National Institute for Health and Care Excellence

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Draft for consultation

Type 2 diabetes

[A] Pharmacological therapies with cardiovascular and other benefits in people with type 2 diabetes.

NICE guideline NG28

Evidence review underpinning recommendations 1.7.4- 1.7.6, 1.7.9, 1.7.12-1.7.16, 1.7.21 and a research recommendation in the NICE guideline

September 2021

Draft for Consultation

This evidence review was developed by the Guideline Updates Team

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1.1 Review question

Which pharmacological therapies are most effective at providing cardiovascular and other benefits in addition to blood glucose control in people with type 2 diabetes?

1.1.1 Introduction

Type 2 diabetes is a chronic metabolic condition characterised by insulin resistance (that is, the body's inability to effectively use insulin) and insufficient pancreatic insulin production, resulting in high blood glucose levels (hyperglycaemia). Type 2 diabetes is commonly associated with obesity, physical inactivity, raised blood pressure, disturbed blood lipid levels and a tendency to develop thrombosis, and is therefore recognised to have an increased cardiovascular risk. Type 2 diabetes has a significant impact on lifestyle, and is associated with major long-term complications, reduced quality of life, and reduced life expectancy (by an average of 5 to 7 years). There are approximately 2.9 million people diagnosed with diabetes in the UK, 90% of adults with diabetes have type 2 diabetes, and incidence is increasing. The condition accounts for 10% of NHS expenditure with complications of type 2 diabetes leading to 5-fold increases in NHS costs and prolonged hospital stays for the individual.

Since the publication of the NICE guideline on Type 2 Diabetes in 2015 (NG28) new glucose lowering drugs (sodium-glucose co-transporter-2 (SGLT2) Inhibitors, Dipeptidyl peptidase-4 (DPP-4) inhibitors and Glucagon-like peptide-1 (GLP-1) agonists) have been licensed. The cardiovascular impact of these drugs has been assessed using a trial design whereby the drug being tested is added to a mixed background of treatments and compared to another drug or placebo on a similar mixed treatment background. These cardiovascular outcome trials (CVOTs) are different in design to trials that compare treatments to each other where everyone in a particular arm is on the same treatment and therefore cannot be combined with these trials directly for analysis. However, the results of these trials can be combined in an economic model to enable an assessment of the effectiveness and cost-effectiveness of the drugs taking the newly identified cardiovascular benefits into account.

This review was carried out to rapidly provide information about the cost-effectiveness of the new drugs, incorporating their cardiovascular benefits, and to use these results to update the pharmacological treatment pathway. Due to the need for a rapid update, the existing evidence base from NG28 has been retained unchanged and only the new evidence from the CVOTs has been added. The protocol for this review is summarised below and presented in detail in Appendix A. Studies which looked these interventions in relation to renal outcomes have been incorporated into a separate review looking at the effectiveness of these drugs in people with type 2 diabetes and chronic kidney disease.

1.1.2 Summary of the protocol

Summary of the review protocol population, intervention, comparator, and outcomes

Population	Adults (aged 18 years and older) with Type 2 diabetes
Intervention	Any of the following treatments added to mixed treatment background: • Thiazolidinedione • Sodium-glucose Cotransporter-2 (SGLT2) Inhibitors • Sulfonylurea (SU) • Glucagon-like peptide-1 (GLP-1) receptor agonists • Dipeptidyl peptidase 4 (DPP-4) inhibitors.

Comparator	Placebo or another drug added to existing therapy
Outcomes	Cardiovascular event outcomes including: • Nonfatal myocardial infarction[1] • Nonfatal stroke or atherosclerotic disease[1] • Unstable angina • Congestive heart failure • Cardiovascular related mortality • 3-point composite outcome (major adverse cardiovascular events) Additional outcomes: • All-cause mortality • Change in weight or body mass index at 1-year • Total discontinuations from each study • Discontinuations from each study due to adverse events • Severe hypoglycaemic events.
[1] Nonfatal events were extracted for inclusion in the network meta-analyses. Where nonfatal MI or stroke was not reported, or the definition was unclear in a study the closest reported outcomes (such as combined fatal **and** nonfatal MI or stroke) were extracted and assessed in pairwise analysis.	

1.1.3 Methods and process

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

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

This review adopted the following additional methods:

1. This review only looked at trials with a design of a (mixed background) versus b (mixed background). This is a different approach to NG28 (2015). In the economic model the results from NG28 have been combined with the results from this review. Please refer to appendix E of NG28 (2015) for the evidence tables of studies included in that work and the full guideline for the results of analyses undertaken at that time.
2. The drugs, routes of administration and doses included in this review are summarised in Table 1.
3. The committee agreed that for the purposes of the evidence review analyses, certain interventions would be analysed at class level (DPP-4s, insulins and sulfonylureas) and the remaining interventions at an individual level (SGLT2s and GLP-1s). All of these drugs were analysed individually in the economic model.
4. After looking at the data provided in the trials for the outcomes of interest, a decision was made about what to extract and analyse based on how the outcomes were reported in the majority of trials. These outcomes were extracted as follows:
    - hospitalisation for unstable angina rather than all unstable angina events
    - hospitalisation for heart failure rather than all heart failure events
    - nonfatal stroke rather than fatal and nonfatal stroke combined
    - nonfatal myocardial infarction rather than fatal and nonfatal myocardial infarction combined.

    The remaining outcomes were extracted for all events. To prevent double counting of fatal events (fatal MI or fatal stroke), events which would also be counted in the CV mortality outcome, the committee agreed that only nonfatal MI and nonfatal stroke events would be extracted and incorporated in an NMA. Where nonfatal MI or stroke was not reported or the definition was unclear in a study the closest reported outcomes (such as combined fatal and nonfatal MI or stroke) were extracted and assessed in pairwise analysis rather than as part of the NMAs. The committee approved of this approach.

5. The committee agreed that the where available, individual components (cardiovascular mortality, nonfatal myocardial infarction, nonfatal stroke and hospitalisation for unstable angina) should be included in the effectiveness analyses in preference to the composite trial outcomes (3- point major adverse cardiovascular events, MACE) for the purpose of network meta-analysis (see protocol deviation below).
6. For trials not reporting these individual component outcomes either because the endpoint is not adequately defined (for example if it is unclear if the event is fatal or nonfatal) or if a slightly different endpoint (combines fatal and nonfatal events), a pairwise analysis would be performed.
7. The committee reviewed the definitions of severe hypoglycaemic events used in the trials. They decided that the definition was sufficiently similar in 13 trials to compare the results in network meta-analysis. The 3 remaining trials (EXAMINE, TECOS and EXSCEL), which differed by specifying that medical intervention (for example hospitalisation) were required, were analysed in a pairwise manner (see section 1.1.6 Table 7 and Table 9).
8. The committee agreed that for the 4 trials which randomised participants to more than 1 dose of active treatment compared to a placebo arm (CANVAS program, EMPA-REG, SUSTAIN-6 and VERTIS-CV), pooled outcome data for the doses could be used for the purposes of the network meta-analysis. The committee agreed that as all the doses used were within the normal range of doses prescribed in practice, and as the doses in the remaining studies in many cases were target doses (doses were titrated to maximum tolerated dose) that this may represent variation in clinical practice.
9. The committee initially identified the outcomes 'total number of dropouts' for any reason and 'dropouts due to adverse events'. Having reviewed the terms used in the included trials the committee agreed to revise the outcomes using the terms 'discontinuation for any reason' and 'discontinuation due to adverse events'.
10. The quality of the evidence for each outcome was assessed using GRADE for the pairwise analyses of comparisons that were not included in the NMA and using a modified form of GRADE for the NMA (see methods in appendix B and results in appendix I).
11. For outcomes with event data presented as risk ratios (RRs) and Hazard ratios (HRs), the committee did not specify particular minimal clinically important differences (MIDs) and the default of 0.8, 1.25 are used (see protocol deviation).
12. The interpretation of NMA and pairwise data used in the summary NMA and pairwise tables is as follows:
    - Improvements in outcomes are represented by two situations:
        - the 95% CI does not cross the line of no effect and the effect estimate meets or exceeds the MID (marked in **bold** text in Table 3)
        - the 95% CI does not cross the line of no effect and the effect estimate is less than the MID (marked in non-bold text in Table 3)
    - Some of the data could not differentiate between treatments (the 95% CI crosses the line of no effect, and it is not completely between the MID, i.e., it crosses one or both MIDs)
    - In other situations, the difference was not meaningful (the 95% CI is completely between the MID).
    - Treatment effects equal to or greater than the MID 0.8, 1.25 were treated as clinically meaningfully.
    - 95% confidence intervals starting or ending with 1.0 were treated as crossing the line of no effect.
    - 95% confidence intervals including 0.8 or 1.25 were downgraded once for imprecision or twice if they included both 0.8 and 1.25.

Protocol deviation

1. The committee requested that the 3 -point MACE outcome be presented in addition to the individual components in the NMA analyses after the protocol was signed off (see section 1.1.11 for details).

Table 1 Acceptable drugs, routes of administration and doses for this review

Drug class	Drug	Route of administration	Recommended daily doses (or weekly dose)
Biguanides	Metformin	Oral	500 to 3000 mg
	Metformin MR	Oral	500 to 2000 mg
Dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors)	Linaglitpin	Oral	5 mg
	Saxagliptin	Oral	5 mg
	Sitagliptin	Oral	100 mg
	Vildagliptin	Oral	100 mg
	Alogliptin	Oral	25 mg
Sulfonylureas	Gliclazide	Oral	40 to 320 mg
	Gliclazide MR	Oral	30 to 120 mg
	Glimepiride	Oral	1 to 6 mg
	Glipizide	Oral	2.5 to 20 mg
	Tolbutamide	Oral	500 to 2000 mg
Thiazolidinediones	Pioglitazone	Oral	15 to 45 mg
Glucagon-like peptide-1 mimetics (GLP-1 mimetics)	Exenatide	Subcutaneous	10 to 20 mcg
	Exenatide MR	Subcutaneous	2 mg once weekly
	Liraglutide	Subcutaneous	0.6 to 1.8 mg
	Lixisenatide	Subcutaneous	10 to 20 mcg
	Dulaglutide	Subcutaneous	0.75 to 4 mg once weekly
	Semaglutide	Subcutaneous	0.25 mg to 1 mg once weekly
		Oral	3 mg to 14 mg
Sodium -glucose co-transporter 2 (SGLT2)	Canagliflozin	Oral	100 to 300 mg
	Dapagliflozin	Oral	10 mg
	Ertugliflozin	Oral	5 to 15 mg
	Empagliflozin	Oral	10 to 25 mg

1.1.4 Effectiveness evidence

1.1.4.1 Included studies

A search to update the NICE guideline on type 2 diabetes (NG28) was undertaken and included 18,333 references which were screened using EPPI-Reviewer software. Priority screening function was used with stopping rules for the CV outcomes review of at least 50% of references screened and at least 1,000 records sifted without a further included trial (sifting stopped at 9,167).

A further 10% random sample of the results were checked (see review protocol for full details). In total 166 results were identified and full text articles of all these were retrieved and checked for inclusion. The evidence search identified 16 double-blind, randomised controlled trials. In 15 trials the intervention was compared with placebo and in 1 trial against an active

comparator. All the trials were conducted across multiple countries and trial sites. As per the review protocol committee members were invited to review the included studies for completeness. The search found no cardiovascular outcome trial (CVOT) evidence for the biguanide class (metformin or metformin modified release), sulfonylureas other than glimepiride (for example gliclazide, glipizide or tolbutamide) and the DPP-4 inhibitor (vildagliptin).

For further details of the included studies please see section 1.1.5 and for details of the literature search please see Appendix C.

1.1.4.2 Excluded studies

For studies excluded from this evidence review with reasons for exclusion please see Appendix M.

1.1.5 Summary of studies included in the effectiveness review

Table 2 Summary of characteristics of the studies included in the effectiveness review (See bottom of table for abbreviations.)

Primary study paper and trial name (study type and no. of countries)	Sample size	Intervention (drug class, mode of administration)	Comparator (drug class, mode of administration)	Population	Duration of follow-up	Outcomes of interest[1]
Dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors)						
Green et al 2015 TECOS (DB, PC, RCT 38 countries)	14,671	Sitagliptin 100 mg (DPP-4, oral[2])	Placebo	Adults with T2D aged ≥50 years with HbA1c of 48-64 mmol/mol (6.5% - 8.0%) with established CVD. Those with an eGFR <30 were excluded.	Median 3.0 years	• CV mortality • MI • Stroke • Hospitalisation for heart failure • Hospitalisation for unstable angina • All-cause mortality • Weight/BMI • Severe hypoglycaemia • Any discontinuation • Discontinuation due to adverse events • 3-point MACE •
Rosenstock et al 2019 CARMELINA (DB, PC, RCT 27 countries)	6,991	Linagliptin 5 mg (DPP-4, once daily oral)	Placebo	Adults with T2D with an HbA1c of 48-86 mmol/mol (6.5% - 10%) with established, or risk factors for, CVD or renal risk factors (only those with eGFR <15 or on dialysis were excluded).	Median 2.2 years	• CV mortality • MI • Stroke • Hospitalisation for heart failure • Hospitalisation for unstable angina • All-cause mortality • Weight/BMI • Severe hypoglycaemia

Primary study paper and trial name (study type and no. of countries)	Sample size	Intervention (drug class, mode of administration)	Comparator (drug class, mode of administration)	Population	Duration of follow-up	Outcomes of interest[1]
						• Any discontinuation • Discontinuation due to adverse events • 3-point MACE
Rosenstock et al 2019 CAROLINA (DB, RCT 43 countries)	6,033	Linagliptin 5 mg (DPP-4, once daily oral)	Glimepiride 4 mg (SU, once daily oral)	Adults with T2D and a HbA1c of 48-70 mmol/mol (6.5% - 8.5%) with established, or risk factors for, CVD or renal risk factors (no exclusions for renal disease reported).	Median 6.3 years	• CV mortality • MI • Stroke • Hospitalisation for heart failure • Hospitalisation for unstable angina • All-cause mortality • Weight/BMI • Severe hypoglycaemia • Any discontinuation • Discontinuation due to adverse events • 3-point MACE
Scirica et al 2013 SAVOR-TIMI 53 (DB, PC, RCT 26 countries)	16,492	Saxagliptin 5 mg[3] (DPP-4, oral[2])	Placebo	Adults with T2D aged ≥40 years with a HbA1c of 48-108 mmol/mol (6.5% - 12%) with established CVD or be older and have risk factors for CVD. Those with end stage renal disease, having had dialysis or transplantation, or who had a serum creatinine above 6.0 mg per decilitre were excluded.	Median 2.1 years	• CV mortality • MI • Stroke • Hospitalisation for heart failure • Hospitalisation for unstable angina • All-cause mortality • Weight/BMI • Severe hypoglycaemia • Any discontinuation • 3-point MACE
White et al 2013	5,380	Alogliptin 25 mg[4]	Placebo	Participants with T2D with an acute coronary syndrome	Median 18 months	• CV mortality

Primary study paper and trial name (study type and no. of countries)	Sample size	Intervention (drug class, mode of administration)	Comparator (drug class, mode of administration)	Population	Duration of follow-up	Outcomes of interest[1]
EXAMINE (DB, PC, RCT 49 countries)		(GLP-1, oral[2])		within the preceding 15 to 90 days (no exclusions for renal disease reported).		• MI • Stroke • Hospitalisation for heart failure • Hospitalisation for unstable angina • All-cause mortality • Weight/BMI • Severe hypoglycaemia • Any discontinuation • Discontinuation due to adverse events • 3-point MACE[5]
Glucagon-like peptide-1 mimetics (GLP-1 mimetics)						
Holman et al 2017 EXSCEL (DB, PC, RCT 35 countries)	14,752	Exenatide 2 mg (GLP-1, once weekly subcutaneous injection)	Placebo	Adults with T2D with a HbA1c of 48-86 mmol/mol (6.5% - 10%), trial designed so that 70% of the population had established CVD. Those with an eGFR <30 were excluded.	Median 3.2 years	• CV mortality • MI • Stroke • Hospitalisation for heart failure • All-cause mortality • Weight/BMI • Severe hypoglycaemia • Any discontinuation • Discontinuation due to adverse events • 3-point MACE
Husain et al 2019 PIONEER-6 (DB, PC, RCT 21 countries)	3,183	Semaglutide 14 mg (GLP-1, once daily oral tablet)	Placebo	Adults with T2D aged ≥50 years with established CVD or renal disease, or aged ≥60 years with CVD risk factors (no exclusions for renal disease reported).	Median 15.9 months	• CV mortality • MI • Stroke • Hospitalisation for heart failure • Hospitalisation for unstable angina

Primary study paper and trial name (study type and no. of countries)	Sample size	Intervention (drug class, mode of administration)	Comparator (drug class, mode of administration)	Population	Duration of follow-up	Outcomes of interest[1]
						• All-cause mortality • Weight/BMI • Severe hypoglycaemia • Any discontinuation • Discontinuation due to adverse events • 3-point MACE
Gerstein et al 2019 REWIND (DB, PC, RCT 24 countries)	9,901	Dulaglutide 1.5 mg (GLP-1, once weekly subcutaneous injection)	Placebo	Adults with T2D aged ≥50 years with a HbA1c ≤81 mmol/mol (≤9.5%) with established CVD or aged ≥60 years with CVD risk factors. Those with an eGFR ≤15 were excluded.	Median 5.4 years	• CV mortality • MI • Stroke • Hospitalisation for heart failure • Hospitalisation for unstable angina • All-cause mortality • Weight/BMI • Severe hypoglycaemia • Any discontinuation • 3-point MACE
Marso et al 2016 LEADER (DB, PC, RCT 32 countries)	9,340	Liraglutide 1.8 mg (GLP-1, once daily subcutaneous injection)	Placebo	Adults with T2D aged ≥50 years with a HbA1c ≥53 mmol/mol (≥7.0%) and ≥1 CVD or ≥60 years with CVD risk factors (no exclusions for renal disease reported).	Median 3.8 years	• CV mortality • MI • Stroke • Hospitalisation for heart failure • Hospitalisation for unstable angina • All-cause mortality • Weight/BMI • Severe hypoglycaemia • Discontinuation due to adverse events • 3-point MACE

Primary study paper and trial name (study type and no. of countries)	Sample size	Intervention (drug class, mode of administration)	Comparator (drug class, mode of administration)	Population	Duration of follow-up	Outcomes of interest[1]
Marso et al 2016 SUSTAIN-6 (DB, PC, RCT 20 countries)	3,297	Semaglutide 0.5 mg or 1.0 mg (GLP-1, once weekly subcutaneous injection)	Placebo	Adults with T2D aged ≥50 years with HbA1c ≥53 mmol/mol (≥7%) with established CVD or renal disease, or aged ≥60 years with CVD risk factors (no exclusions for renal disease reported).	Planned 109-week treatment and follow-up period.	• CV mortality • MI • Stroke • Hospitalisation for heart failure • Hospitalisation for unstable angina • All-cause mortality • Weight/BMI • Severe hypoglycaemia • Any discontinuation • Discontinuation due to adverse events • 3-point MACE
Pfeffer et al 2015 ELIXA (DB, PC, RCT 49 countries)	6,068	Lixisenatide 10 – 20 mg (GLP-1, once daily subcutaneous injection)	Placebo	Adults with T2D aged ≥30 years and an acute coronary event in the preceding 180 days. Those with an eGFR <30 were excluded.	Median 25 months	• CV mortality • MI • Stroke • Hospitalisation for heart failure • Hospitalisation for unstable angina • All-cause mortality • Weight/BMI • Severe hypoglycaemia • Any discontinuation • Discontinuation due to adverse events
Sodium -glucose co-transporter 2 (SGLT2) studies						
Cannon et al 2020 VERTIS-CV (DB, PC, RCT	8,246	Ertugliflozin 5 mg or 15 mg (SGLT2, oral[2])	Placebo	Adults with T2D aged ≥40 years with a HbA1c of 53-92 mmol/mol (7.0% - 10.5%) and	Mean 3.5 years	• CV mortality • MI • Stroke

Primary study paper and trial name (study type and no. of countries)	Sample size	Intervention (drug class, mode of administration)	Comparator (drug class, mode of administration)	Population	Duration of follow-up	Outcomes of interest[1]
34 countries)				established CVD. Those with an eGFR <30 were excluded.		• Hospitalisation for heart failure • All-cause mortality • Weight/BMI • Severe hypoglycaemia • Any discontinuation • 3-point MACE
Mahaffey et al 2018 CANVAS program (DB, PC, RCT 30 countries)	10,142 4,330 (CANVAS) 5,812 (CANVAS-R)	Canagliflozin 100 mg or 300 mg (SGLT2, oral[2])	Placebo	Adults with T2D aged ≥30 years with a history of CVD or aged ≥50 years with ≥2 or more CVD risk factors. The study excluded people with an eGFR <30.	Mean 188.2 weeks	• CV mortality • MI • Stroke • Hospitalisation for heart failure • All-cause mortality • Weight/BMI • Severe hypoglycaemia • Any discontinuation • Discontinuation due to adverse events • 3-point MACE
Wiviott et al 2019 DECLARE-TIMI 58 (DB, PC, RCT 33 countries)	17,160	Dapagliflozin 10 mg (SGLT2, oral)	Placebo	Adults with T2D aged ≥40 years with a HbA1c of 48-108 mmol/mol (6.5% - 12%) and a creatinine clearance of ≥60 ml/minute.	Median 4.2 years	• CV mortality • MI • Stroke • Hospitalisation for heart failure • All-cause mortality • Weight/BMI • Severe hypoglycaemia • Any discontinuation • Discontinuation due to adverse events • 3-point MACE

Primary study paper and trial name (study type and no. of countries)	Sample size	Intervention (drug class, mode of administration)	Comparator (drug class, mode of administration)	Population	Duration of follow-up	Outcomes of interest[1]
Zinman et al 2015 EMPA-REG (DB, PC, RCT 42 countries)	7,020	Empagliflozin 10 mg or 25 mg (SGLT2, oral[2])	Placebo	Adults with T2D aged ≥18 years and with a BMI ≤45 and established CVD. Those with an eGFR <30 were excluded.	Median 3.1 years	• CV mortality • MI • Stroke • Hospitalisation for heart failure • Hospitalisation for unstable angina • All-cause mortality • Weight/BMI • Severe hypoglycaemia • Any discontinuation • Discontinuation due to adverse events • 3-point MACE
Thiazolidinediones						
Wilcox et al 2008 PROactive (DB, PC, RCT 19 European countries)	5,238	Pioglitazone 15 mg to 45 mg[6] (Thiazolidinedione, oral)	Placebo	Adults with T2D aged 35 to 75 years with a HbA1c >48 mmol/mol (>6.5%) with established macrovascular disease. Those having had haemodialysis were excluded.	Mean 34.5 months	• CV mortality • MI • Stroke • All-cause mortality • Weight/BMI • Severe hypoglycaemia • Any discontinuation • Discontinuation due to adverse events • 3-point MACE

***Abbreviations**: DB, Double blind; PC, Placebo controlled; RCT, Randomised Controlled Trial, mg, Milligrams; T2D, Type 2 diabetes; CV or CVD, Cardiovascular or cardiovascular disease; eGFR, Estimated glomerular filtration rate (ml per minute per 1.73 m^2 of body surface area); HbA1c, Glycated haemoglobin; ml, Millilitre; BMI, Body mass index (Kg/m^2); MI, Myocardial infarction; SU= Sulphonylurea; DPP-4, Dipeptidyl peptidase-4 inhibitors; GLP-1, glucagon-like peptide 1; SGLT2, sodium-glucose co-transporter-2 inhibitors.

[1] These outcomes are the ones specified in the review protocol (see Appendix A).

Primary study paper and trial name (study type and no. of countries)	Sample size	Intervention (drug class, mode of administration)	Comparator (drug class, mode of administration)	Population	Duration of follow-up	Outcomes of interest[1]
[2] Not stated if oral in study but available as tablet in BNF. [3] Dose adjusted according to eGFR either 2.5 mg (eGFR ≤50 ml/minute) or 5 mg [4] Dose adjusted according to eGFR either 6.25 mg, 12.5 mg or 25 mg daily. [5] 3-point MACE data not included in NMA as 95% confidence interval was not reported. [6] Titrated according to tolerability.						

1 See Appendix E for full evidence tables.

1.1.6 Summary of the effectiveness evidence

Network meta-analysis (NMA) summary tables

Table 3 Summary of NMA results with GRADE quality ratings showing where treatments are better than another treatment based on the use of MIDs.

The following outcomes use the default MIDs of 0.8, 1.25. The columns list the treatments, and the rows list the outcomes. Within each box, the treatments listed represent results where there was an improvement in that outcome (the text in **bold** represents situations where the 95% CI does not cross the line of no effect **and** the effect treatment point estimate meets or exceeds the MID; the text which is not bold represents situations where the 95% CI does not cross the line of no effect **and** the effect point estimate of the treatment is less than the MID). Results have been reversed where necessary to ensure that they are presented as improvements. Boxes with dashes represent cases where the NMA could not differentiate between treatments (the 95% CI crosses the line of no effect, and it is not completely within the MID) or in cases where the difference was not meaningful (the 95% CI is completely within the MID).

Abbreviations are as follows: PLAC, Placebo; PIO, Pioglitazone; LIXI, Lixisenatide; LIRA, Liraglutide; EXEN, Exenatide; ERTU, Ertugliflozin; EMPA, Empagliflozin; DULA, Dulaglutide; DPP-4, Dipeptidyl peptidase-4 inhibitors; DAPA, Dapagliflozin; CANA, Canagliflozin; SU, Sulphonylurea; SEMAo, Oral semaglutide; SEMAi, Injected semaglutide. N/A is used when the treatment was not represented in the NMA. See section 1.1.3 for more details on the interpretation of results.

TREATMENTS															
OUTCOME	**PLAC**	**CANA**	**DPP-4**	**DAPA**	**LIXI**	**EMPA**	**EXEN**	**LIRA**	**SEMAo**	**SEMAi**	**PIO**	**DULA**	**ERTU**	**SU**	**GRADE Quality**
IMPROVEMENTS COMPARED TO:															
All-cause mortality	-	**SU**	-	-	-	**SU DPP-4 PLAC CANA DAPA DULA**	**SU** DPP-4 PLAC	**SU** DPP-4 PLAC	**SU DPP-4 PLAC CANA DAPA DULA**	-	-	SU	-	-	High

TREATMENTS															
OUTCOME	**PLAC**	**CANA**	**DPP-4**	**DAPA**	**LIXI**	**EMPA**	**EXEN**	**LIRA**	**SEMAo**	**SEMAi**	**PIO**	**DULA**	**ERTU**	**SU**	**GRADE Quality**
						ERTU EXEN LIXI PIO SEMAi			**ERTU EXEN LIXI PIO SEMAi**						
Cardiovascular mortality	-	**-**	-	-	-	**SU DPP-4 PLAC CANA DAPA LIXI DULA ERTU EXEN PIO**	-	**DPP-4 PLAC**	**SU DPP-4 PLAC DAPA LIXI**	-	-	-	-	-	High
Any discontinuation	**SEMAo**	**SEMAo** LIXI	**SEMAo** SEMAi **LIXI**	**SEMAo SEMAi LIXI** CANA PIO	**SEMAo** SU	**SEMAo SEMAi LIXI** CANA PIO DULA EXEN SU **PLAC**	**SEMAo** SEMAi LIXI	N/A	-	**SEMAo**	**SEMAo**	**SEMAo** SEMAi LIXI	**SEMAo SEMAi LIXI** CANA PIO SU PLAC	**SEMAo** SEMAi LIXI	High
Discontinuation due to advers	**SEMAo SEMAi LIXI CANA** DAPA **LIRA**	**SEMAi**	**SEMAo SEMAi LIXI CANA DAPA LIRA**	**SEMAo SEMAi LIXI**	**-**	**SEMAo SEMAi LIXI CANA DAPA LIRA**	**SEMAo SEMAi LIXI CANA LIRA**	**SEMAo SEMAi**	-	-	**SEMAo SEMAi LIXI**	N/A	**SEMAo SEMAi LIXI CANA**	**SEMAo SEMAi LIXI CANA LIRA**	High

TREATMENTS															
OUTCOME	**PLAC**	**CANA**	**DPP-4**	**DAPA**	**LIXI**	**EMPA**	**EXEN**	**LIRA**	**SEMAo**	**SEMAi**	**PIO**	**DULA**	**ERTU**	**SU**	**GRADE Quality**
e events			**PIO**			**PIO**									
Hospitalisation for heart failure	-	**DPP-4 PLAC**	-	**DPP-4 PLAC**	-	**DPP-4 PLAC**	-	-	-	-	N/A	-	**DPP-4**	-	Moderate
Hospitalisation for unstable angina	-	N/A	-	N/A	-	-	N/A	-	-	-	N/A	-	N/A	-	Moderate
Nonfatal MI	-	**DPP-4**	-	N/A	N/A	-	-	**DPP-4**	-	-	-	-	-	-	High
Nonfatal stroke	-	-	-	N/A	N/A	-	-	-	-	**EMPA PLAC**	N/A	**EMPA PLAC**	-	-	High
Severe hypoglycaemia	**SU**	**SU**	**SU**	**SU PLAC DPP-4 PIO SEMAi SEMAo**	**SU PIO SEMAo**	**SU**	N/A	**SU PLAC DPP-4 PIO SEMAi SEMAo**	**SU**	**SU**	**SU**	**SU**	**SU DPP-4**	-	High
3-POINT mace	-	DPP-4 PLAC	-	-	N/A	PLAC	-	DPP-4 PLAC	-	**DPP-4 PLAC SU**	DPP-4 PLAC	PLAC	-	-	High

See Appendix G for the NMA results, Appendix I for full GRADE tables and section 1.1.11.3 Benefits and harms: discussion of the NMA and pairwise analysis results for more information.

Pairwise meta-analysis summary GRADE tables

These tables only show the pairwise results for treatments that could not be included in the relevant NMA. The results are interpreted as follows:

- The evidence could not differentiate between treatments where the 95% CI crosses the line of no effect, and it is not completely between the MID, (i.e., it crosses one or both MIDs).
- There was no meaningful difference where the 95% CI is completely between the MID.

See section 1.1.3 for more details on the interpretation of results and the other categories (effects greater or less than the MID and clinically meaningful effects).

Dapagliflozin versus placebo

Table 4 Dapagliflozin versus placebo

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk intervention (95% CI)	Interpretation	Quality
Myocardial infarction (unclear if fatal or nonfatal)							
1[a]	RCT	17,160	HR 0.89 (0.78 to 1.02)	51 per 1000	45 per 1000 (40 to 52)	The evidence could not differentiate between comparators for myocardial infarction.	Moderate
Ischaemic stroke (unclear if fatal or nonfatal)							
1[a]	RCT	17,160	HR 1.01 (0.84 to 1.21)	27 per 1000	27 per 1000 (23 to 33)	The evidence found no meaningful difference between comparators for stroke.	High
[a] Wiviott et al 2019 (DECLARE-TIMI 58)							

Saxagliptin versus placebo

Table 5 Saxagliptin versus placebo

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk intervention (95% CI)	Interpretation	Quality
Myocardial infarction (unclear if fatal or nonfatal)							
1[a]	RCT	16,492	HR 0.95 (0.80 to 1.12)	34 per 1000	32 per 1000 (27 to 38)	The evidence could not differentiate between comparators for myocardial infarction.	Moderate

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk intervention (95% CI)	Interpretation	Quality
Stroke (unclear if fatal or nonfatal)							
1[a]	RCT	16,492	HR 1.11 (0.88 to 1.40)	17 per 1000	19 per 1000 (15 to 24)	The evidence could not differentiate between comparators for stroke.	Moderate
[a] Scirica et al 2013 (SAVOR-TIMI 53)							

Lixisenatide versus placebo

Table 6 Lixisenatide versus placebo

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk intervention (95% CI)	Interpretation	Quality
Myocardial infarction (fatal and nonfatal)							
1[a]	RCT	6,068	HR 1.03 (0.87 to 1.22)	86 per 1000	89 per 1000 (75 to 105)	The evidence found no meaningful difference between comparators for myocardial infarction.	High
Stroke (fatal and nonfatal)							
1[a]	RCT	6,068	HR 1.12 (0.79 to 1.58)	20 per 1000	22 per 1000 (16 to 32)	The evidence could not differentiate between comparators for stroke.	Low
[a] Pfeffer et al 2013 (ELIXA)							

DPP-4 versus placebo

Table 7 DPP-4 versus placebo

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk intervention (95% CI)	Interpretation	Quality
Sitagliptin							
Myocardial infarction (fatal and nonfatal)							

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk intervention (95% CI)	Interpretation	Quality
1[a]	RCT	14,671	HR 0.95 (0.81 to 1.11)	43 per 1000	41 per 1000 (35 to 48)	The evidence found no meaningful difference between comparators for myocardial infarction.	High
Stroke (fatal and nonfatal)							
1[a]	RCT	14,671	HR 0.97 (0.79 to 1.19)	25 per 1000	24 per 1000 (20 to 30)	The evidence could not differentiate between comparators for stroke.	Moderate
DPP-4 (Sitagliptin; Alogliptin)							
Severe hypoglycaemia							
2[a,b]	RCT	19,903	RR 1.15 (0.92 to 1.44)	14 per 1000	16 per 1000 (13 to 20)	The evidence could not differentiate between comparators for severe hypoglycaemia.	Moderate
[a] Green et al 2013 (TECOS) [b] White et al 2013 (EXAMINE)							

Pioglitazone versus placebo

Table 8 Pioglitazone versus placebo

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk intervention (95% CI)	Interpretation	Quality
Stroke (not further defined)							
1[a]	RCT	5,238	HR 0.81 (0.61 to 1.07)	41 per 1000	33 per 1000 (25 to 44)	The evidence could not differentiate between comparators for stroke.	Moderate
[a] Wilcox et al 2008 (PROactive)							

1 ***Exenatide versus placebo***

2 **Table 9 Exenatide versus placebo**

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk intervention (95% CI)	Interpretation	Quality
Severe hypoglycaemia							
1[a]	RCT	14,716	RR 1.13 (0.95 to 1.35)	30 per 1000	34 per 1000 (29 to 41)	The evidence could not differentiate between comparators for severe hypoglycaemia.	Moderate
[a] Holman et al 2017 (EXSCEL)							

3 See Appendix I for full GRADE tables.

1.1.7 Economic evidence

A systematic review was conducted to identify economic evaluations for this review question. A date filter was applied to exclude papers which were incorporated in the previous iteration of the guideline and the search was based on the clinical search with a health economic filter applied. The search yielded 382 unique citations.

In order to assist the committee's decision making it was specified that only UK based studies should be included. As the scope of the guideline includes a wide variety of drug classes, it was felt that multiple pairwise cost-utility analyses (CUAs), with varying underlying models would hinder, as opposed to aid decision making. Hence only studies which included all comparators of interest were included. The committee also stressed the importance of incorporating evidence directly from CVOTs where available as opposed to using surrogate models, which have been shown to perform poorly (Si et al. 2020) and do not appear to fully capture the treatment effects for newer drug classes.

This search criteria resulted in 0 CUAs being included.

It is somewhat surprising that despite the proliferation of CVOTs no existing CUAs provide comparisons between all treatment classes. Whilst they did not reach the threshold for inclusion based on the pairwise nature of the analysis, three studies were found which employed a similar hybrid approach of surrogate modelling combined with direct CVOT trial results.

Ramos et al. (2019) compared the cost-effectiveness of empagliflozin compared with sitagliptin or saxagliptin. The IQVIA Core Diabetes Model (CDM) was calibrated to replicate CVOT hazard ratios until a patient reached the HbA1c intensification threshold (70 mmol/mol or 8.5%). After this point the UKPDS risk equations were applied. Empagliflozin was found to be cost-effective versus both sitaglitpin and saxagliptin, with results robust to sensitivity analysis. This study was funded by the manufacturer of empagliflozin.

Ramos et al. (2020) compared the cost-effectiveness of empagliflozin + standard of care (SoC) with liraglutide + SoC and SoC in patients with established cardiovascular disease. The CDM was calibrated to replicate outcomes from the EMPA-REG and LEADER trials with the treatment effect applied until a patient reached the HbA1c intensification threshold (70 mmol/mol or 8.5%). Empagliflozin +SoC dominated liraglutide + SoC and empagliflozin + SoC was associated with a base-case ICER of £6428 versus SoC alone. A minimum approach to estimate utilities was applied, meaning that for a patient with a history of multiple events the lowest value was used. The study was funded by the manufacturers of empagliflozin.

McEwan et al. (2020) assessed the cost-effectiveness of SGLT2 inhibitors using clinical trial and real-world evidence. The Cardiff T2 model was adapted to incorporate the survival curves from real-world studies and trials involving SGLT2s. In a UK setting SGLT2s were found to be highly cost-effective in a UK setting. It is notable that the majority of the cost reduction using SGLT2s was as a result of reduced CKD (including ESRD). The study was funded by the manufacturers of dapagliflozin.

Further details of excluded studies are outlined in Appendix M.

1.1.8 Summary of included economic evidence

As outlined in Section 1.1.7, no directly applicable CUAs including all interventions were identified for this review question. For this reason, an original economic model was developed to support the guideline.

1.1.9 Economic model

The economic model comprises of two modules which incorporate the evidence from the cardiovascular outcome trials (CVOTs) alongside evidence for treatments without CVOTs taken from NG28.

The committee felt that where available, the modelling of direct CVOT outcomes (such as MI or stroke) was more informative for decision making as opposed to the traditional modelling of surrogate outcomes (such as HbA1c) commonly employed in diabetes modelling.

This cost-utility analysis has a time horizon of 40 years, uses an NHS and personal social services perspective and a discount rate of 3.5% for both costs and QALYs.

Interventions are explored both as additions to the standard care comparator treatments and as replacements of components of standard care. As well as the total population, four subgroups are modelled.

