changes in cardiac biomarkers or postmortem pathological findings); and
- Supporting information derived from the clinical presentation, ECG changes, or the results of myocardial or coronary artery imaging

The totality of the clinical, ECG, and cardiac biomarker information should be considered to determine whether or not a MI has occurred. Specifically, timing and trends in cardiac biomarkers and ECG information require careful analysis. The adjudication of MI should also take into account the clinical setting in which the event occurs. MI may be adjudicated for an event that has characteristics of a MI but which does not meet the strict definition because biomarker or ECG results are not available. Likewise, the committee may consider information based on its source and its likely reliability without requiring a specific source document; for example, if there is a note from a specialist that “troponins are increased” or “ECG suggests acute MI”, additional documentation is generally not necessary.

2. Criteria for MI

a. Clinical Presentation

The clinical presentation should be consistent with diagnosis of myocardial ischemia and infarction. Other findings that might support the diagnosis of MI should be taken into account because a number of conditions are associated with elevations in cardiac biomarkers (e.g., trauma, surgery, pacing, ablation, CHF, hypertrophic cardiomyopathy, pulmonary embolism, severe pulmonary hypertension, stroke or subarachnoid hemorrhage, infiltrative and inflammatory disorders of cardiac muscle, drug toxicity, burns, critical illness, extreme exertion, and chronic kidney disease). Supporting information can also be considered from myocardial imaging and coronary imaging. The totality of the data may help differentiate acute MI from the background disease process.

b. Biomarker Elevations

For cardiac biomarkers, laboratories should report an upper reference limit (URL). If the 99th percentile of the URL from the respective laboratory performing the assay is not available, then the URL for myocardial necrosis from the laboratory should be used. If the 99th percentile of the URL or the URL for myocardial necrosis is not available, the MI decision limit for the particular laboratory should be used as the URL. Laboratories can also report both the 99th percentile of the upper reference limit and the MI decision limit. Reference limits from the laboratory performing the assay are preferred over the manufacturer’s listed reference limits in an assay’s instructions

for use. Creatine-kinase (CK)-MB and troponin are preferred, but CK may be used in the absence of CK-MB and troponin.

For MI subtypes, different biomarker elevations for CK, CK-MB, or troponin will be important sources of information. The specific criteria will be referenced to the URL.

In many studies, particularly those in which patients present acutely to hospitals that are not participating sites, it is not practical to stipulate the use of a single biomarker or assay, and the locally available results are to be used as the basis for adjudication. However, if possible, using the same cardiac biomarker assay and preferably, a core laboratory, for all measurements reduces interassay variability.

Since the prognostic significance of different types of MIs (e.g., periprocedural MI versus spontaneous MI) may be different, consider evaluating outcomes for these subsets of patients separately.

c. Electrocardiogram (ECG) Changes

ECG changes can be used to support or confirm an MI. Supporting evidence may be ischemic changes, and confirmatory information may be new Q waves.

- **Criteria for acute myocardial ischemia (in absence of left ventricular hypertrophy [LVH] and LBBB):**
  - ST elevation
  - New ST elevation at the J point in 2 anatomically contiguous leads with the cut-off points: ≥0.2 mV in men (>0.25 mV in men <40 years) or ≥0.15 mV in women in leads V2-V3 and/or ≥0.1 mV in other leads.
  - ST depression and T wave changes
  - New horizontal or down-sloping ST depression ≥0.05 mV in 2 contiguous leads; and/or new T inversion ≥0.1 mV in 2 contiguous leads.

  The above ECG criteria illustrate patterns consistent with myocardial ischemia. In patients with abnormal biomarkers, it is recognized that lesser ECG abnormalities may represent an ischemic response and may be accepted under the category of abnormal ECG findings.