Interventions: Anti-diabetic treatments studied in cardiovascular outcome trials (CVOTs), expected to include:

- DPP-4 inhibitors (sitagliptin, saxagliptin, lingagliptin, alogliptin)
- GLP-1 receptor agonists (exenatide, liraglutide, lixisenatide, dulaglutide, semaglutide (injectable), semaglutide (oral))
- SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin)
- Pioglitazone

Comparators: Some treatments modelled in NG28 that have not been studied in CVOT trials. Comparators differ by level of treatment intensification:

- Initial therapy (metformin/ placebo)
- First intensification (metformin/ metformin + sulfonylurea)
- Second intensification (metformin + NPH insulin /metformin + sulfonylurea + NPH insulin)

Subgroups:

- High BMI
- Primary prevention - Patients with high cardiovascular risk based on cardiovascular risk factors
- Secondary prevention - Patients with a history of cardiovascular events
- High CV Risk – a combination of primary a secondary prevention

For non-CVOT treatments an implementation of the UKPDS risk equations was developed and used the surrogate biomarker changes extracted for the NG28 clinical review to predict baseline event rates over time to which the CVOT hazard ratios are applied. Cardiovascular events (MI, stroke, IHD and CHF) and microvascular events (Blindness, Amputation and Ulcers) and renal failure are modelled for the non-CVOT drugs, with hazard ratios extracted from the clinical review for MI, stroke, IHD and CHF applied to the CVOT drugs.

Short term in-year events are also modelled. Costs and QALYs relating to rates of hypoglycaemia, treatment-related change in BMI and injections are applied to living patients in each modelled year and relevant costs and QALYs are applied.

In order to apply the CVOT hazard the UKPDS individual patient-level outputs are converted to states in a multi-state model which allows full incorporation of all CVOT hazard ratios.

The multi-state model contains states which track events and history of events (e.g. the state of suffering an in-year MI with a history of heart failure is different to the state of suffering an in-year MI with no event history). This structure allows the direct application of CVOT hazard ratios to align with the outcomes the committee valued most highly.

At £20,000-£30,000 per QALY gained, the only drugs cost-effective in any of the base-case analyses were the SGLT2s. Table 10 to Table 15 outline the ICERs for the CVOT interventions compared to non-CVOT regimens for each intensification level, stratified into scenarios where the CVOT replaces a component of the non-CVOT regimen and where the CVOT is added to the non-CVOT regimen. Results are presented for all subgroups. Net monetary benefit rankings are presenting in the column next to the ICERs. Note that the net monetary benefit ranking of the non-CVOT regimen is not shown in the table below. See the health economic model report for further details on the methods and economic model results.

Sensitivity analyses were used to explore the effect of removing parameters associated with uncertainty that were known drivers of the results. The sensitivity analyses performed showed that removing hypos makes pioglitazone highly cost-effective, whereas other drugs typically gain or lose a proportion of their QALYs with no clear within-class trends. Removing the QALYs associated with injections leads to a QALY gain for the injectable GLP-1s, with injectable semaglutide being associated with the lowest ICER within the GLP-1s. Typically the higher cost of GLP-1s compared with SGLT-2s prevents them from being associated with the lowest ICERs. Removing the QoL impact of BMI change has a small overall impact however as GLPL-1s are associated with the highest weight loss they lose more QALYs in this scenario than other treatments. The sensitivity analyses were designed to be exploratory and explored the model's sensitivity to extreme scenarios where parameters were removed, and as such did not reflect the committee's preferred model assumptions.

Table 10: Initial therapy - replacement

Drug	All T2 patients		High CV risk – no prior event		High CV risk – prior event		All high CV risk		High BMI	
Alogliptin	Dominated	9	Dominated	9	Dominated	8	Dominated	9	Dominated	9
Linagliptin	£265,517	8	£185,349	8	Dominated	9	£253,835	8	£203,470	7
Saxagliptin	Dominated	12	Dominated	13	Dominated	12	Dominated	13	Dominated	13
Sitagliptin	£119,284	7	£106,167	7	£85,445	7	£114,125	7	£127,721	8
Dulaglutide	£85,134	10	£71,385	11	£65,338	11	£69,112	10	£87,684	10
Exenatide	£164,207	13	£128,525	12	£113,955	13	£128,188	12	£170,510	12
Liraglutide	Dominated	16	Dominated	16	£355,776	16	Dominated	16	Dominated	16
Lixisenatide	Dominated	14	Dominated	14	Dominated	14	Dominated	14	Dominated	14
Semaglutide (injection)	£90,451	11	£71,498	10	£44,778	10	£73,417	11	£114,951	11
Semaglutide (oral)	Dominated	15	Dominated	15	Dominated	15	Dominated	15	Dominated	15
Pioglitazone	Dominated	6	£116,326	5	£21,069	3	£100,244	5	Dominated	6
Canagliflozin	£25,504	4	£20,769	3	£21,666	4	£20,988	3	£24,270	5
Dapagliflozin	£17,670	1	£16,443	1	£16,916	1	£16,556	1	£16,839	1
Empagliflozin	£26,730	5	£25,330	6	£22,676	5	£25,438	6	£23,806	4
Ertugliflozin	£25,400	3	£22,525	4	£33,510	6	£22,821	4	£22,772	3

Table 11: Initial therapy - addition

Drug	All T2 patients		High CV risk – no prior event		High CV risk – prior event		All high CV risk		High BMI	
Alogliptin	Dominated	9	Dominated	9	Dominated	8	Dominated	9	Dominated	9
Linagliptin	£249,251	7	£181,635	7	Dominated	9	£246,734	7	£198,449	7
Saxagliptin	Dominated	12	Dominated	13	Dominated	12	Dominated	13	Dominated	13
Sitagliptin	£192,598	8	£152,891	8	£113,281	7	£168,493	8	£217,300	8
Dulaglutide	£80,221	10	£69,092	10	£62,777	11	£67,023	10	£82,414	10
Exenatide	£215,778	13	£157,100	12	£135,114	13	£156,496	12	£228,497	12
Liraglutide	Dominated	15	£3,504,735	15	£275,683	15	£2,855,842	15	Dominated	15
Lixisenatide	Dominated	14	Dominated	14	Dominated	14	Dominated	14	Dominated	14
Semaglutide (injection)	£103,323	11	£79,699	11	£47,685	10	£81,630	11	£135,153	11
Semaglutide (oral)	Dominated	16	Dominated	16	Dominated	16	Dominated	16	Dominated	16
Pioglitazone	Dominated	6	Dominated	6	£75,098	6	Dominated	6	Dominated	6
Canagliflozin	£31,914	5	£24,923	5	£25,041	4	£25,132	5	£30,357	5
Dapagliflozin	£16,145	1	£15,376	1	£15,695	1	£15,464	1	£15,435	1
Empagliflozin	£25,950	4	£25,017	4	£22,067	3	£25,076	4	£23,264	4
Ertugliflozin	£24,274	3	£22,008	3	£31,441	5	£22,283	3	£21,952	3

Table 12: First intensification - replacement

Drug	All T2 patients		High CV risk – no prior event		High CV risk – prior event		All high CV risk		High BMI	
Alogliptin	Dominated	9	Dominated	9	Dominated	8	Dominated	9	Dominated	9
Linagliptin	£222,240	7	£140,587	7	Dominated	9	£363,173	8	£185,291	7
Saxagliptin	Dominated	12	Dominated	13	Dominated	12	Dominated	13	Dominated	13
Sitagliptin	£118,518	8	£110,651	8	£87,744	7	£116,919	7	£126,945	8
Dulaglutide	£82,736	11	£70,764	11	£63,019	11	£67,923	11	£85,965	10
Exenatide	£163,702	13	£132,781	12	£115,352	13	£131,946	12	£171,785	12
Liraglutide	Dominated	16	Dominated	16	£385,874	16	Dominated	16	Dominated	16
Lixisenatide	Dominated	14	Dominated	14	Dominated	14	Dominated	14	Dominated	14

Drug	All T2 patients		High CV risk – no prior event		High CV risk – prior event		All high CV risk		High BMI	
Semaglutide (injection)	£81,100	10	£70,189	10	£42,441	10	£66,319	10	£101,227	11
Semaglutide (oral)	Dominated	15	Dominated	15	Dominated	15	Dominated	15	Dominated	15
Pioglitazone	Dominated	6	Dominated	5	£23,674	3	£204,705	5	Dominated	6
Canagliflozin	£26,793	4	£22,190	4	£23,920	4	£22,939	3	£25,571	5
Dapagliflozin	£17,787	1	£16,551	1	£17,878	1	£16,972	1	£16,979	1
Empagliflozin	£28,395	5	£26,835	6	£26,293	5	£27,857	6	£25,087	4
Ertugliflozin	£26,049	3	£22,732	3	£38,983	6	£24,537	4	£23,421	3

Table 13: First intensification - addition

Drug	All T2 patients		High CV risk – no prior event		High CV risk – prior event		All high CV risk		High BMI	
Alogliptin	Dominated	9	Dominated	9	Dominated	8	Dominated	9	Dominated	9
Linagliptin	£180,999	6	£122,531	7	Dominated	9	£263,975	7	£153,134	6
Saxagliptin	Dominated	13	Dominated	13	Dominated	12	Dominated	13	Dominated	13
Sitagliptin	£259,172	8	£221,947	8	£142,327	7	£246,451	8	£301,735	8
Dulaglutide	£72,035	10	£62,864	10	£57,370	10	£60,718	10	£74,315	10
Exenatide	£228,660	12	£172,601	12	£146,081	13	£171,452	12	£243,498	12
Liraglutide	£1,114,410	15	£555,294	15	£227,151	15	£531,758	15	£1,022,648	15
Lixisenatide	Dominated	14	Dominated	14	Dominated	14	Dominated	14	Dominated	14
Semaglutide (injection)	£92,797	11	£79,368	11	£45,838	11	£74,342	11	£119,629	11
Semaglutide (oral)	Dominated	16	Dominated	16	Dominated	16	Dominated	16	Dominated	16
Pioglitazone	Dominated	7	Dominated	6	Dominated	6	Dominated	6	Dominated	7
Canagliflozin	£34,644	5	£27,464	5	£29,470	5	£28,544	5	£32,593	5
Dapagliflozin	£14,756	1	£13,814	1	£15,415	1	£14,181	1	£14,129	1
Empagliflozin	£24,975	4	£23,582	4	£24,140	3	£24,494	4	£22,259	4
Ertugliflozin	£22,396	3	£19,742	2	£32,252	4	£21,169	3	£20,289	3

Table 14: Second intensification - replacement

Drug	All T2 patients		High CV risk – no prior event		High CV risk – prior event		All high CV risk		High BMI	
Alogliptin	Dominated	9	Dominated	9	Dominated	8	Dominated	9	Dominated	9
Linagliptin	£176,942	7	£106,118	7	Dominated	9	£300,837	7	£151,193	7
Saxagliptin	Dominated	13	Dominated	13	Dominated	12	Dominated	13	Dominated	13
Sitagliptin	£139,652	8	£138,361	8	£108,998	7	£144,023	8	£148,308	8
Dulaglutide	£74,699	10	£65,799	10	£56,633	11	£62,626	10	£76,697	10
Exenatide	£171,084	12	£145,252	12	£121,124	13	£141,808	12	£175,782	12
Liraglutide	£6,334,180	15	£1,046,000	15	£262,166	15	£791,498	15	£3,377,498	15
Lixisenatide	Dominated	14	Dominated	14	Dominated	14	Dominated	14	Dominated	14
Semaglutide (injection)	£74,532	11	£69,441	11	£42,448	10	£62,559	11	£89,597	11
Semaglutide (oral)	Dominated	16	Dominated	16	Dominated	16	Dominated	16	Dominated	16
Pioglitazone	Dominated	6	Dominated	6	£46,163	4	Dominated	6	Dominated	6
Canagliflozin	£28,922	5	£24,721	4	£26,039	5	£25,591	4	£26,974	5
Dapagliflozin	£16,343	1	£15,150	1	£16,598	1	£15,612	1	£15,567	1
Empagliflozin	£27,394	4	£25,871	5	£26,083	3	£26,930	5	£24,041	4
Ertugliflozin	£24,322	3	£21,077	3	£34,694	6	£23,240	3	£21,782	3

Table 15: Second intensification - addition

Drug	All T2 patients		High CV risk – no prior event		High CV risk – prior event		All high CV risk		High BMI	
Alogliptin	Dominated	8	Dominated	9	Dominated	9	Dominated	9	Dominated	8
Linagliptin	£157,990	6	£98,646	6	Dominated	8	£243,671	6	£136,238	6
Saxagliptin	Dominated	13	Dominated	14	Dominated	12	Dominated	13	Dominated	14
Sitagliptin	£390,845	7	£380,237	7	£205,586	7	£417,921	8	£469,520	7
Dulaglutide	£64,196	10	£56,984	10	£50,836	10	£54,794	10	£65,732	10
Exenatide	£240,722	12	£190,794	12	£153,393	13	£185,744	12	£250,564	12
Liraglutide	£391,861	15	£289,677	15	£166,180	15	£270,891	15	£372,298	15
Lixisenatide	Dominated	14	Dominated	13	Dominated	14	Dominated	14	Dominated	13

Drug	All T2 patients		High CV risk – no prior event		High CV risk – prior event		All high CV risk		High BMI	
Semaglutide (injection)	£78,902	11	£72,389	11	£44,076	11	£65,240	11	£96,461	11
Semaglutide (oral)	Dominated	16	Dominated	16	Dominated	16	Dominated	16	Dominated	16
Pioglitazone	Dominated	9	Dominated	8	Dominated	6	Dominated	7	Dominated	9
Canagliflozin	£38,727	5	£31,780	5	£32,899	5	£33,098	5	£35,449	5
Dapagliflozin	£13,548	1	£12,591	1	£14,200	1	£13,020	1	£12,974	1
Empagliflozin	£24,376	4	£23,071	4	£23,912	3	£24,083	4	£21,602	4
Ertugliflozin	£21,204	3	£18,549	2	£29,290	4	£20,287	3	£19,162	2

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1.1.10 Evidence statements

Summaries of the clinical evidence are presented in section 1.1.6.

As outlined in section 1.1.7, a review of the economic literature did not return any directly applicable CUAs including all interventions relevant to the review question.

1.1.11 The committee's discussion and interpretation of the evidence

This discussion includes consideration of the clinical effectiveness evidence (see section 1.1.4) and health economic evidence (see section 1.1.7) presented in this review.

1.1.11.1. The outcomes that matter most

From the review protocol the committee agreed that the key outcomes for decision making were cardiovascular events (cardiovascular mortality, myocardial infarction, stroke, unstable angina and congestive heart failure) and all-cause mortality. (The renal benefits of these drugs are being considered in another review for in people with type 2 diabetes and chronic kidney disease (CKD) as part of an update of the CKD guideline. This is because cardiovascular events are common in type 2 diabetes and related to increased morbidity and reduced life expectancy. The committee noted that the primary cause of mortality in type 2 diabetes were cardiovascular events but agreed that both types of mortality (all-cause mortality and cardiovascular mortality) carried equal weight. The committee also discussed the key issue that people with type 2 diabetes may prioritise the relative importance of mortality and clinical outcomes differently to clinicians and may place more emphasis on quality-of-life issues such as weight gain or loss, the tolerability of a drug and any side effects or adverse events related to taking the drug. The committee also agreed that the relative importance of these outcomes to an individual may be affected by personal factors such as the person's age, the duration of their diabetes diagnosis and their current level of cardiovascular risk. In addition, the committee discussed that for a person with type 2 diabetes, willingness to accept more intensive drug therapy with increased side effects may depend on their perceived level, and attitude towards, risk of a cardiovascular event.

The committee agreed that hypoglycaemia unawareness (a complication of diabetes in which people, with diabetes do not show the usual adrenergic hypoglycaemia symptoms in response to a rapid or large reduction in blood glucose) is also an important outcome for people with type 2 diabetes. However, it is a relatively rare complication in comparison to people with type 1 diabetes and was not prioritised by the committee because it is not an outcome routinely reported in the included RCTs. Hypoglycaemia unawareness was therefore not included in the review protocol because the economic modelling for the outcomes can only consider a limited number of clinical factors.

1.1.11.2 The quality of the evidence

The committee noted that the quality of the evidence in the pairwise analyses was moderate and in the network meta-analyses (NMA) this ranged from moderate to high as assessed using a modified form of GRADE (please see Table 17 and the section on Modified GRADE for intervention studies analysed using network meta-analysis in appendix B for more details). Two outcomes were downgraded to moderate quality in the NMAs, hospitalisation for heart failure, which was downgraded due to heterogeneity between the medications (I^2>50%) and hospitalisation for unstable angina which was downgraded for imprecision. The pairwise analyses were all downgraded to moderate quality due to imprecision. Two NMA outcomes (severe hypoglycaemia and any discontinuation) had sensitivity analyses conducted using random effects models to confirm their findings, as the heterogeneity was assessed as close to the I^2 model choice threshold of 50%. The NMA for hospitalisation for

heart failure had a sensitivity analysis conducted using a fixed effects model (removing 1 trial which caused significant heterogeneity in the NMA model).

The evidence was provided by 16 double blind, randomised controlled trials. In 15 of the trials the comparator was placebo and in 1 trial the comparator was an active drug. Following the review protocol outcomes which were reported the same way across the trials were analysed using NMAs to assess the relative effectiveness of each treatment versus other treatments or placebo (see section 1.1.3 Methods and process for more details on which outcomes were extracted and in what format). Although the committee were interested in all recorded events of unstable angina or congestive heart failure, they noted that the majority of the trials reported hospitalisation for these events. They agreed that in the absence of data on all the events the data for hospitalisation still provided useful information about the impact of the drugs on these outcomes. For myocardial infarction and stroke non-fatal event data was extracted to prevent double counting with the cardiovascular normality outcome and used in the NMAs. Outcomes which were unclear or different between the trials (for example if it was unclear if an event was fatal or nonfatal for stroke and myocardial infarction, or, if events were reported as both fatal and nonfatal) were reported separately to the NMA as pairwise comparisons.

The committee noted that there was no cardiovascular outcome trial evidence for some of the treatments listed in the review protocol (biguanides, sulfonylureas other than glimepiride, and vildagliptin). The committee also noted that not every RCT contributed to each NMA due to different outcomes being reported by each trial.

The committee noted that 6 of the 16 RCTs only included people with established cardiovascular disease (CVD) (secondary prevention group) and that the remaining 10 trials included people with both established CVD and those at high risk due to being older age and/or having additional CVD risk factors. However, the committee noted that in 7 of the 10 trials most participants also had established CVD with percentages of participants with established CVD ranging from 57% - 85%. The committee discussed whether people with type 2 diabetes and CV risk factors are likely to respond in the same way to treatment interventions to those people with established CVD. The committee agreed that for the treatments under review in this update it was reasonable to assume that the relative treatment effects would be similar, but that baseline risks may be different between these CVD risk groups. They noted that this difference in baseline risks is being considered as part of the economic modelling work. They therefore agreed that pooled data covering both groups of people from these studies could be used in the analyses alongside the data from studies that only included people with established CVD. The committee agreed that because of the inclusion criteria of these trials caution may be needed when generalising the findings of these trials beyond people with type 2 diabetes who are at high or very high risk of CVD events.

The committee discussed the difference in kidney function of the included study populations at baseline between the RCTs (as measured using estimated glomerular filtration rate [eGFR]). Where reported, the proportion of people with an eGFR <60 ml/min varied between trials from 10% to 60%, reflecting differences in the severity of their chronic kidney disease (CKD). Eight of the studies also reported urine albumin-to-creatinine ratio (UACR), but the method of reporting varied making comparison across studies harder (see evidence table baseline characteristics for this information where it is available). The committee noted that some drugs can be used in people with very reduced kidney function, while the use of other drugs should be avoided below a certain eGFR level. The committee agreed that the differences in eGFR inclusion criteria and baseline levels between the RCTs most likely represented the use of each drug in people with reduced kidney function based on the licences of the individual drugs. Although there were differences in the baseline levels of kidney dysfunction between trials the committee agreed these differences were not so pronounced that the data from these trials could not be pooled for analysis for comparison using NMAs, although they agreed that the variation in inclusion criteria between trials for

kidney function and for CV risk was a limitation. The committee also noted that in practice they would expect around 40% of people with type 2 diabetes to have some kidney dysfunction during their lifetime although this may be increasing as more younger people develop the disease and that people with type 2 diabetes who had higher CV risk or established CVD were more likely to have CKD. The severity of CKD as shown by baseline eGFR was not seen to be unrepresentative of people with type 2 diabetes with high CV risk and therefore the committee agreed the quality of the evidence should not be downgraded.

The committee also discussed the racial and ethnic populations in the included trials. All the trials were conducted in multiple countries and often across different continents. Caucasian participants made up the majority of the studied populations in all trials (approx. 67-99%, [99% in 1 RCT of thiazolidinedione]) with much smaller percentages of Black (approx. 3-7%) and Asian participants (ranging from approximately 6-22%). These percentages may be approximately representative of the ethnicities of the populations in the countries the participants were recruited from, but the committee noted that in the UK a higher proportion of people from the Asian and Black communities may have a predisposition to type 2 diabetes, and that as a result they are likely to be underrepresented in the trials. In addition, they noted that the differences in racial and ethnic recruitment to the trials could affect event rates as certain racial and ethnic groups may have a higher baseline risk of cardiovascular events in type 2 diabetes than others. However, the committee decided that this evidence was still generalisable to the UK and agreed not to downgrade the results of the NMAs and pairwise analyses.

The committee agreed to group DPP-4 and sulfonylureas (SU) as drug classes for the purpose of the network meta-analyses, as it was expected that there would be limited difference between the effectiveness of the individual drugs in each class. However, these drugs were analysed separately in the economic model in case differences did exist. The committee noted that only 1 sulfonylurea glimepiride was included in the RCTs which is used less commonly than, for example, sulfonylurea gliclazide in some areas of the UK. The committee considered whether glimepiride alone was sufficient to represent all sulfonylureas but decided that on balance that it was likely that any differences in outcomes between sulfonylureas would be small and therefore they agreed that this data could still be used to represent SUs as a class.

The committee noted that 2 trials had lower numbers of participants and events than other trials (PIONEER-6 and SUSTAIN-6). They also noted that 2 outcomes had fewer events than other outcomes (stroke and hospitalised for unstable angina) across most of the trials. This may increase uncertainty in the outcomes from these trials and as smaller numbers of events lead to wider 95% confidence intervals. The committee noted that there might be greater uncertainty around the results of the NMAs for comparisons that included these trials and they agreed to take this into account when looking at the results of the NMAs and economic model.

Overall, the committee agreed that despite the caveats with the evidence discussed above the CVOT data was directly applicable to the UK population and of sufficient quality to be used to inform the economic model.

1.1.11.3 Benefits and harms: discussion of the NMA and pairwise analysis results

The committee discussed the evidence from the NMAs and the pairwise evidence that was used to inform them. There were 16 trials included in the analyses and the numbers of participants in these trials ranged from 3,183 (PIONEER-6) to 17,160 (DECLARE-TIMI 58) with the majority of trials having over 6,000 participants. The PIONEER-6 and SUSTAIN- 6 trials for oral and injectable semaglutide respectively had lower number of participants (see above for more discussion about the impact this could have on the certainty of the results).

Please see section 1.1.3 Methods and process for a description of the interpretation of the results using the minimal clinically important differences. For an effect to be described as

clinically meaningful it had to be greater than the MID. The results are summarised in Table 3.

The NMA for all-cause mortality (Figure 1) and cardiovascular mortality (Figure 3) included all 16 trials, their interventions and comparators. These networks were star shaped and had a thicker connection between DPP-4 and placebo, denoting the 4 trials for the DPP-4 class compared to placebo. The other comparisons all consisted of data from single trials. The star shaped network displays graphically how almost all the comparisons were between the intervention and placebo; with the exception of a single spur for DPP-4 compared to sulfonylurea there were no other direct drug-drug comparisons. Therefore, the only direct comparisons were intervention to placebo apart from the single DPP-4 to sulfonylurea study. The remaining evidence for drugs versus other drugs in the network came from indirect evidence. This is shown clearly when we examine the proportions of the NMA evidence that are derived from direct and indirect evidence for each network. Since there were no loops in the network inconsistency between direct and indirect estimates of effect was not possible and so no inconsistency checks were carried out.

The committee discussed the high-quality evidence from the NMA for all-cause mortality presented in the caterpillar plot (see Figure 2) and noted that no treatment was worse than placebo. The committee noted that 4 interventions showed a reduction in the risk of all-cause mortality compared with placebo (empagliflozin and oral semaglutide with clinically meaningful effects greater than the minimal important difference (MID), and a reduction of less than the MID for exenatide and liraglutide). The committee noted that in the NMA results shown in the relative effectiveness table (Table 19) empagliflozin and oral semaglutide showed a clinically meaningful reduction in the risk of all-cause mortality compared with exenatide with an effect greater than MID but could not be differentiated compared to each other. Liraglutide could not be differentiated from oral semaglutide and from empagliflozin. The committee noted that while oral semaglutide showed a clinically meaningful reduction in risk of all-cause mortality estimate against placebo, it had greater imprecision (broader 95% confidence intervals; HR 0.51, [0.31 to 0.84]) than was seen for empagliflozin versus placebo (HR 0.68, [0.57 to 0.82]). The committee noted the probability that oral semaglutide (P score=0.9773) and empagliflozin (P score=0.9259) were most effective compared to other treatments and that both DPP-4 and sulfonylurea were ranked worse than placebo. However, the committee noted the lack of 95% CI for the P scores (Table 20) that would allow them to determine whether there were overlaps in ranking between any of the treatments (for example in the relative effectiveness chart (Table 19) the results could not differentiate between oral semaglutide and empagliflozin). They were careful to take this limitation into account when interpreting the table and comparing it to the relative effectiveness results.

Similar findings were noted by the committee for the high-quality evidence from the NMA for the cardiovascular mortality outcome where 3 interventions (empagliflozin, liraglutide and oral semaglutide) showed a clinically meaningful reduction in the risk of CV mortality compared to placebo with effects greater than the MID (Figure 4) but could not be differentiated from each other in terms of relative effectiveness in the NMA (Table 21). Again, no intervention was worse than placebo. The committee noted that the probability ranking showed that oral semaglutide (P score=0.9552) and empagliflozin (P score=0.9322) (Table 22) were likely to be the most effective interventions compared to other treatments and this was in agreement with the relative effectiveness results that showed that these drugs were better than placebo and multiple other drugs. Liraglutide (P score = 0.7818) was less likely to be the most effective and this was reflected in the relative effectiveness data where it was only better than placebo and DPP-4.

Oral semaglutide showed a clinically meaningful reduction in the risk of all-cause mortality compared to placebo. In contrast, the effects of injectable semaglutide could not be differentiated from placebo. In addition, oral semaglutide showed a clinically meaningful reduction in the risk of all-cause mortality compared to injectable semaglutide (HR 2.06, [1.12 to 3.79]). The committee agreed that it was unexpected that there was such a pronounced

difference in effectiveness between oral and injectable forms of semaglutide for the all-cause mortality outcome compared to each other and to placebo given that they are the same drug. The committee discussed possible reasons to explain this including whether there were differences in trial populations. The results for these drugs came from 2 trials, one of each intervention which compared to other trials in the review were the 2 smallest; N=3,183 [oral semaglutide] and N=3,297 [injectable semaglutide]). However, the committee did not identify any major differences between the trials. Alternatively, the committee discussed whether the pharmacokinetics related to the different routes of administration could lead to differences in effectiveness, but they thought this was unlikely given that they were meant to both deliver an effective dose of drug. The committee looked at the results for cardiovascular mortality to see if these differences were maintained. They noted that in the NMA relative effectiveness chart cardiovascular mortality could not be differentiated between the oral and injectable forms of semaglutide (Table 21). Furthermore, the committee noted that the 2 forms of semaglutide could not be differentiated for any other outcome relevant to each other, apart from the outcome of any discontinuation where injected semaglutide showed a clinically meaningful reduction in discontinuations (HR 0.72, [0.57 to 0.91]) compared to oral semaglutide (Table 23). The committee also noted the uncertainty due to wide 95% CI for many outcomes with these drugs, due to the smaller numbers of participants and events in the trials (see section 1.1.11.2 above). (This was also the case for the comparison of oral semaglutide compared to injectable semaglutide for all-cause mortality (HR 2.06, [1.12 to 3.79]), although the point estimate fell outside the MID). Taking the above into account, the committee were less certain that any differences seen in all-cause mortality between the 2 forms of semaglutide were real and decided not to place undue weight on this.

For both all-cause mortality and CV mortality, empagliflozin showed a clinically meaningful reduction in the risk of all-cause mortality and CV mortality compared with other SGLT2 drugs. The committee discussed why empagliflozin (an SGLT2) might be more effective than other drugs of the SGLT2 class for these outcomes. The committee noted that the EMPA-REG (empagliflozin) trial was in a population (N=7,020) with established CVD only. However, the committee noted that another SGLT2 trial (ertugliflozin in the VERTIS-CV [N=8,246]) also included people with only established CVD, and this did not have the same effects versus placebo or relative to other SGLT2 drugs. The population in the VERTIS-CV trial was similar to the EMPA-REG trial. Both trials included people with established CVD only, but the population in the VERTIS-CV trial had higher rates of heart failure at baseline than the EMPA-REG trial (approximately 24% versus 10%) and slightly more events in the control arm (all-cause mortality 9.2% compared with 8.3%; and CV mortality 6.7% compared with 5.9%) than the EMPA-REG trial. The other 2 SGLT2 trials (CANVAS and DECLARE-TIMI 58) were both conducted in mixed populations of people with and without established CVD. The DECLARE-TIMI 58 (dapagliflozin) trial had the lowest proportion of people (<41%) with established CVD at baseline and much lower control arm events rates for both outcomes. The CANVAS trial (canagliflozin) had higher rates of established CVD at baseline (65.6%) but again had lower control arm event rates for the all-cause and CV mortality outcomes. The committee thought that differences between the study populations and the event rates might explain the observed differences in effects seen for these outcomes for canagliflozin and dapagliflozin compared to empagliflozin. They were less certain about the reason for the differences between empagliflozin and ertugliflozin. The committee noted that the difference in effectiveness between empagliflozin and the other SGLT2s was not sustained consistently across the remaining outcomes and agreed to look at the results of the economic model, which would integrate the effects of the drugs across all the outcomes, before making decisions about whether to treat the SGLT2s as a class or as individual drugs when making recommendations.

The committee noted that the network for hospitalisation for heart failure was similarly shaped to the ones for mortality (Figure 10) but contained only 15 trials as this outcome was not reported for pioglitazone. The committee noted that the moderate quality evidence of effectiveness from the NMA for hospitalisation for heart failure, favoured the SGLT2 class of drugs (canagliflozin, dapagliflozin and empagliflozin all showing clinically meaningful effects

greater than the MID) in comparison to placebo and that no intervention was worse than placebo (Figure 11). The committee noted that canagliflozin, dapagliflozin, empagliflozin and ertugliflozin showed a clinically meaningful reduction in the risk of hospitalisation due to heart failure against DPP-4 in the NMA but could not be differentiated from each other (Table 29). These 4 SGLT2s also ranked best compared to other treatments (Table 30). The committee also noted that for this outcome injectable semaglutide and the DPP-4 were ranked lower than placebo but noted that injectable semaglutide could not be differentiated from placebo in the relative effectiveness chart and that the difference was not clinically meaningful between DPP-4 and placebo (Table 29). However, it was noted that there is heterogeneity between the 4 DPP-4 trials in the NMA for this outcome, particularly between the largest trial (SAVOR-TIMI 53, saxagliptin) and the remaining 3 DPP-4 trials. In this model the effects of the SAVOR-TIMI trial in causing a statistically significant increase in hospitalisation for heart failure (HR 1.27, [1.07 to 1.51] in the trial) is drawn towards the estimate of effect of treatment in the remaining smaller DPP-4 trials. This was noted as a limitation by the committee and a sensitivity analysis was conducted to look at the effects of removing the SAVOR-TIMI trial on the heterogeneity and the results (Figure 12). As expected, this reduced the heterogeneity (I^2=0.0%) and so a fixed effect model was now appropriate. The sensitivity analysis emphasised the statistically significant and clinically meaningful reduction in hospitalisation for heart failure for each of the SGLT2 compared with placebo (Figure 13), but again the SGLT2s could not be differentiated from each other (Table 33). In the ranking table (Table 34) it was noted that the SGLT2 were still ranked highest of all interventions and that the DPP-4 were now ranked higher than placebo. The committee agreed that these findings supported the use of SGLT2s in type 2 diabetes for people with CVD or high CV risk and noted that a specific SGLT2 (dapagliflozin) is used in people with heart failure (NICE TA679).

The committee noted the network for hospitalisation due to unstable angina was sparser than previous networks including data from 11 trials because there was no data for this outcome for canagliflozin, dapagliflozin, exenatide or ertugliflozin (Figure 14). They agreed that the findings of the moderate quality evidence for the outcome of hospitalisation for unstable angina were unsurprising. No effects could be differentiated between any intervention and placebo in the caterpillar plot, apart from DPP-4 which had no clinically meaningful difference compared to placebo, (Figure 15), or compared to any other comparator in the NMA relative effectiveness chart results (Table 33). However, no intervention was worse than placebo except in the probability ranking (Table 34) where 3 interventions (lixisenatide, dulaglutide and oral semaglutide) ranked lower. However, because of the lack of detectable differences in relative effectiveness between drugs the committee agreed that the ranking was unhelpful for this outcome. The committee attributed this to the action of the drugs not impacting on the mechanisms underlying unstable angina.

The committee discussed the high-quality NMA evidence for the outcomes of nonfatal myocardial infarction (MI) and the moderate quality evidence from the pairwise analyses for other MI outcomes (appendix F). The committee noted that the network was composed of 12 trials, but there was no data for dapagliflozin or lixisenatide (Figure 16). The committee noted that no effect could be differentiated between any intervention and placebo apart from exenatide which had no clinically meaningful difference compared to placebo (Figure 17), and only 2 interventions (canagliflozin and liraglutide) showed a clinically meaningful reduction in the risk of nonfatal MI, , both compared to DPP-4 (Table 35). The probability ranking showed that injectable semaglutide was ranked first (P score = 0.8651) but that oral semaglutide ranked second lowest (P score = 0.2104), amongst 4 drugs that ranked lower than placebo. Again, the committee were surprised at the difference in ranking for the same drug administered differently, but due to the lack of 95% CI could not tell how much overlap between rankings exists (Table 36). In addition, they noted that in the relative effectiveness chart only canagliflozin and liraglutide were more effective than another treatment and they therefore did not place much weight on the results of this particular probability ranking table.

The committee noted the network for nonfatal stroke (Figure 18) comprised data from 11 RCTs, but there was no data for dapagliflozin, lixisenatide or pioglitazone which was

analysed in pairwise analysis (see appendix F). Only 2 interventions showed a clinically meaningful reduction in the risk of nonfatal stroke, (dulaglutide and injectable semaglutide, both GLP-1s) compared with placebo, and no intervention was worse than placebo (Figure 19). In the NMA analysis both dulaglutide and injectable semaglutide showed a clinically meaningful reduction in the risk of nonfatal stroke compared to empagliflozin (Table 37). Empagliflozin was the only intervention ranked lower than placebo (Table 38) but it could not be differentiated from placebo in the relative effectiveness chart. The committee discussed whether the specific mode of action of SGLT2s could be linked to the results for this outcome in comparison to the GLP-1s dulaglutide and injectable semaglutide. However, as the result was specific to empagliflozin only and was not seen for other drugs in the SGLT2 class they agreed that this was unlikely.

The committee agreed that the small number of clinically meaningful differences between comparators seen for both non-fatal MI and non-fatal stroke outcomes was unsurprising as they did not expect to observe major differences between most of the drugs for these outcomes. They noted that there may have been relatively few events for both outcomes over the duration of the trials, especially where the trial population was small, even when longer follow up times were used. In addition, most of the trials included composite (major adverse cardiovascular events or MACE) outcomes as their primary outcome rather than the individual components of the 3-point MACE (CV mortality, nonfatal MI and nonfatal stroke) and therefore the trials may have been designed to be powered around the composite outcome. The committee therefore requested a protocol deviation to include an NMA for 3-point MACE. The committee agreed that for the purposes of informing the NICE economic analyses these outcomes have been separated as they have different costs and effects on quality of life.

The committee noted the high-quality evidence for the NMA outcome of 3-point MACE, the network for 3-point MACE (Figure 24) comprised of data from 14 trials, but there was no data for lixisenatide or alogliptin for this outcome. The committee noted that the EXAMINE trial does report a hazard ratio for alogliptin (a DPP-4) versus placebo (HR 0.96), but only reported an upper boundary of the one-sided repeated CI at an alpha level of 0.01 (≤1.16) rather than a 95% CI which could be included in the NMA. The committee agreed that it was therefore appropriate to exclude this drug from the NMA and that as the as DPP-4s were analysed at class level there would still be results for this comparison from the NMA. The committee noted that 5 interventions (canagliflozin, empagliflozin, liraglutide, pioglitazone and dulaglutide) showed a reduction in 3-point MACE compared with placebo that was less than the MID, but injectible semaglutide showed a clinically meaningful reduction (Figure 24) compared to placebo. In the NMA relative effectiveness chart there were relatively few differences noted between interventions and only 2 comparisons, favouring injectible semaglutide, versus both DPP-4 and sulfonylurea had clinically meaningful effects (Table 43). The committee noted that injectible semaglutide, pioglitazone and oral semaglutide were the 3 highest ranked interventions for this outcome but due to the lack of statistically significant differences in the relative effectiveness chart between these they did not place much weight on the results of the probability ranking table (Table 44).

The committee discussed high-quality evidence from the NMA for the outcome of any discontinuation. The committee noted the network (Figure 5) contained data from 15 RCTs, but there was no data for liraglutide. The committee noted that the definition of any discontinuation was the concluding of participation, before completing all protocol-required elements, in a trial by an enrolled subject. Discontinuation does not necessarily imply the exclusion of the subject's data from analyses and is not necessarily due to adverse events, (these are analysed in a separate NMA below). The committee noted that empagliflozin and ertugliflozin showed a reduction in the risk of any discontinuation compared to placebo but only empagliflozin showed a clinically meaningful reduction. In contrast, oral semaglutide showed a clinically meaningful increase compared to placebo (Figure 6). The effect of the remaining interventions was not clinically meaningfully different from placebo, apart from injectable semaglutide which could not be differentiated from placebo. The committee noted

that there was an increased risk of any discontinuation with oral semaglutide, injectable semaglutide and lixisenatide compared to most of the other interventions (Table 23) and that often the risk was greater than the MID (see Table 3 in section 1.1.6 for full details). The committee noted that the 3 interventions ranked best were SGLT2s (empagliflozin, dapagliflozin and ertugliflozin) and that 3 interventions ranked worse than placebo (oral and injectable semaglutide, and lixisenatide; Table 24). These rankings also reflected the relative effectiveness data as although the results for injectable semaglutide could not be differentiated from placebo, the lower 95% CI was 0.99 and the point estimate was 1.13, and this treatment was less effective than many other treatments. The committee noted the consistency between the results of the caterpillar plot, relative effectiveness chart and the probability rankings which increased their confidence in the results of the probability rankings. As the NMA model heterogeneity (I^2=48%) was near to the model choice threshold (I^2>50%) for using random effects a sensitivity analyses using random effects model was conducted. There was little change in the results compared to placebo from the fixed effects model, except exenatide could no longer be differentiated from placebo (Figure 7). Similarly, there was little change in the relative effectiveness of the interventions (Table 25) and the probability rankings (Table 26).

The committee noted that the network for discontinuation due to adverse events (Figure 8) contained data from 13 trials but there was no data for dulaglutide. The NMA evidence was rated as high-quality. The committee noted that, as they expected, many drugs showed an increase in the risk of discontinuation due to adverse events when directly compared to placebo (Figure 9). The committee noted that for canagliflozin, lixisenatide, liraglutide, and oral and subcutaneous semaglutide the effect was clinically meaningful. The committee commented that the result for empagliflozin reducing the risk compared to placebo was surprising as this is not seen in clinical practice in their experience and was not seen for other drugs of the SGLT2 class. However, they noted that as the 95% CI for empagliflozin was contained within the defined MID this effect was not clinically meaningful. The committee also discussed whether the results for pioglitazone were borne out in clinical practice as they may have expected more discontinuations for this compared to other interventions (see relative effectiveness chart, Table 27). However, the committee agreed that this may be more common in certain areas of practice such as heart failure where pioglitazone may be stopped due to weight gain or exacerbation of heart failure and noted that it still ranked below placebo in the probability ranking (Table 28). In addition, the committee noted that when the default MIDs were considered in the pairwise and NMA results, oral and subcutaneous semaglutide and lixisenatide increased the risk of discontinuation due to adverse events compared with other interventions often by greater than the MID (Table 3). The committee discussed at what point people discontinued the medication due to adverse events and agreed that some interventions are tolerable for longer than others. However, the event data provided by the trials was over the entire follow-up period for each trial and therefore the time course for discontinuation due to adverse events could not be examined using this data and was not reflected in the NMA. The committee made recommendations about checking tolerability of drug treatments and retained existing recommendations that mention tolerability (see section on 1.1.11.5 Balancing the benefits and harms to make recommendations for more details).

The committee noted the network for severe hypoglycaemia (Figure 20) was derived from 13 RCTs but there was no data for exenatide. They reviewed the high-quality evidence, and the results were largely consistent with the committees' expectations. The committee were made aware that 1 trial (SUSTAIN-6) had higher rate of severe hypoglycaemia (>20% in both arms) compared to the other trials (typically 2% to 3%), this may be due to definitional differences in this trial compared to other trials, but that this has not led to clinically meaningful differences compared to placebo and other interventions as the rate of events was similar in both intervention and control arms but note this as a limitation. (See below for the results of a sensitivity analysis using a random effects model and also economic model sensitivity analyses for hypoglycaemia in section 1.1.11.4 Cost effectiveness and resource use.)

The committee noted that 2 interventions, dapagliflozin and liraglutide, showed a clinically meaningful reduction in severe hypoglycaemia, with effects greater than the defined MID, compared with placebo (Figure 21). In addition, there were clinically meaningful reductions in severe hypoglycaemia seen with dapagliflozin, lixisenatide, liraglutide and ertugliflozin compared to other interventions in the relative effectiveness chart (Table 39) (see also Table 3). The committee also noted that, sulfonylurea (glimepiride) increased the risk of severe hypoglycaemia compared to placebo and every other comparator and ranked lowest on the probability ranking for this outcome (Table 40). However, there are limitations in the NMA model related to the shape of the model and that Glimepiride is a spur from the star shape; firstly, as there are no loops in the model inconsistency could not be assessed. Secondly, there is heterogeneity in the rates of severe hypoglycaemia in the DPP-4 class to which glimepiride is compared which may affect the estimates. Finally, differences in the baseline event rates between trials could have affected the estimates for glimepiride. The committee commented that although glimepiride is not as commonly used in UK practice as gliclazide, in their opinion it probably causes fewer hypoglycaemic events than other sulfonylureas. In this respect the committee agreed that it is probably conservatively representative for this outcome of other drug in its class and all sulfonylureas can cause hypoglycaemia, especially in those with renal impairment, so the result was not unexpected. The committee agreed that these findings were in line with their clinical experience, and they had reasonable confidence in the data.

The NMA model heterogeneity (I^2=49.9%) was near to the model choice threshold (I^2>50%) for using random effects for the severe hypoglycaemia outcome. This may have been due in part to the differences between the SUSTAIN- 6 trial and DPP-4 trials compared to the other included trials. To try to determine whether allowing for the increased heterogeneity as part of the model choice would affect the results, we carried out a sensitivity analysis using a random effects model. The results of the random effects model caterpillar plot showed that both dapagliflozin and liraglutide were no longer meaningfully different to placebo (Figure 1) with sulfonylureas remaining clinically meaningfully worse than placebo. There was little change in the relative effectiveness (Table 43) and the probability rankings (Table 44) of the interventions. The results of the 2 analyses confirm the main findings and increased the committee certainty with regards to the results.

1.1.11.4 Cost effectiveness and resource use

The committee were presented with ICERs and net monetary benefit rankings for all individual CVOT drugs compared with a non-CVOT treatment regimen which was stratified by treatment level (metformin at first line treatment, metformin and sulfonylurea at second line treatment, and metformin, sulfonylurea and NPH insulin at third line therapy). Results were further stratified into scenarios where the CVOT drug replaced a component of the non-CVOT treatment regimen and where the CVOT drug was added to the non-CVOT treatment regimen. The base-case analysis included all patients with Type 2 diabetes. Subgroup analyses were presented for patients with a BMI ≥30 and patients at high risk of cardiovascular events with and/or without previous cardiovascular events. One-way sensitivity analyses explored the removal of quality-of-life decrements associated with injections, hypoglycaemic events and change in BMI. The sensitivity analyses were designed to be exploratory and to indicate the likely 'direction of travel' from changes to parameters that were associated with substantial uncertainty and were known drivers of the results. A probabilistic sensitivity analysis was run for the Type 2 diabetes population at second intensification, as this was the treatment stage in which the most patient time was spent in the model.

The committee were asked whether there were any populations or treatment stages at which it would be appropriate to compare any of the individual CVOT drugs against each other. The committee considered that although CVOT drugs were used in clinical practice, prescribing was done on an individual patient basis and that there were no specific patient groups in whom use of CVOTs were considered established clinical practice. On this basis, committee

decision making was informed by comparisons of CVOT compared to non-CVOT treatment regimens. The committee was however presented with the net monetary benefit rankings which were considered during the decision-making process.

The committee were aware that there was substantial uncertainty around several of the model inputs, especially the wide confidence intervals around estimates taken from the clinical review. The committee were presented with sensitivity analyses exploring the effect of changing model parameters and assumptions that were associated with substantial uncertainty. The assumptions explored were the removal of the utility decrement associated with additional injections, the removal of hypoglycaemic events, the removal of the effects of change in BMI, adding in the effects of adverse events and using an alternative assumption around the modelling of cardiovascular mortality. The committee considered the sensitivity analyses during decision making to assess how much these assumptions were driving the results. In general, the committee preferred to base its decisions on the results from the base-case analysis as these were aligned to the preferred model assumptions that had been chosen before seeing the results. When considering the sensitivity analyses, the committee noted the uncertainty in the estimates of hypoglycaemic event rates and agreed that some of the modelled rates were higher than they would expect to see in clinical practice. Although aware that the sensitivity analyses were only intended to be exploratory, the committee noted that the ICERs for several drugs decreased when this parameter was removed. The drugs with lower ICERs in the hypoglycaemia sensitivity analyses were canagliflozin, exenatide, pioglitazone, injectable semaglutide and sitagliptin. The committee concluded that the base-case ICERs for these drugs may be higher than if they had been based on hypoglycaemic rates observed in clinical practice.

When considering the base-case analyses for the total Type 2 diabetes population and subgroups, the committee noted that the only class of drugs with ICERs that fell below £30,000 in any of the analyses were the SGLT2s, and so these were the only drugs with any potential to be cost-effective. The committee discussed whether any recommendations for SGLT2s should be class based or based on individual drugs. Although the cost-effectiveness estimates differed across individual SGLT2s, the committee considered that the differences were predominately driven by differences in costs and so preferred to make recommendations on a class level. To address the differences in cost-effectiveness, and mindful of future price changes and new treatments entering the market, the committee agreed that wherever an SGLT2s was suitable for people at high CV risk, the SGLT2 with the lowest acquisition cost should be used. The NG28 2015 recommendation on choosing drugs already states that the drug with the lowest acquisition cost should be used if 2 options from the same class are under consideration and this was retained by the committee as part of the current update. With this proviso in place, the committee were comfortable basing recommendations on the most cost-effective member of the class in any analysis.

The committee were mindful of potential the resource impact of any recommendations made due to the large population numbers of people with Type 2 diabetes. When developing recommendations, the committee took into account the principles outlined in Section 6.2.14 of the NICE Guide to the methods of technology appraisal; that the committee would want to be increasingly certain of the cost effectiveness of a technology as the resource impact of adoption increases. As the CVOTs informing the clinical review were only studied in people with high cardiovascular risk, the committee considered that there was more uncertainty in the cost effectiveness estimates for the populations outside this group (the total population of people with Type 2 diabetes and the subgroup with BMI ≥30 to whom the trial data was then extrapolated in the economic model). On this basis, the committee placed more weight on the cost-effectiveness estimates for the high cardiovascular risk subgroups. In the economic model, the high cardiovascular risk subgroups were based on clinical criteria determined by the committee (outlined in Sections 3.1.2 to 3.1.4 of the Economic Model Report). However, the committee considered that these criteria might not be practical for clinicians to use when assessing patients in clinical practice. The committee instead decided that any recommendations made for the high cardiovascular risk subgroups should be aligned to

assessment of cardiovascular risk using the QRISK2 algorithm already widely used in the NHS,

The scope of the work in this guideline update is compatible with two 'worldviews' on the role of evidence from the CVOTs:

1. The primary purpose of glycaemic control is to prevent future cardiovascular and diabetic events, rather than being a goal in itself (other than for avoiding hypo/hyperglycaemic events). Because of this, evidence of treatment effects on 'hard' cardiovascular events takes priority over evidence on measures of glycaemic control (such as HbA1c) which only serve as surrogates for predicting hard events.
2. There is inherent merit to achieving glycaemic control over and above its potential to prevent future cardiovascular and diabetic events. Because of this, evidence on treatment effects on cardiovascular events supplements evidence on measures of glycaemic control but does not take priority.

The chosen worldview about the CVOT evidence determines whether evidence from the clinical review and economic model supports recommendations that supersede previous recommendations based on evidence about glycaemic control.

The committee discussed the positions and concluded that option 2 best represented their views for the main Type 2 population, but that option 1 was true for patients at high cardiovascular risk. Because of this, the committee felt the evidence supported recommendations for treatments given with the intention to improve cardiovascular protection in patients at high cardiovascular risk. The committee did not consider the evidence to support recommendations for treatments given with the intention of improving glycaemic control and so opted not to adapt recommendations from NG28 that were based on evidence on glycaemic control.

The committee were aware that in clinical practice GLP-1s are sometimes used more broadly than currently recommended in the current NG28 (2015) pathway. Based on the economic analysis, the committee considered that GLP-1s were not likely to be cost-effective in improving the cardiovascular prognosis of people with Type 2 diabetes. The committee recognised that it had not seen evidence on the use of GLP-1s when given with the intention to improve glycaemic control, and so restricted its recommendation not to use GLP-1s to apply only when given solely for cardiovascular risk reduction.

The committee also noted that in the sensitivity analysis where the effects of hypoglycaemic events were excluded, pioglitazone became highly cost-effective in all subgroups across all levels of treatment intensification. The committee considered that the base-case ICERs for pioglitazone may have been less favourable than if they had been based on hypoglycaemic rates observed in clinical practice but noted that in the base-case pioglitazone was predicted to cost more and be less effective than standard care. The committee were uncertain of the most plausible ICER for pioglitazone but noted that pioglitazone is already recommended as an option if further interventions are needed after first line therapy (and as an option for initial therapy in people who cannot have metformin) in the 2015 NG28 pathway and that these recommendations were retained in this update; because of this, the committee did not make a further recommendation for pioglitazone.

1.1.11.5 Balancing the benefits and harms to make recommendations

The committee used the information provided by the NMAs (discussed above) and the economic model (see the section on cost effectiveness and resource use below) to draft their recommendations. The evidence from the CVOTs was primarily about CV benefits, and so the consideration of effectiveness focused on the treatment effect on CV protection in this review.

There was an existing recommendation on the factors to take into account when choosing drug treatments and the committee agreed that these were still relevant. However, they noted that the cardiovascular benefits (as reflected in the evidence from the NMAs that several treatments reduce the risk of an adverse cardiovascular event in both primary prevention and secondary prevention cohorts) were not covered by the existing recommendation. They therefore agreed that it is important to expand consideration of effectiveness to include the effects on cardiovascular protection and this has been added to recommendation 1.7.1 in the update as an amendment. The committee also amended the recommendation to take account of 2 additional factors to be considered when choosing a drug treatment. Firstly, any contraindication to a drug listed in its summary of product characteristics (SPC) or the British National Formulary (BNF) would mean that the drug should not be used because of the potential to cause harm to that person. Secondly, monitoring requirements, which differ between drugs, may impact negatively upon quality of life and affect drug choice.

The person's preferences and needs should be considered as part of a shared decision-making process, as well as focusing on clinical needs, effectiveness, safety and cost. The committee included a cross reference to the NICE guideline on shared decision making to emphasise this point and to ensure that the person with type 2 diabetes is empowered to be involved in the choice being made. For women with type 2 diabetes the committee also added a cross reference to the safety of medicines section in the NICE guideline on diabetes in pregnancy as some type 2 diabetes drugs may be safer to use during pregnancy than others, and so may require current treatment to be switched if the person becomes pregnant or is planning a pregnancy.

First line drug treatment

The committee discussed the results from the economic model for the replacement of metformin with one of the other drugs in the analysis at treatment initiation. They noted that although the analysis looked at 5 populations of people with type 2 diabetes (a high cardiovascular (CV) risk population with a prior event, a high CV risk population without a prior event, a pooled high CV risk population, one with BMI greater than or equal to 30 and one representing everyone with type 2 diabetes), the ICER results for each drug were similar across the population groups. All of the ICER results were greater than £20,000 with the exception of Dapagliflozin which had ICERs for all groups less than £20,000. The other SGLT2s had higher ICERs but these were £21,000- £33,000, compared to ICERs of over £50,000 (and in some cases over £100,000) for other drug options. A similar pattern was seen with the analysis for adding a drug to metformin for initial therapy (i.e., starting with dual therapy). In this scenario, ICERs for the SGLT2s ranged from £15,000- £32,000. Further details of results in this population are outlined in the Economic Model Report.

The committee discussed whether the clinical trial data that was used in the economic model and analysed in the NMAs (discussed above) could be generalised to everyone with type 2 diabetes. They noted that the trials all recruited people with established CV disease and a proportion also included people with high CV risk, but no prior CV event. They agreed that there was highest certainty that the results of the NMAs, the economic model and any CV benefits identified applied to people with established CV disease and that the uncertainty increased as the populations in the model became more removed from this group.

The committee noted the economic model findings which suggested that replacing metformin as initial therapy in the treatment of all adults with type 2 diabetes with the SGLT2 dapagliflozin was cost effective (ICER £17,670). However, the committee noted that metformin is very effective at controlling blood glucose levels and they agreed that changing to initial therapy with an SGLT2 for these people would not be appropriate because there was less certainty that they would benefit from this change due to their reduced CV risk compared to the people with type 2 diabetes who have established CV disease or high risk of CV disease who were studied in the CVOT trials. In addition, the cost impact of using

dapagliflozin as first line therapy in place of metformin would be substantial, with a significant opportunity cost to the NHS. The committee therefore agreed that standard release metformin should remain the standard of care first-line drug treatment for newly, or recently, diagnosed adults with type 2 diabetes if diet and lifestyle changes alone are insufficient to control glycaemia and the patient is not at high CV risk (see below for the definition of high CV risk). The committee therefore agreed that the existing recommendations in NG28 (2015) concerning the use of metformin as initial therapy, increasing the dose of metformin over several weeks, when to consider a modified release metformin or reducing or stopping metformin according to kidney function were still applicable and did not make any amendments to them.

The committee agreed that the results of the analyses carried out in this review and the associated model are most applicable to people with established CV disease and high risk of developing CV disease (collectively referred to as high CV risk in the sections below). As a result of this decision, they retained the existing NG28 pathway for drug treatment, including for those people who are metformin intolerant or contraindicated, but developed new recommendations for people with established CV disease and high risk of developing CV disease. The following sections of this discussion focus on the development of new recommendations specific to people with high CV risk (those who have congestive heart failure, established atherosclerotic cardiovascular disease or a high risk of developing cardiovascular disease).

The committee agreed that it was important to assess the cardiovascular status (presence of established atherosclerotic cardiovascular disease or not) and risk of developing cardiovascular disease before determining which treatments would be offered to people with type 2 diabetes. The committee agreed that adults with type 2 diabetes are all generally regarded as being at high cardiovascular risk. However, they noted that certain people (for example younger people, those with a shorter history of diabetes, those without concomitant renal disease) who would not fit into a highest CV risk category, which might include people with previous atherosclerotic disease, congestive heart failure or chronic kidney disease. The committee discussed that type 2 diabetes is progressive and although much can be done to slow disease progression, cardiovascular risk tends to increase with duration of disease and highlighted the importance of not just current cardiovascular risk but lifetime risk of cardiovascular disease.

The committee deliberated over the definition of high CV risk (high risk of future major adverse cardiovascular event such as an MI or stroke) to capture this population. They agreed that a QRISK2 score of >10% might be appropriate because this score takes into account most of the factors that were used to define this population in the economic model (see Economic Model Report section 3.1.2 for information on the modelled population) and factors such as age, gender and ethnicity. However, they agreed that for people aged under 40 years old the lifetime risk of CV disease may be underestimated. They therefore included a point about using clinical judgment to assess lifetime risk in these people and suggested a number of factors (hypertension, dyslipidaemia, smoking, family history (in a first degree relative) of premature cardiovascular disease and obesity) to take into account. Most of these criteria were used in the cardiovascular outcome trials that contained primary prevention cohorts, although definitions varied (including the SGLT2 trials, CANVAS and DECLARE-TIMI 58). The committee agreed that prescribers and people with type 2 diabetes who wanted further guidance on the assessment of risk of cardiovascular disease in adults with type 2 diabetes should see the recommendations in the NICE guideline on Cardiovascular disease: risk assessment and reduction, including lipid modification (CG181) and a cross reference was made to this guideline as part of the recommendation on assessing CV status and risk.

The committee discussed whether there was sufficient evidence to justify replacing metformin or initiating treatment with dual therapy in subgroups of adults diagnosed with type 2 diabetes who have a higher cardiovascular risk. The committee agreed that given the

benefits of metformin for blood glucose management and the similar ICERs for replacing metformin with another drug or adding another drug to metformin that it would be more appropriate to start a person with type 2 diabetes and high CV risk on dual therapy. To simplify the pathway, they retained the existing 2015 recommendation on the use of metformin as first line treatment for adults with type 2 diabetes but made an additional recommendation on the use of SGLT2s in addition to metformin for people with high CV risk or with established CVD.

The committee noted that the economic model suggested that only the SGLT2s were close to being cost effective as a class solely based on cardiovascular outcomes when modelled as additional therapy to metformin in those at higher risk (as a pooled group and separately for people with people with and without prior CV events). However, the committee thought that the ICERs might be slightly overestimated due to the modelling of hypoglycaemia and so thought the 'true' ICER would be slightly lower (see the section on cost effectiveness and resource use for more details).

The committee also noted the clinical evidence from the NMA that SGLT2s reduced hospitalisation for heart failure in adults with type 2 diabetes compared with placebo and other drugs based on trial data from people with higher cardiovascular risk (see above on benefits and harms). The committee were aware that all of the CVOT trials included people with established CV disease, and some of the CVOT trials had a broader population comprising of people at high risk of developing CV disease but that the definitions for the broader group varied across trials. The subgroups in the economic model categorised patients with prior CV events (including myocardial infarction, stroke and congestive heart failure) as having established CV disease; this subgroup was therefore most representative of the trial populations. The committee agreed that there was sufficient certainty in the evidence to recommend initial dual therapy with metformin and an SGLT2 in adults with type 2 diabetes with congestive heart failure or established atherosclerotic cardiovascular disease, who correspond the population with established CV disease (secondary prevention group) in the trials and in the economic model and therefore they made a strong recommendation to offer an SGLT2 with metformin as initial therapy for these people. The committee discussed whether to recommend an individual SGLT2, as canagliflozin in particular had the lowest ICER, but noted that there was significant uncertainty in the modelling which meant that small changes in price of individual SGLT2 drugs may result in changes to the cost effectiveness. Therefore, the committee agreed that, as all the SGLT2 were more effective than placebo but could not differentiated from each other for hospitalisation for heart failure, the SGLT2 with the lowest acquisition cost be selected by the prescriber. This point is already covered in an existing recommendation to use the lowest cost drug within a class if they are all appropriate (see the general recommendation on choosing drug treatments).

Although the SGLT2 ICERs for people without established CVD who were at increased risk of developing CVD were almost identical to the ICERs for the established CVD group, the committee noted that there was greater uncertainty for this group because they were included in a lower proportion in many of the trials and not included in 6 trials at all. The committee agreed that prescribers, in discussion with their patients, may want to think about early dual therapy to help prevent poor cardiovascular outcomes in the future and they made a weaker recommendation for initial dual therapy with SGLT2s and metformin for this population.

The committee agreed that to allow assessment of the tolerability of each drug for the person with type 2 diabetes, the dual therapy should be introduced sequentially rather than at the same time and that it would likely begin with metformin. The committee noted that the effectiveness of the drugs at controlling blood glucose levels can be assessed by measuring HbA1c levels, but the effects of SGLT2s on CV outcomes could only be assumed based on trial evidence and would be expected to lead to improved CV outcomes in the long term. They also agreed that the recommendations about initiating metformin treatment in the

general population applied to people with high CV risk. If metformin is not tolerated, then a trial with a modified-release form may be considered (as per an existing 2015 recommendation) before the SGLT2 inhibitor is added for these people.

The committee noted that SGLT2s have been approved by NICE as monotherapy if metformin, sulfonylurea, and pioglitazone are contraindicated or not tolerated, and if a DPP-4 would otherwise have been prescribed. (See NICE technology appraisals for Canagliflozin, dapagliflozin and empagliflozin as monotherapies for treating type 2 diabetes [TA390] and Ertugliflozin as monotherapy or with metformin for treating type 2 diabetes [TA572] for details). They noted that the results of the economic model did not directly provide evidence for the most effective treatments for people with high CV risk in whom metformin is contraindicated or not tolerated. Although metformin being contraindicated or not tolerated was not an exclusion criterion for the CVOTs, it was expected that the majority of participants in these trials would be able to take metformin and data was not reported separately by ability to take metformin. The committee therefore agreed that in the absence of specific evidence for these people that it would be appropriate to use SGLT2 drugs as the preferred option as they offer cardiovascular benefit (as seen in the NMAs) and were most likely to be cost effective in the NICE economic model as monotherapy (replacing metformin analysis in model). The committee agreed that there was more certainty in the evidence for people who have congestive heart failure or established CVD than for people who have a high risk of developing CV disease (see above for more discussion about this point). They extrapolated these findings to people in whom metformin is contraindicated or not tolerated and therefore made a stronger 'offer' recommendation for the former group, and a separate weaker 'consider' recommendation for the latter group. The committee also agreed that if an SGLT2 was not appropriate (contraindicated or not tolerated) then a DDP-4, pioglitazone or a sulfonylurea would be suitable as alternative monotherapies but did not include this in the recommendation because they wanted to keep the pathway as simple as possible and they agreed that it would not be possible to do this if alternative options were provided every time a drug was not contradicted or not tolerated. They agreed that it was appropriate to have recommendations for metformin being contradicted or not tolerated because this is the drug that the majority of people would take as first-line therapy.

The committee noted that although the DPP-4 drugs did not offer clinically significant cardiovascular benefits in the NMAs and were often dominated for outcomes in the economic model (meaning they were more expensive and less effective than other treatment options), they have a place in therapy due to their effectiveness at lowering glycaemia without a high burden of adverse events, particularly in older and more frail adults. The committee also noted that in the base case economic model pioglitazone was not cost effective as monotherapy for replacing metformin, but that it became highly cost effective in the sensitivity analysis where quality-of-life decrements associated with hypoglycaemia were removed. In addition, the rates of severe hypoglycaemia in the PROactive trial were for pioglitazone given as combination therapy. In the committees' experience, in clinical practice, the rates of severe hypoglycaemia when pioglitazone is used as monotherapy are much lower. On this basis, the committee considered that the 'true' ICER for pioglitazone was plausibly cost-effective. However, pioglitazone still has contraindications to its use in certain people.

The committee discussed additional safety and monitoring issues raised by the use of SGLT2s. The committee noted the MHRA/CHM advice on the Risk of diabetic ketoacidosis with sodium-glucose co-transporter 2 (SGLT2) inhibitors (canagliflozin, dapagliflozin or empagliflozin). The committee were aware that the SGLT2 inhibitors are a relatively new class of drugs and clinical experience with their use is low. They noted that in their experience there have been multiple instances of avoidable diabetic ketoacidosis resulting in hospital admission. Diabetic ketoacidosis (DKA) is a rare (in type 2 diabetes) but potentially life-threatening side effect of treatment due to build-up of ketones in the body. The committee noted that taking an SGLT2 inhibitors along with a ketogenic diet has been seen to increase the risk DKA in clinical practice. The committee agreed that prescribers should check that a person is not on a ketogenic diet before commencing treatment with an SGLT2. Similarly, the

committee agreed that people with type 2 diabetes taking an SGLT2 should be advised by the prescriber not to commence very low carbohydrate or ketogenic diet without first discussing this with a health professional because it would be advisable to suspend SGLT2 treatment to avoid DKA before starting the diet. The committee noted that these diets are often used in remission treatment for type 2 diabetes and that treatment with SGLT2 should not be a barrier to access to such programmes.

The committee noted that all manufacturers of SGLT2 inhibitors advise the avoidance of their use during pregnancy and breastfeeding due to toxicity and the presence of the drugs in breast milk being observed in animal studies (see the BNF for details). Therefore, it is essential that prescribers check with the person who has type 2 diabetes before initiating treatment with an SGLT2 that they are not pregnant, breastfeeding, or planning a pregnancy. In addition, they noted that an unplanned pregnancy could occur and would be problematic when taking an SGLT2 inhibitor, so they recommended checking with the person whether advice about contraception is needed to prevent this happening. The committee advised that prescribers should also see NICE guideline on diabetes in pregnancy.

The committee agreed that as SGLT2 inhibitors can have adverse effects on renal function prescribers should monitor the person's renal function, including the estimated glomerular filtration rate (eGFR). They also noted that monitoring requirements vary between SGLT2 inhibitor treatments in the SPCs. The committee agreed that for those with reduced renal function dose adjustment or avoidance of SGLT2 inhibitor treatment may be required depending on the SGLT2 inhibitor selected and the renal function test results obtained (as detailed in the summary of product characteristics (SPC) for the proposed SGLT2 inhibitor). The committee decided against making a recommendation for monitoring to be carried out at specific time intervals because the appropriate timing would need to be tailored to the needs of the individual, taking into account their clinical factors and baseline renal function. Instead, the committee made a recommendation to warn clinicians about the need for monitoring when SGLT2 inhibitors are used.

The committee discussed that due to their mechanism of action in increasing urinary glucose excretion (osmotic diuresis) SGLT2 inhibitors may reduce blood pressure. The committee agreed that certain groups may require more careful monitoring of fluid volume status (for example physical examination, blood pressure checks, blood tests including renal function, haematocrit, and serum electrolytes). These groups may include older adults (aged 65 years and above), those with established cardiovascular disease, those with an eGFR <60 mL/min/1.73m^2, patients taking antihypertensive therapy with a history of hypotension, and those on diuretics. In particular, the committee noted that people aged 65 and over, people who are frail or at risk of dehydration are commonly encountered in clinical practice and are vulnerable to DKA. The committee agreed that prescribers should be aware of the additional monitoring requirements listed in the SPCs for the above groups, but they included fluid volume depletion in the 'be aware' recommendation to emphasise this point.

The committee noted that SGLT2s could lead to an increased risk of dehydration and DKA if taken by a person during an acute illness, particularly if there is reduced intake of fluids from nausea or vomiting and diarrhoea. The committee therefore recommended that prescribers should advise people commencing SGLT2 treatment about suspending this if they become ill.

Reviewing drug treatments

The committee discussed the importance of reviewing treatments regularly to ensure that they remain optimised to the individual. They noted that this process is particularly important when a change in treatment is being considered because the lack of effectiveness of the current regimen could be due to poor adherence and that this could in turn be linked to adverse effects. In these cases, it would be appropriate to explore other treatment options involving the same line of therapy before thinking about adding a drug or moving to treatment with insulin. The committee noted that treatment reviews can also involve the removal of

ineffective or unnecessary treatments or those that are not tolerated. They agreed that some changes in clinical circumstances (such as losing weight) could lead to a degree of remission and the possibility of de-escalating/ reducing treatment.

The committee agreed that a number of factors should be taken into account as part of the optimisation process before changing treatments is considered. These included adherence to existing medication, prescribed doses and formulations, and adverse effects. They were also aware of the NICE guideline on medicines optimisation which has a relevant section on medication review and of the recommendations on reviewing medications and supporting adherence in the NICE guideline on medicines adherence and included cross references to these guidelines They agreed that the list of factors was not intended to be exhaustive and that the NICE guidelines mentioned would provide additional information to support the implementation of this recommendation. The committee also agreed that the effectiveness of the treatments and individual clinical factors were important considerations. This latter category covers both the individual's medical history and the current medical situation. However, as these were both covered by the existing 2015 recommendation on choosing drug treatments the committee included a cross reference to this recommendation rather than duplicating content. In addition, they agreed that the other factors listed in that recommendation were also relevant at the treatment review stage.

Adding an SGLT2 inhibitor at any stage after first-line treatment has been started

In order to ensure that people with type 2 diabetes who have either congestive heart failure or established cardiovascular disease and are already on drug therapy are able to benefit from the use of SGLT2s similar to people at treatment initiation, the committee included a recommendation to offer therapy with an SGLT2 to these people based on the clinical (cardiovascular benefit) and cost effectiveness evidence of benefit in this subgroup. Similarly, for those adults with type 2 diabetes already on drug therapy who are at high risk of developing cardiovascular disease, therapy with an SGLT2 should be considered based on the lower certainty evidence of cost-effectiveness in this subgroup. However, it may be the case that a person who is already taking treatment for type 2 diabetes develops congestive heart failure or established atherosclerotic cardiovascular disease or becomes at high risk of developing cardiovascular disease. In these cases, it is now appropriate for these people to have access to SGLT2 inhibitors as well and the committee included these scenarios in the recommendation to ensure that this could happen. The differing strengths of the recommendations for people with established CVD or at high risk of developing CVD was based on the different levels of confidence the committee had in the results for these groups due to the populations in the CVOTs and the economic model (see above for more discussion about this point). The committee discussed that in line with the recommendation on reviewing drug treatments it may be appropriate to replace an existing therapy with an SGLT2 inhibitor rather than to add it to the existing treatment regimen. This choice would be dependent on the persons individual clinical circumstances, needs and preferences and should be made as part of a shared decision-making process.

Treatment options if further interventions are required

The committee agreed that it was unnecessary to have separate recommendations for people at high risk of developing cardiovascular disease who had congestive heart failure or established atherosclerotic cardiovascular disease for later stages of treatment for several reasons. Firstly, because the evidence from the clinical review and economic model continued to show that the SGLT2 inhibitors were likely to be the most cost-effective options for these people. Secondly, the recommendations the committee had made on first-line treatment using SGLT2 inhibitors (with metformin if it is not contradicted or not tolerated or alone otherwise) and for switching or adding these drugs at later stages meant that these people would be able to access SGLT2 inhibitors without adding this consideration to the existing recommendations. Finally, the alternative treatment options for people with and without increased cardiovascular risk remained the same for later treatment stages.

Therefore, the committee agreed to retain the existing 2015 NG28 recommendations for treatment options if further interventions are required without editing them to refer to cardiovascular risk.

The committee agreed with the existing 2015 recommendation that if dual therapy with metformin and another oral drug was not sufficient to control the HbA1c to below the persons agreed threshold for intervention then triple therapy by adding a DPP-4 inhibitor, pioglitazone, or sulfonylurea would be appropriate. Based on the earlier recommendations that the committee made as part of this update, people with established atherosclerotic CVD, or who were at high risk of developing CVD, would be expected to be taking an SGLT2 inhibitor already. In further support of this the economic model showed that a combination of metformin, sulfonylurea and an SGLT2 inhibitor was more likely to be cost effective compared to metformin, sulfonylurea, and any other drug class studied in the CVOTs (if the SGLT2 inhibitor with the lowest acquisition cost was used) for adults with type 2 diabetes and established CVD or those who were at high risk of developing CVD. However, the ICERs varied within the class and some drugs had ICERs of more than £20,000 for the three high risk CV populations. As before, the committee thought that the ICERs might be slightly overestimated due to the modelling of hypoglycaemia and so thought the 'true' ICER would be slightly lower (see the section 1.1.11.14 on Cost effectiveness and resource use for more details). Although it was not included in the model, the committee also agreed that commencing insulin therapy may be an option for these groups, based on the existing recommendations in NG28 (2015). People who were not in these groups but met the criteria in a relevant NICE technology appraisal (TA315, TA418, TA336, or TA583) could also take an SGLT2 inhibitor as part of their combination therapy at this stage.

The committee agreed that, where possible, the recommendations for people in whom metformin was contraindicated or not tolerated should be merged with the recommendations for people who could take metformin because after first-line treatment the same options applied as seen with the recommendations in NG28 (2015). By doing this they aimed to simplify the pathway to make it more user friendly. The committee noted that these options were the same if first-line monotherapy (either metformin or another monotherapy if metformin was contraindicated or not tolerated) was not sufficient to control the HbA1c to below the persons agreed threshold. They therefore merged recommendations 1.6.25 and 1.6.26 from the 2015 version of NG28. However, they were unable to merge the later recommendations because, based on the existing 2015 recommendations, the treatment option was limited to insulin for people in whom metformin was contraindicated or not tolerated if dual therapy was not effective. In contrast, the options were wider and included triple therapy or insulin for people who could take metformin. The committee did not look at evidence that would allow them to update these options as part of the current work. Therefore, the recommendations were retained with minor amendments (for example, adding the SGLT2 inhibitor TAs as options if people meet the criteria specified in the TAs).

The committee noted that evidence for the use of GLP1 mimetics to reduce cardiovascular risk suggested that they are not cost-effective at the current cost at any stage in the treatment pathway and therefore recommended against the use of GLP-1 mimetics solely to reduce cardiovascular risk. For the analysis adding a GLP-1 mimetic to metformin and sulfonylurea the ICERs were dominated or over £ 50,000 for dulaglutide to over £200,000 for liraglutide. For the analyses where a GLP-1 mimetic was added to, or replaced a component of, metformin, sulfonylurea and NPH insulin the ICERs were either dominated or fell in a range between £50,000 to £6,334,180. However, the committee agreed that there may be wider benefits from using GLP-1 mimetics that are not captured in the clinical evidence included in the current evidence review and the economic model, although these drugs are unlikely to ever be cost-effective at their current prices unless they are used in a very restricted population who lack other treatment options.

The evidence that was reviewed as part of this update was limited to the cardiovascular benefits of GLP1-mimetics. The committee noted that people should be aware that evidence

for the use of GLP1 mimetics to control blood glucose levels was not looked at as part of the update to the guidance. As a result, the committee were unable to update the existing 2015 GLP-1 mimetic recommendations for the wider type 2 diabetes population and they were retained as before. The committee were aware that in practice GLP-1 mimetics are being used in populations outside those specified in the existing recommendations in the NICE guideline NG28 (2015). These recommendations set tight limits to the populations that should be offered a GLP-1 mimetic, based on the analyses in NG28 that showed that GLP-1s mimetics were not cost-effective in the main type 2 diabetes population. However, the committee were concerned that, as currently written, the existing (2015) recommendation would mean that people taking newer drugs with proven cardiovascular benefit, such as SGLT2 inhibitors, would have to switch to a combination of metformin, a sulfonylurea and a GLP-1 mimetic which they felt might be inappropriate and not in keeping with current clinical practice. The committee were able to amend this recommendation to remove the requirement for this specific combination of treatment options, but the rest of the recommendation and the other recommendations for GLP-1 mimetics were out of scope and as a result, the criteria for accessing a GLP-1 mimetic remained unchanged.

1.1.11.6 Other factors the committee took into account

There was a lack of evidence for people in whom metformin was contraindicated or not tolerated. The committee therefore had to extrapolate the evidence from the economic model that did not include these people as a separate group. This was in turn based on data from the CVOTs that included people who could take metformin and may also have included people who could not take metformin but did not present the results separately. Although there was a lack of evidence the committee decided against making a specific research recommendation to determine the most effective treatments for these people because most people can tolerate and are not contraindicated for metformin and so this would be a relatively small population to recruit for a trial. In addition, there are multiple other treatment options licensed as monotherapy and combination therapy which could be used, and the committee agreed that in practice if a particular drug is contraindicated or not tolerated the clinician would select the next most effective and appropriate treatment in discussion with the person who has type 2 diabetes. Therefore, they agreed that additional clinical trials would be of low priority compared to other areas that need research. They also noted that it would be unlikely that the relevant drug companies would run such trials.

In addition, the committee discussed whether GLP-1 mimetics might be cost-effective at later treatment stages compared to insulin therapy. They noted that adults with type 2 diabetes may prefer to take GLP-1 mimetics instead of insulin due to weekly rather than daily injections, and the association of GLP-1 mimetics with weight loss. In contrast, insulins are associated with weight gain, need blood glucose monitoring and may lead to restrictions on activities of daily living such as driving. However, this comparison was not included in the economic modelling and the relevant clinical evidence was not searched for or examined as part of this update. The committee therefore made a research recommendation for this analysis (see Appendix O for more details).