- **Criteria for pathological Q wave**
  - Any Q-wave in leads V2-V3 ≥0.02 seconds or QS complex in leads V2 and V3
  - Q-wave ≥0.03 seconds and ≥0.1 mV deep or QS complex in leads I, II, aVL, aVF, or V4-V6 in any two leads of a contiguous lead grouping (I, aVL, V6; V4-V6; II, III, and aVF). (The same criteria are used for supplemental leads V7-V9, and for the Cabrera frontal plane lead grouping.)
- **Criteria for prior MI**
  - Pathological Q waves, as defined above
  - R-wave ≥0.04 seconds in V1-V2 and R/S ≥1 with a concordant positive T-wave in the absence of a conduction defect

MI Subtypes

Several MI subtypes are commonly reported in clinical investigations and each is defined below:

a. Spontaneous MI

1) Detection of rise and/or fall of cardiac biomarkers with at least one value above the URL with at least one of the following:

- Clinical presentation consistent with ischemia
- ECG evidence of acute myocardial ischemia
- New pathological Q waves
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
- Autopsy evidence of acute MI

2) If biomarkers are elevated from a prior infarction, then a spontaneous MI is defined as:

a) One of the following:

- Clinical presentation consistent with ischemia
- ECG evidence of acute myocardial ischemia
- New pathological Q waves
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
- Autopsy evidence of acute MI

AND

b) Both of the following:

- Evidence that cardiac biomarker values were decreasing (e.g., 2 samples 3-6 hours apart) prior to the suspected MI (if biomarkers are increasing or peak is not reached, then a definite diagnosis of recurrent MI is generally not possible)
- ≥20% increase (and >URL) in troponin or CK-MB between a measurement made at the time of the initial presentation and a further sample taken 3-6 hours later

b. PCI-related MI

Peri-PCI MI is defined by any of the following criteria. Symptoms of cardiac ischemia are not required.

1) Biomarker elevations within 48 hours of PCI:

- Troponin or CK-MB (preferred) >3 × URL AND
- No evidence that cardiac biomarkers were elevated prior to the procedure;

OR

- Both of the following must be true:
  - ≥50% increase in the cardiac biomarker result (data should be collected in such a way that analyses using ≥20% or ≥50% could both be performed)
  - Evidence that cardiac biomarker values were decreasing (e.g., 2 samples 3-6 hours apart) prior to the suspected MI

2) New pathological Q waves

3) Autopsy evidence of acute MI

c. CABG-Related MI

Peri-CABG MI is defined by the following criteria. Symptoms of cardiac ischemia are

not required.

1) Biomarker elevations within 72 hours of CABG:

- Troponin or CK-MB (preferred) >5 × URL AND
- No evidence that cardiac biomarkers were elevated prior to the procedure;

OR

- Both of the following must be true:
  - ≥50% increase in the cardiac biomarker result (data should be collected in such a way that analyses using ≥20% or ≥50% could both be performed)
  - Evidence that cardiac biomarker values were decreasing (e.g., 2 samples 3-6 hours apart) prior to the suspected MI.

AND

2) One of the following:

- New pathological Q waves persistent through 30 days
- New persistent non–rate-related LBBB
- Angiographically documented new graft or native coronary artery occlusion
- Other complication in the operating room resulting in loss of myocardium
- Imaging evidence of new loss of viable myocardium

OR

3) Autopsy evidence of acute MI

4. Clinical Classification of Different Types of MI

a. Particular categories of MI will be distinguished using the following guidelines:

- Type 1

  Spontaneous MI related to ischemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection

- Type 2

  MI secondary to ischemia due to either increased oxygen demand or decreased supply (e.g., coronary artery spasm, coronary embolism, anemia, arrhythmias, hypertension, or hypotension)

- Type 3

  Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischemia, accompanied by presumably new ST elevation, or new LBBB, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood

- Type 4a

  MI associated with PCI

- Type 4b

  MI associated with stent thrombosis as documented by angiography or at autopsy

- Type 5

  MI associated with CABG

b. For each MI identified, the type of MI will also be described as:

- ST-Elevation MI (STEMI)
  - Also categorize as:
    - Q wave
    - Non–Q wave
    - Unknown (no ECG or ECG not interpretable)
- Non-ST-Elevation MI (NSTEMI)
  - Also categorize as:
    - Q wave
    - Non–Q wave
    - Unknown (no ECG or ECG not interpretable)
- Unknown (no ECG or ECG not interpretable)

C. Stroke

A nonfatal stroke is an event that meets the current classification definition below and does not result in death within 30 days from onset. Stroke will also be classified by the EAC according to historical criteria. Any recurrence or exacerbation of the condition within 30 days is considered part of the original episode, whereas beyond that time period it is considered a separate event.

Transient Ischemic Attack

Transient ischemic attack (TIA) is defined as a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction.

The distinction between a TIA and an ischemic stroke is the presence of infarction, not the transience of the symptoms. In addition to laboratory documentation of infarction, persistence of symptoms is an acceptable indicator of infarction. Thus, symptoms lasting ≤24 hours versus >24 hours may be used by the EAC to distinguish between transient ischemia and infarction. The committee will endeavor to review any relevant documentation of the cerebrovascular event. However, in the absence of documentation regarding duration of the symptoms, the committee may on occasion use any other reliable source of information such as the diagnosis of the treating physician to determine if the event was a TIA or stroke.

Stroke

1. Historical classification

   An acute disturbance of focal neurological function resulting in symptoms lasting more than 24 hours.

2. Current classification

   Stroke is defined as an acute episode of neurological dysfunction caused by focal or global brain, spinal cord, or retinal vascular injury.

   a. Ischemic stroke

      Ischemic stroke is defined as an acute episode of focal cerebral, spinal, or retinal dysfunction caused by an infarction of central nervous system tissue.

      Hemorrhage may be a consequence of ischemic stroke. In this situation, the stroke is an ischemic stroke with hemorrhagic transformation and not a hemorrhagic stroke.

   b. Hemorrhagic stroke

Hemorrhagic stroke is defined as an acute episode of focal or global cerebral or spinal dysfunction caused by a nontraumatic intraparenchymal, intraventricular, or subarachnoid hemorrhage.

c. Undetermined stroke

Undetermined stroke is defined as a stroke with insufficient information to allow categorization as ischemic or hemorrhagic.

General Considerations

Evidence of vascular central nervous system injury without recognized neurological dysfunction may be observed. Examples include microhemorrhage, silent infarction, and silent hemorrhage. When encountered, the clinical relevance of these findings may be unclear. If observed, they should be precisely defined and categorized by the EAC.

D. Hospitalized Congestive Heart Failure

HF requiring hospitalization is defined as an event that meets the following criteria:

1. Requires hospitalization defined as an admission to an inpatient unit or a visit to an emergency department that results in at least a 24-hour stay (or a date change if the time of admission/discharge is not available).

AND

2. Clinical symptoms of HF, including ≥1 of the following new or worsening conditions:

- Dyspnea
- Orthopnea
- Paroxysmal nocturnal dyspnea
- Increasing fatigue/worsening exercise tolerance

AND

3. Physical signs of HF, including ≥2 of the following:

- Edema (greater than 2+ lower extremity)
- Pulmonary crackles greater than basilar (pulmonary edema must be sufficient to cause tachypnea and distress not occurring in the context of an acute MI or as the consequence of an arrhythmia occurring in the absence of worsening HF)
- Jugular venous distension
- Tachypnea (respiratory rate >20 breaths/minute)
- Rapid weight gain
- S3 gallop
- Increasing abdominal distension or ascites
- Hepatojugular reflux
- Radiological evidence of worsening HF
- A right heart catheterization within 24 hours of admission showing a pulmonary capillary wedge pressure (pulmonary artery occlusion pressure) ≥18 mmHg or a cardiac output <2.2 l/min/m2

Note: biomarker results (e.g., brain natriuretic peptide [BNP]) consistent with CHF will be supportive of this diagnosis, but the elevation in BNP cannot be due to other conditions such as cor pulmonale, pulmonary embolus, primary pulmonary hypertension, or congenital heart

disease. Increasing levels of BNP, although not exceeding the ULN, may also be supportive of the diagnosis of CHF in selected cases (e.g., morbid obesity).

AND

4. Need for additional/increased therapy

- Initiation of, or an increase in, treatment directed at HF or occurring in a patient already receiving maximal therapy for HF and including ≥1 of the following:
    - Initiation of or a significant augmentation in oral therapy for the treatment of CHF
    - Initiation of intravenous diuretic, inotrope, or vasodilator therapy
    - Up-titration of intravenous therapy, if already on therapy
    - Initiation of mechanical or surgical intervention (mechanical circulatory support, heart transplantation or ventricular pacing to improve cardiac function), or the use of ultrafiltration, hemofiltration, or dialysis that is specifically directed at treatment of HF.