1.1.12 Recommendations supported by this evidence review

This evidence review supports new recommendations 1.7.4- 1.7.6, 1.7.9, 1.7.12-1.7.16, 1.7.21 and the research recommendation on GLP-1 receptor agonists compared to insulin.

1.1.13 References – included studies

1.1.13.1 Effectiveness

Key paper for each study used for data extraction (matches summary evidence table)

CANVAS

Mahaffey Kenneth, W, Neal, Bruce, Perkovic, Vlado et al. (2018) Canagliflozin for Primary and Secondary Prevention of Cardiovascular Events: Results From the CANVAS Program (Canagliflozin Cardiovascular Assessment Study). Circulation 137(4): 323-334

CARMELINA

Rosenstock, Julio, Perkovic, Vlado, Johansen Odd, Erik et al. (2019) Effect of Linagliptin vs Placebo on Major Cardiovascular Events in Adults With Type 2 Diabetes and High Cardiovascular and Renal Risk: The CARMELINA Randomized Clinical Trial. JAMA 321(1): 69-79

CAROLINA

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DECLARE-TIMI

Wiviott Stephen, D, Raz, Itamar, Bonaca Marc, P et al. (2019) Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. The New England journal of medicine 380(4): 347-357

ELIXA

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EMPA-REG

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EXAMINE

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EXSCEL

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LEADER

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PIONEER-6

Husain, Mansoor, Birkenfeld Andreas, L, Donsmark, Morten et al. (2019) Oral Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. The New England journal of medicine 381(9): 841-851

PROactive

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SAVOR-TIMI 53

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SUSTAIN-6

Marso Steven, P, Daniels Gilbert, H, Brown-Frandsen, Kirstine et al. (2016) Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. The New England journal of medicine 375(4): 311-22

TECOS

Green Jennifer, B, Bethel M, Angelyn, Armstrong Paul, W et al. (2015) Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes. The New England journal of medicine 373(3): 232-42

VERTIS-CV

Cannon Christopher, P, Pratley, Richard, Dagogo-Jack, Samuel et al. (2020) Cardiovascular Outcomes with Ertugliflozin in Type 2 Diabetes. The New England journal of medicine 383(15): 1425-1435

All included papers (includes all identified references for each of the studies above)

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Appendices

Appendix A – Review protocols

Review protocol for the most effective pharmacological therapies with cardiovascular and other benefits for people with type 2 diabetes

ID	Field	Content
0.	PROSPERO registration number	Not relevant
1.	Review title	Pharmacological therapies with cardiovascular and other benefits in people with type 2 diabetes.
2.	Review question	Which pharmacological therapies are most effective at providing cardiovascular and other benefits in addition to blood glucose control in people with type 2 diabetes?
3.	Objective	To determine which pharmacological therapies are most effective at providing cardiovascular and other benefits in addition to blood glucose control in people with type 2 diabetes.
4.	Searches	The following databases will be searched for the clinical review: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • Medline in Process • Medline EPub Ahead of Print

		For the economics review the following databases will be searched: • Embase • MEDLINE • Medline in Process • Medline EPub Ahead of Print • Econlit • NHS EED (legacy records) • INAHTA Searches will be restricted by: • Studies reported in English • Study design RCT and SR 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 will be set • Economic evaluations and quality of life filters for the economic search Other searches: • None identified The searches will be re-run 6 weeks before final submission of the review and further studies retrieved for inclusion. The full search strategies for MEDLINE database will be published in the final review.
5.	Condition or domain being studied	Pharmacological treatments for people with Type 2 Diabetes.
6.	Population	Inclusion: Adults (aged 18 years and older) with Type 2 diabetes Exclusion: - Children and young people aged younger than 18 years with type 2 diabetes. - Pregnant women with type 2 diabetes.

		- People with type 1 diabetes. - People with type 2 diabetes who are hyperglycaemic and require rescue treatment.

7.	Interventions	One of the following treatments added to existing therapy:
		
		• Thiazolidinediones
		  ○ Pioglitazone
		• SGLT2 inhibitors
		  ○ Canagliflozin
		  ○ Dapagliflozin
		  ○ Ertugliflozin
		  ○ Empagliflozin
		• Sulfonylurea
		  ○ Gliclazide (standard and modified release)
		  ○ Glimepiride
		  ○ Glipizide
		  ○ Tolbutamide
		
		GLP-1 agonists will be considered added to any anti-diabetic licenced for type 2 diabetes but not DPP4 inhibitors:
		  ○ Liraglutide
		  ○ Dulaglutide
		  ○ Semaglutide
		  ○ Exenatide (standard and modified release)
		  ○ Lixisenatide
		
		DPP4 inhibitors will be considered added to any anti-diabetic licenced for type 2 diabetes but not GLP-1 agonists:
		  ○ Saxagliptin
		  ○ Vildagliptin
		  ○ Sitagliptin
		  ○ Alogliptin
		  ○ Linagliptin

		Both standard and modified release preparations of drugs listed which are available in the UK will be considered. Both oral and injectable modes of administration of drugs listed which are available in the UK will be considered.
8.	Comparators	Placebo or another drug added to existing therapy
9.	Types of study to be included	- Randomised controlled trials - Systematic reviews of randomised controlled trials (including published NMAs) - Studies must include time to event data (Kaplan Meier curves, HRs with a minimum follow up duration of 15 months - Studies must be in the format of A (mixed background) versus B or placebo (mixed background) [a +(b or b+c or b+c+d) versus x +(b or b+c or b+c+d)]
10.	Other exclusion criteria	- Non-randomised evidence (including observational, cohort, case–control and case series studies, uncontrolled or single arm trials), narrative reviews, conference abstracts, letters, editorials and trial protocols. - Studies including a mixed population of people with type 1 and 2 diabetes, unless subgroup analyses were reported or 85% or more of the study population have type 2 diabetes. - Studies including a mixed population of people with and without diabetes will be excluded. - Comparisons with unlicensed modes of delivery (for example, inhaled insulin) - Crossover trials, (unless the duration of one or both interventions is at least 15 months and there is a washout period of at least 6 weeks between interventions). - Trials where there is unclear washout of existing drug treatments, where a proportion or all participants continued previous medicines that will likely confound study results (papers were excluded unless this represented a small proportion of patients that is less than 5%). - Trials where drugs are compared with each other or placebo but the treatments are the same within each treatment arm (a vs b or placebo) - Trials that have a treatment and follow up period of less than 15 months - Trials where rescue medication was given and it is unclear if analyses were adjusted. - Systematic reviews that did not include at least one RCT of at least 15 months duration - Dose finding trials where both arms would be combined in a single node in the NMA. (Three arm trials may be included if they connect to the network and provide useful information.) - Trials with no information relating to doses. - Other methodological reasons (e.g. no explicit inclusion/exclusion criteria - Trials of Treatments which are not available, or no longer available, in the UK including:

		○ Glibenclamide ○ Chlorpropamide ○ Nateglinide ○ Miglitol ○ Omarigliptin ○ Albiglutide - Trials of treatments that are rarely used in the UK: ○ Repaglinide ○ Acarbose - Trials of combinations of drugs which include one or more drug that is not available in the UK, no longer available in the UK or are rarely used in the UK. - Trials of combinations of drugs within the same class due to the therapeutic overlap. - Trials of combinations of a GLP-1 analogue with a DPP4 inhibitor due to the therapeutic overlap. - Trials that were not reported in English
11.	Context	Since the publication of the 2015 guideline, new blood-glucose lowering medicines have been developed, and there is new evidence on cardiovascular and renal outcomes. This new evidence may affect which medicines should be offered, and which combinations should be used at each stage of treatment.
12.	Primary outcomes (critical outcomes)	Outcomes to take from CVOTs: • Cardiovascular outcomes (event rates of the following during trial duration): • Myocardial infarction • Stroke, or atherosclerotic disease • Unstable angina • Congestive heart failure • Cardiovascular-related mortality The outcomes will be presented as reported in the majority of trials to facilitate comparison. Where possible and appropriate, they will include all non-fatal reported events, not just those events leading to hospitalisation. Since cardiovascular mortality is a separate outcome, they will be limited to non-fatal events, where possible, to prevent double counting.

		• All-cause mortality Other outcomes to take from CVOTs (even if there are NG28 surrogate trials for these drugs): • Change in weight or Body Mass Index (BMI) at 1 year • Total discontinuations • Discontinuations due to adverse events • Severe hypoglycaemic events Drug type specific adverse events will be accounted for in the economic model if appropriate. The economists will carry out a brief, non-systematic review to identify this data.
13.	Secondary outcomes (important outcomes)	None
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. This review will make use of the priority screening functionality within the EPPI-reviewer software. A stopping rule will be used to terminate screening if the following criteria are met: • At least 50% of the database has been screened and • 1,000 records have been screened with no further included studies (this 1,000 can fall within the 50%) A further 10% random screen of remaining records will be undertaken. If any additional records are identified, then the remaining records will be screened in full. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). Extracted information for the quantitative review will include: study type; study setting; study population and participant demographics and baseline characteristics; details of the intervention and comparator used; inclusion and exclusion

		criteria; recruitment and study completion rates; outcomes and times of measurement and information for assessment of the risk of bias.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using appropriate checklists as described in Developing NICE guidelines: the manual. Risk of bias in RCTs will be assessed using the Cochrane risk of bias version 2 tool. Risk of bias in systematic reviews and meta-analyses of RCTs will be assessed using ROBIS checklist.
16.	Strategy for data synthesis	Where appropriate pairwise meta-analyses will be performed in Cochrane Review Manager V5.3. A pooled relative risk will be calculated for dichotomous outcomes (using the Mantel–Haenszel method) reporting numbers of people having an event. A pooled mean difference will be calculated for continuous outcomes (using the inverse variance method) when the same scale is used to measure an outcome across different studies. Where different studies presented continuous data measuring the same outcome but using different numerical scales these outcomes will be all converted to the same scale before meta-analysis is conducted on the mean differences. Where outcomes measured the same underlying construct but used different instruments/metrics, data will be analysed using standardised mean differences (SMDs, Hedges' g). Fixed effects models will be fitted unless there is significant statistical heterogeneity in the meta-analysis, defined as I2≥50%, when random effects models will be used instead. GRADE will be used to assess the quality of the pairwise outcomes. Outcomes using evidence from RCTs will be rated as high quality initially and downgraded from this point. Reasons for upgrading the certainty of the evidence will also be considered. Where 10 or more studies are included as part of a single meta-analysis, a funnel plot will be produced to graphically assess the potential for publication bias. Network meta-analysis (NMAs) may be used to synthesise direct evidence about pairs of interventions that originate from two or more separate studies and indirect evidence.

		The quality of the NMA networks will be assessed using a modified form of GRADE.
17.	Analysis of sub-groups	None
18.	Type and method of review	☒ Intervention ☐ Diagnostic ☐ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service Delivery ☐ Other (please specify)
19.	Language	English
20.	Country	England
21.	Anticipated or actual start date	December 2020
22.	Anticipated completion date	June 2021

23.	Stage of review at time of this submission	**Review stage**	**Started**	**Completed**
		Preliminary searches	☑	☑
		Piloting of the study selection process	☑	☑
		Formal screening of search results against eligibility criteria	☑	☑
		Data extraction	☑	☐
		Risk of bias (quality) assessment	☑	☐
		Data analysis	☐	☐

24.	Named contact	**5a. Named contact** NICE Guideline Updates Team **5b Named contact e-mail** T2DAmedupdate@nice.org.uk **5e Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE) and NICE Guideline Updates Team
25.	Review team members	From the Guideline Updates team: • Technical lead, Marie Harrisingh • Medicines analyst, Greg Moran • Health economics lead, Lucy Beggs • Health economics analyst, Thomas Jones • Information specialist, Sarah Glover
26.	Funding sources/sponsor	This systematic review is being completed by the Guideline Updates team which receives funding from NICE.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10160

29.	Other registration details	None
30.	Reference/URL for published protocol	None
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
32.	Keywords	Diabetes type 2, adults, pharmacological treatment, cardiovascular outcome trials.
33.	Details of existing review of same topic by same authors	None
34.	Current review status	☒ Ongoing ☐ Completed but not published ☐ Completed and published ☐ Completed, published and being updated ☐ Discontinued
35..	Additional information	None

36.	Details of final publication	www.nice.org.uk

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Appendix B – Methods

Reviewing research evidence

Review protocols

Review protocols were developed with the guideline committee to outline the inclusion and exclusion criteria used to select studies for each evidence review.

Searching for evidence

Evidence was searched for each review question using the methods specified in the 2020 NICE guidelines manual.

Selecting studies for inclusion

All references identified by the literature searches and from other sources (for example, previous versions of the guideline or studies identified by committee members) were uploaded into EPPI reviewer software (version 5) and de-duplicated. Titles and abstracts were assessed for possible inclusion using the criteria specified in the review protocol. 10% of the abstracts were reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer.

The following evidence reviews made use of the priority screening functionality within the EPPI-reviewer software: [insert links to evidence reviews that used the priority screening functionality in EPPI]. This functionality uses a machine learning algorithm (specifically, an SGD classifier) to take information on features (1-, 2- and 3-word blocks) in the titles and abstract of papers marked as being 'includes' or 'excludes' during the title and abstract screening process, and re-orders the remaining records from most likely to least likely to be an include, based on that algorithm. This re-ordering of the remaining records occurs every time 25 additional records have been screened. Research is currently ongoing as to what are the appropriate thresholds where reviewing of abstracts can be stopped, assuming a defined threshold for the proportion of relevant papers it is acceptable to miss on primary screening. As a conservative approach until that research has been completed, the following rules were adopted during the production of this guideline:

- At least 50% of the identified abstracts (or 1,000 records, if that is a greater number) were always screened.
- After this point, screening was only terminated if a pre-specified threshold was met for a number of abstracts being screened without a single new include being identified. This threshold was set according to the expected proportion of includes in the review (with reviews with a lower proportion of includes needing a higher number of papers without an identified study to justify termination) and was always a minimum of 250.

As an additional check to ensure this approach did not miss relevant studies, systematic reviews (or qualitative evidence syntheses in the case of reviews of qualitative studies) were included in the review protocol and search strategy for all review questions. Relevant systematic reviews or qualitative evidence syntheses were used to identify any papers not found through the primary search. Committee members were also consulted to identify studies that were missed. If additional studies were found that were erroneously excluded during the priority screening process, the full database was subsequently screened.

The full text of potentially eligible studies was retrieved and assessed according to the criteria specified in the review protocol. A standardised form was used to extract data from included studies. Study investigators were contacted for missing data when time and resources allowed (when this occurred, this was noted in the evidence review and relevant data was included).

Incorporating published evidence syntheses

For all review questions where a literature search was undertaken looking for a particular study design, published evidence syntheses (quantitative systematic reviews or qualitative evidence syntheses) containing studies of that design were also included. All included studies from those syntheses were screened to identify any additional relevant primary studies not found as part of the initial search. Evidence syntheses that were used solely as a source of primary studies were not formally included in the evidence review (as they did not provide additional data) and were not quality assessed.

Methods of combining evidence

Data synthesis for intervention studies

Where possible, meta-analyses were conducted to combine the results of quantitative studies for each outcome. Network meta-analyses was considered in situations where the following criteria were met:

- At least three treatment alternatives.
- The aim of the review was to produce recommendations on the most effective option, rather than simply describe the effectiveness of treatment alternatives.

In other situations, pairwise meta-analysis was used to compare interventions.

Pairwise meta-analysis

Pairwise meta-analyses were performed in Cochrane Review Manager V5.3. A pooled relative risk was calculated for dichotomous outcomes (using the Mantel–Haenszel method) reporting numbers of people having an event, and a pooled incidence rate ratio was calculated for dichotomous outcomes reporting total numbers of events. Both relative and absolute risks were presented, with absolute risks calculated by applying the relative risk to the risk in the comparator arm of the meta-analysis (calculated as the total number events in the comparator arms of studies in the meta-analysis divided by the total number of participants in the comparator arms of studies in the meta-analysis).

Fixed- and random-effects models were fitted, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence. Fixed-effects models were the preferred choice to report, but in situations where the assumption of a shared mean for fixed-effects model were clearly not met, even after appropriate pre-specified subgroup analyses were conducted, random-effects results are presented. Fixed-effects models were deemed to be inappropriate if there was significant statistical heterogeneity in the meta-analysis, defined as $I^2 \geq 50\%$.

However, in cases where the results from individual pre-specified subgroup analyses were less heterogeneous (with $I^2 < 50\%$) the results from these subgroups were reported using fixed effects models. This may have led to situations where pooled results were reported from random-effects models and subgroup results were reported from fixed-effects models.

Network meta-analysis

Frequentist NMAs were undertaken using the netmeta package in R v3.6.2. This uses a graph-theoretical method which is mathematically equivalent to frequentist network meta-analysis (Rücker 2012). Inconsistency was assessed using the overall I^2 value for the whole network, which is a weighted average of the I^2 value for all comparisons where there are multiple trials (both direct and indirect), and random-effects models were used if the I^2 value was above 50% (as for pairwise meta-analyses, this was interpreted as showing the assumption of consistent, shared underlying means was not met, and therefore a fixed-effects model was inappropriate). In addition, the Cochrane Q and p-value were also examined to check that these were in agreement with the I^2 results and if this was not the case then a random effects model was used.

Appraising the quality of evidence

Intervention studies (relative effect estimates)

RCTs were quality assessed using the Cochrane Risk of Bias Tool. Evidence on each outcome for each individual study was classified into one of the following groups:

- Low risk of bias – The true effect size for the study is likely to be close to the estimated effect size.
- Moderate risk of bias – There is a possibility the true effect size for the study is substantially different to the estimated effect size.
- High risk of bias – It is likely the true effect size for the study is substantially different to the estimated effect size.

Each individual study was also classified into one of three groups for directness, based on if there were concerns about the population, intervention, comparator and/or outcomes in the study and how directly these variables could address the specified review question. Studies were rated as follows:

- Direct – No important deviations from the protocol in population, intervention, comparator and/or outcomes.
- Partially indirect – Important deviations from the protocol in one of the following areas: population, intervention, comparator and/or outcomes.
- Indirect – Important deviations from the protocol in at least two of the following areas: population, intervention, comparator and/or outcomes.

Minimally important differences (MIDs) and clinical decision thresholds

The Core Outcome Measures in Effectiveness Trials (COMET) database was searched to identify published minimal clinically important difference thresholds relevant to this guideline that might aid the committee in identifying clinical decision thresholds for the purpose of GRADE. Identified MIDs were assessed to ensure they had been developed and validated in a methodologically rigorous way, and were applicable to the populations, interventions and outcomes specified in this guideline. In addition, the Guideline Committee were asked to prospectively specify any outcomes where they felt a consensus clinical decision threshold could be defined from their experience. In particular, any questions looking to evaluate non-inferiority (that one treatment is not meaningfully worse than another) required a clinical decision threshold to be defined to act as a non-inferiority margin.

No clinical decision thresholds were identified thought his process of by the committee. For relative risks and hazard ratios, a default clinical decision threshold for dichotomous outcomes of 0.8 to 1.25 was used.

GRADE for intervention studies analysed using pairwise analysis

GRADE was used to assess the quality of evidence for the outcomes specified in the review protocol. Data from randomised controlled trials were initially rated as high quality while data from other study types were initially rated as low quality. The quality of the evidence for each outcome was downgraded or not from this initial point, based on the criteria given in Table 16.

Table 16: Rationale for downgrading quality of evidence for intervention studies

GRADE criteria	Reasons for downgrading quality
Risk of bias	Not serious: If less than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from studies at high risk of bias, the outcome was downgraded two levels. Extremely serious: If greater than 33.3% of the weight in a meta-analysis came from studies at critical risk of bias, the outcome was downgraded three levels Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies at high and low risk of bias.
Indirectness	Not serious: If less than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from indirect studies, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between direct and indirect studies.
Inconsistency	Concerns about inconsistency of effects across studies, occurring when there is unexplained variability in the treatment effect demonstrated across studies (heterogeneity), after appropriate pre-specified subgroup analyses have been conducted. This was assessed using the I^2 statistic. N/A: Inconsistency was marked as not applicable if data on the outcome was only available from one study.

GRADE criteria	Reasons for downgrading quality
	Not serious: If the I^2 was less than 33.3%, the outcome was not downgraded. Serious: If the I^2 was between 33.3% and 66.7%, the outcome was downgraded one level. Very serious: If the I^2 was greater than 66.7%, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies with the smallest and largest effect sizes.
Imprecision	If an MID other than the line of no effect was defined for the outcome, the outcome was downgraded once if the 95% confidence interval for the effect size crossed one line of the MID, and twice if it crosses both lines of the MID. If the line of no effect was defined as an MID for the outcome, it was downgraded once if the 95% confidence interval for the effect size crossed the line of no effect (i.e., the outcome was not statistically significant), and twice if the sample size of the study was sufficiently small that it is not plausible any realistic effect size could have been detected. Outcomes meeting the criteria for downgrading above were not downgraded if the confidence interval was sufficiently narrow that the upper and lower bounds would correspond to clinically equivalent scenarios.
Publication bias	Where 10 or more studies were included as part of a single meta-analysis, a funnel plot was produced to graphically assess the potential for publication bias. When a funnel plot showed convincing evidence of publication bias, or the review team became aware of other evidence of publication bias (for example, evidence of unpublished trials where there was evidence that the effect estimate differed in published and unpublished data), the outcome was downgraded once. If no evidence of publication bias was found for any outcomes in a review (as was often the case), this domain was excluded from GRADE profiles to improve readability.

Modified GRADE for intervention studies analysed using network meta-analysis

A modified version of the standard GRADE approach for pairwise interventions was used to assess the quality of evidence across the network meta-analyses. While most criteria for pairwise meta-analyses still apply, it is important to adapt some of the criteria to take into consideration additional factors, such as how each 'link' or pairwise comparison within the network applies to the others. As a result, the following criteria (Table 17) was used when modifying the GRADE framework to a network meta-analysis. It is designed to provide a single overall quality rating for an NMA to judge the overall strength of evidence.

Table 17: Rationale for downgrading quality of evidence for network meta-analysis

GRADE criteria	Reasons for downgrading quality
Risk of bias	Not serious: If fewer than 33.3% of the studies in the network meta-analysis were at moderate or high risk of bias, the overall network was not downgraded. Serious: If greater than 33.3% of the studies in the network meta-analysis were at moderate or high risk of bias, the network was downgraded one level. Very serious: If greater than 33.3% of the studies in the network meta-analysis were at high risk of bias, the network was downgraded two levels.
Indirectness	Not serious: If fewer than 33.3% of the studies in the network meta-analysis were partially indirect or indirect, the overall network was not downgraded. Serious: If greater than 33.3% of the studies in the network meta-analysis were partially indirect or indirect, the network was downgraded one level. Very serious: If greater than 33.3% of the studies in the network meta-analysis were indirect, the network was downgraded two levels.
Inconsistency	N/A: Inconsistency was marked as not applicable if there were no links in the network where data from multiple studies (either direct or indirect) were synthesised. For network meta-analyses conducted under a frequentist framework, the network was downgraded one level if the I^2 was greater than 50%. In addition, the direct and indirect treatment estimates were compared as a check on the consistency of the network.
Imprecision	95% confidence intervals were used to assess imprecision. Not serious: The data were sufficiently precise to allow the committee to draw conclusions from the results of the NMA. (At least one comparison had a 95% CI that did not cross the line of no effect.) Serious: Imprecision had a moderate impact on the ability of the committee to draw conclusions from the results of the NMA. Very serious: Imprecision had a substantial impact on the committee to draw conclusions from the results of the NMA.

References

Follmann D, Elliott P, Suh I, Cutler J (1992) Variance imputation for overviews of clinical trials with continuous response.Journal of Clinical Epidemiology 45:769–73

Fu R, Vandermeer BW, Shamliyan TA, et al. (2013) Handling Continuous Outcomes in Quantitative Synthesis In: Methods Guide for Effectiveness and Comparative Effectiveness Reviews [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2008-. Available from: http://www.ncbi.nlm.nih.gov/books/NBK154408/

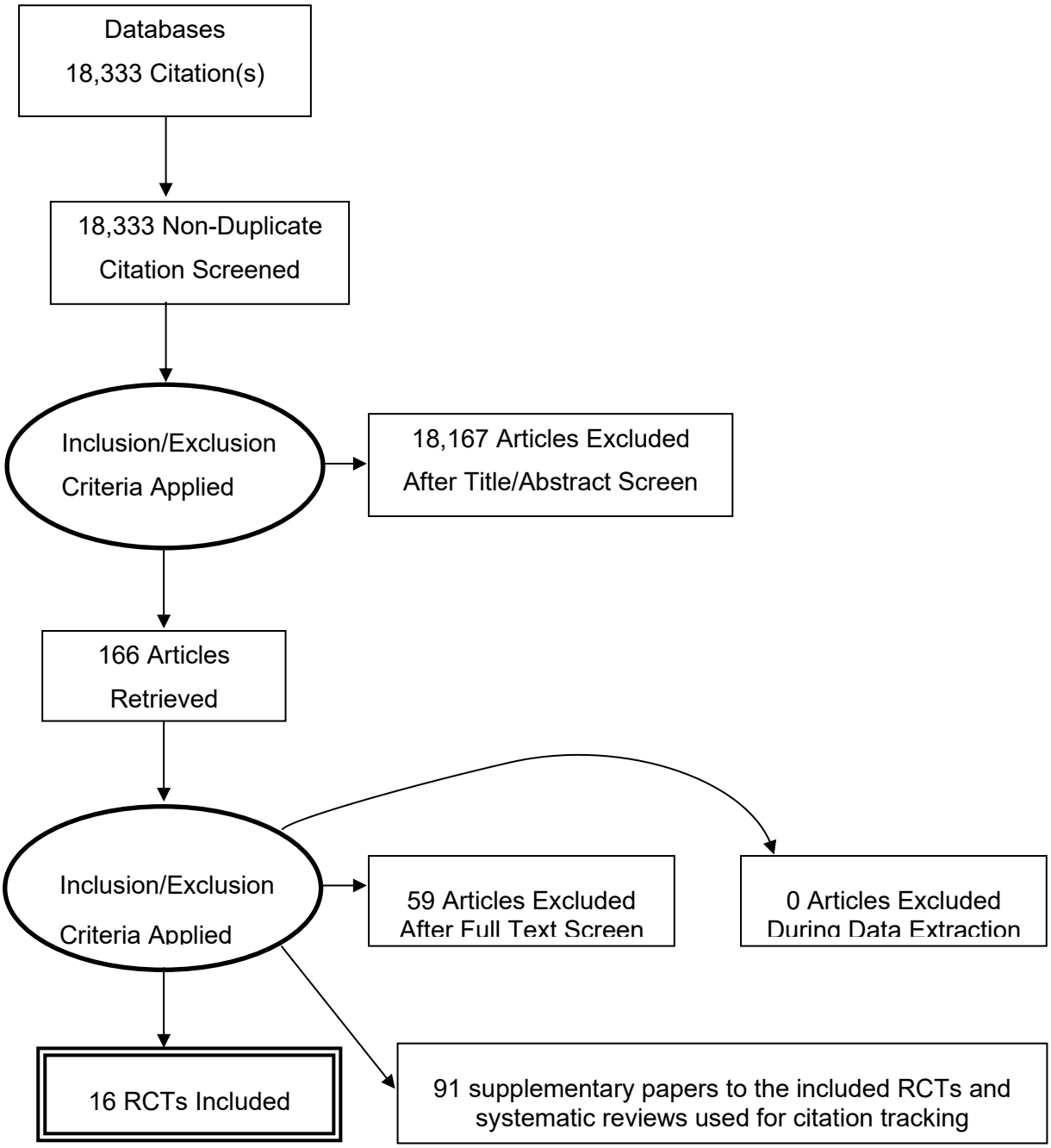
Appendix C – Literature search strategies

The MEDLINE strategy below was run on the 30th November 2020. It was translated into all the databases that were searched.

1 exp Diabetes Mellitus, Type 2/
2 (Type* adj4 ("2" or "II" or two*) adj4 (diabete* or diabetic*)).tw.
3 ((Maturit* or adult* or slow*) adj4 onset* adj4 (diabete* or diabetic*)).tw.
4 ((Ketosis-resistant* or stable*) adj4 (diabete* or diabetic*)).tw.
5 ((Non-insulin* or Non insulin* or Noninsulin*) adj4 depend* adj4 (diabete* or diabetic*)).tw.
6 NIDDM.tw.
7 or/1-6
8 exp Glucagon-Like Peptide 1/
9 (Glucagon* adj Like adj Peptide adj "1").tw.
10 (GLP* adj "1").tw.
11 GLP1*.tw.
12 Exenatide/
13 (Exenatide* or Byetta* or Bydureon* or Saxenda*).tw.
14 (Liraglutide* or Victoza*).tw.
15 (Dulaglutide* or Trulicity*).tw.
16 (Semaglutide* or Ozempic* or Rybelsus*).tw.
17 (Lixisenatide* or Lyxumia*).tw.
18 Sodium-Glucose Transporter 2/
19 (Sodium* adj4 Glucose* adj4 Transporter* adj4 "2").tw.
20 (Sodium* adj4 Glucose* adj4 (co-transporter* or cotransporter* or co transporter*) adj4 "2").tw.
21 (SGLT* or gliflozin*).tw.
22 Canagliflozin/
23 (Canagliflozin* or Invokana* or Dapagliflozin* or Forxiga* or Ertugliflozin* or Steglatro* or Empagliflozin* or Jardiance* or Glyxambi*).tw.
24 exp Sulfonylurea Compounds/tu [Therapeutic Use]
25 (Sulfonylurea* or Sulphonylurea*).tw.
26 (Gliclazide* or Diamicron*).tw.
27 (Glimepiride* or Amaryl*).tw.
28 (Glipizide* or Minodiab*).tw.
29 Tolbutamide*.tw.
30 Thiazolidinediones/
31 (Thiazolidinedione* or Glitazone*).tw.
32 Pioglitazone/
33 (Pioglitazone* or Actos*).tw.
34 exp Dipeptidyl-Peptidase IV Inhibitors/ or Dipeptidyl Peptidase 4/
35 (Dipeptidyl* adj2 Peptidase* adj2 ("4" or "iv") adj Inhibitor*).tw.
36 (DPP* adj2 ("4" or "iv")).tw.
37 gliptin*.tw.
38 (Saxagliptin* or Onglyza* or Komboglyze* or Qtern*).tw.
39 (Vildagliptin* or Galvus*).tw.
40 (Sitagliptin* or Januvia*).tw.
41 (Alogliptin* or Vipdomet*).tw.
42 (Linagliptin* or Trajenta* or Jentadueto*).tw.
43 Metformin/
44 (Metformin* or Glucophage*).tw.

45 (Competact* or Janumet* or Eucreas* or Synjardy* or Vokanamet* or Xigduo*).tw.
46 Biguanides/
47 Biguanide*.tw.
48 exp Glycoside Hydrolase Inhibitors/
49 glycosid*.tw.
50 (glycosyl adj4 hydrolases).tw.
51 ((intestinal adj4 alpha adj4 amylase adj4 inhibitor*) or (intestinal adj4 alpha-amylase adj4 inhibitor*)).tw.
52 ((pancreatic adj4 alpha adj4 amylase adj4 inhibitor*) or (pancreatic adj4 alpha-amylase adj4 inhibitor*)).tw.
53 Acarbose/
54 (Acarbose* or Glucobay*).tw.
55 exp Insulins/ad, tu [Administration & Dosage, Therapeutic Use]
56 exp Insulin/ad, tu [Administration & Dosage, Therapeutic Use]
57 Insulin Infusion Systems/
58 (Insulin* adj4 (treat* or therap* or administrat* or dos* or human* or analogue* or biphasic* or basal* or protamine* or isophane* or inject* or pen* or deliver* or device* or system* or pump* or syringe* or needle* or infusion*)).tw.
59 (Insulin* adj4 (Intermediate* or shortact* or short-act* or short act* or longact* or long-act* or long act* or ultralong* or ultra-long* or ultra long* or rapidact* or rapid-act* or rapid act*)).tw.
60 (Actrapid* or Humulin* or Hypurin*).tw.
61 Aspart*.tw.
62 (Glulisine* or Apidra*).tw.
63 (Lispro* or Humalog*).tw.
64 (Insulin* adj4 zinc* adj4 (suspension* or protamine*)).tw.
65 (Detemir* or Levemir*).tw.
66 (Glargine* or Lantus* or Toujeo*).tw.
67 (Degludec* or Tresiba*).tw.
68 (Isophane* or Insulatard* or Insuman* or Novomix*).tw.
69 (Fiasp* or Lyumjev* or Suliqua* or Xultophy* or NovoRapid*).tw.
70 (LY2963016 or Abasaglar* or MYK-1501D or MYK1501D or Semglee*).tw.
71 Biosimilar pharmaceuticals/
72 (biosimilar* or biologics).tw.
73 Nateglinide/
74 (Meglitinide* or Repaglinide* or Nateglinide*).tw.
75 or/8-74
76 7 and 75
77 animals/ not humans/
78 76 not 77
79 limit 78 to english language
80 randomized controlled trial.pt.
81 randomi?ed.mp.
82 placebo.mp.
83 or/80-82
84 (MEDLINE or pubmed).tw.
85 systematic review.tw.
86 systematic review.pt.
87 meta-analysis.pt.
88 intervention$.ti.
89 or/84-88
90 79 and 83
91 79 and 89

Appendix D – Effectiveness evidence study selection



Appendix E – Effectiveness evidence

Cannon Christopher, 2020

Bibliographic Reference	Cannon Christopher, P; Pratley, Richard; Dagogo-Jack, Samuel; Mancuso, James; Huyck, Susan; Masiukiewicz, Urszula; Charbonnel, Bernard; Frederich, Robert; Gallo, Silvina; Cosentino, Francesco; Shih Weichung, J; Gantz, Ira; Terra Steven, G; Cherney David Z, I; McGuire Darren, K; VERTIS, CV; Investigators; Cardiovascular Outcomes with Ertugliflozin in Type 2 Diabetes.; The New England journal of medicine; 2020; vol. 383 (no. 15); 1425-1435

Study details

Other publications associated with this study included in review	Cannon et al. 2018; Cosentino et al. 2020
Trial registration number and/or trial name	ClinicalTrials.gov number, NCT01986881 - Vertis-CV
Study type	Randomised controlled trial (RCT)
Study location	34 countries
Study setting	567 centers (no further details reported)
Study dates	December 2013 through July 2015 and from June 2016 through April 2017; The final follow-up window was from September 2019 through December 2019; the last patient visit took place on December 27, 2019.
Sources of funding	Merck Sharp & Dohme and Pfizer
Inclusion criteria	Adults (aged 40 year or older) with type 2 diabetes At least 40 years of age and had type 2 diabetes (with a glycated haemoglobin level of 7.0 to 10.5%) and established atherosclerotic cardiovascular disease involving the coronary, cerebrovascular, or peripheral arterial systems.
Exclusion criteria	**People with type 1 diabetes** History of type 1 diabetes or ketoacidosis **Renal** Estimated glomerular filtration rate below 30 ml per minute per 1.73 m2 of body-surface area

Intervention(s)	5 mg or 15 mg of ertugliflozin once daily, added to background standard-of-care treatment
Comparator	Matching placebo once daily, added to background standard-of-care treatment
Outcomes of interest	Myocardial infarction Stroke, or atherosclerotic disease Cardiovascular-related mortality All-cause mortality Change in weight or Body Mass Index (BMI) at 1 year Total dropouts Hypoglycaemic event rates Hospitalization for heart failure 3-point MACE
Number of participants	8250 Underwent randomization; 8246 Were included in the intention-to-treat population
Duration of follow-up	3.5 years (mean)
Loss to follow-up	13% (n=358/2747) in the placebo arm, 12% (n=330/2752) in the ertugliflozin, 5 mg/day are and 12.6% (n=346/2747) ertugliflozin, 15 mg/day arm did not complete the study. ITT analysis undertaken
Methods of analysis	Stratified Cox proportional-hazards model that included the trial group as a covariate and cohort of enrolment as the stratification factor was used to evaluate the primary outcome. The Kaplan–Meier method was used to estimate the cumulative incidence (first occurrence) of an outcome event over time in each trial group.