AND

5. No other noncardiac etiology (such as chronic obstructive pulmonary disease, hepatic cirrhosis, acute renal failure, or venous insufficiency) and no other cardiac etiology (such as pulmonary embolus, cor pulmonale, primary pulmonary hypertension, or congenital heart disease) for signs or symptoms is identified.

Note: it is recognized that some patients may have multiple simultaneous disease processes. Nevertheless, for the endpoint event of HF requiring hospitalization, the diagnosis of CHF would need to be the primary disease process accounting for the above signs and symptoms.

Appendix L – Cardiovascular definitions from EMPA-REG-OUTCOME trial

The following definitions were taken from the supplementary appendix of Zinman B, Wanner C, Lachin JM, et al. (2015) Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. The New England journal of medicine 373(22):2117-28.

Definition of high risk of cardiovascular events

High risk of cardiovascular events was defined as the presence of ≥1 of the following:

- History of myocardial infarction >2 months prior to informed consent
- Evidence of multi-vessel coronary artery disease i.e. in ≥2 major coronary arteries or the left main coronary artery, documented by any of the following:
    - Presence of significant stenosis: ≥50% luminal narrowing during angiography (coronary or multi-slice computed tomography)
    - Previous revascularization (percutaneous transluminal coronary angioplasty ±stent or coronary artery bypass graft >2 months prior to consent
    - The combination of revascularization in one major coronary artery and significant stenosis (≥50% luminal narrowing) in another major coronary artery
- Evidence of single-vessel coronary artery disease, ≥50% luminal narrowing during angiography (coronary or multi-slice computed tomography) not subsequently successfully revascularised, with at least 1 of the following:
    - A positive non-invasive stress test for ischemia

- Hospital discharge for unstable angina ≤12 months prior to consent
- Unstable angina >2 months prior to consent with evidence of single- or multi-vessel coronary artery disease
- History of stroke (ischemic or haemorrhagic) >2 months prior to consent
- Occlusive peripheral artery disease documented by any of the following:
  - Limb angioplasty, stenting, or bypass surgery
  - Limb or foot amputation due to circulatory insufficiency
  - Evidence of significant peripheral artery stenosis (>50% on angiography, or >50% or hemodynamically significant via non-invasive methods) in 1 limb
  - Ankle brachial index <0.9 in ≥1 ankle

Definitions of clinical outcomes

Cardiovascular death

The cause of death was determined by the principal condition that caused the death, not the immediate mode of death. Clinical Events Committee (CEC) members reviewed all available information and used their clinical expertise to adjudicate the cause of death. All deaths not attributed to the categories of CV death and not attributed to a non-CV cause were presumed CV deaths. Death certificates or summary, if possible, were provided for all patients who died, including date and details surrounding death. However, if a death certificate was the only information available for review besides the patient profile in the clinical trial database, the CEC may have decided not to use this information as cause of death if another aetiology appeared more plausible. The following definitions were used for the adjudication of fatal cases:

Sudden cardiac death

Death that occurs unexpectedly in a previously stable patient and includes the following deaths:

- Witnessed and instantaneous without new or worsening symptoms
- Witnessed within 60 minutes of the onset of new or worsening cardiac symptoms
- Witnessed and attributed to an identified arrhythmia (e.g., captured on ECG recording or witnessed on a monitor by either a medic or paramedic)
- Subjects unsuccessfully resuscitated from cardiac arrest or successfully resuscitated from cardiac arrest but who die within 24 hours without identification of a non-cardiac aetiology
- Unwitnessed death and there is no conclusive evidence of another, non-CV, cause of death (i.e. presumed CV death)

Sudden death due to acute MI (MI type 3)

Sudden death occurring up to 14 days after a documented acute MI (verified either by the diagnostic criteria outlined for acute MI or by autopsy findings showing recent MI or recent coronary thrombus) and where there is no conclusive evidence of another cause of death. If death occurs before biochemical confirmation of myocardial necrosis can be obtained, adjudication should be based on clinical presentation and ECG evidence.

Death due to heart failure or cardiogenic shock

Death occurring in the context of clinically worsening symptoms and/or signs of congestive heart failure (CHF) without evidence of another cause of death.

New or worsening signs and/or symptoms of CHF include any of the following:

- New or increasing symptoms and/or signs of heart failure requiring the initiation of, or an increase in, treatment directed at heart failure or occurring in a patient already receiving maximal therapy for heart failure
- Heart failure symptoms or signs requiring continuous intravenous therapy or oxygen administration
- Confinement to bed predominantly due to heart failure symptoms
- Pulmonary oedema sufficient to cause tachypnea and distress not occurring in the context of an acute myocardial infarction or as the consequence of an arrhythmia occurring in the absence of worsening heart failure
- Cardiogenic shock not occurring in the context of an acute MI or as the consequence of an arrhythmia occurring in the absence of worsening heart failure
    - Cardiogenic shock is defined as SBP <90 mmHg for more than 1 hour, not responsive to fluid resuscitation and/or heart rate correction, and felt to be secondary to cardiac dysfunction and associated with at least one of the following signs of hypoperfusion:
        - Cool, clammy skin
        - Oliguria (urine output < 30 mL/hour)
        - Altered sensorium
        - Cardiac index < 2.2 L/min/m^2
    - Cardiogenic shock can also be defined in the presence of SBP ≥90 mmHg or for a time period <1 hour if the blood pressure measurement or the time period is influenced by the presence of positive inotropic or vasopressor agents alone and/or with mechanical support <1 hour. The outcome of cardiogenic shock will be based on CEC assessment and must occur after randomization. Episodes of cardiogenic shock occurring before and continuing after randomization will not be part of the study outcome. This category will include sudden death occurring during an admission for worsening heart failure

Death due to stroke, cerebrovascular event

Death occurring up to 30 days after a stroke that is either due to the stroke or caused by complication of the stroke.

Death due to other CV causes

Death must be due to a fully documented CV cause not included in the above categories (e.g. dysrhythmia, pulmonary embolism, or CV intervention). Death due to a MI that occurs as a direct consequence of a CV investigation/procedure/ operation will be classified as death due to other CV cause.

Myocardial infarction (MI) (non-fatal)

The term MI should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia. Under these conditions, any one of the following criteria A to C meets the diagnosis for myocardial infarction.

Criteria A: Spontaneous MI (type 1)

To identify a type 1 MI, patients should demonstrate spontaneous symptoms of myocardial ischemia unprovoked by supply/demand inequity, together with ≥1 of the following criteria:

- Cardiac biomarker elevation: Troponin is the preferred marker for use to adjudicate the presence of acute myocardial infarction. At least one value should show a rise and/or fall above the lowest cut-point providing 10% imprecision (typically the upper reference limit for the troponin run per standard of clinical care). Creatine kinase-MB is a secondary choice to troponin; a rise of CK-MB above the local upper reference limit would be consistent with myocardial injury
- ECG changes consistent with new ischemic changes
  - ECG changes indicative of new ischemia (new ST-T changes or new left bundle branch block [LBBB]) or ECG manifestations of acute myocardial ischemia (in absence of left ventricular hypertrophy [LVH] and LBBB):
  - Development of pathological Q waves in the ECG
    - Any Q-wave in leads V2-V3 ≥0.02 seconds or QS complex in leads V2 and V3
    - Q-wave ≥ 0.03 seconds and ≥0.1 mV deep or QS complex in leads I, II, aVL, aVF, or V4-V6 in any two leads of a contiguous lead grouping (I, aVL, V6; V4-V6; II, III, and aVF)
  - ST elevation: New ST elevation at the J-point in two contiguous leads with the cut-off points: ≥0.2 mV in men or ≥ 0.15 mV in women in leads V2-V3 and/or ≥0.1 mV in other leads
  - ST depression and T-wave changes: New horizontal or down-sloping ST depression ≥0.05 mV in two contiguous leads; and/or T inversion ≥0.1 mV in two contiguous leads with prominent R-wave or R/S ratio >1
- Imaging evidence of new non-viable myocardium or new wall motion abnormality

Criteria B: "Demand" related (type 2) MI

- Patients with type 2 MI should be considered with similar diagnostic criteria as a type 1 MI, however type 2 MI should be considered present when myocardial ischemia and infarction are consequent to supply/demand inequity, rather than a spontaneous plaque rupture and coronary thrombosis.