1 **Study arms**

Ertugliflozin (5 mg and 15 mg) (N = 5499) Ertugliflozin (5 mg n=2752 and 15 mg n=2747) with standard care of treatment
Placebo (N = 2747) with standard-of-care treatment

2 **Characteristics**

3 **Arm-level characteristics**

	Ertugliflozin (5 mg and 15 mg) (N = 5499)	**Placebo (N = 2747)**
% Female *(Percentage)*		
Nominal	29.7	30.7

	Ertugliflozin (5 mg and 15 mg) (N = 5499)	Placebo (N = 2747)
Mean age (SD) *(years)*		
Mean/SD	64.4 (8.1)	64.4 (8)
BMI or weight *(kg/m2)* Data were available for 5496 patients in the ertugliflozin group and 2747 patients in the placebo group.		
Mean/SD	31.9 (5.4)	32 (5.5)
Comorbidities		
Duration of type 2 diabetes - years Data were available for 5493 patients in the ertugliflozin group and 2745 patients in the placebo group.		
Mean/SD	12.9 (8.3)	13.1 (8.4)
Glycated haemoglobin %		
Mean/SD	8.2 (1)	8.2 (0.9)
Estimated GFR — ml/min/1.73 m2 (mean/SD) The estimated glomerular filtration rate (GFR) was calculated with the Modification of Diet in Renal Disease equation. Data were available for 5498 patients in the ertugliflozin group and 2747 patients in the placebo group.		
Mean/SD	76.1 (20.9)	75.7 (20.8)
Coronary artery disease %		
Nominal	75.4	76.9
Cerebrovascular disease %		
Nominal	23.2	22.3
Peripheral arterial disease %		
Nominal	18.7	18.6
Heart failure %		
Nominal	23.4	24.5
Myocardial infarction %		
Nominal	47.7	48.4
Coronary revascularization %		
Nominal	57.8	58.7
Stroke %		

	Ertugliflozin (5 mg and 15 mg) (N = 5499)	Placebo (N = 2747)
Nominal	21.5	20.3
Race / Ethnicity %		
White %		
Nominal	87.8	87.9
Black %		
Nominal	3	2.5
Asian %		
Nominal	6.1	5.9
Other %		
Nominal	3.1	3.7

1

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Multicentre, double-blind, randomized, placebo-controlled, event-driven, noninferiority trial; Randomization was performed at a central location with the use of an interactive voice-response system and was based on a computer-generated schedule with randomly permuted blocks, stratified according to geographic region; Study described the baseline characteristics of the patients as well balanced between the ertugliflozin group and the placebo group; However the use of diuretics, were used more often in the placebo group than in the ertugliflozin group at the end of the trial but this is not considered a to be a source of bias.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Multicentre, double-blind, randomized, placebo-controlled, event-driven, noninferiority trial; Randomization was performed at a central location with the use of an interactive voice-response system and was based on a computer-generated schedule with randomly permuted blocks, stratified according to geographic region; Intention to treat analysis undertaken that considered 99.9% of randomized participants (n=4 participants were excluded post randomization due to being enrolled twice; involved in another ertugliflozin trial))*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Intention to treat analysis undertaken that considered 99.9% of those randomized; The non-inferiority analysis for the primary outcome*

Section	Question	Answer
		considered participants who at received at least one dose of treatment/placebo (99.9%); 12.5% (n=1034) participant did not complete the trial)
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Clinical event rates were used to measure all predefined and prespecified outcomes, with all the primary and secondary outcome events centrally adjudicated on by a cardiovascular adjudication committee in a blinded manner; The study is outlined as a multicentre, double-blind, randomized, placebo-controlled, event-driven, noninferiority trial. Randomization was performed at a central location with the use of an interactive voice-response system and was based on a computer-generated schedule with randomly permuted blocks, stratified according to geographic region.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(Pre-specified analysis plan is outlined in the paper and published in Cannon et al 2018, with the analysis undertaken is in line with this plan. Primary and secondary outcomes were all prespecified with outcome measures assessed via clinical event rates with all the primary and secondary outcome events centrally adjudicated on by a cardiovascular adjudication committee in a blinded manner.)*
Overall bias and Directness	Risk of bias judgement	Low
	Overall Directness	Directly applicable

1

Gerstein Hertzel, 2019

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

2 **Study details**

Other publications associated with this study included in review	Gerstein et al. 2019b; Cukierman-Yaffe et al. 2020; Dagenais et al. 2020; Gerstein et al 2018

Trial registration number and/or trial name	ClinicalTrials.gov, number NCT01394952; REWIND
Study type	Randomised controlled trial (RCT)
Study location	24 countries
Study setting	371 sites
Study dates	Aug 18, 2011, and Aug 14, 2013, 12 133 patients were screened; Follow-up ended on Aug 21, 2018.
Sources of funding	Eli Lilly and Company
Inclusion criteria	Adults (aged 50 year or older) with type 2 diabetes Previous/new type 2 diabetes with HbA1c <81 mmol/mol (<9.5%); Stable dose of 0, 1 or 2 oral glucose lowering drugs +/- basal insulin for > 3 months; Body mass index > 23 kg/m2; If age > 50, at least 1 of: prior MI; prior ischemic stroke; coronary revascularization > 2 years earlier; carotid, or peripheral revascularization > 2 months earlier; unstable angina hospitalization; image proven myocardial ischemia; or percutaneous coronary intervention; If age > 55, any of the above or at least 1 of: documented myocardial ischemia by stress test or imaging; >50% coronary, carotid, or lower extremity artery stenosis; ankle-brachial index <0.9; eGFR persistently <60 mL/minute/1.73m2; hypertension with LV hypertrophy; or persistent albuminuria; If age > 60, any of the above or at least 2 of: any tobacco use; use of lipid modifying therapy or a documented untreated LDL ≥3.4 mmol/L (130 mg/dL) within the past 6 months; HDL-C <1.0 mmol/L (40 mg/dL) for men and <1.3 mmol/L (50 mg/dL) for women or triglycerides ≥2.3 mmol/L (200 mg/dL) within the past 6 months; use of > 1 blood pressure drug or untreated SBP ≥140 mm Hg or DBP ≥95 mmHg; or waist-to-hip ratio >1.0 (men) and >0.8 (women); Run-in adherence to study drug = 100%
Exclusion criteria	**Renal** eGFR <15 ml/min/1.73 m2 or on dialysis Cardiovascular or cerebrovascular event within 8 weeks of randomization **Cancer** Family history of/or C cell hyperplasia or medullary thyroid cancer or MEN 2A or 2B or calcitonin value ≥20 pg/mL; Cancer within prior 5 years **Treatment** Unwilling to stop GLP-1 RA or DPP-4 inhibitor or weight loss drug **Hypoglycaemia** Uncontrolled diabetes Pancreatitis

	Prior pancreatitis/concordant symptoms **Liver disease** Liver disease or ALT ≥3.0 X normal **Pregnant** Pregnant or not using reliable birth control **Life expectancy** Life expectancy < 1 year
Intervention(s)	Dulaglutide: 1.5 mg weekly via subcutaneous injection
Comparator	Placebo
Outcomes of interest	Myocardial infarction Stroke, or atherosclerotic disease Cardiovascular-related mortality All-cause mortality Change in weight or Body Mass Index (BMI) at 1 year Total dropouts Hypoglycaemic event rates Hospitalization for unstable angina Hospitalization for heart failure Composite renal and retinal microvascular outcome Composite Microvascular Outcome: diabetic retinopathy needing laser, anti VEGF therapy, or vitrectomy; or clinical proteinuria; or a 30% decline in eGFR; or chronic renal replacement therapy Angina Unstable angina hospitalization Non-fatal stroke
Number of participants	9901
Duration of follow-up	5.4 years (median)
Loss to follow-up	ITT undertaken for all randomized participants; 0.3% (n=34) final status across arms was unknown; 2.9% (n=291) did not provide primary outcome at final visit or died.

Methods of analysis	All efficacy and safety analyses will be conducted using an intention-to-treat approach that includes all randomized participants regardless of adherence; The effect of the intervention on the time to the first occurrence of the primary outcome analysed via Cox proportional hazards models with the only independent variable being allocation to dulaglutide versus placebo. The proportional hazard assumption assessed graphically. Kaplan-Meier curves generated along with log-rank P-values. The incidence rate per 100 person years calculated for each treatment group for all key outcomes.
Additional comments	

1 **Study arms**

Dulaglutide (N = 4949)
Placebo (N = 4952)

2 **Characteristics**

3 **Arm-level characteristics**

	Dulaglutide (N = 4949)	**Placebo (N = 4952)**
% Female		
Nominal	46.6	46.1
Mean age (SD)		
Mean/SD	66.2 (6.5)	66.2 (6.5)
BMI or weight		
Mean/SD	32.3 (5.7)	32.3 (5.8)
Comorbidities		
Current tobacco use %		
Nominal	14	14.4
Cardiovascular disease % Myocardial infarction, ischaemic stroke, unstable angina with electrocardiogram changes, myocardial ischaemia on imaging or stress test, or coronary, carotid, or peripheral re-vascularisation		
Nominal	31.5	31.4
Cardiovascular event % Myocardial infarction or ischemic stroke		
Nominal	20.8	20.3
Hypertension %		
Nominal	93	93.3

	Dulaglutide (N = 4949)	Placebo (N = 4952)
Previous heart failure %		
Nominal	8.5	8.7
Duration of diabetes (years) Data are mean (SD).		
Mean/SD	10.5 (7.3)	10.6 (7.2)
eGFR <60 ml/min/1.73 m2 Percentage		
Nominal	21.8	22.6
Urinary albumin-to-creatinine ratio (mg/mmol)		
Nominal	1.80 (0.70 - 6.60)	1.88 (0.70 - 7.38)
Race % *(Percentage)*		
White %		
Nominal	75.9	75.6

1

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Randomized, double-blind, placebo-controlled trial. Randomization was done by a computer-generated random code with an interactive web response system with stratification by site. All investigators and participants were masked to treatment allocation. There were no between-group differences in use of other medications at baseline)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Randomized, double-blind, placebo-controlled trial. Randomization was done by a computer-generated random code with an interactive web response system with stratification by site. All investigators and participants were masked to treatment allocation. All efficacy and safety analyses were done according to an intention-to-treat approach that included all randomly assigned participants irrespective of adherence, as described in the protocol and prespecified statistical analysis plan.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(ITT undertaken with all randomized participant accounted for in final analysis for all predefined and prespecified outcomes)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for	Low *(Clinical event rates used to calculate the prespecified clinical and biochemical outcomes. All*

Section	Question	Answer
	measurement of the outcome	*deaths and cardiovascular, pancreatic, and thyroid events were adjudicated by an external adjudication committee, which is blinded to treatment allocation.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(Pre-specified plan published (Gerstein et al 2018); Analysis undertaken in line with this. Clinical event rates used to calculate the prespecified clinical and biochemical outcomes. All deaths and cardiovascular, pancreatic, and thyroid events were adjudicated by an external adjudication committee, which is blinded to treatment allocation.)*
Overall bias and Directness	Risk of bias judgement	Low
	Overall Directness	Directly applicable

1

Green Jennifer, 2015

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

2 **Study details**

Other publications associated with this study included in review	Bethel et al. 2017; Bethel et al. 2018; McAlister et al. 2020; Nauck et al. 2019: Pagidipati et al. 2017; Standl et al. 2018.
Trial registration number and/or trial name	ClinicalTrials.gov number, NCT00790205 - TECOS
Study type	Randomised controlled trial (RCT)
Study location	38 countries
Study setting	673 sites
Study dates	Patients underwent randomization from December 2008 through July 2012; The study was closed in March 2015, after the requisite minimum of 1300 patients were confirmed to have had a primary composite outcome.

Sources of funding	Merck Sharp & Dohme; TECOS
Inclusion criteria	Adults (aged 50 year or older) with type 2 diabetes Participants had type 2 diabetes with established cardiovascular disease (history of major coronary artery disease, ischemic cerebrovascular disease, or atherosclerotic peripheral arterial disease) at least 50 years of age, with a glycated hemoglobin level of 6.5 to 8.0% when treated with stable doses of one or two oral antihyperglycemic agents (metformin, pioglitazone, or sulfonylurea) or insulin (with or without metformin).
Exclusion criteria	Renal: Estimated glomerular filtration rate (eGFR) was less than 30 ml per minute per 1.73 m2 of body-surface area at baseline Treatment: DPP-4 inhibitor, glucagon-like peptide-1 receptor agonist, or thiazolidinedione (other than pioglitazone) during the preceding 3 months Hypoglycaemia: History of two or more episodes of severe hypoglycaemia (defined as requiring third party assistance) during the preceding 12 months;
Intervention(s)	Sitagliptin 100 mg daily (50 mg according to eGFR) - route of administration not specified but available as a tablet (BNF)
Comparator	Placebo
Outcomes of interest	Myocardial infarction Stroke, or atherosclerotic disease Cardiovascular-related mortality All-cause mortality Change in weight or Body Mass Index (BMI) at 1 year Total dropouts Dropouts due to adverse events Hypoglycaemic event rates Hospitalization for unstable angina Hospitalization for heart failure
Number of participants	14,735 Patients underwent randomization; 14,671 Were included in the intention-to-treat population
Duration of follow-up	3.0 years (median)
Loss to follow-up	Of those randomized to sitagliptin (n=7332) 4.9% (n=360) did not complete the study; Of those randomized to placebo (n=7339) 5.9% (n=434).

Methods of analysis	Cox proportional-hazards model to calculate hazard ratios and two-sided 95% confidence intervals, stratified according to region.

1 **Study arms**

Sitagliptin (N = 7332)
Placebo (N = 7339)

2 **Characteristics**

3 **Arm-level characteristics**

	Sitagliptin (N = 7332)	**Placebo (N = 7339)**
% Female		
Nominal	29.1	29.5
Mean age (SD)		
Mean/SD	65.4 (7.9)	65.5 (8)
BMI or weight *(kg/m2)*		
Mean/SD	30.2 (5.6)	30.2 (5.7)
Comorbidities		
Duration of diabetes (years) (year of randomization – year of diagnosis) + 1.		
Mean/SD	11.6 (8.1)	11.6 (8.1)
Qualifying HbA1c (%)		
Mean/SD	7.2 (0.5)	7.2 (0.5)
eGFR (mL/min/1.73 m2) MDRD formula used to calculate eGFR. Site-reported values are presented.		
Mean/SD	74.9 (21.3)	74.9 (20.9)
Urinary albumin: creatinine ratio (mg/g) Median		
Nominal	10.3	11.4
Range	3.5 to 34.6	3.6 to 36.2
Prior cardiovascular disease % Myocardial infarction, >50% coronary stenosis, Prior PCI, CABG		
Nominal	73.6	74.5
Prior cerebrovascular disease %		

	Sitagliptin (N = 7332)	Placebo (N = 7339)
Nominal	24.6	24.3
Cigarette smoking % Never smoked		
Nominal	48.9	48.6
Prior congestive heart failure %		
Nominal	17.8	18.3
Race / Ethnicity		
White %		
Nominal	67.6	68.2
Black %		
Nominal	2.8	3.3
Asian %		
Nominal	22.6	22
Other %		
Nominal	7.1	6.6
Hispanic / Latino %		
Nominal	12.1	12.4

1

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Randomized, double-blind, placebo-controlled; An interactive voice-response system assigned the study medication in a double-blind manner, blocked within each site. The characteristics of the patients at baseline were well balanced between the study groups with respect to demographic characteristics and the use of antihyperglycemic agents and secondary cardiovascular prevention medications - analysis not specified.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Randomized, double-blind, placebo-controlled; An interactive voice-response system assigned the study medication in a double-blind manner, blocked within each site. per protocol and ITT undertaken for all outcomes)*

Section	Question	Answer
assignment to intervention)		
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Intention to treat analysis undertaken considering all randomized participants; 14,735 Patients underwent randomization; 14,671 Were included in the intention-to-treat population; Of those randomized to sitagliptin (n=7332) 4.9% (n=360) did not complete the study; Of those randomized to placebo (n=7339) 5.9% (n=434) did not complete the study.)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Clinical event rates were used to measure predefined and prespecified outcomes, with an independent clinical events classification committee whose members were unaware of study-group assignments adjudicating all events of death, myocardial infarction, stroke, hospitalization for unstable angina, hospitalization for heart failure, acute pancreatitis, and cancers (other than nonmelanoma skin cancers).)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(The study refers to a pre-specified analytical plan; Randomized, double-blind, placebo-controlled; An interactive voice-response system assigned the study medication in a double-blind manner, blocked within each site. All prespecified and predefined outcomes have been reported on in line with a pre specified plan. Clinical event rates were used to measure predefined and prespecified outcomes, overseen by an independent clinical events classification committee who were unaware of study-group assignments.)*
Overall bias and Directness	Risk of bias judgement	Low
	Overall Directness	Directly applicable

1

Holman Rury, 2017

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

2 **Study details**

Other publications associated	Holman et al. 2016; Clegg et al. 2019 Badjatiya et al. 2019; Bethel et al. 2019; Fudim et al. 2019; Gaebler et al. 2012; Mentz et al. 2017; Mentz et al. 2018; Reed et al. 2020; Standl et al. 2020; Wittbrodt et al. 2018

with this study included in review	
Trial registration number and/or trial name	ClinicalTrials.gov number - NCT01144338
Study type	Randomised controlled trial (RCT)
Study location	35 countries - North America, Latin America, Europe, Asia/Pacific
Study setting	687 sites - no further details
Study dates	Randomization June 18, 2010, through September 16, 2015. The planned closeout of follow-up of the patients was from December 5, 2016 to May 11, 2017.
Sources of funding	Amylin Pharmaceuticals
Inclusion criteria	Adults (aged 18 years and older) with type 2 diabetes Adults with type 2 diabetes (defined as a glycated haemoglobin level of 6.5 to 10.0% [48 to 96 mmol per mole]); 70% had previous cardiovascular events (history of major clinical manifestation of coronary artery disease, ischemic cerebrovascular disease, or atherosclerotic peripheral arterial disease) 30% not have had previous cardiovascular events. Patients were permitted to receive up to three oral glucose-lowering agents or to receive insulin, either alone or in combination with up to two oral glucose-lowering agents.
Exclusion criteria	**Renal** End-stage renal disease estimated glomerular filtration rate (eGFR) at entry of less than 30 ml per minute per 1.73 m2 of body-surface area **Cancer** Personal or family history of medullary thyroid carcinoma; multiple endocrine neoplasia type 2 **Treatment** Previous treatment with a GLP-1 receptor agonist **Hypoglycaemia** Two or more episodes of severe hypoglycaemia (defined as hypoglycaemia for which a patient received third-party assistance) during the preceding 12 months, **Calcitonin level** Baseline calcitonin level of greater than 40ng per litre

Intervention(s)	Subcutaneous injections of extended release exenatide at a dose of 2 mg weekly
Comparator	Subcutaneous injections of placebo
Outcomes of interest	Myocardial infarction Stroke, or atherosclerotic disease Cardiovascular-related mortality All-cause mortality Change in weight or Body Mass Index (BMI) at 1 year Total dropouts Dropouts due to adverse events Hypoglycaemic event rates Hospitalization for heart failure
Number of participants	14752 randomised
Duration of follow-up	3.2 years (median)
Loss to follow-up	14,187 patients (96.2%) completed the trial - 565 did not complete the trial (3.8%); vital status was obtained for 98.8% of the patients.
Methods of analysis	Time-to-event analyses were performed with Cox proportional-hazards model for primary, secondary, and exploratory outcomes in the intention-to-treat population, stratified according to history of cardiovascular disease, with trial regimen as an explanatory variable. The Kaplan–Meier method was used to calculate event rates

1 **Study arms**

Exenatide (N = 7356) Subcutaneous injections of extended release exenatide at a dose of 2 mg once weekly
Placebo (N = 7396) Subcutaneous injections of 2 mg placebo once weekly

2 **Characteristics**

3 **Arm-level characteristics**

	Exenatide (N = 7356)	**Placebo (N = 7396)**
% Female		
Nominal	38	38
Median age (IQR)		

	Exenatide (N = 7356)	Placebo (N = 7396)
Age at randomization	62.0 (56.0, 68.0)	62.0 (56.0, 68.0)
BMI or weight BMI 30 or over (%)		
Median (IQR)	31.8 (28.2 to 36.2)	31.7 (28.2 to 36.1)
Comorbidities		
Previous cardiovascular event at randomization (%) Prior CV event at randomization based on IVRS.		
Nominal	73.3	72.9
History of congestive heart failure		
Nominal	15.8	16.6
Duration of diabetes 15 years or greater		
Nominal	36.7	37.1
Race / Ethnicity %		
White %		
Nominal	75.5	76
Black %		
Nominal	6	5.9
Asian %		
Nominal	9.9	9.8
Indian (American) or Alaskan Native %		
Nominal	0.5	0.5
Native Hawaiian or Other Pacific Islander %		
Nominal	0.2	0.2
Hispanic %		
Nominal	7.8	7.5
eGFR (MDRD) % *(ml/min/1.73m2 of body surface area)*		
Median (IQR)	76.6 (61.3 to 92)	76 (61 to 92)
HbA1c (%) *(median)*		
Median (IQR)	8 (7.3 to 8.9)	8 (7.3 to 8.9)

1

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Double blind randomized control trial; An interactive voice-response system assigned patients on the basis of computer-generated block randomization within each site; The demographic, disease, and clinical characteristics of the patients did not differ significantly between the groups with the exception of lipid-lowering medications and SGLT2 inhibitors - this is not consider to be a source of bias.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Double-blind randomized control study; interactive voice-response system assigned patients on the basis of computer-generated block randomization within each site; ITT undertaken considering all randomized participants within the analysis)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(ITT used for analysis of primary and secondary outcomes; ITT population includes all randomized participants)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Double blind randomized control trial; interactive voice-response system assigned patients on the basis of computer-generated block randomization within each site; Clinical event rates; all outcomes pre-defined; An independent clinical events classification committee whose members were unaware of the trial-group assignments adjudicated all the components of the primary composite outcome, secondary outcomes, ventricular arrhythmias that led to intervention, neoplasms, and pancreatitis)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(Numerical result outlined is in line with the prespecified analytical plan; All Clinical event rates used outcomes which were pre-defined are reported on; An independent clinical events classification committee whose members were unaware of the trial-group assignments adjudicated all the components of the primary composite outcome, secondary outcomes.)*
Overall bias and Directness	Risk of bias judgement	Low
	Overall Directness	Directly applicable

2

Husain, 2019

Bibliographic Reference	Husain, Mansoor; Birkenfeld Andreas, L; Donsmark, Morten; Dungan, Kathleen; Eliaschewitz Freddy, G; Franco Denise, R; Jeppesen Ole, K; Lingvay, Ildiko;

Mosenzon, Ofri; Pedersen Sue, D; Tack Cees, J; Thomsen, Mette; Vilsboll, Tina; Warren Mark, L; Bain Stephen, C; PIONEER, 6; Investigators; Oral Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes.; The New England journal of medicine; 2019; vol. 381 (no. 9); 841-851

1 **Study details**

Other publications associated with this study included in review	Rodbard et al. 2019; Thethi et al. 2020; Bain et al. 2018.
Trial registration number and/or trial name	ClinicalTrials.gov number, NCT02692716 - PIONEER6
Study type	Randomised controlled trial (RCT)
Study location	21 countries - Africa, Asia, Europe, Latin America, North America and the Middle East.
Study setting	214 sites
Study dates	Participants (n=3183) randomized between January and August 2017; Last point of data collection/follow-up not specified
Sources of funding	Novo Nordisk
Inclusion criteria	Adults (aged 50 year or older) with type 2 diabetes 50 years of age or older, had established cardiovascular disease or chronic kidney disease, or 60 years of age or older and had cardiovascular risk factors only
Exclusion criteria	**Renal** Long-term or intermittent haemodialysis or peritoneal dialysis, or severe renal impairment (estimated glomerular filtration rate [GFR], <30 ml per minute per 1.73 m2 of body surface area) Cardiovascular or cerebrovascular event within 8 weeks of randomization Myocardial infarction, stroke, or hospitalization for unstable angina or transient ischemic attack within 60 days before screening **Treatment** Treatment with any GLP-1 receptor agonist, dipeptidyl peptidase 4 inhibitor, or pramlintide within 90 days before screening **Heart failure**

	New York Heart Association class 4 heart failure Planned coronary revascularization procedure within 90 days after screening Planned coronary-artery, carotid-artery, or peripheral-artery revascularization within 60 days before screening **Retinopathy or maculopathy** Proliferative retinopathy or maculopathy resulting in active treatment
Intervention(s)	Once-daily oral Semaglutide (target dose, 14 mg)
Comparator	Placebo
Outcomes of interest	Myocardial infarction Stroke, or atherosclerotic disease Non-fatal Cardiovascular-related mortality All-cause mortality A composite of death from any cause, nonfatal myocardial infarction, or nonfatal stroke Change in weight or Body Mass Index (BMI) at 1 year Total dropouts Dropouts due to adverse events Hypoglycaemic event rates Hospitalization for unstable angina Hospitalization for heart failure
Number of participants	3183 patients were randomly assigned to oral semaglutide (1591 patients) or placebo (1592 patients)
Duration of follow-up	15.9 months (median)
Loss to follow-up	3172 patients (99.7%) completed the trial (n=11 loss to follow-up); 1347 (84.7%) completed the trial regimen with oral semaglutide (n=144 did not complete treatment) and 1435 (90.1%) with placebo (n=156 did not complete treatment - placebo)
Methods of analysis	A stratified Cox proportional hazards model was used for the primary analysis, with treatment group as a fixed factor, and stratification based on evidence of cardiovascular disease/advanced chronic kidney disease at screening
Additional comments	

1 **Study arms**

Semaglutide (N = 1592) 14 mg orally once daily (target dose) in addition to standard of care treatment
Placebo (N = 1592) in addition to standard of care treatment

1 **Characteristics**

2 **Arm-level characteristics**

	Semaglutide (N = 1592)	Placebo (N = 1592)
% Female		
Nominal	31.9	31.4
Mean age (SD)		
Mean/SD	66 (7)	66 (7)
BMI or weight *(Kilograms)* Body weight		
Mean/SD	91 (21.4)	90.8 (21)
Comorbidities		
Type 2 diabetes Duration — yr		
Mean/SD	14.7 (8.5)	15.1 (8.5)
Cardiovascular risk stratum % Age ≥50 yr and established CVD or chronic kidney disease %		
Nominal	84.9	84.5
Current smoker %		
Nominal	11.6	10.4
Cardiovascular risk stratum % Age ≥60 yr and cardiovascular risk factors only		
Nominal	15.1	15.5
Chronic heart failure NYHA class 2-3 (%)		
Nominal	11.8	12.6
Race / Ethnicity %		
White %		
Nominal	72.2	72.4

	Semaglutide (N = 1592)	Placebo (N = 1592)
Black or African American %		
Nominal	5.6	6.5
Asian %		
Nominal	20.4	19.2
Other %		
Nominal	1.9	1.9
eGFR *(ml/min/1.73m2 of body surface area)*		
Mean/SD	74 (21)	74 (21)

1

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Double blind randomized trial - Patients were randomly assigned (in a 1:1 ratio); Randomization was stratified according to evidence of established cardiovascular disease or chronic kidney disease or the presence of cardiovascular risk factors only and performed using an interactive voice/web response system (IV/WRS).)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Double blind randomized trial - Patients were randomly assigned (in a 1:1 ratio); Randomization was stratified according to evidence of established cardiovascular disease or chronic kidney disease or the presence of cardiovascular risk factors only and performed using an interactive voice/web response system (IV/WRS). Blinding of trial staff is maintained by using IV/WRS. ITT undertaken)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(ITT undertaken; 99.7% of participants randomized completed the trial; 87% of participants randomized completed treatment)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Clinical event rates used to assess prespecified outcomes. Cardiovascular and other selected events were adjudicated by an independent, external event-adjudication committee whose members were unaware of the trial-group assignments. Blinding of trial staff was maintained by using IV/WRS for dispensing of trial drug and through the use of visually identical oral semaglutide and placebo tablets in identical packaging.)*

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(All pre-specified outcomes are reported based on clinical event rates for those outcomes as outlined in the pre-specified analytical plan. All non-primary outcomes were not controlled for multiple comparisons within the stratified Cox proportional-hazards model and are outlined as exploratory.)*
Overall bias and Directness	Risk of bias judgement	Low
	Overall Directness	Directly applicable

1

Mahaffey Kenneth, 2018

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

2 **Study details**

Other publications associated with this study included in review	Arnott et al. 2020; Figtree et al. 2019; Fulcher et al. 2015a; Fulcher et al. 2015b; Matthews et al. 2019; Matthews et al. 2020; Neal et al. 2015; Neal et al. 2016; Neal et al. 2017; Neuen et al. 2018; Neuen et al. 2020; Perkovic et al. 2018; Radholm et al. 2018; Watts et al. 2016; Wittbrodt et al. 2018; Yale et al. 2017; Zhou et al. 2019
Trial registration number and/or trial name	NCT01032629 and NCT01989754.
Study type	Randomised controlled trial (RCT)
Study location	667 centres in 30 countries - Not further specified
Study setting	Not specified
Study dates	Not specified
Sources of funding	Supported by Janssen Research & Development, LLC. Medical writing support was funded by Janssen Global Services, LLC. Canagliflozin has been developed by Janssen Research & Development, LLC, in collaboration with Mitsubishi Tanabe Pharma Corp.
Inclusion criteria	Adults (aged 18 years and older) with type 2 diabetes

	Men and women with type 2 diabetes mellitus (glycohemoglobin ≥7.0% and ≤10.5%) who were either ≥30 years of age with a history of symptomatic atherosclerotic cardiovascular events defined as stroke, MI, hospitalization for unstable angina, coronary artery bypass grafting, percutaneous coronary intervention, peripheral revascularization (surgical or percutaneous), and symptomatic with documented hemodynamically significant carotid or peripheral vascular disease or amputation secondary to vascular disease (secondary prevention cohort); or ≥50 years of age with no prior cardiovascular events but with ≥2 of the following cardiovascular risk factors: duration of diabetes mellitus ≥10 years, systolic blood pressure >140 mm Hg on ≥1 antihypertensive agents, current smoker, microalbuminuria or macroalbuminuria, or high-density lipoprotein cholesterol <1 mmol/L (primary prevention cohort).
Exclusion criteria	People with type 1 diabetes **Renal** Requiring renal dialysis or transplantation or eGFR <30 ml/min/1.73m2 Pregnant (or intending), breastfeeding, not using adequate contraception **Life expectancy** Less than 1 year Current or prior use of sodium glucose co-transporter 2 inhibitor
Intervention(s)	Canagliflozin 300 mg or canagliflozin 100 mg.
Comparator	Placebo
Outcomes of interest	Myocardial infarction Stroke, or atherosclerotic disease Cardiovascular-related mortality All-cause mortality Change in weight or Body Mass Index (BMI) at 1 year Total dropouts Dropouts due to adverse events Hypoglycaemic event rates Hospitalization for heart failure
Number of participants	10142 participants with type 2 diabetes mellitus
Duration of follow-up	Mean: 188 weeks
Loss to follow-up	Discontinuation of the study drug was similar with placebo and canagliflozin in the overall population (30% versus 29%) and in the secondary prevention (29% versus 30%) and primary prevention cohorts (31% versus 28%)

Methods of analysis	Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated for participants; Cardiovascular, death, and safety outcomes were analysed using a stratified Cox proportional hazards regression model; Renal outcomes were analysed using a stratified Cox proportional hazards model with treatment and the stage of baseline chronic kidney disease measured by estimated glomerular filtration rate (<60 or ≥60 mL/min/1.73 m^2) as the exploratory variables and study as the stratification factor. Homogeneity of treatment effects across the primary and secondary prevention groups was examined via a test for the treatment-by-prevention interaction by adding this term and the prevention cohort as covariates to the respective Cox proportional hazards model. The risk differences were calculated by subtracting the incidence rate (per 1000 patient-years) with placebo from the incidence rate with canagliflozin and multiplying by 5 years. Similarly, the CI was estimated by multiplying the lower and upper CI values by 5 years.
Additional comments	

1 **Study arms**

Canagliflozin (N = 5795) Randomized to receive either 100 mg or 300 mg
Placebo (N = 4347) Randomized to placebo arm

2 **Characteristics**

3 **Arm-level characteristics**

	Canagliflozin (N = 5795)	**Placebo (N = 4347)**
% Female *(Percentage)*		
Nominal	35.1	36.7
Mean age (SD) *(Mean (SD))*		
Mean/SD	63.2 (8.3)	63.4 (8.2)
BMI or weight *(Mean (SD))*		
Mean/SD	31.9 (5.9)	32 (6)
Comorbidities		
eGFR *(ml/min/1.73m2 of body surface area)*		
Mean/SD	76.7 (20.3)	76.2 (20.8)
Current smokers *(Percentage)*		
Nominal	17.6	18.1
Established CVD *(Percentage)*		

	Canagliflozin (N = 5795)	Placebo (N = 4347)
Nominal	64.8	66.7
Nephropathy *(Percentage)*		
Nominal	17.2	17.9
Median albumin-to-creatinine ratio (IQR)		
Median (IQR)	12.4 (6.71-40.9)	12.1 (6.57-43.9)
History of Heart Failure %		
Nominal	13.9	15.1
Race / Ethnicity % *(Percentage)* Race was determined by investigator inquiry of the participant. Other includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, multiple races, other race, and unknown.		
White %		
Nominal	77.8	79
Asian %		
Nominal	13.4	11.7
Black %		
Nominal	3	3.7
Other		
Nominal	5.8	5.6

1

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Randomization was performed through a central web-based system and used a computer-generated randomization schedule; CANVAS Program outlined as a double-blind comparison of the effects of canagliflozin versus placebo made by combining data from 2 large-scale trials; Blinding and concealment protocols not specified in this paper; Authors outlined that within each of the primary and secondary prevention cohorts, participant characteristics were all well balanced across canagliflozin and placebo groups.)*
Domain 2a: Risk of bias due to deviations from the intended	Risk of bias for deviations from the intended interventions	Low *(Limited details in the paper but outlines a double-blind procedure; Study highlights that all analyses of the effects of canagliflozin compared with placebo*

Section	Question	Answer
interventions (effect of assignment to intervention)	(effect of assignment to intervention)	*on cardiovascular and renal outcomes were based on the intention-to-treat principle using all follow-up time (on or off study treatment) for all randomized participants)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(All analyses of the effects of canagliflozin compared with placebo on cardiovascular and renal outcomes were based on the intention-to-treat principle using all follow-uptime (on or off study treatment) for all randomized participants.)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Study utilized a double-blind method; Event rates of clinical outcomes measured with major cardiovascular events, renal outcomes, and deaths as well as selected safety outcomes (diabetic ketoacidosis, acute pancreatitis, and fracture) were assessed by Endpoint Adjudication Committees blinded to therapy.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(Study outlines that evaluation of outcomes in the primary and secondary prevention participants were prespecified with all analyses of the effects of canagliflozin compared with placebo on cardiovascular and renal outcomes based on the intention-to-treat principle using all follow-up time (on or off study treatment) for all randomized. participants. Findings presented for all pre-specified efficacy outcomes: composite of cardiovascular mortality, nonfatal MI, or nonfatal stroke; the individual components of the composite; hospitalization for heart failure; and all-cause mortality. Effects on the kidney, and safety events)*
Overall bias and Directness	Risk of bias judgement	Low
	Overall Directness	Directly applicable

1

Marso Steven, 2016

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

2 **Study details**

Other publications associated with this study	Vilsboll et al. 2017; Jodar et al. 2019; Leiter et al. 2019

included in review	
Trial registration number and/or trial name	ClinicalTrials.gov number, NCT01720446 - SUSTAIN-6
Study type	Randomised controlled trial (RCT)
Study location	20 countries not specified
Study setting	230 sites not specified
Study dates	February 2013 through December 2013 patients were screened; the last patient visit was March 15, 2016
Sources of funding	Novo Nordisk
Inclusion criteria	Adults (aged 50 year or older) with type 2 diabetes Patients with type 2 diabetes and a glycated haemoglobin level of 53 mmol/mol (7%) or more were eligible if they had not been treated with an antihyperglycemic drug or had been treated with no more than two oral antihyperglycemic agents, with or without basal or premixed insulin. Key inclusion criteria were an age of 50 years or more with established cardiovascular disease (previous cardiovascular, cerebrovascular, or peripheral vascular disease), chronic heart failure (New York Heart Association class II or III), or chronic kidney disease of stage 3 or higher or an age of 60 years or more with at least one cardiovascular risk factor
Exclusion criteria	**Renal** Long-term dialysis Cardiovascular or cerebrovascular event within 8 weeks of randomization A history of an acute coronary or cerebrovascular event within 90 days before randomization **Treatment** Treatment with a dipeptidyl-peptidase 4 inhibitor within 30 days before screening or with a GLP-1–receptor agonist or insulin other than basal or premixed within 90 days before screening **Revascularization** Planned revascularization of a coronary, carotid, or peripheral artery
Intervention(s)	Subcutaneous semaglutide 0.5 mg or 1.0 mg once weekly
Comparator	Volume-matched Placebo

Outcomes of interest	Myocardial infarction Stroke, or atherosclerotic disease Cardiovascular-related mortality All-cause mortality Change in weight or Body Mass Index (BMI) at 1 year Total dropouts Dropouts due to adverse events Hypoglycaemic event rates Hospitalization for unstable angina Hospitalization for heart failure
Number of participants	3297
Duration of follow-up	109 weeks
Loss to follow-up	Vital status was known for 99.6%; 2% (n=65) randomized participants did not complete the trial due to withdrawal of consent or lost to follow-up.
Methods of analysis	Prespecified statistical analysis plan utilizing Cox proportional-hazards model, with pooled treatment (semaglutide vs. placebo) as a fixed factor and categorized according to all possible combinations of stratification factors used for randomization.
Additional comments	

1 **Study arms**

Semaglutide (0.5 mg) (N = 826)
Semaglutide (1.0 mg) (N = 822)
Placebo (0.5 mg) (N = 824)
Placebo (1.0 mg) (N = 825)

2 **Characteristics**

3 **Arm-level characteristics**

	Semaglutide (0.5 mg) (N = 826)	**Semaglutide (1.0 mg) (N = 822)**	**Placebo (0.5 mg) (N = 824)**	**Placebo (1.0 mg) (N = 825)**
% Female				
Nominal	40.1	37	41.5	39.5

	Semaglutide (0.5 mg) (N = 826)	Semaglutide (1.0 mg) (N = 822)	Placebo (0.5 mg) (N = 824)	Placebo (1.0 mg) (N = 825)
Mean age (SD) Age in years				
Mean/SD	64.6 (7.3)	64.7 (7.1)	64.8 (7.6)	64.4 (7.5)
BMI or weight *(Kilograms)* Weight (kg)				
Mean/SD	91.8 (20.3)	92.9 (21.1)	91.8 (20.3)	91.9 (20.8)
Comorbidities				
Never smoked %				
Nominal	47.2	44.3	47.5	42.2
History of Ischemic heart disease %				
Nominal	59.7	60.2	61.9	60.1
History of MI %				
Nominal	32.2	32.1	32.4	33.3
History of heart failure %				
Nominal	24.3	21.9	23.1	25
Ischemic stroke %				
Nominal	10.8	10.8	11.7	13.2
Haemorrhagic stroke %				
Nominal	3.4	2.9	3.3	3.5
Hypertension %				
Nominal	93.5	93.8	91.7	92.1
Normal eGFR ≥90 (%) *(ml/min/1.73m2 of body surface area)*				
Nominal	29.9	29.9	29.7	30.5
Ethnicity *(Percentage)*				
Hispanic / Latino Percentage				
Nominal	16	15.1	14.2	16.6
Not Hispanic / Latino				

	Semaglutide (0.5 mg) (N = 826)	Semaglutide (1.0 mg) (N = 822)	Placebo (0.5 mg) (N = 824)	Placebo (1.0 mg) (N = 825)
Percentage				
Nominal	84	84.9	85.8	83.4
Race *(Percentage)*				
White %				
Nominal	83.9	84.1	82	81.9
Black/African American				
Nominal	6.5	6.6	6.6	7.2
Asian %				
Nominal	7.6	7.1	9.7	8.7
Other				
Nominal	1.9	2.3	1.7	2.2
Duration of diabetes *(years (mean))*				
Mean/SD	14.3 (8.21)	14.1 (8.17)	14 (8.54)	13.2 (7.44)

1

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Randomized, double-blind, placebo-controlled, parallel-group trial - method of randomization and allocation concealment not specified. The study outlines that demographic and clinical characteristics of the patients at baseline were similar across treatment groups - method of analysis not outlined.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Randomized, double-blind, placebo-controlled, parallel-group trial - method of randomization and allocation concealment not specified. All results were analysed on an intention-to-treat basis that included all patients who underwent randomization according to the planned treatment with the exception of adverse events leading to premature discontinuation, which were included in the as-treated safety analysis.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Vital status was known for 99.6%; 2% (n=65) randomized participants did not complete the trial due to withdrawal of consent or lost to follow-up. ITT undertaken on all participants randomized)*

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Clinical event rates used to measure the predefined and prespecified outcomes; Each outcome, except for peripheral revascularization, was adjudicated in a blinded fashion by an external, independent event-adjudication committee. Randomized, double-blind, placebo-controlled, parallel-group trial - method of randomization and allocation concealment not specified.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(Clinical event rates used to measure the predefined and prespecified outcomes; All outcomes prespecified are outlined. Each outcome, except for peripheral revascularization, was adjudicated in a blinded fashion by an external, independent event-adjudication committee.)*
Overall bias and Directness	Risk of bias judgement	Low
	Overall Directness	Directly applicable

1

Marso Steven, 2016

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

2 **Study details**

Other publications associated with this study included in review	Daniels et al. 2015; Dhatariya et al. 2018; Hegedus et al. 2018; Hinton et al. 2019; Mann et al. 2017; Mann et al. 2018; Marso et al. 2018; Marso et al. 2020; Masmiquel et al. 2016; Mosenzon et al. 2020; Nuack et al. 2018; Nuack et al. 2018; Nuack et al. 2018; Nauck et al. 2019; Petrie et al. 2016; Rutten et al. 2016; Satman et al. 2016; Steinberg et al. 2014; Steinberg et al. 2017; Verma et al. 2018; Verma et al. 2018; Verma et al. 2019; Zinman et al. 2018; Zinman et al. 2018.
Trial registration number and/or trial name	ClinicalTrials.gov number, NCT01179048 - LEADER
Study type	Randomised controlled trial (RCT)
Study location	32 countries (Canada, USA, Mexico, Brazil, South Africa, Romania, Greece, Serbia, Italy, Austria, Spain, France, Ireland, United Kingdom, Belgium, Netherlands, Denmark, Norway, Sweden, Finland, Germany, Poland, Czech Rep, Russian Federation, China, India, Taiwan, South Korea, Australia, UAE, Turkey, Israel)
Study setting	410 sites - no further detail.