Criteria C: Percutaneous Coronary Intervention (PCI)-related MI (type 4a/4b)

- For PCI in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL within 24 hours of the procedure are indicative of peri-procedural myocardial necrosis. By convention, increases of biomarkers >3 x 99th percentile URL (troponin or CK-MB >3 x 99th percentile URL) are consistent with PCI-related MI.
- If the cardiac biomarker is elevated prior to PCI, a ≥20% increase of the value in the second cardiac biomarker sample within 24 hours of PCI and documentation that cardiac biomarker values were decreasing (two samples ≥6 hours apart) prior to the suspected recurrent MI is consistent with PCI-related MI.
- Symptoms of cardiac ischemia are not required.

Criteria D: Coronary Artery Bypass Grafting (CABG)-related MI (type 5)

- For CABG in patients with normal baseline troponin values, elevation of cardiac biomarkers above the 99th percentile URL within 72 hours of the procedure is indicative of peri-procedural myocardial necrosis. By convention, an increase of biomarkers >5 x 99th percentile URL (troponin or CK-MB >5 x 99th percentile URL) plus at least one of the following

- New pathological Q waves in at least 2 contiguous leads on the electrocardiogram that persist through 30 days or new LBBB
- Angiographically documented new graft or native coronary artery occlusion
- Imaging evidence of new loss of viable myocardium is consistent with CABG-related MI

- If the cardiac biomarker is elevated prior to CABG, a ≥20% increase of the value in the second cardiac biomarker sample within 72 hours of CABG and documentation that cardiac biomarker values were decreasing (two samples ≥6 hours apart) prior to the suspected recurrent MI plus new pathological Q waves in ≥2 contiguous leads on the electrocardiogram or new LBBB, angiographically documented new graft or native coronary artery occlusion, or imaging evidence of new loss of viable myocardium is consistent with a peri-procedural MI after CABG. Symptoms of cardiac ischemia are not required.

Clinical classification of acute MI

For every MI identified by the CEC, one of the following will be assigned:

- Type 1: Spontaneous MI related to ischemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection
- Type 2: MI secondary to ischemia due to either increased oxygen demand or decreased supply, e.g. coronary artery spasm, coronary embolism, anaemia, arrhythmias, hypertension, or hypotension
- Type 3: Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischemia, accompanied by presumably new ST elevation, or new LBBB, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood
- Type 4a: MI associated with PCI
- Type 4b: MI associated with stent thrombosis as documented by angiography or at autopsy
- Type 5: MI associated with CABG

Heart Failure (HF) requiring hospitalization

The date of this event is the day of hospitalization of the patient including any overnight stay at an emergency room or chest pain unit. HF requiring hospitalization is defined as an event that meets all of the following criteria:

- Requires hospitalization defined as an admission to an inpatient unit or a visit to an emergency department that results in at least a 12-hour stay (or a date change if the time of admission/discharge is not available)
- Clinical manifestations of heart failure (new or worsening) including at least one of the following:
  - Dyspnoea
  - Orthopnoea
  - Paroxysmal nocturnal dyspnoea
  - Oedema
  - Pulmonary basilar crackles
  - Jugular venous distension
  - Third heart sound or gallop rhythm
  - Radiological evidence of worsening heart failure

- Additional/increased therapy: at least one of the following:
  - Initiation of oral diuretic, intravenous diuretic, inotrope, or vasodilator therapy
  - Uptitration of oral diuretic or intravenous therapy, if already on therapy
  - Initiation of mechanical or surgical intervention (mechanical circulatory support, heart transplantation or ventricular pacing to improve cardiac function), or the use of ultrafiltration, hemofiltration, or dialysis that is specifically directed at treatment of heart failure

Changes in biomarker (e.g., brain natriuretic peptide) consistent with CHF will support this diagnosis.

Coronary revascularization procedure

Either CABG or PCI (e.g., angioplasty, coronary stenting).

- CABG: the successful placement of ≥1 conduit with either a proximal and distal anastomosis or a distal anastomosis only
- PCI: Successful balloon inflation with or without stenting and the achievement of a residual stenosis <50%. The balloon inflation and/or stenting could have been preceded by device activation (e.g., angiojet, directional coronary atherectomy, or rotational atherectomy)

In cases where the procedure leads to a MI (type 4a, 4b or 5) the event will be adjudicated as an MI.

Stroke

Stroke: the rapid onset of a new persistent neurologic deficit attributed to an obstruction in cerebral blood flow and/or cerebral haemorrhage with no apparent non-vascular cause (e.g., trauma, tumour, or infection). Available neuroimaging studies are considered to support the clinical impression and to determine if there is a demonstrable lesion compatible with an acute stroke. Strokes are classified as ischemic, haemorrhagic, or unknown.

Diagnosis of stroke

For the diagnosis of stroke, the following 4 criteria should be fulfilled:

- Rapid onset of a focal/global neurological deficit with at least one of the following:
  - Change in level of consciousness
  - Hemiplegia
  - Hemiparesis
  - Numbness or sensory loss affecting one side of the body
  - Dysphasia/aphasia
  - Hemianopia (loss of half of the field of vision of one or both eyes)
  - Other new neurological sign(s)/symptom(s) consistent with stroke

NOTE: If the mode of onset is uncertain, a diagnosis of stroke may be made provided that there is no plausible non-stroke cause for the clinical presentation

- Duration of a focal/global neurological deficit ≥24 hours OR < 24 hours if this is because of at least one of the following therapeutic interventions:
  - Pharmacologic (i.e., thrombolytic drug administration)
  - Non-pharmacologic (i.e., neurointerventional procedure [e.g. intracranial angioplasty])

OR

- Available brain imaging clearly documents a new haemorrhage or infarct

OR

- The neurological deficit results in death

- No other readily identifiable non-stroke cause for the clinical presentation (e.g., brain tumour, trauma, infection, hypoglycaemia, peripheral lesion)
- Confirmation of the diagnosis by at least one of the following:
  - Neurology or neurosurgical specialist
  - Brain imaging procedure (at least one of the following):
    - CT scan
    - MRI scan
    - Cerebral vessel angiography
  - Lumbar puncture (i.e. spinal fluid analysis diagnostic of intracranial haemorrhage)

If a stroke is reported but evidence of confirmation of the diagnosis by the methods outlined above is absent, the event will be discussed at a full CEC meeting. In such cases, the event may be adjudicated as a stroke on the basis of the clinical presentation alone, but full CEC consensus is mandatory.

If the acute focal signs represent a worsening of a previous deficit, these signs must have either

- Persisted for more than one week

OR

- Persisted for more than 24 hours and were accompanied by an appropriate new CT or MRI finding

Classification of stroke

Strokes are sub-classified as follows:

- Ischemic (non-haemorrhagic): A stroke caused by an arterial obstruction due to a thrombotic (e.g., large vessel disease/atherosclerotic or small vessel disease/lacunar) or embolic aetiology. This category includes ischemic strokes with haemorrhagic transformation (i.e. no evidence of haemorrhage on an initial imaging study but appearance on a subsequent scan)
- Haemorrhagic: A stroke due to a haemorrhage in the brain as documented by neuroimaging or autopsy. This category includes strokes due to primary intracerebral haemorrhage (intraparenchymal or intraventricular) and primary subarachnoid haemorrhage
- Not assessable: The stroke type could not be determined by imaging or other means (e.g., lumbar puncture, neurosurgery, or autopsy) or no imaging was performed

Investigator-reported heart failure

Based on narrow standardised MedDRA query (SMQ) “cardiac failure”, which comprised these preferred terms: acute pulmonary oedema; cardiac failure; cardiac failure, acute; cardiac failure, chronic; cardiac failure, congestive; cardiogenic shock; cardiopulmonary failure; left ventricular failure; pulmonary oedema; right ventricular failure.