Study dates	Randomization from September 2010 through April 2012; The planned closeout of follow-up of the patients was from August 2014 through December 2015.
Sources of funding	Novo Nordisk and the National Institutes of Health
Inclusion criteria	Adults (aged 50 year or older) with type 2 diabetes Patients with type 2 diabetes who had a glycated haemoglobin level of 7.0% or more were eligible if they either had not received drugs for this condition previously or had been treated with one or more oral antihyperglycemic agents or insulin (human neutral protamine Hagedorn, long-acting analogue, or premixed) or a combination of these agents. The major inclusion criteria: an age of 50 years or more with at least one cardiovascular coexisting condition (coronary heart disease, cerebrovascular disease, peripheral vascular disease, chronic kidney disease of stage 3 or greater, or chronic heart failure of New York Heart Association class II or III) or an age of 60 years or more with at least one cardiovascular risk factor (investigator determined: microalbuminuria or proteinuria, hypertension and left ventricular hypertrophy, left ventricular systolic or diastolic dysfunction, or an ankle–brachial index of less than 0.9).
Exclusion criteria	People with type 1 diabetes Cardiovascular or cerebrovascular event within 8 weeks of randomization Within 14 days before screening and randomization **Cancer** Familial or personal history of multiple endocrine neoplasia type 2 or medullary thyroid cancer; **Treatment** Use of GLP-1–receptor agonists, dipeptidyl peptidase 4 (DPP-4) inhibitors, pramlintide **Insulin therapy** Rapid-acting insulin
Intervention(s)	Liraglutide, an analogue of human glucagon-like peptide 1 (GLP-1)
Comparator	Placebo
Outcomes of interest	Myocardial infarction Stroke, or atherosclerotic disease Primary composite outcome: first occurrence of death from cardiovascular causes, nonfatal (including silent) myocardial infarction, or nonfatal stroke Expanded composite cardiovascular outcome (death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or hospitalization for unstable angina pectoris or heart failure), Cardiovascular-related mortality

	Primary composite outcome: first occurrence of death from cardiovascular causes, nonfatal (including silent) myocardial infarction, or nonfatal stroke Expanded composite cardiovascular outcome (death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or hospitalization for unstable angina pectoris or heart failure), All-cause mortality Change in weight or Body Mass Index (BMI) at 1 year Dropouts due to adverse events Hypoglycaemic event rates Hospitalization for unstable angina Expanded composite cardiovascular outcome (death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or hospitalization for unstable angina pectoris or heart failure), Hospitalization for heart failure
Number of participants	9340 patients underwent randomization; liraglutide n=4668 and placebo n=4672
Duration of follow-up	Minimum follow-up period 42 months, median follow-up 3.8 years
Loss to follow-up	A total of 96.8% (n=9041) of the patients completed a final visit, died, or had a primary outcome (loss to follow-up of 3.2%; n=299); The vital status was known in 99.7% of the patients.
Methods of analysis	The primary and exploratory analyses for the outcomes in the time-to-event analyses were based on a Cox proportional-hazards model with treatment as a covariate
Additional comments	

1 **Study arms**

Liraglutide (N = 4668) 1.8 mg via subcutaneous injection
Placebo (N = 4672)

2 **Characteristics**

3 **Arm-level characteristics**

	Liraglutide (N = 4668)	**Placebo (N = 4672)**
% Female		
Nominal	35.5	36

	Liraglutide (N = 4668)	Placebo (N = 4672)
Mean age (SD)		
Mean/SD	64.2 (7.2)	64.4 (7.2)
BMI or weight BMI		
Mean/SD	32.5 (6.3)	32.5 (6.3)
Comorbidities		
Established CVD (age >50) % Includes: Prior myocardial infarction, Prior stroke or transient ischemic attack, Prior revascularization, >50% stenosis of coronary, carotid, or lower extremity arteries, documented symptomatic CHD, documented asymptomatic cardiac ischemia, Heart failure NYHA II – III, Chronic kidney disease		
Nominal	82.1	80.6
CVD risk factors (age >60) % Includes: Microalbuminuria or proteinuria, Hypertension and left ventricular hypertrophy, Left ventricular systolic or diastolic dysfunction, Ankle-brachial index <0.9.		
Nominal	17.9	19.4
Renal function Normal (eGFR >90) %		
Nominal	34.7	35.4
Heart failure (NYHA class I, II and III) %		
Nominal	17.9	17.8

1

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Double-blind, placebo-controlled trial - randomized in a 1:1 manner using a interactive voice/web response system. The demographic and clinical characteristics of the patients were similar in the two groups)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Double-blind, placebo-controlled trial - randomized in a 1:1 manner using a interactive voice/web response system; ITT undertaken with subject evaluated as randomized)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Marso et al 2013 outlines that the full analysis set includes all randomized subjects with evaluation by intention-to-treat, with subjects evaluated as randomized.)*

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Clinical event rates used to assess prespecified outcomes which were adjudicated in a blinded fashion by an external, independent event-adjudication committee; Double blind randomized study)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(Results outlined align with those prespecified in the analytical plan and the prespecified outcomes which were assessed via clinical event rates which were adjudicated in a blinded fashion by an external, independent event-adjudication committee)*
Overall bias and Directness	Risk of bias judgement	Low
	Overall Directness	Directly applicable

1

Pfeffer Marc, 2015

Bibliographic Reference	Pfeffer Marc, A; Claggett, Brian; Diaz, Rafael; Dickstein, Kenneth; Gerstein Hertzel, C; Kober Lars, V; Lawson Francesca, C; Ping, Lin; Wei, Xiaodan; Lewis Eldrin, F; Maggioni Aldo, P; McMurray John J, V; Probstfield Jeffrey, L; Riddle Matthew, C; Solomon Scott, D; Tardif, Jean-Claude; ELIXA, Investigators; Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome.; The New England journal of medicine; 2015; vol. 373 (no. 23); 2247-57

2 **Study details**

Other publications associated with this study included in review	Bentley-Lewis et al. 2015; Serferovic et al. 2018; Wijkman et al. 2020; Wittbrodt et al. 2018; Wolsk et al 2017.
Trial registration number and/or trial name	ClinicalTrials.gov number, NCT01147250
Study type	Randomised controlled trial (RCT)
Study location	49 countries (not specified)
Study setting	Not specified - study refers to 'multicentre'
Study dates	Enrolment occurred between July 9, 2010, and August 2, 2013; end-of-study visits initiated from November 11, 2014 with the last patient visit occurring on February 11, 2015.

Sources of funding	Funded by Sanofi
Inclusion criteria	Adults (aged 30 years or older) with type 2 diabetes Eligible patients had type 2 diabetes and had had an acute coronary event within 180 days before screening.
Exclusion criteria	Renal Estimated glomerular filtration rate (eGFR) of less than 30 ml per minute per 1.73 m2 of body surface area age <30 years Percutaneous coronary intervention within the previous 15 days Coronary-artery bypass graft surgery within the previous 15 days Planned coronary revascularization procedure within 90 days after screening Glycated haemoglobin level of less than 5.5% or more than 11.0%,
Intervention(s)	Lixisenatide, a once-daily GLP-1–receptor agonist, effective in reducing the glycated haemoglobin level in patients with type 2 diabetes by lowering both the fasting and the postprandial blood glucose levels
Comparator	Placebo
Outcomes of interest	Myocardial infarction Stroke, or atherosclerotic disease non-fatal stroke Cardiovascular-related mortality All-cause mortality Change in weight or Body Mass Index (BMI) at 1 year Total dropouts Dropouts due to adverse events Hypoglycaemic event rates Hospitalization for unstable angina Hospitalization for heart failure
Number of participants	6068
Duration of follow-up	Median 25 months

Loss to follow-up	5/6068 did not receive at least one does of treatment (Placebo n=2; lixisenatide n=3); 96.3% in the lixisenatide arm and 96.1% in the placebo arm completed the study
Methods of analysis	The primary analysis was conducted in the intention-to-treat population with the use of the Cox proportional-hazards model, with study group and geographic region as the covariates, to estimate the hazard ratio for the comparison of lixisenatide with placebo
Additional comments	

1 **Study arms**

Lixisenatide (N = 3034) A starting dose of 10 µg of lixisenatide per day was administered via subcutaneous injection during the first 2 weeks and then increased, at the investigator's discretion, to a maximum dose of 20 µg of lixisenatide per day.
Placebo (N = 3034) A starting dose of 10 µg of volume matched placebo was administered during the first 2 weeks and then increased, at the investigator's discretion, to a maximum dose of 20 µg volume-matched placebo.

2 **Characteristics**

3 **Arm-level characteristics**

	Lixisenatide (N = 3034)	**Placebo (N = 3034)**
% Female		
Nominal	30.4	34.9
Mean age (SD)		
Mean/SD	59.9 (9.7)	60.6 (9.6)
BMI or weight		
Mean/SD	30.1 (5.6)	30.2 (5.8)
Comorbidities		
Current smoking %		
Nominal	11.7	11.7
Myocardial infarction before index ACS %		
Nominal	22.1	22.1
Urinary albumin: creatinine ratio (Median) measured in milligrams and creatinine in grams.		

	Lixisenatide (N = 3034)	Placebo (N = 3034)
Nominal	10.2	10.5
Hypertension % Medical history at randomization		
Nominal	75.6	77.1
Percutaneous coronary intervention %		
Nominal	67.6	66.8
Heart failure %		
Nominal	22.5	22.3
Stroke %		
Nominal	4.7	6.2
Peripheral arterial disease % included amputation due to a cause other than trauma		
Nominal	7.8	7.5
Atrial fibrillation %		
Nominal	5.8	6.3
eGFR *(ml/min/1.73m2 of body surface area)*		
Mean/SD	76.7 (21.3)	75.2 (21.4)
Race / Ethnicity % Race and ethnic group were self-reported.		
Asian %		
Nominal	13.3	12.1
Black %		
Nominal	3.9	3.4
Other		
Nominal	8.4	8.1
White %		
Nominal	74.4	76.4

1

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Outlined as a multicentre, randomized, double-blind, placebo-controlled trial. Randomization was performed with the use of a centralized assignment system. The characteristics of the study groups are outlined as 'generally balanced at baseline' however nominally significant between-group differences were observed in 4/35 baseline comparisons (age, eGFR, glycated haemoglobin, level, and prior stroke).)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Outlined as a multicentre, randomized, double-blind, placebo-controlled trial; Concealment protocols not specified; Intention to treat adopted for the primary analysis)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(5/6068 participants did not receive at least one dose of treatment or placebo; ITT adopted for primary analysis; data reported for all randomized participants (n=6068) - unclear how 3/5 participants randomized to the treatment arm but did not receive the treatment were considered in the data collection or analysis - this represents 0.1% of the treatment arm - not considered to be a source of bias)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Outlined as a multicentre, randomized, double-blind, placebo-controlled trial; Concealment protocols not specified. Prespecified outcomes measured via clinical event rates with a separate independent committee blinded to treatment allocations adjudicated potential cardiovascular, pancreatic, and allergic events.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(Pre-specified primary outcomes are all reported based on clinical event rates. Study outlined as a double-blind study; Some additional analysis were undertaken which were not outlined in the pre-specified analytic plan including the use of Student's t-tests, Wilcoxon rank-sum tests, and chi-square tests. These additional analysis are not a source of bias.)*
Overall bias and Directness	Risk of bias judgement	Low
	Overall Directness	Directly applicable

1

Rosenstock, 2019

Bibliographic Reference	Rosenstock, J; Kahn S, E; Johansen O, E; Zinman, B; Espeland M, A; Woerle H, J; Pfarr, E; Keller, A; Mattheus, M; Baanstra, D; Meinicke, T; George J, T; Von Eynatten, M; McGuire D, K; Marx, N; Effect of Linagliptin vs Glimepiride on Major

Adverse Cardiovascular Outcomes in Patients with Type 2 Diabetes: The CAROLINA Randomized Clinical Trial; JAMA - Journal of the American Medical Association; 2019; vol. 322 (no. 12); 1155-1166

1 **Study details**

Other publications associated with this study included in review	Kadowaki et al. 2021; Espeland et al. 2020; Biessels et al. 2018; Biessels et al. 2021; Chilton et al. 2013; Janssen et al. 2018; Marx et al. 2015
Trial registration number and/or trial name	ClinicalTrials.gov Identifier: NCT01243424
Study type	Randomised controlled trial (RCT)
Study location	43 countries not specified but covering Europe, North America, New Zealand, or Australia, Asia, South America and Mexico, Africa (Tunisia and South Africa)
Study setting	607 centres not specified
Study dates	Participants were screened from November 2010 through December 2012, with final follow-upon August 21, 2018.
Sources of funding	This study was sponsored by Boehringer Ingelheim and Eli Lilly and Company.
Inclusion criteria	Adults (aged 18 years and older) with type 2 diabetes Adults with type 2 diabetes, glycated haemoglobin (HbA1c) level of 48-70 mmol/mol (6.5% to 8.5%), and high cardiovascular risk were eligible for inclusion. Participants naive to sulfonylurea or glinide therapy had to have a HbA1c level of 48-70 mmol/mol (6.5% to 8.5%), while participants who were currently treated with a sulfonylurea or glinide as monotherapy or in a dual combination with metformin or α-glucosidase inhibitor (who also were eligible for the trial) had to have an HbA1c level of 48-59 mmol/mol (6.5% to 7.5%).
Exclusion criteria	Insulin therapy exposure to DPP-4 inhibitors exposure to glucagonlikepeptide-1 exposure to receptor agonists exposure to thiazolidinediones **Heart failure** New York Heart Association class III to IV heart failure
Intervention(s)	Linagliptin orally 5 mg once daily
Comparator	Glimepiride orally 1 to 4 mg once daily

Outcomes of interest	Myocardial infarction Non-fatal myocardial infarction Stroke, or atherosclerotic disease Non-fatal (secondary) Fatal or non-fatal stroke (secondary) Cardiovascular-related mortality Part of MACE Transient ischemic attack Secondary All-cause mortality Secondary outcome Total dropouts Dropouts due to adverse events Hypoglycaemic event rates Hospitalization for unstable angina Hospitalization for heart failure
Number of participants	6033
Duration of follow-up	6.3 years (median)
Loss to follow-up	9/6033 participants were not included in the analysis 239/6033 did not complete the study (112/6033 withdrew consent; 127/6033 lost to follow-up)
Methods of analysis	Time-to-event outcomes were analysed using a Cox proportional hazards model, with treatment assignment as a factor in the model. For all Cox proportional hazards analyses, the proportional hazard assumption was met. Proportional hazards assumptions were explored by plotting log (−log [survival function]) against the log of time*treatment group and checked for parallelism. Schoenfeld residuals were plotted against time and log(time). Subgroup analyses included additional factors for subgroup and treatment by subgroup interaction. Kaplan-Meier estimates are presented
Additional comments	

1 **Study arms**

Linagliptin (N = 3028)

5 mg once daily
Glimepiride (N = 3014) 1 to 4 mg once daily

1 **Characteristics**

2 **Arm-level characteristics**

	Linagliptin (N = 3028)	**Glimepiride (N = 3014)**
% Female *(%)*		
Nominal	39.2	40.8
Mean age (SD) *(years)*		
Mean/SD	63.9 (9.5)	64.2 (9.5)
BMI or weight		
Sample Size	n = 3012; % = 99.5	n = 2997; % = 99.6
Mean/SD	30.2 (5.2)	30 (5.1)
Comorbidities		
Smoking status Never smoker %		
Nominal	45	48.1
Sample Size	n = 3014; % = 99.7	n = 3000; % = 99.7
Vascular disease %		
Nominal Sample Size	34.8	34.5
Multiple cardiovascular risk factors %		
Nominal Sample Size	37.4	36.9
Microvascular disease % Any (Diabetic neuropathy, Diabetic nephropathy; Diabetic retinopathy)		
Nominal Sample Size	28.1	29.4
Atherosclerotic cardiovascular disease % Any (Coronary artery disease; Cerebrovascular disease; Peripheral artery disease)		

	Linagliptin (N = 3028)	Glimepiride (N = 3014)
Nominal Sample Size	42.2	41.7
eGFR (MDRD) *(ml/min/1.73m2 of body surface area)*		
Mean/SD	76.5 (19.7)	77 (19.8)
Urinary albumin-to-creatinine ratio (mg/mL)		
Median (IQR)	9.7 (5.3, 31.8)	9.7 (5.3, 30.1)
History of heart failure %		
Nominal	4.1	5.0
Race % *(Percentage)*		
White %		
Nominal	73.6	73
Asian %		
Nominal	17.6	17.7
Black %		
Nominal	5.1	5.6
American Indian / Alaska native %		
Nominal	3.5	3.6
Hawaiian/Pacific Islander %		
Nominal	0.2	0.1
Ethnicity %		
Nominal	3014	3000
Not Hispanic / Latino %		
Nominal	82.8	82.9
Hispanic / Latino %		
Nominal	17.2	17.1

1

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Study outlined as multicentre, randomized, double-blind, active controlled clinical trial. Randomization and allocation protocols outlined. Baseline clinical characteristics balanced between groups)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Study described as multicentre, randomized, double-blind, active controlled clinical trial indicating adequate allocation concealment, but specific methods not outlined; ITT undertaken)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Data provided for all primary (Cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke [3P-MACE]) and secondary end points accounting for 99.9% (6033/6042) of participants randomized.)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Clinical event rates and objective measures of safety coded using the Medical Dictionary for Drug Regulatory Activities version were utilized to measure pre-specified outcomes. Study described as multicentre, randomized, double-blind, active controlled clinical trial indicating adequate allocation concealment, but specific methods not outlined.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(Evidence of prespecified analytical plan and prespecified outcomes, and the data presented aligns with prespecified plans)*
Overall bias and Directness	Risk of bias judgement	Low *(Study described as multicentre, randomized, double-blind, active controlled clinical trial indicating adequate allocation concealment, but specific methods not outlined; ITT undertaken; Data provided for all primary (Cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke [3P-MACE]) and secondary end points accounting for 99.9% (6033/6042) of participants randomized. Clinical event rates and objective measures of safety coded (using the Medical Dictionary for Drug Regulatory Activities version) were utilized to measure pre-specified outcomes. Evidence of prespecified analytical plan and prespecified outcomes (Marx et al 2015), and the data presented, and methods of analysis outlined aligns with prespecified plans.)*
	Overall Directness	Directly applicable

1

Rosenstock, 2019

Bibliographic Reference	Rosenstock, Julio; Perkovic, Vlado; Johansen Odd, Erik; Cooper Mark, E; Kahn Steven, E; Marx, Nikolaus; Alexander John, H; Pencina, Michael; Toto Robert, D; Wanner, Christoph; Zinman, Bernard; Woerle Hans, Juergen; Baanstra, David; Pfarr, Egon; Schnaidt, Sven; Meinicke, Thomas; George Jyothis, T; von Eynatten, Maximilian; McGuire Darren, K; CARMELINA, Investigators; Effect of Linagliptin vs Placebo on Major Cardiovascular Events in Adults With Type 2 Diabetes and High Cardiovascular and Renal Risk: The CARMELINA Randomized Clinical Trial.; JAMA; 2019; vol. 321 (no. 1); 69-79

1 **Study details**

Other publications associated with this study included in review	Rosenstock et al. 2018; Perkovic et al. 2020; McGuire et al. 2019; Biessels et al. 2019; Inagaki et al. 2020; Cooper et al. 2020; Verhagen et al. 2020
Trial registration number and/or trial name	ClinicalTrials.gov Identifier: NCT01897532
Study type	Randomised controlled trial (RCT)
Study location	27 countries (not specified)
Study setting	605 clinic sites (no further information)
Study dates	August 2013 to August 2016. Final follow-up occurred on January 18, 2018.
Sources of funding	Study was sponsored by Boehringer Ingelheim and Eli Lilly.
Inclusion criteria	Adults (aged 18 years and older) with type 2 diabetes
Exclusion criteria	People with type 1 diabetes End-stage renal disease eGFR <15ml/min/1.73m2 Pregnant (or intending), breastfeeding, not using adequate contraception
Intervention(s)	Linagliptin is a selective, once-daily, DPP-4 inhibitor approved for glycaemic management of type 2 diabetes
Comparator	Placebo
Outcomes of interest	Myocardial infarction Primary outcome: time to first occurrence of CV death, nonfatal myocardial infarction Stroke, or atherosclerotic disease

	Primary outcome: nonfatal stroke (3-point major adverse CV event [MACE]). Coronary heart failure Hospitalization for heart failure Cardiovascular-related mortality All-cause mortality Tertiary or exploratory outcomes all-cause death Change in weight or Body Mass Index (BMI) at 1 year Total dropouts Dropouts due to adverse events Hypoglycaemic event rates Additional tertiary outcomes: change from baseline in HbA1c. Hospitalization for unstable angina
Number of participants	6991 randomized
Duration of follow-up	Median 2.2 years
Loss to follow-up	1.3% (n=12) did not receive at least one dose and were not included in the primary analysis; (27% [n=1880] did not provided primary data or discontinued treatment before the end of the study [n=91 participants did not have primary outcome data; n=1789 discontinued treatment before the end of the study])
Methods of analysis	Hazard ratio with 95% CI outlined based on cox regression analysis based on patients treated with at least 1 dose of study drug; Adverse event assessments were conducted using descriptive statistics
Additional comments	Protocol amendment (via steering group) in 2016 based on emerging evidence that a primary outcome definition based on 3-point MACE was preferred by regulators and consistent with other CV outcome trials - the original protocol included hospitalization for unstable angina pectoris in the primary outcome (a 4-point MACE). Assessment of outcome change - Death due to renal failure: The eGFR criterion was changed from the original decrease of at least 50% in eGFR in accord with National Kidney Foundation and the US Food and Drug Administration (FDA) recommendations. Use of the originally planned decrease of at least 50% in eGFR in the kidney composite was evaluated as a tertiary outcome.

1 **Study arms**

Linagliptin (N = 3499) DPP-4 inhibitor approved for glycaemic management of type 2 diabetes (5 mg once daily orally)

Placebo (N = 3492)

1 **Characteristics**

2 **Arm-level characteristics**

	Linagliptin (N = 3499)	Placebo (N = 3492)
% Female		
Nominal	38.5	35.7
Mean age (SD)		
Mean/SD	66.1 (9.1)	65.6 (9.1)
BMI or weight		
Mean/SD	31.4 (5.3)	31.3 (5.4)
Comorbidities		
Never smoker %		
Nominal	54.3	53.3
History of heart failure %		
Nominal	27.2	26.4
Ischemic heart disease %		
Nominal	58.1	58.9
History of hypertension %		
Nominal	90.8	91.2
Atrial fibrillation %		
Nominal	9.1	10.2
eGFR (MDRD) %		
Nominal	25.1	24.9
Urinary albumin-to-creatinine ratio (mg/g)		
Median (IQR)	162 (43, 700)	162 (44, 750)
Race / Ethnicity % Other - American Indian/Alaska Native or Native Hawaiian/other Pacific Islander.		
White %		

	Linagliptin (N = 3499)	Placebo (N = 3492)
Nominal	80.9	79.5
Asian %		
Nominal	8.8	9.6
Black, African American		
Nominal	5.6	6.2
Other		
Nominal	4.8	4.8

1

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Randomized double-blind study, No reference to a analysis of difference. Study outlines that baseline clinical characteristics were balanced between groups and patients' CV and kidney disease risk factors were well managed overall)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Randomized double blinded study; computer generated allocations and ITT undertaken with analysis undertaken based on the groups patients were randomized to.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Data available for all prespecified outcomes; n=12 (1.3%) participants were not included in the primary analysis; ITT undertaken (27% [n=1880] did not provided primary data or discontinued treatment before the end of the study [n=91 participants did not have primary outcome data; n=1789 discontinued treatment before the end of the study]))*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Study outlines double-blind methods and computerized participant allocation process. Clinical event rates; Definitions of all clinical outcomes assessed as well as a complete list of all predefined end points are detailed in statistical analyses plans; Adverse events were assessed based on reported events, coded using the Medical Dictionary for Drug Regulatory Activities, version 20.1. An independent, unmasked data monitoring committee regularly reviewed trial data throughout the study.)*

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(Reference made to prespecified definitions of outcomes and analytical plans. Prespecified outcomes are assessed by clinical event rates and all prespecified outcomes have been reported.)*
Overall bias and Directness	Risk of bias judgement	Low
	Overall Directness	Directly applicable

1

Scirica Benjamin, 2013

Bibliographic Reference	Scirica Benjamin, M; Bhatt Deepak, L; Braunwald, Eugene; Steg P, Gabriel; Davidson, Jaime; Hirshberg, Boaz; Ohman, Peter; Frederich, Robert; Wiviott Stephen, D; Hoffman Elaine, B; Cavender Matthew, A; Udell Jacob, A; Desai Nihar, R; Mosenzon, Ofri; McGuire Darren, K; Ray Kausik, K; Leiter Lawrence, A; Raz, Itamar; SAVOR-TIMI 53 Steering Committee, and; Investigators; Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus.; The New England journal of medicine; 2013; vol. 369 (no. 14); 1317-26

2 **Study details**

Other publications associated with this study included in review	Scirica et al. 2014; Scirica et al. 2018; Mosenzon et al. 2017; Leiter et al. 2015; Leibowitz et al. 2015; Cavender et al. 2016; Berg et al. 2019; Bergmark et al. 2019; Mosenzon et al. 2015; Scirica et al. 2016; Udell et al. 2015; Xia et al. 2017
Trial registration number and/or trial name	ClinicalTrials.gov number, NCT01107886 SAVOR-TIMI 53
Study type	Randomised controlled trial (RCT)
Study location	26 countries not specified
Study setting	788 sites not specified
Study dates	May 2010 through December 2011 patients underwent randomization.
Sources of funding	AstraZeneca and Bristol-Myers Squibb;
Inclusion criteria	Adults (aged 40 year or older) with type 2 diabetes History of documented type 2 diabetes mellitus, a glycated haemoglobin level of 6.5% to 12.0%, and either a history of established cardiovascular disease (at least 40 years old and have a history of a clinical event associated with atherosclerosis involving the coronary, cerebrovascular, or peripheral vascular system) or multiple

	risk factors for vascular disease (at least 55 years of age [men] or 60 years of age [women] with at least one of the following additional risk factors: dyslipidaemia, hypertension, or active smoking).
Exclusion criteria	Renal End-stage renal disease and were undergoing long-term dialysis, had undergone a renal transplantation, or had a serum creatinine level higher than 6.0 mg per decilitre (530 µmol per litre). Treatment Patients were ineligible if they were currently receiving or had received within the previous 6 months an incretin-based therapy
Intervention(s)	Saxagliptin: Dose of 5 mg daily (or 2.5 mg daily in patients with an estimated glomerular filtration rate [GFR] of =50 ml per minute)
Comparator	Matching placebo
Outcomes of interest	Myocardial infarction Stroke, or atherosclerotic disease Cardiovascular-related mortality All-cause mortality Change in weight or Body Mass Index (BMI) at 1 year Total dropouts Hypoglycaemic event rates Hospitalization Hospitalization for unstable angina Hospitalization for heart failure
Number of participants	16492
Duration of follow-up	2.1 years (median)
Loss to follow-up	A final vital status was assessed in 99.1% of the patients. A total of 28 patients were lost to follow-up. The study drug was discontinued prematurely less frequently among patients assigned to saxagliptin than among patients assigned to placebo (1527 patients [18.4%] vs. 1705 patients [20.8%], P<0.001).
Methods of analysis	Cox proportional-hazards model, with stratification according to baseline renal-impairment category and baseline cardiovascular risk group and with treatment as a model term.
Additional comments	

1 **Study arms**

Saxagliptin (N = 8280)

Placebo (N = 8212)

1 **Characteristics**

2 **Arm-level characteristics**

	Saxagliptin (N = 8280)	Placebo (N = 8212)
% Female		
Nominal	33.4	32.7
Mean age (SD)		
Mean/SD	65.1 (8.5)	65 (8.6)
BMI or weight (BMI)		
Mean/SD	31.5 (5.5)	31.2 (5.7)
Comorbidities		
Duration of diabetes (median - years) Data were available for 8270 patients in the saxagliptin group and 8207 in the placebo group		
Nominal	10.3	10.3
Established atherosclerotic disease %		
Nominal	78.4	78.7
Hypertension %		
Nominal	81.2	82.4
Dyslipidaemia %		
Nominal	71.2	71.2
Prior myocardial infarction %		
Nominal	38	37.6
Prior heart failure %		
Nominal	12.8	12.8
Prior coronary revascularization %		
Nominal	43.1	43.3
Glycated haemoglobin		
Mean/SD	8 (1.4)	8 (1.4)

	Saxagliptin (N = 8280)	Placebo (N = 8212)
Fasting serum glucose — mg/dl Data were available for 7892 patients in the saxagliptin group and 7805 in the placebo group		
Mean/SD	156 (56)	157 (57)
Estimated glomerular filtration rate		
Mean/SD	72.5 (22.6)	72.7 (22.6)
Albumin-to-creatinine ratio		
Median (IQR)	1.8 (0.7, 7.5)	1.9 (0.7, 7.9)
Race % *(Percentage)*		
White % Race and ethnic group were self-reported.		
Nominal	75.4	75.1
Hispanic % Race and ethnic group were self-reported.		
Nominal	21.5	21.5

1

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Randomized, double-blind, placebo-controlled; Randomization was performed by means of a central computerized telephone or Web-based system in blocks of 4; Method of allocation concealment not specified; The baseline characteristics of the patients who underwent randomization were outlined as well balanced between the two groups. Analysis not outlined)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Randomized, double-blind, placebo-controlled; Randomization was performed by means of a central computerized telephone or Web-based system in blocks of 4. Method of allocation concealment not specified. The primary safety and efficacy analyses were performed according to the intention-to-treat principle on data from all patients who underwent randomization.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(The primary safety and efficacy analyses were performed according to the intention-to-treat principle on data from all patients who underwent randomization. A final vital status was assessed in 99.1% of the patients. A total of 28 patients were lost to follow-up.)*

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Clinical event rates used to assess predefined and prespecified outcomes; A clinical events committee comprising specialists in cardiovascular and pancreatic medicine, all of whom were unaware of the study group assignments, adjudicated all components of the primary composite and secondary efficacy end points and all cases of pancreatitis. Randomized, double-blind, placebo-controlled; Randomization was performed by means of a central computerized telephone or Web-based system in blocks of 4; Method of allocation concealment not specified;)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(Prespecified analytical plan outlined and published which reported outcomes align with; Clinical event rates used to assess impact of interventions on prespecified and predefined outcomes; A clinical events committee comprising specialists in cardiovascular and pancreatic medicine, all of whom were unaware of the study group assignments, adjudicated all components of the primary composite and secondary efficacy end points and all cases of pancreatitis.)*
Overall bias and Directness	Risk of bias judgement	Low
	Overall Directness	Directly applicable

1

White William, 2013

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

2 **Study details**

Secondary publication of another included study- see primary study for details	
Other publications associated with this study	Cavender et al. 2017; Elharram et al. 2020; Ferreira et al. 2020; Hwang et al. 2017; Jarolim et al. 2018; Kay et al. 2017; Sharma et al. 2018; Sharma et al. 2020; Shimada et al.2016; White et al. 2011; White et al. 2016; White et al. 2018; White et al. 2018; Zannad et al. 2015

included in review	
Trial registration number and/or trial name	ClinicalTrials.gov number, NCT00968708
Study type	Randomised controlled trial (RCT)
Study location	49 countries; United States and Canada; Western Europe, Australia, New Zealand, and Middle East; Central and South America and Mexico; Eastern Europe and Africa; Asia and Pacific Islands
Study setting	898 centres; Described as multicentre; reference made to outpatient visits - no further details
Study dates	Recruitment undertaken from October 2009 to March 2013; last patient visit June 18, 2013
Sources of funding	Takeda Development Center Americas
Inclusion criteria	Adults (aged 18 years and older) with type 2 diabetes Received a diagnosis of type 2 diabetes mellitus (glycated haemoglobin level of 6.5 to 11.0% at screening, or if the antidiabetic regimen included insulin, a glycated haemoglobin level of 7.0 to 11.0%, receiving antidiabetic therapy (other than a DPP-4 inhibitor or GLP-1 analogue), and had had an acute coronary syndrome (acute myocardial infarction and unstable angina requiring hospitalization within 15 to 90 days before randomization.
Exclusion criteria	People with type 1 diabetes Diagnosis **Renal** Dialysis within 14 days before screening **Heart failure** New York Heart Association class IV heart failure Refractory angina Uncontrolled arrhythmias Critical valvular heart disease Severe uncontrolled hypertension
Intervention(s)	Alogliptin - Selective inhibitor of dipeptidyl peptidase 4 (DPP-4) that is approved for the treatment of type 2 diabetes. Dose of alogliptin was adjusted to eGFR from 6.25 mg, 12.5 mg and 25 mg daily. Route of administration not stated (BNF - Oral) in addition to standard-of-care treatment for type 2 diabetes mellitus
Comparator	Placebo in addition to standard-of-care treatment for type 2 diabetes mellitus

Outcomes of interest	Myocardial infarction Stroke, or atherosclerotic disease Cardiovascular-related mortality All-cause mortality Change in weight or Body Mass Index (BMI) at 1 year Total dropouts Dropouts due to adverse events Hypoglycaemic event rates Hospitalization for unstable angina Hospitalization for heart failure
Number of participants	5380 (Placebo: n=2679; Alogliptin: n=2701)
Duration of follow-up	18 months (median)
Loss to follow-up	606/2679 (Placebo arm [22.6%]) and 564/2701 (Alogliptin are [20.9%]) prematurely discontinued study drug
Methods of analysis	Cox proportional-hazards models were used to analyse the time to the first occurrence of a primary or secondary end-point event among all randomly assigned patients, with stratification according to geographic region and renal function at baseline.

1 **Study arms**

Alogliptin (N = 2701) Alogliptin (Selective inhibitor of dipeptidyl peptidase 4 (DPP-4) that is approved for the treatment of type 2 diabetes) in addition to standard-of-care treatment for type 2 diabetes mellitus. Dose of alogliptin was adjusted to eGFR from 6.25 mg, 12.5 mg and 25 mg daily. Route of administration not stated (BNF - Oral)
Placebo (N = 2679) in addition to standard-of-care treatment for type 2 diabetes mellitus

2 **Characteristics**

3 **Arm-level characteristics**

	Alogliptin (N = 2701)	**Placebo (N = 2679)**
% Female		
Nominal	32.3	32
Mean age (SD)		

	Alogliptin (N = 2701)	**Placebo (N = 2679)**
Median (IQR)	61 (*not reported*)	61 (*not reported*)
BMI or weight *(BMI - Median (range))*		
Nominal	28.7	28.7
Range	15.7 to 55.9	15.6 to 68.3
Comorbidities		
Current smoker %		
Nominal	13	14.3
Hypertension %		
Nominal	82.5	83.6
Myocardial infarction % Values include the index event of the acute coronary syndrome.		
Nominal	88.4	87.5
Percutaneous coronary intervention % Values include the index event of the acute coronary syndrome		
Nominal	62.5	62.8
Coronary-artery bypass grafting % Values include the index event of the acute coronary syndrome		
Nominal	12.8	12.7
Congestive heart failure %		
Nominal	28	27.8
Stroke %		
Nominal	7.2	7.2
Peripheral arterial disease %		
Nominal	9.7	9.4
Estimated glomerular filtration rate - Median — ml/min/1.73 m2 calculated with the use of the Modification of Diet in Renal Disease formula		
Nominal	71.1	71.2
% Aged 65 and over		
Nominal	36.0	34.9
Race / Ethnicity %		

	Alogliptin (N = 2701)	Placebo (N = 2679)
Race or ethnic group was self-reported.		
White %		
Nominal	72.8	72.5
Black %		
Nominal	3.7	4.3
Asian %		
Nominal	20.3	20.2
Native American %		
Nominal	2.1	2
Other		
Nominal	1.1	0.9

1

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Randomized, double-blind trial - method of randomization not specified; analysis of post-randomization baseline characteristics not outlined)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Randomized, double-blind trial; method of blinding and concealment not specified; No reference to analysis to account for randomization but participants appear to be analysed in the arms they were randomized to.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Data for all participants randomized is outlined in the arms randomized to. However, no reference made to ITT or mITT and 1170 participants prematurely discontinued allocated treatment (approximately 22%))*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Double blind randomized trial; Outcome measurements were clinical event rate with an independent central adjudication committee adjudicated all suspected primary end-point events and other cardiovascular end points, as well as all deaths.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(Pre-specified analytical plan was outlined in White et al 2011; Analysis utilized based on*

Section	Question	Answer
		pre-specified outcomes based on a composite of clinical events which were also reported individually.)
Overall bias and Directness	Risk of bias judgement	Low
	Overall Directness	Directly applicable

1

Wilcox, 2008

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

2 **Study details**

Other publications associated with this study included in review	Wilcox et al. 2007; Spanheimer et al. 2009; Ferrannini et al. 2011; Erdmann et al. 2010; Erdmann et al. 2007; Erdmann et al. 2007; Dormandy et al. 2005; Doehner et al. 2011; Charbonnel et al. 2004; Erdmann et al. 2007; Schneider et al. 2007.
Trial registration number and/or trial name	PROspective pioglitAzone Clinical Trial In macroVascular Events 04; International Standard Randomized Controlled Trial (ISRCTN NCT00174993
Study type	Randomised controlled trial (RCT)
Study location	19 European countries
Study setting	321 clinical sites across
Study dates	Not specified
Sources of funding	Takeda Europe R&D Centre Ltd, London, United Kingdom, and Eli Lilly and Company, Indianapolis, IN.
Inclusion criteria	Adults (aged 30 years or older) with type 2 diabetes Participants included with type 2 diabetes (haemoglobin A1c level above the upper limit of normal; i.e., the local equivalent of 6.5% for a DCCT traceable assay) and with an established history of macrovascular disease (MI, stroke, percutaneous coronary intervention (PCI), or coronary artery bypass graft (CABG) ≥6 months before entering the study; ACS ≥3 months before entering the study; Objective evidence of coronary artery disease (positive exercise test or scintigraphy, or angiography showing at least one lesion N50% stenosis); Peripheral arterial

	obstructive disease of the leg (previous leg amputation above the ankle, or intermittent claudication with an ankle or toe brachial pressure index N0.9).
Exclusion criteria	People with type 1 diabetes including any history of ketoacidosis or requirement for insulin therapy within 1 year of diagnosis **Renal** Haemodialysis; or significantly impaired hepatic function (defined as serum alanine aminotransferase >2.5 times the upper limit of normal) **Treatment** Insulin as sole therapy for diabetes **Heart failure** Symptomatic heart failure (New York Heart Association class II or above) Planned coronary revascularization procedure within 90 days after screening Planned revascularization - no time frame Leg ulcers, gangrene, or pain at rest
Intervention(s)	Pioglitazone dose was force-titrated from 15 to 45 mg/d during the first 2 months, depending upon tolerability
Comparator	Placebo
Outcomes of interest	Myocardial infarction Stroke, or atherosclerotic disease Nonfatal stroke Cardiovascular-related mortality All-cause mortality Change in weight or Body Mass Index (BMI) at 1 year Total dropouts Dropouts due to adverse events Hypoglycaemic event rates
Number of participants	5238
Duration of follow-up	34.5 months (mean)
Loss to follow-up	All randomized participants provided outcome data with no documentation of loss to follow-up

Methods of analysis	Kaplan-Meier estimates of the 3-year event rates were calculated; Time-to-event analyses were carried out by fitting proportional hazards survival models with “treatment” as the only covariate, and estimated hazard ratios (HRs) and 95% CIs were calculated.
Additional comments	

1 **Study arms**

Pioglitazone (N = 2605)
Placebo (N = 2633)

2 **Characteristics**

3 **Study-level characteristics**

	Pioglitazone	**Placebo**
% Female *(Percentage)*		
Nominal	33	34
Mean age (SD) *(years (mean))*		
Mean/SD	61.9 (7.6)	61.6 (7.8)
BMI or weight *(kg/m2)*		
Mean/SD	30.7 (4.7)	31.0 (4.8)
Comorbidities		
Previous MI %		
Nominal	47	46
Previous stroke %		
Nominal	19	19
Micral test negative %		
Nominal	54	54
Hypertension %		
Nominal	75	76
Previous percutaneous intervention or CABG %		
Nominal	31	31
Hypertension %		

	Pioglitazone	Placebo
Nominal	75	76
Current smoking %		
Nominal	13	14
Race %		
White %		
Nominal	98	99
Duration of diabetes (median - years) *(median)*		
Median IQR	8 (4 to 13)	8 (4 to 14)

1

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Study described as randomized prospective, double-blind, multicentre, placebo controlled. Method of randomization and allocation concealment not specified. Study outlines that there were no relevant differences between the treatment groups in any of the baseline characteristics, medical history, or existing medication use. The analysis undertaken to establish this has not been specified.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Study described as randomized prospective, double-blind, multicentre, placebo controlled. Method of randomization and allocation concealment not specified. All study outcomes analysed on an intention-to-treat basis, defined as a patient having received at least one dose of study medication (Charbonnel et al 2004).)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(All study outcomes analysed on an intention-to-treat basis, defined as a patient having received at least one dose of study medication (Charbonnel et al 2004). All participants randomized are accounted for in the analysis.)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(A composite cardiovascular disease end point is used from randomization to the first occurrence of any of the events in the composite based on clinical event rates. The end points are adjudicated by an independent panel. Secondary end points include the individual components of the primary end point and cardiovascular mortality. Safety evaluations were undertaken (serious and non-serious adverse events). Study described as randomized*

Section	Question	Answer
		prospective, double-blind, multicentre, placebo controlled. Method of randomization and allocation concealment not specified.)
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(The study was analysed in accordance with a pre-specified and published (Charbonnel et al 2004) plan. All pre-specified outcomes are reported on as outlined in pre-specified plan. Outcomes are based on clinical event rates which were adjudicated by an independent panel)*
Overall bias and Directness	Risk of bias judgement	Low
	Overall Directness	Directly applicable

1

Wiviott Stephen, 2019

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

2 **Study details**

Other publications associated with this study included in review	Zelniker et al. 2020; Mosenzon et al. 2019; Kato et al. 2019; Furtado et al. 2019; Cahn et al. 2020; Bonaca et al. 2020; Cahn et al.2020; Berg et al. 2019; Wittbrodt et al. 2018; Wiviott eal. 2018
Trial registration number and/or trial name	ClinicalTrials.gov number, NCT01730534
Study type	Randomised controlled trial (RCT)
Study location	33 countries (regions: N. America; Europe; Latin America; Asia-Pacific)
Study setting	882 sites (not specified)
Study dates	Not reported
Sources of funding	Funded by AstraZeneca

Inclusion criteria	Adults (aged 40 year or older) with type 2 diabetes 40 years of age or older and had type 2 diabetes, a glycated haemoglobin level of at least 6.5% but less than 12.0%, and a creatinine clearance of 60 ml or more per minute. Eligible patients also had multiple risk factors for atherosclerotic cardiovascular disease or had established atherosclerotic cardiovascular disease (defined as clinically evident ischemic heart disease, ischemic cerebrovascular disease, or peripheral artery disease).
Exclusion criteria	People with type 1 diabetes Renal creatinine clearance (CrCl) <60 mL/min Cancer lifetime history of bladder cancer; history of any malignancy within 5 years Recurrent UTI Recurrent urinary tract infections Treatment Use of an open-label SGLT2 inhibitor, pioglitazone, or rosiglitazone Pregnant
Intervention(s)	Dapagliflozin - 10 mg daily orally
Comparator	Placebo
Outcomes of interest	Myocardial infarction Stroke, or atherosclerotic disease Cardiovascular-related mortality All-cause mortality Change in weight or Body Mass Index (BMI) at 1 year Total dropouts Dropouts due to adverse events Hypoglycaemic event rates Hospitalization for unstable angina Hospitalization for heart failure
Number of participants	n=17160

Duration of follow-up	Median: 4.2 years
Loss to follow-up	A total of 3962 patients discontinued the trial regimen prematurely; 1811/8574 patients (21.1%) in the dapagliflozin group and 2151/8569 (25.1%) in the placebo group.
Methods of analysis	Hazard ratios, 95% confidence intervals, and P values for time-to-event analyses are reported for the primary outcomes and were derived from a Cox proportional-hazards model in the overall population
Additional comments	

1 **Study arms**

Dapagliflozin (N = 8582)
10 mg daily orally
Placebo (N = 8578)

2 **Characteristics**

3 **Arm-level characteristics**

	Dapagliflozin (N = 8582)	**Placebo (N = 8578)**
% Female		
Nominal	36.9	37.9
Mean age (SD)		
Mean/SD	63.9 (6.8)	64 (6.8)
BMI or weight (BMI)		
Mean/SD	32.1 (6)	32 (6.1)
Comorbidities		
Established atherosclerotic cardiovascular disease %		
Nominal	40.5	40.8
History of coronary artery disease %		
Nominal	32.9	33
History of peripheral artery disease %		
Nominal	6.1	5.9
History of cerebrovascular disease %		

	Dapagliflozin (N = 8582)	Placebo (N = 8578)
Nominal	7.6	7.6
History of heart failure %		
Nominal	9.9	10.2
eGFR *(ml/min/1.73m2 of body surface area)*		
Mean/SD	85.4 (15.8)	85.1 (16)
Race % Race was reported by the patient.		
White %		
Nominal	79.7	79.4
Black %		
Nominal	3.4	3.6
Asian %		
Nominal	13.4	13.5
Other		
Nominal	3.4	3.6

1

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Eligible patients were enrolled in a 4-to-8-week, single-blind run-in period during which all patients received placebo, and blood and urine testing was performed. Patients who remained eligible after the run-in period were randomly assigned in a 1:1 ratio, in a double-blind fashion. Balanced baseline characteristics across arms post randomization)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Study outlined as randomized and utilizing double blind approach; Methods for allocation concealment not specified; ITT adopted)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Analyses were performed according to the intention-to-treat principle with the use of adjudicated events)*

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Clinical event rates with primary and secondary outcomes prespecified. Outcomes and their measurement included oversight from the clinical-events committee of the TIMI Study Group who adjudicated all components of the primary outcomes and key components of other safety and efficacy outcomes. Study is outlined as double blind, but methods of concealment not specified)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(Reference made to pre-specified outcomes and statistical analysis plan; Trial registered; Results outlined are in line with the pre-specified outcomes and analytical plan)*
Overall bias and Directness	Risk of bias judgement	Low
	Overall Directness	Directly applicable

1

Zinman, 2015

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

2 **Study details**

Other publications associated with this study included in review	Bohm et al. 2020; Ceriello et al. 2020; Cherney et al. 2017; Fitchett et al 2016; Inzucchi et al. 2019; Kadowaki et al. 2019; Kaku et al. 2017; Mancia et al. 2016; Mayer et al. 2019; McGuire et al. 2020; Monteiro et al. 2019; Ridderstrale et al. 2018; Sattar et al. 2018; Wanner et al. 2016; Wanner et al. 2018a; Chilton et al. 2016; Wanner et al. 2018b; Wanner et al. 2020
Trial registration number and/or trial name	ClinicalTrials.gov number, NCT01131676
Study type	Randomised controlled trial (RCT)
Study location	42 countries - not specified
Study setting	590 sites - North America [plus Australia and New Zealand], Latin America, Europe, Africa, or Asia
Study dates	Randomization from September 2010 through April 2013; date for last data collection point and follow-up not outlined

Sources of funding	Supported by Boehringer Ingelheim and Eli Lilly
Inclusion criteria	Adults (aged 18 years and older) with type 2 diabetes BMI 45 or less and an estimated glomerular filtration rate (eGFR) of at least 30 ml per minute per 1.73 m2 of body-surface area, according to the Modification of Diet in Renal Disease criteria.
Exclusion criteria	**Renal** Glomerular filtration rate (eGFR) of <30 ml per minute per 1.73 m2 of body-surface area, according to the Modification of Diet in Renal Disease criteria Cancer Received glucose-lowering agents for at least 12 weeks before randomization and had a glycated haemoglobin level of at <53 mmol/mol and >86 mmol/mol (<7.0% and > than 10.0%). No glucose-lowering agents for at least 12 weeks before randomization, glycated haemoglobin level of at <53 mmol/mol and >75 mmol/mol (<7.0% and > 9.0%). Liver disease Pregnant (or intending), breastfeeding, not using adequate contraception
Intervention(s)	Empagliflozin 10 mg (n=2345) or 25 mg (n=2342)
Comparator	Placebo (n=2333)
Outcomes of interest	Myocardial infarction Stroke, or atherosclerotic disease Fatal or nonfatal stroke; Nonfatal stroke Cardiovascular-related mortality All-cause mortality Change in weight or Body Mass Index (BMI) at 1 year Total dropouts Dropouts due to adverse events Hypoglycaemic event rates Hospitalization for unstable angina Hospitalization for heart failure
Number of participants	7028 patients underwent randomization; 7020 were treated and included in the primary analysis
Duration of follow-up	3.1 years (mean)

Loss to follow-up	8/7020 randomized were not included in the primary analysis (0.1%). 97.0% of patients completed the study (n=6809), with 25.4% of patients prematurely discontinuing a study drug (n=1780). Final vital status was available for 99.2% of patients (n=6967).
Methods of analysis	Cox proportional-hazards model, with study group, age, sex, baseline body-mass index, baseline glycated haemoglobin level, baseline eGFR, and geographic region as factors; Kaplan–Meier estimates for death from any cause;
Additional comments	

1 **Study arms**

Empagliflozin (N = 4687) Empagliflozin an inhibitor of sodium–glucose cotransporter 2, patients to receive 10 mg (n=2345) or 25 mg (n=2342) of empagliflozin
Placebo (N = 2333)

2 **Characteristics**

3 **Arm-level characteristics**

	Empagliflozin (N = 4687)	**Placebo (N = 2333)**
% Female		
Nominal	29	28
Mean age (SD)		
Mean/SD	63.1 (8.6)	63.2 (8.8)
BMI or weight		
Mean/SD	30.6 (5.3)	30.7 (5.2)
Comorbidities		
CV risk factor % 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; Cardiac failure		
Nominal	99.4	98.9
Glycated haemoglobin %		
Mean/SD	8.07 (0.85)	8.08 (0.84)
eGFR (MDRD) *(ml/min/1.73m2 of body surface area)*		
Mean/SD	74.2 (21.6)	73.8 (21.1)

	Empagliflozin (N = 4687)	Placebo (N = 2333)
Urinary albumin-to-creatinine ratio (<30 mg/g) %		
Nominal	59.5	59.2
Cardiac failure %		
Nominal	9.9	10.5
Race %		
White %		
Nominal	72.6	71.9
Asian %		
Nominal	21.5	21.9
Black/African American		
Nominal	5.1	5.1
Other/missing		
Nominal	0.9	1

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Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Randomized, double-blind, placebo-controlled trial. Randomization process outlined, but protocol for allocation concealment not specified. No significant differences outlined for baseline characteristics post randomisation)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Randomized, double-blind, placebo-controlled trial. Randomization process outlined, but protocol for allocation concealment not specified. mITT undertaken for primary analysis)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Data presented for n=7020 participants for all outcomes accept silent myocardial infarction (n=3589); 97.0% of patients completed the study (n=6809), with 25.4% of patients prematurely discontinuing a study drug (n=1780). Final vital status was available for 99.2% of patients (n=6967).)*

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Study outlined as a double-blind randomized controlled trial. Clinical event rates were the measures for the primary outcome and secondary outcome. Definitions of major clinical outcomes prespecified. Cardiovascular outcome events and deaths were prospectively adjudicated by two clinical-events committees.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(Evidence of prespecified analytical plan; Outcomes reported for most participants against prespecified and clearly defined outcomes using clinical event rates.)*
Overall bias and Directness	Risk of bias judgement	Low
	Overall Directness	Directly applicable

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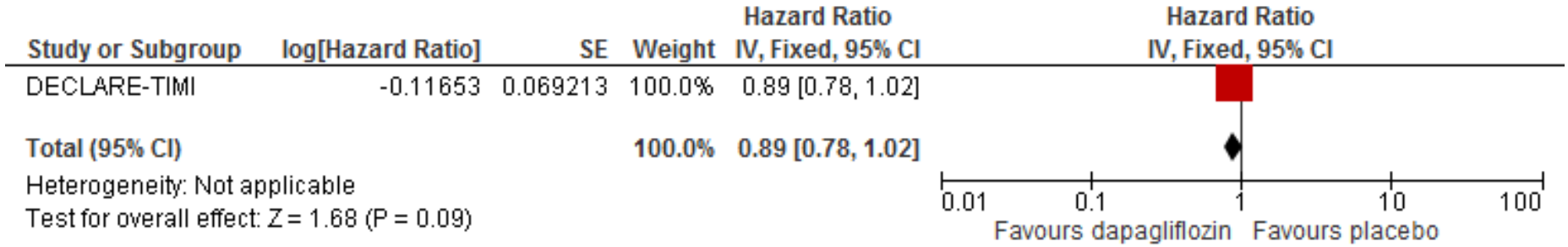
Appendix F – Forest plots

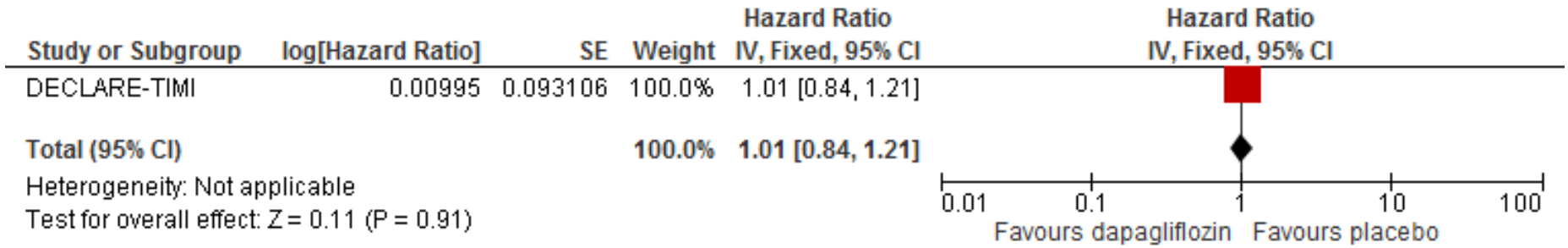
Pairwise forest plots

Dapagliflozin versus placebo

Outcome: Myocardial infarction (unclear if fatal or nonfatal).



Outcome: Stroke (unclear if fatal or nonfatal).

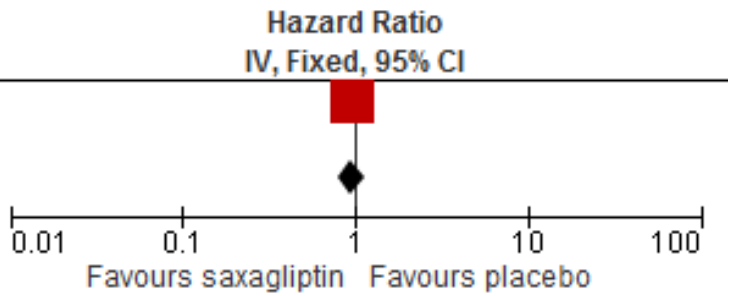


Saxagliptin versus placebo

Outcome: Myocardial infarction (unclear if fatal or nonfatal).

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
SAVOR-TIMI	-0.05129	0.085835	100.0%	0.95 [0.80, 1.12]
Total (95% CI)			**100.0%**	**0.95 [0.80, 1.12]**

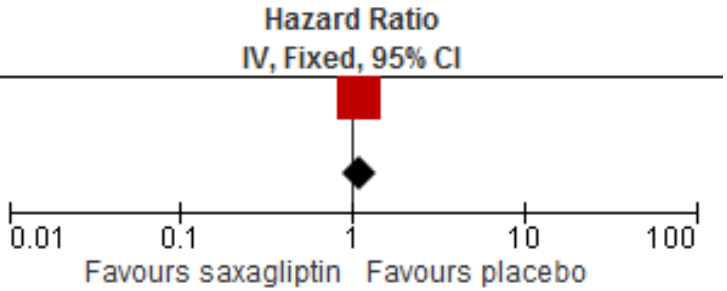
Heterogeneity: Not applicable
Test for overall effect: Z = 0.60 (P = 0.55)



Outcome: Stroke (unclear if fatal or nonfatal).

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
SAVOR-TIMI	0.10436	0.116617	100.0%	1.11 [0.88, 1.40]
Total (95% CI)			**100.0%**	**1.11 [0.88, 1.40]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.89 (P = 0.37)

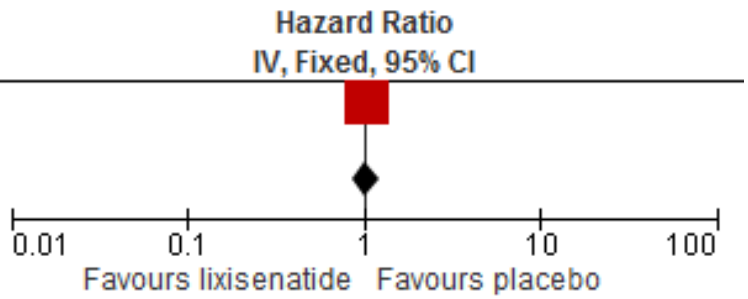


Lixisenatide versus placebo

Outcome: Myocardial infarction (unclear if fatal or nonfatal).

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
ELIXA	0.029559	0.086253	100.0%	1.03 [0.87, 1.22]
Total (95% CI)			**100.0%**	**1.03 [0.87, 1.22]**

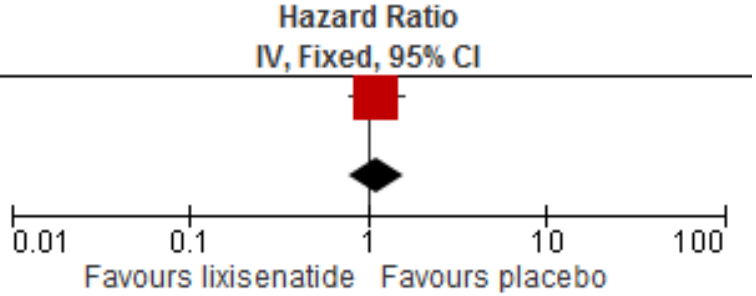
Heterogeneity: Not applicable
Test for overall effect: Z = 0.34 (P = 0.73)



Outcome: Stroke (unclear if fatal or nonfatal).

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
ELIXA	0.113329	0.176823	100.0%	1.12 [0.79, 1.58]
Total (95% CI)			**100.0%**	**1.12 [0.79, 1.58]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.64 (P = 0.52)

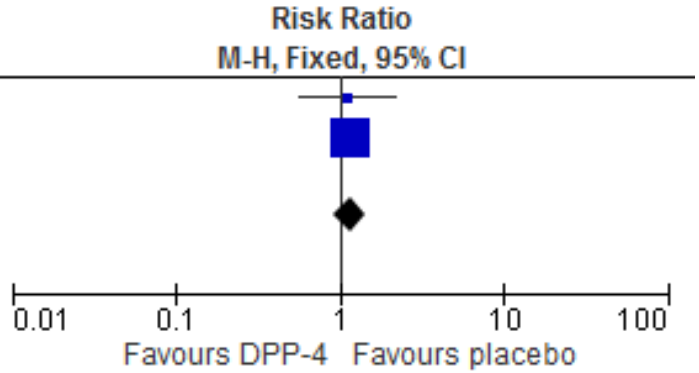


DPP-4 versus placebo

Outcome: Severe hypoglycaemia. The data for these studies for the outcome of severe hypoglycaemia was not included in the NMA as the committee agreed that this may be a subgroup of more severe hypoglycaemia defined as requiring medical intervention.

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
EXAMINE	18	2701	16	2679	11.4%	1.12 [0.57, 2.18]
TECOS	144	7257	125	7266	88.6%	1.15 [0.91, 1.46]
Total (95% CI)		**9958**		**9945**	**100.0%**	**1.15 [0.92, 1.44]**
Total events	162		141			

Heterogeneity: Chi² = 0.01, df = 1 (P = 0.93); I² = 0%
Test for overall effect: Z = 1.22 (P = 0.22)



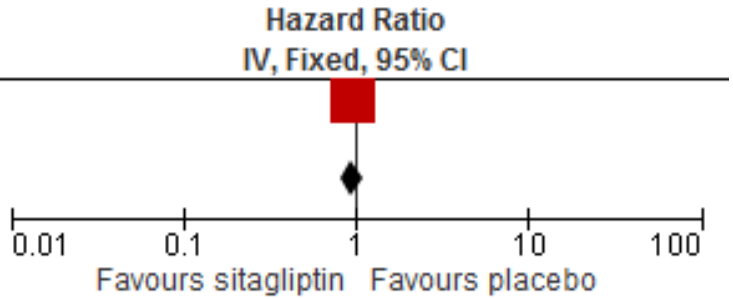
The interventions in the trials were Alogliptin (EXAMINE) and sitagliptin (TECOS).

Sitagliptin versus placebo

Outcome: Myocardial infarction (fatal and nonfatal).

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
TECOS	-0.05129	0.080378	100.0%	0.95 [0.81, 1.11]
Total (95% CI)			**100.0%**	**0.95 [0.81, 1.11]**

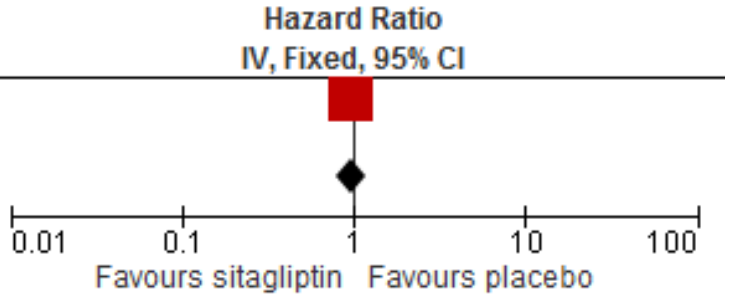
Heterogeneity: Not applicable
Test for overall effect: Z = 0.64 (P = 0.52)



Outcome: Stroke (fatal and nonfatal).

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
TECOS	-0.03046	0.104509	100.0%	0.97 [0.79, 1.19]
Total (95% CI)			**100.0%**	**0.97 [0.79, 1.19]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.29 (P = 0.77)

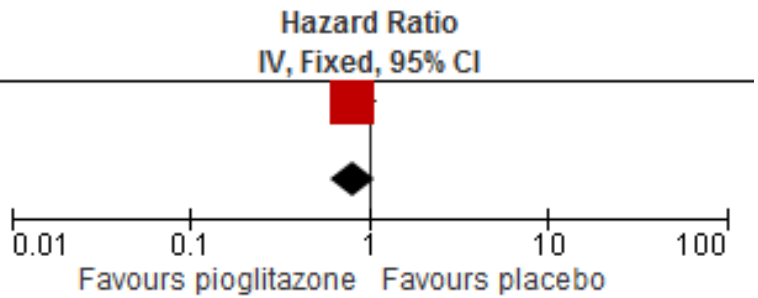


Pioglitazone versus placebo

Outcome: Stroke (all).

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
PROactive	-0.21072	0.143356	100.0%	0.81 [0.61, 1.07]
Total (95% CI)			**100.0%**	**0.81 [0.61, 1.07]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.47 (P = 0.14)

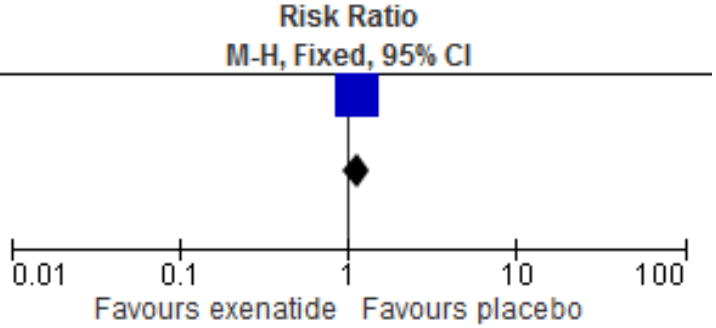


Exenatide versus placebo

Outcome: Severe hypoglycaemia. The data for this study for the outcome of severe hypoglycaemia was not included in the NMA as the committee agreed that this may be a subgroup of more severe hypoglycaemia defined as requiring medical intervention.

	Experimental		Control			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
EXSCEL	247	7344	219	7372	100.0%	1.13 [0.95, 1.35]
Total (95% CI)		**7344**		**7372**	**100.0%**	**1.13 [0.95, 1.35]**
Total events	247		219			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.36 (P = 0.17)



Appendix G – NMA results

Network meta-analysis methodological considerations

The committee noted that most trials (15 out of 16) compared an active treatment against placebo. One trial compared two active treatments: CAROLINA, which compared linagliptin (a DPP-4) to glimepiride (a sulfonylurea). These outcomes of interest were useful, but the trials largely did not directly compare drugs against each other. The committee agreed it would be helpful if the results for each outcome of interest could be pooled to give effectiveness estimates which would allow a meaningful comparison between the drugs. The committee agreed that for the purposes of the evidence review analyses that certain interventions would be analysed at class level (DPP-4, insulins and sulfonylureas) and the remining interventions at an individual level (all SGLT2 and GLP-1 interventions).

Since the resultant networks were star shaped without loops no inconsistency checking was necessary or possible. Additionally, this meant that comparisons of indirect versus direct evidence did not add extra information as the comparisons with placebo were direct and comparison between interventions were indirect, with the exception of linagliptin to glimepiride (trial data was included for this comparison). Therefore, these results are not presented.

See methods and processes and the methods in Appendix B for more details.

Abbreviations used in figures and tables: PLAC, Placebo; PIO, Pioglitazone; LIXI, Lixisenatide; LIRA, Liraglutide; EXEN, Exenatide; ERTU, Ertugliflozin; EMPA, Empagliflozin; DULA, Dulaglutide; DPP-4, Dipeptidyl peptidase-4 inhibitors; DAPA, Dapagliflozin; CANA, Canagliflozin; SU, Sulphonylurea; SEMAo, Oral semaglutide; SEMAi, Injected semaglutide.

NMA model choice

We undertook frequentist network meta-analyses (NMA) using the netmeta package in R, with placebo as the reference treatment. Heterogeneity was assessed using the I^2 statistic and either a fixed effects or random effects model was selected as appropriate. Random effects models were used when I^2 was high (≥50%) and there were sufficient studies to estimate a distribution for the random effects (>2 studies on the relevant treatment comparison) with the Q statistic also reported. See Table 18 below for a summary of the models chosen for each outcome.

Table 18 Model choice for each outcome

No of studies	Outcome	Heterogeneity	Model used
16 trials	All-cause mortality	I^2= 14.1% Total Q 3.49 (3 *df*), p=0.3219)	Fixed effects model
15 trials	Any discontinuation	I^2= 48.4% Total Q 5.81 (*3 df*), p=0.1213	Fixed effects model [a]
16 trials	Cardiovascular mortality	I^2= 6.0% Total Q 3.19 (*3 df*), p=0.3632	Fixed effects model
13 trials	Discontinued due to adverse events	I^2= 0.0% Total Q 0.70 (1 *df*), p=0.4014	Fixed effects model

15 trials	Hospitalization for heart failure	I^2= 60.0% Total Q 7.5 (3 *df*), p=0.0576	Random effects model [b]
11 trials	Hospitalization for unstable angina	I^2= 0.0% Total Q 2.68 (3 *df*), p=0.4436	Fixed effects model
12 trials	Nonfatal myocardial infarction	I^2= 0.0% Total Q 0.16 (1 df), p=0.6925	Fixed effects model
11 trials	Nonfatal stroke	I^2= 0.0% Total Q 0.01 (1 *df*), p=0.9132	Fixed effects model
13 trials	Severe hypoglycaemia	I^2= 49.9% Total Q 2.00 (1 *df*), p=0.1575	Fixed effects model [a]
14 trials	3-point MACE (composite outcome)	I^2= 0.0% Total Q 0.11 (2 *df*), p=0.9459	Fixed effects model
[a] Sensitivity analyses are presented for outcomes with I^2 within a few points of 50% either side. [b] Additional sensitivity analysis excluding 1 DPP-4 trial which caused heterogeneity, using fixed effects model (I^2= 0.0%, Total Q 1.1 (2 df), p=0.5773)			
Abbreviations: df, degrees of freedom; p, P-value; MACE, Major adverse cardiovascular outcomes.			

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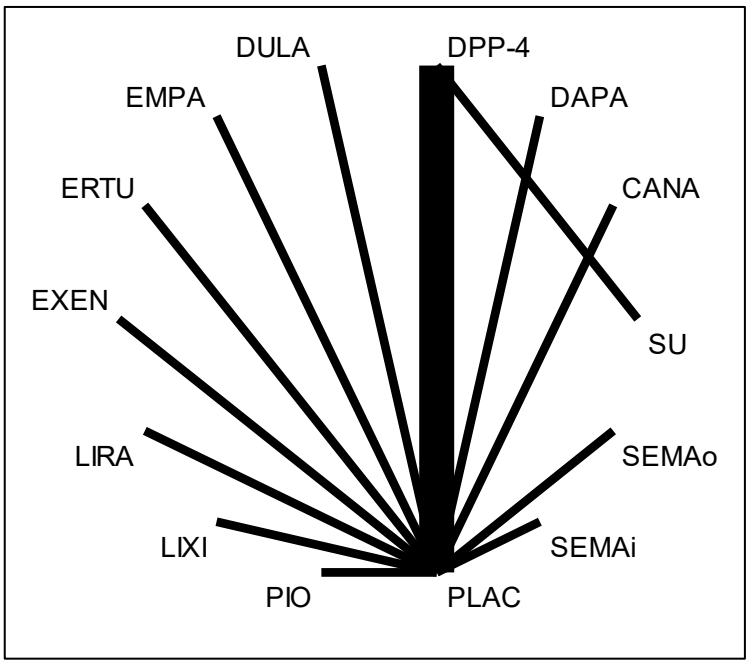
All-cause mortality

The fixed effects model for all-cause mortality generated a network diagram (see Figure 1). Data for this outcome was included from all 16 RCTs. As specified by the committee, both the sulfonylureas and DPP-4 drugs were analysed at the class level, assuming the treatments within the class have the same effectiveness. Five trials included DPP-4 interventions, whilst the sulfonylurea class consisted of a single treatment (glimepiride). Other drugs were analysed at the individual level.

Abbreviations used in figures and tables: PLAC, Placebo; PIO, Pioglitazone; LIXI, Lixisenatide; LIRA, Liraglutide; EXEN, Exenatide; ERTU, Ertugliflozin; EMPA, Empagliflozin; DULA, Dulaglutide; DPP-4, Dipeptidyl peptidase-4 inhibitors; DAPA, Dapagliflozin; CANA, Canagliflozin; SU, Sulphonylurea; SEMAo, Oral semaglutide; SEMAi, Injected semaglutide.

Network diagram for all-cause mortality

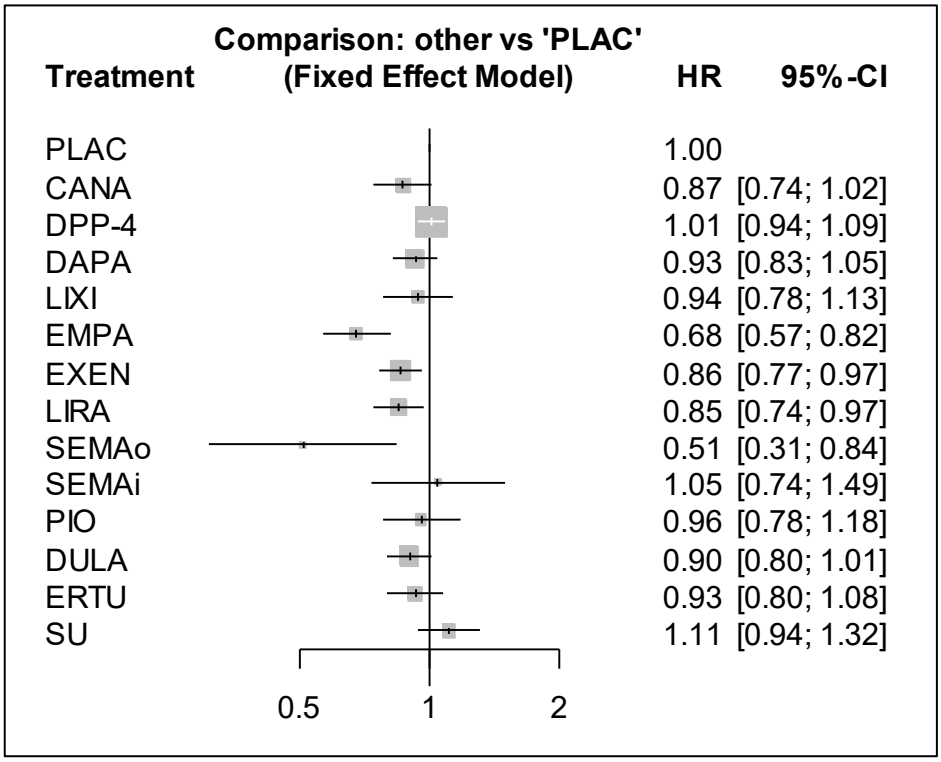
Figure 1 Network diagram for all-cause mortality[1].



[1] Line width is proportional to the number of trials comparing every pair of treatments.

Caterpillar plot for all-cause mortality

Figure 2 Relative effectiveness of all options versus placebo. (Hazard ratios with 95% confidence intervals and line of no effect as the vertical line at 1).



Relative effectiveness chart for all-cause mortality

Table 19 Relative effectiveness of all pairwise combinations for all-cause mortality. Upper diagonal: hazard ratios (HR) with 95% confidence intervals from the pair-wise meta-analysis. HR less than 1 favour the row defining treatment. HRs greater than 1 favour the column defining treatment.) Lower diagonal: HR with 95% confidence intervals from the from the NMA results. HRs greater than 1 favour the row defining treatment, HRs less than 1 favour the column defining treatment.

	CANA	DAPA	DPP-4	DULA	EMPA	ERTU	EXEN	LIRA	LIXI	PIO	SEMAi	SEMAo	SU	Placebo
CANA														0.87 (0.74; 1.02)
DAPA	0.94 (0.77; 1.14)													0.93 (0.83; 1.05)
DPP-4	0.86 (0.72; 1.02)	0.92 (0.80; 1.06)											0.91 (0.78; 1.06)	1.01 (0.94; 1.09)
DULA	0.97 (0.80; 1.17)	1.03 (0.87; 1.22)	1.12 (0.98; 1.29)											0.90 (0.80; 1.01)
EMPA	1.28 (1.01; 1.63)	1.37 (1.10; 1.70)	1.49 (1.22; 1.81)	1.32 (1.07; 1.64)										0.68 (0.57; 0.82)
ERTU	0.94 (0.75; 1.16)	1.00 (0.83; 1.21)	1.09 (0.92; 1.29)	0.97 (0.80; 1.17)	0.73 (0.58; 0.93)									0.93 (0.80; 1.08)
EXEN	1.01 (0.83; 1.23)	1.08 (0.92; 1.28)	1.18 (1.03; 1.35)	1.05 (0.89; 1.23)	0.79 (0.64; 0.98)	1.08 (0.89; 1.31)								0.86 (0.77; 0.97)
LIRA	1.02 (0.83; 1.26)	1.09 (0.91; 1.31)	1.19 (1.02; 1.39)	1.06 (0.89; 1.27)	0.80 (0.64; 1.00)	1.09 (0.89; 1.34)	1.01 (0.85; 1.21)							0.85 (0.74; 0.97)
LIXI	0.93 (0.73; 1.18)	0.99 (0.79; 1.23)	1.08 (0.88; 1.31)	0.96 (0.77; 1.19)	0.72 (0.56; 0.94)	0.99 (0.78; 1.26)	0.91 (0.74; 1.14)	0.90 (0.72; 1.14)						0.94 (0.78; 1.13)
PIO	0.91 (0.70; 1.17)	0.97 (0.76; 1.23)	1.05 (0.85; 1.31)	0.94 (0.74; 1.19)	0.71 (0.54; 0.93)	0.97 (0.75; 1.25)	0.90 (0.71; 1.14)	0.89 (0.69; 1.13)	0.98 (0.74; 1.29)					0.96 (0.78; 1.18)
SEMAi	0.83 (0.56; 1.22)	0.89 (0.61; 1.29)	0.96 (0.67; 1.38)	0.86 (0.59; 1.24)	0.65 (0.44; 0.96)	0.89 (0.60; 1.30)	0.82 (0.56; 1.19)	0.81 (0.55; 1.18)	0.90 (0.60; 1.33)	0.91 (0.61; 1.38)				1.05 (0.74; 1.49)
SEMAo	1.71 (1.01; 2.88)	1.82 (1.09; 3.04)	1.99 (1.20; 3.28)	1.76 (1.06; 2.94)	1.33 (0.78; 2.27)	1.82 (1.08; 3.07)	1.69 (1.01; 2.81)	1.67 (0.99; 2.79)	1.84 (1.08; 3.14)	1.88 (1.10; 3.23)	2.06 (1.12; 3.79)			0.51 (0.31; 0.84)
SU	0.78 (0.62; 0.98)	0.84 (0.68; 1.03)	0.91 (0.78; 1.06)	0.81 (0.66; 0.99)	0.61 (0.48; 0.78)	0.84 (0.67; 1.05)	0.77 (0.63; 0.95)	0.76 (0.61; 0.95)	0.84 (0.66; 1.09)	0.86 (0.66; 1.13)	0.94 (0.64; 1.40)	0.46 (0.27; 0.78)		
Placebo	0.87 (0.74; 1.02)	0.93 (0.83; 1.05)	1.01 (0.94; 1.09)	0.90 (0.80; 1.01)	0.68 (0.57; 0.82)	0.93 (0.80; 1.08)	0.86 (0.77; 0.97)	0.85 (0.74; 0.97)	0.94 (0.78; 1.13)	0.96 (0.78; 1.18)	1.05 (0.74; 1.49)	0.51 (0.31; 0.84)	1.11 (0.94; 1.32)	

Probability ranking for all-cause mortality

Table 20 Probability that each intervention is one of the best treatments. Higher probabilities indicate that the intervention would be ranked as more effective.

Treatment	P-score (fixed effects)
SEMAo	0.9773
EMPA	0.9259
LIRA	0.6956
EXEN	0.6764
CANA	0.6351
DULA	0.5590
DAPA	0.4660
ERTU	0.4638
LIXI	0.4346
PIO	0.3841
SEMAi	0.2518
PLAC	0.2398
DPP-4	0.2133
SU	0.0773

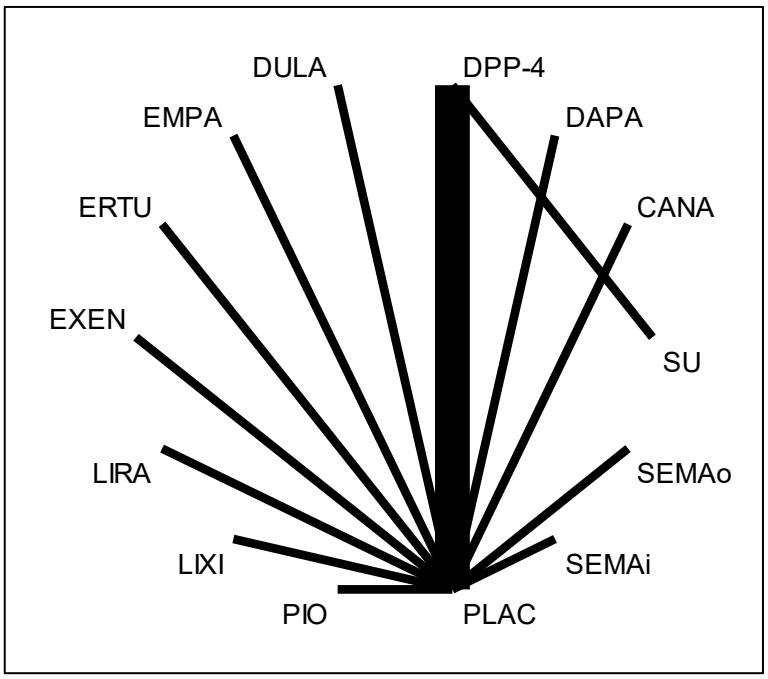
Cardiovascular mortality

The fixed effects model for cardiovascular (CV) mortality generated a network diagram (see Figure 3). Data for this outcome was included from all 16 RCTs. As specified by the committee, both the sulfonylureas and DPP-4 drugs were analysed at the class level, assuming the treatments within the class have the same effectiveness. Five trials included DPP-4 interventions, whilst the sulfonylurea class consisted of a single treatment (glimepiride). Other drugs were analysed at the individual level.

Abbreviations used in figures and tables: PLAC, Placebo; PIO, Pioglitazone; LIXI, Lixisenatide; LIRA, Liraglutide; EXEN, Exenatide; ERTU, Ertugliflozin; EMPA, Empagliflozin; DULA, Dulaglutide; DPP-4, Dipeptidyl peptidase-4 inhibitors; DAPA, Dapagliflozin; CANA, Canagliflozin; SU, Sulphonylurea; SEMAo, Oral semaglutide; SEMAi, Injected semaglutide.

Network diagram for CV mortality

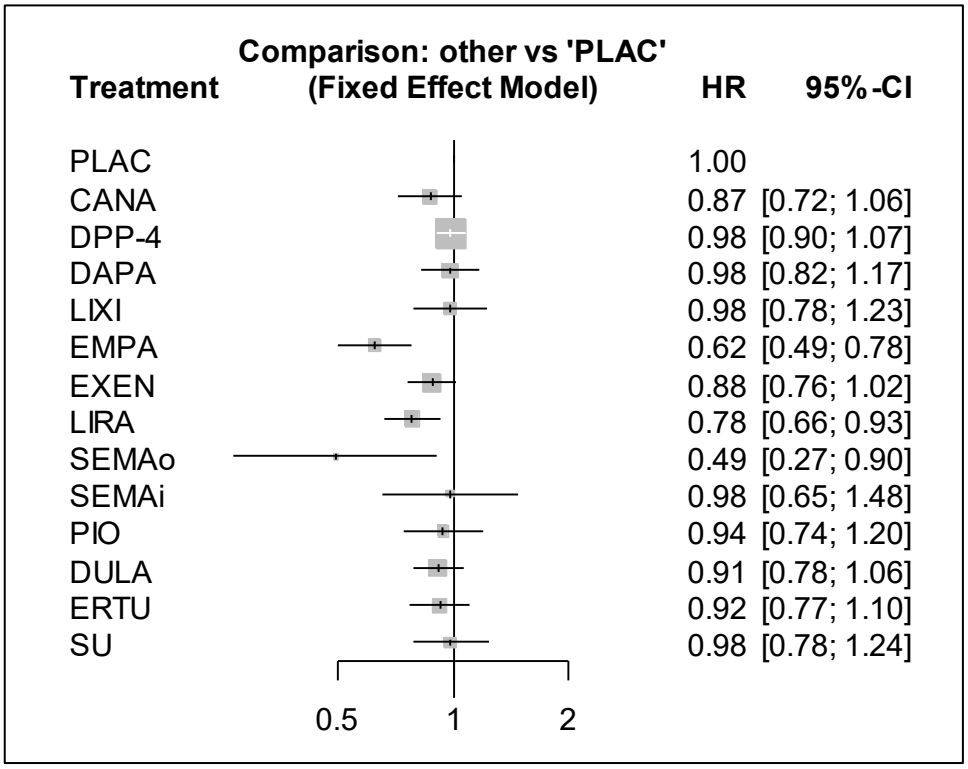
Figure 3 Network diagram for CV mortality[1]



[1] Line width is proportional to the number of trials comparing every pair of treatments.

Caterpillar plot for CV Mortality

Figure 4 Relative effectiveness of all options versus placebo. (Hazard ratios with 95% confidence intervals and line of no effect as the vertical line at 1).



Relative effectiveness chart for CV mortality

Table 21 Relative effectiveness of all pairwise combinations for CV mortality. Upper diagonal: hazard ratios (HR) with 95% confidence intervals from the pair-wise meta-analysis. HR less than 1 favour the row defining treatment. HRs greater than 1 favour the column defining treatment.) Lower diagonal: HR with 95% confidence intervals from the from the NMA results. HRs greater than 1 favour the row defining treatment, HRs less than 1 favour the column defining treatment.

	CANA	DAPA	DPP-4	DULA	EMPA	ERTU	EXEN	LIRA	LIXI	PIO	SEMAi	SEMAo	SU	Placebo
CANA														0.87 (0.72; 1.06)
DAPA	0.89 (0.68; 1.15)													0.98 (0.82; 1.17)
DPP-4	0.88 (0.71; 1.09)	1.00 (0.82; 1.21)											1.00 (0.81; 1.24)	0.98 (0.90; 1.07)
DULA	0.96 (0.75; 1.22)	1.08 (0.85; 1.36)	1.08 (0.91; 1.29)											0.91 (0.78; 1.06)
EMPA	1.40 (1.04; 1.89)	1.58 (1.19; 2.11)	1.59 (1.25; 2.02)	1.47 (1.12; 1.93)										0.62 (0.49; 0.78)
ERTU	0.95 (0.72; 1.23)	1.07 (0.83; 1.37)	1.07 (0.87; 1.31)	0.99 (0.78; 1.26)	0.67 (0.50; 0.90)									0.92 (0.77; 1.10)
EXEN	0.99 (0.78; 1.26)	1.11 (0.88; 1.40)	1.12 (0.94; 1.33)	1.03 (0.84; 1.28)	0.70 (0.54; 0.92)	1.05 (0.83; 1.32)								0.88 (0.76; 1.02)
LIRA	1.12 (0.86; 1.44)	1.26 (0.98; 1.61)	1.26 (1.04; 1.53)	1.17 (0.93; 1.47)	0.79 (0.60; 1.06)	1.18 (0.92; 1.52)	1.13 (0.90; 1.41)							0.78 (0.66; 0.93)
LIXI	0.89 (0.66; 1.19)	1.00 (0.75; 1.33)	1.00 (0.79; 1.28)	0.93 (0.71; 1.22)	0.63 (0.46; 0.87)	0.94 (0.70; 1.25)	0.90 (0.69; 1.17)	0.80 (0.60; 1.06)						0.98 (0.78; 1.23)
PIO	0.93 (0.68; 1.26)	1.04 (0.77; 1.41)	1.05 (0.81; 1.35)	0.97 (0.73; 1.29)	0.66 (0.47; 0.92)	0.98 (0.72; 1.33)	0.94 (0.71; 1.24)	0.83 (0.62; 1.12)	1.04 (0.75; 1.45)					0.94 (0.74; 1.20)
SEMAi	0.89 (0.56; 1.40)	1.00 (0.64; 1.57)	1.00 (0.66; 1.53)	0.93 (0.60; 1.44)	0.63 (0.40; 1.01)	0.94 (0.60; 1.47)	0.90 (0.58; 1.39)	0.80 (0.51; 1.24)	1.00 (0.63; 1.60)	0.96 (0.60; 1.55)				0.98 (0.65; 1.48)
SEMAo	1.78 (0.93; 3.38)	2.00 (1.06; 3.79)	2.01 (1.08; 3.73)	1.86 (0.99; 3.49)	1.27 (0.66; 2.43)	1.88 (0.99; 3.56)	1.80 (0.96; 3.37)	1.59 (0.84; 3.01)	2.00 (1.04; 3.84)	1.92 (0.99; 3.71)	2.00 (0.96; 4.18)			0.49 (0.27; 0.90)
SU	0.88 (0.65; 1.19)	1.00 (0.74; 1.33)	1.00 (0.81; 1.24)	0.92 (0.70; 1.22)	0.63 (0.46; 0.87)	0.93 (0.70; 1.25)	0.89 (0.68; 1.18)	0.79 (0.59; 1.06)	1.00 (0.72; 1.37)	0.96 (0.68; 1.33)	1.00 (0.62; 1.60)	0.50 (0.26; 0.96)		
Placebo	0.87 (0.72; 1.06)	0.98 (0.82; 1.17)	0.98 (0.90; 1.07)	0.91 (0.78; 1.06)	0.62 (0.49; 0.78)	0.92 (0.77; 1.10)	0.88 (0.76; 1.02)	0.78 (0.66; 0.93)	0.98 (0.78; 1.23)	0.94 (0.74; 1.20)	0.98 (0.65; 1.48)	0.49 (0.27; 0.90)	0.98 (0.78; 1.24)	

Probability ranking for CV mortality

Table 22 Probability that each intervention is one of the best treatments. Higher probabilities indicate that the intervention would be ranked as more effective.

Treatment	P-score (fixed effects)
SEMAo	0.9552
EMPA	0.9322
LIRA	0.7818
CANA	0.5890
EXEN	0.5790
DULA	0.4967
ERTU	0.4642
PIO	0.4110
SEMAi	0.3526
LIXI	0.3180
SU	0.3104
DAPA	0.3085
DPP-4	0.2820
PLAC	0.2195

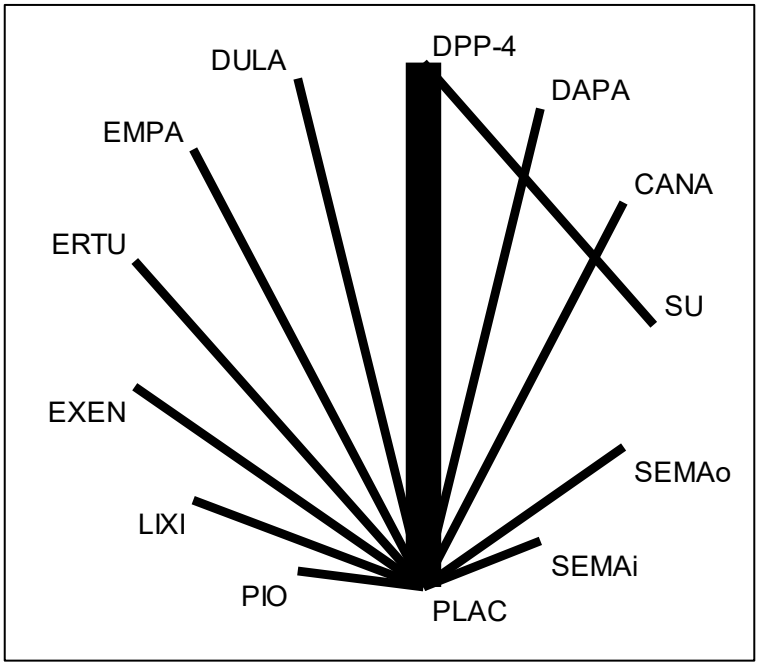
Any discontinuation

The fixed effects model for any discontinuation generated a network diagram (see Figure 5). Data for this outcome was included from 15 RCTs. As specified by the committee, both the sulfonylureas and DPP-4 drugs were analysed at the class level, assuming the treatments within the class have the same effectiveness. Five trials included DPP-4 interventions, whilst the sulfonylurea class consisted of a single treatment (glimepiride). GLP-1 and SGLT-2 drugs were analysed as separate interventions, each with evidence from a single trial.

Abbreviations used in figures and tables: PLAC, Placebo; PIO, Pioglitazone; LIXI, Lixisenatide; LIRA, Liraglutide; EXEN, Exenatide; ERTU, Ertugliflozin; EMPA, Empagliflozin; DULA, Dulaglutide; DPP-4, Dipeptidyl peptidase-4 inhibitors; DAPA, Dapagliflozin; CANA, Canagliflozin; SU, Sulphonylurea; SEMAo, Oral semaglutide; SEMAi, Injected semaglutide.

Network diagram for any discontinuation

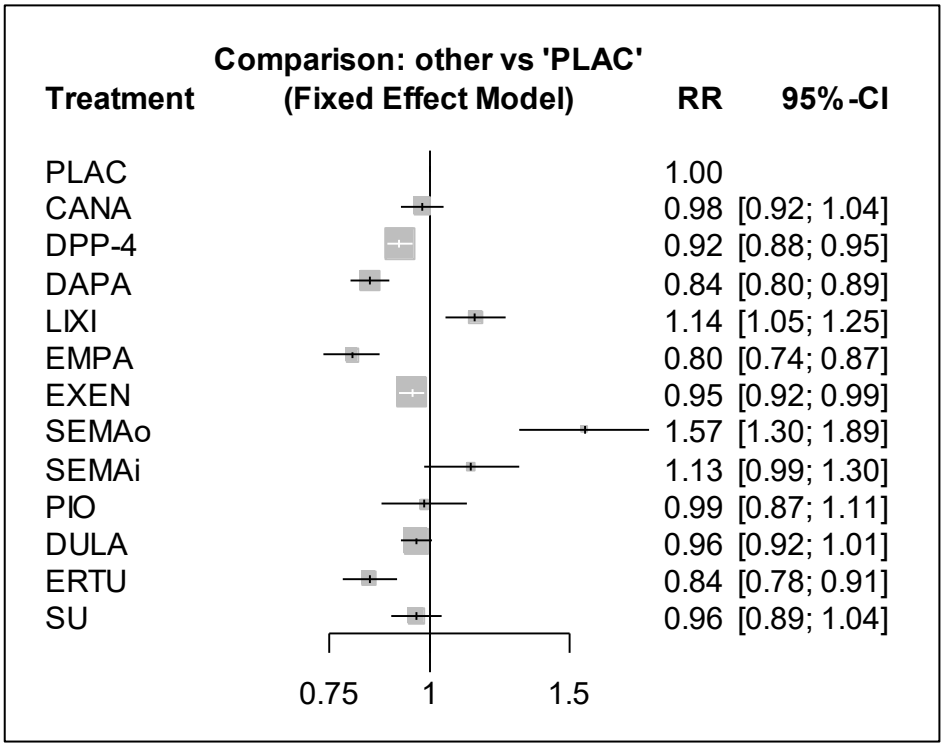
Figure 5 Network diagram for any discontinuation[1]



[1] Line width is proportional to the number of trials comparing every pair of treatments.

Caterpillar plot for any discontinuation

Figure 6 Relative effectiveness of all options versus placebo. (Risk ratios with 95% confidence intervals and line of no effect as the vertical line at 1).



Relative effectiveness chart for any discontinuation

Table 23 Relative effectiveness of all pairwise combinations for any discontinuation. Upper diagonal: risk ratios (RR) with 95% confidence intervals from the pair-wise meta-analysis. RR less than 1 favour the row defining treatment. RRs greater than 1 favour the column defining treatment.) Lower diagonal: RR with 95% confidence intervals from the from the NMA results. RRs greater than 1 favour the row defining treatment, RRs less than 1 favour the column defining treatment.

	CANA	DAPA	DPP-4	DULA	EMPA	ERTU	EXEN	LIXI	PIO	SEMAi	SEMAo	SU	Placebo
CANA													0.98 (0.92; 1.04)
DAPA	1.16 (1.07; 1.26)												0.84 (0.80; 0.89)
DPP-4	1.07 (1.00; 1.15)	0.92 (0.86; 0.98)										0.95 (0.89; 1.02)	0.92 (0.88; 0.95)
DULA	1.02 (0.94; 1.10)	0.87 (0.81; 0.94)	0.95 (0.90; 1.01)										0.96 (0.92; 1.01)
EMPA	1.22 (1.11; 1.36)	1.05 (0.95; 1.16)	1.15 (1.05; 1.25)	1.21 (1.10; 1.32)									0.80 (0.74; 0.87)
ERTU	1.16 (1.06; 1.28)	1.00 (0.91; 1.10)	1.09 (1.00; 1.19)	1.15 (1.05; 1.25)	0.95 (0.85; 1.06)								0.84 (0.78; 0.91)
EXEN	1.03 (0.96; 1.10)	0.88 (0.83; 0.94)	0.96 (0.92; 1.01)	1.01 (0.96; 1.07)	0.84 (0.77; 0.92)	0.88 (0.81; 0.96)							0.95 (0.92; 0.99)
LIXI	0.86 (0.77; 0.95)	0.74 (0.67; 0.82)	0.80 (0.73; 0.88)	0.84 (0.77; 0.93)	0.70 (0.62; 0.79)	0.74 (0.66; 0.83)	0.83 (0.76; 0.91)						1.14 (1.05; 1.25)
PIO	0.99 (0.87; 1.14)	0.85 (0.75; 0.98)	0.93 (0.82; 1.06)	0.98 (0.86; 1.11)	0.81 (0.70; 0.94)	0.85 (0.74; 0.99)	0.97 (0.85; 1.10)	1.16 (1.00; 1.35)					0.99 (0.87; 1.11)
SEMAi	0.87 (0.75; 1.01)	0.74 (0.64; 0.86)	0.81 (0.70; 0.93)	0.85 (0.74; 0.99)	0.71 (0.60; 0.83)	0.74 (0.64; 0.87)	0.84 (0.73; 0.97)	1.01 (0.86; 1.19)	0.87 (0.73; 1.05)				1.13 (0.99; 1.30)
SEMAo	0.63 (0.51; 0.76)	0.54 (0.44; 0.65)	0.59 (0.48; 0.71)	0.62 (0.51; 0.75)	0.51 (0.42; 0.63)	0.54 (0.44; 0.66)	0.61 (0.50; 0.74)	0.73 (0.59; 0.90)	0.63 (0.50; 0.79)	0.72 (0.57; 0.91)			1.57 (1.30; 1.89)
SU	1.02 (0.93; 1.12)	0.87 (0.80; 0.96)	0.95 (0.89; 1.02)	1.00 (0.92; 1.09)	0.83 (0.74; 0.93)	0.87 (0.79; 0.97)	0.99 (0.91; 1.07)	1.19 (1.06; 1.33)	1.02 (0.89; 1.18)	1.17 (1.01; 1.37)	1.63 (1.33; 1.99)		
Placebo	0.98 (0.92; 1.04)	0.84 (0.80; 0.89)	0.92 (0.88; 0.95)	0.96 (0.92; 1.01)	0.80 (0.74; 0.87)	0.84 (0.78; 0.91)	0.95 (0.92; 0.99)	1.14 (1.05; 1.25)	0.99 (0.87; 1.11)	1.13 (0.99; 1.30)	1.57 (1.30; 1.89)	0.96 (0.89; 1.04)	

Probability ranking for any discontinuation

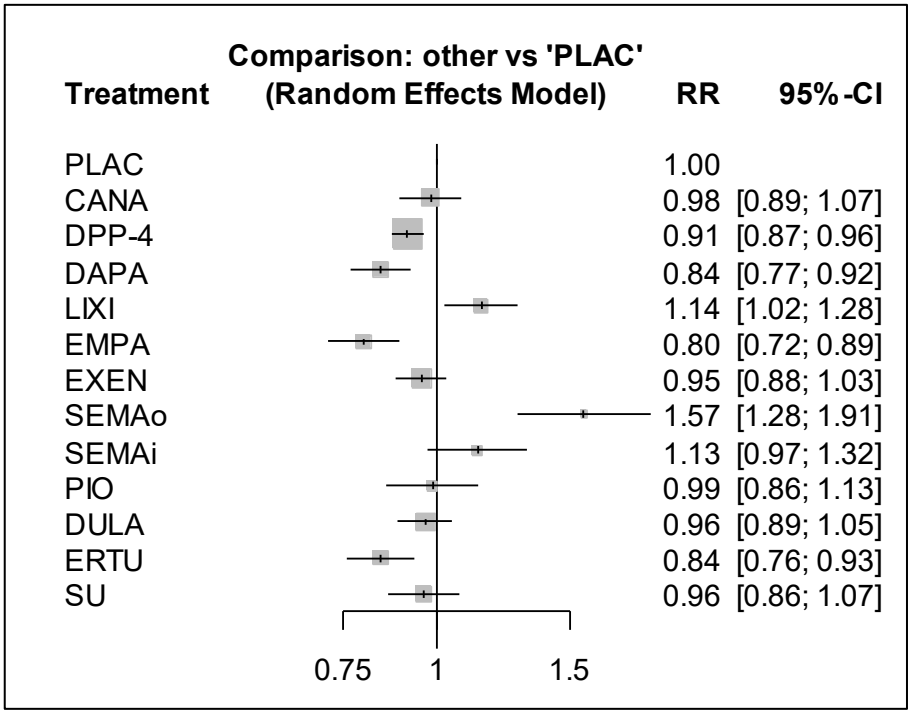
Table 24 Probability that each intervention is one of the best treatments. Higher probabilities indicate that the intervention would be ranked as more effective.

Treatment	P-score (fixed effects)
EMPA	0.9711
ERTU	0.8872
DAPA	0.8858
DPP-4	0.7231
EXEN	0.5693
SU	0.5071
DULA	0.5055
CANA	0.4335
PIO	0.4300
PLAC	0.3190
SEMAi	0.1452
LIXI	0.1228
SEMAo	0.0004

Sensitivity analysis: any discontinuation (using random effects model)

Caterpillar plot any discontinuation

Figure 7 Relative effectiveness of all options versus placebo. (Risk ratios with 95% confidence intervals and line of no effect as the vertical line at 1).



Relative effectiveness chart for any discontinuation (sensitivity analysis using random effects model)

Table 25 Relative effectiveness of all pairwise combinations for any discontinuation. Upper diagonal: risk ratios (RR) with 95% confidence intervals from the pair-wise meta-analysis. RR less than 1 favour the row defining treatment. RRs greater than 1 favour the column defining treatment.) Lower diagonal: RR with 95% confidence intervals from the from the NMA results. RRs greater than 1 favour the row defining treatment, RRs less than 1 favour the column defining treatment.

	CANA	DAPA	DPP-4	DULA	EMPA	ERTU	EXEN	LIXI	PIO	SEMAi	SEMAo	SU	PLAC
CANA													0.98 (0.89; 1.07)
DAPA	1.16 (1.02; 1.32)												0.84 (0.77; 0.92)
DPP-4	1.07 (0.96; 1.19)	0.92 (0.83; 1.02)										0.95 (0.87; 1.05)	0.91 (0.87; 0.96)
DULA	1.02 (0.90; 1.15)	0.87 (0.77; 0.99)	0.95 (0.86; 1.05)										0.96 (0.89; 1.05)
EMPA	1.22 (1.06; 1.41)	1.05 (0.92; 1.21)	1.14 (1.01; 1.29)	1.21 (1.05; 1.38)									0.80 (0.72; 0.89)
ERTU	1.16 (1.01; 1.34)	1.00 (0.87; 1.15)	1.09 (0.97; 1.22)	1.15 (1.00; 1.31)	0.95 (0.82; 1.10)								0.84 (0.76; 0.93)
EXEN	1.03 (0.91; 1.16)	0.88 (0.78; 1.00)	0.96 (0.87; 1.06)	1.01 (0.90; 1.14)	0.84 (0.74; 0.96)	0.88 (0.78; 1.01)							0.95 (0.88; 1.03)
LIXI	0.86 (0.74; 0.99)	0.74 (0.64; 0.85)	0.80 (0.71; 0.90)	0.84 (0.73; 0.97)	0.70 (0.60; 0.82)	0.74 (0.63; 0.86)	0.83 (0.73; 0.95)						1.14 (1.02; 1.28)
PIO	0.99 (0.84; 1.18)	0.85 (0.72; 1.01)	0.93 (0.80; 1.08)	0.98 (0.83; 1.15)	0.81 (0.68; 0.97)	0.85 (0.72; 1.02)	0.97 (0.82; 1.13)	1.16 (0.97; 1.39)					0.99 (0.86; 1.13)
SEMAi	0.87 (0.72; 1.04)	0.74 (0.62; 0.89)	0.81 (0.69; 0.95)	0.85 (0.72; 1.02)	0.71 (0.59; 0.85)	0.74 (0.62; 0.90)	0.84 (0.71; 1.00)	1.01 (0.84; 1.22)	0.87 (0.71; 1.07)				1.13 (0.97; 1.32)
SEMAo	0.63 (0.50; 0.78)	0.54 (0.43; 0.67)	0.58 (0.47; 0.72)	0.62 (0.50; 0.77)	0.51 (0.41; 0.64)	0.54 (0.43; 0.67)	0.61 (0.49; 0.75)	0.73 (0.58; 0.92)	0.63 (0.49; 0.80)	0.72 (0.56; 0.93)			1.57 (1.28; 1.91)
SU	1.02 (0.89; 1.18)	0.88 (0.76; 1.01)	0.95 (0.87; 1.05)	1.01 (0.88; 1.15)	0.83 (0.72; 0.97)	0.88 (0.75; 1.02)	0.99 (0.87; 1.13)	1.19 (1.02; 1.39)	1.03 (0.86; 1.23)	1.18 (0.98; 1.42)	1.63 (1.30; 2.05)		
PLAC	0.98 (0.89; 1.07)	0.84 (0.77; 0.92)	0.91 (0.87; 0.96)	0.96 (0.89; 1.05)	0.80 (0.72; 0.89)	0.84 (0.76; 0.93)	0.95 (0.88; 1.03)	1.14 (1.02; 1.28)	0.99 (0.86; 1.13)	1.13 (0.97; 1.32)	1.57 (1.28; 1.91)	0.96 (0.86; 1.07)	

Probability ranking for any discontinuation (sensitivity analysis using random effects model)

Table 26 Probability that each intervention is one of the best treatments. Higher probabilities indicate that the intervention would be ranked as more effective.

Treatment	P-score (fixed effects)
EMPA	0.9553
DAPA	0.8802
ERTU	0.8773
DPP-4	0.6986
EXEN	0.5497
SU	0.5142
DULA	0.5017
CANA	0.4471
PIO	0.4383
PLAC	0.3510
SEMAi	0.1563
LIXI	0.1296
SEMAo	0.0008

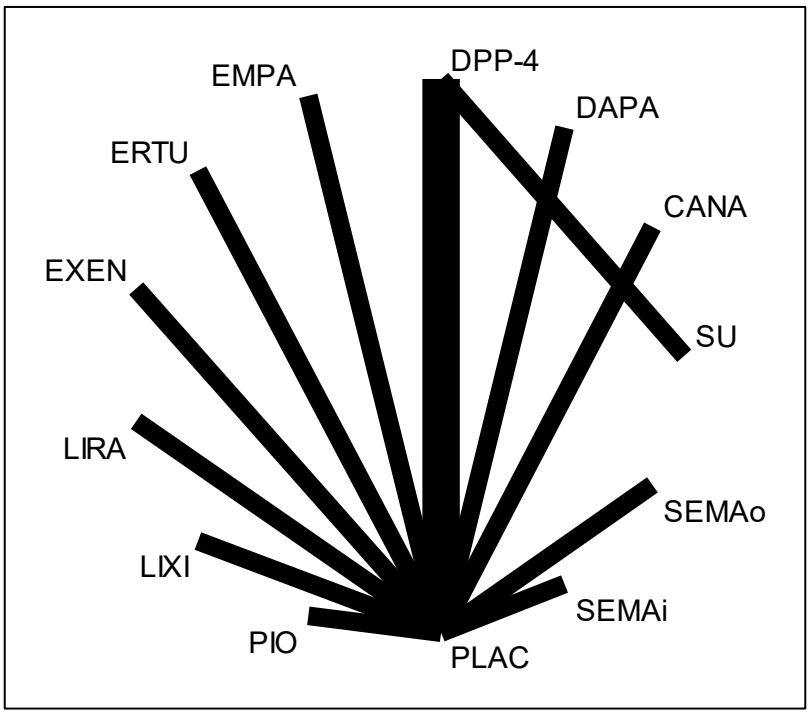
Discontinuation due to adverse events

The fixed effects model for discontinuation due to adverse events generated a network diagram (see Figure 8). Data for this outcome was included from 13 RCTs. As specified by the committee, both the sulfonylureas and DPP-4 drugs were analysed at the class level, assuming the treatments within the class have the same effectiveness. Five trials included DPP-4 interventions, whilst the sulfonylurea class consisted of a single treatment (glimepiride). Other drugs were analysed at the individual level.

Abbreviations used in figures and tables: PLAC, Placebo; PIO, Pioglitazone; LIXI, Lixisenatide; LIRA, Liraglutide; EXEN, Exenatide; ERTU, Ertugliflozin; EMPA, Empagliflozin; DULA, Dulaglutide; DPP-4, Dipeptidyl peptidase-4 inhibitors; DAPA, Dapagliflozin; CANA, Canagliflozin; SU, Sulphonylurea; SEMAo, Oral semaglutide; SEMAi, Injected semaglutide.

Network diagram for discontinuation due to adverse events

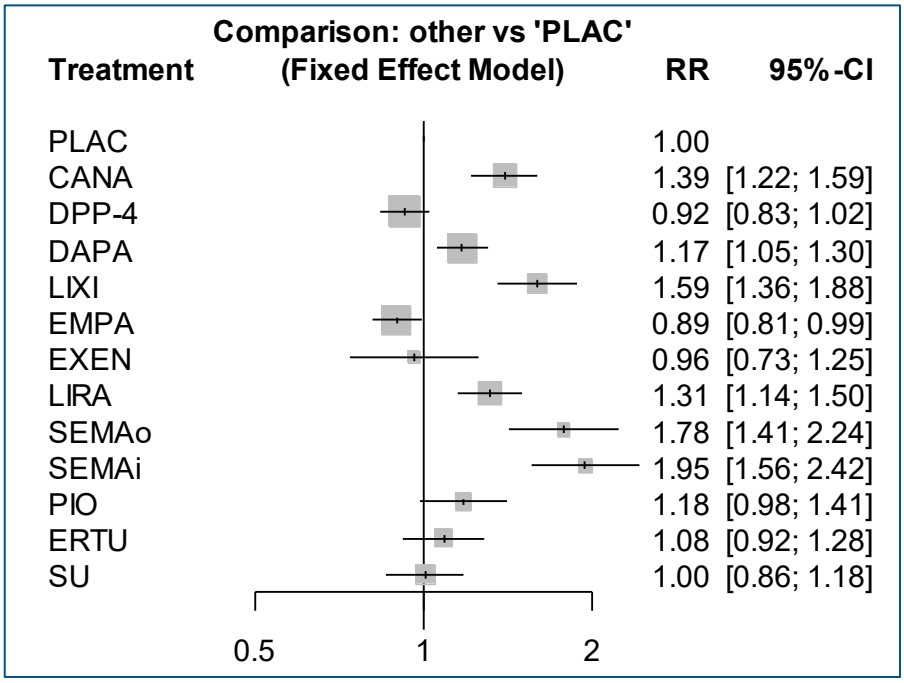
Figure 8 Network diagram for discontinuation due to adverse events[1]



[1] Line width is proportional to the number of trials comparing every pair of treatments.

Caterpillar plot for discontinuation due to adverse events

Figure 9 Relative effectiveness of all options versus placebo. (Risk ratios with 95% confidence intervals and line of no effect as the vertical line at 1).



Relative effectiveness chart for discontinuation due to adverse events

Table 27 Relative effectiveness of all pairwise combinations for discontinuation due to adverse events. Upper diagonal: risk ratios (RR) with 95% confidence intervals from the pair-wise meta-analysis. RR less than 1 favour the row defining treatment. RRs greater than 1 favour the column defining treatment.) Lower diagonal: RR with 95% confidence intervals from the from the NMA results. RRs greater than 1 favour the row defining treatment, RRs less than 1 favour the column defining treatment.

	CANA	DAPA	DPP-4	EMPA	ERTU	EXEN	LIRA	LIXI	PIO	SEMAi	SEMAo	SU	PLAC
CANA													1.39 (1.22; 1.59)
DAPA	1.19 (1.00; 1.41)												1.17 (1.05; 1.30)
DPP-4	1.51 (1.27; 1.79)	1.27 (1.09; 1.47)										0.92 (0.81; 1.04)	0.92 (0.83; 1.02)
EMPA	1.56 (1.32; 1.85)	1.31 (1.13; 1.52)	1.03 (0.89; 1.20)										0.89 (0.81; 0.99)
ERTU	1.28 (1.04; 1.59)	1.08 (0.89; 1.31)	0.85 (0.70; 1.04)	0.82 (0.68; 1.00)									1.08 (0.92; 1.28)
EXEN	1.45 (1.08; 1.96)	1.22 (0.91; 1.63)	0.96 (0.72; 1.28)	0.93 (0.70; 1.24)	1.13 (0.83; 1.55)								0.96 (0.73; 1.25)
LIRA	1.06 (0.88; 1.29)	0.89 (0.75; 1.06)	0.71 (0.59; 0.84)	0.68 (0.57; 0.81)	0.83 (0.67; 1.03)	0.73 (0.54; 0.99)							1.31 (1.14; 1.50)
LIXI	0.87 (0.71; 1.08)	0.73 (0.60; 0.89)	0.58 (0.48; 0.70)	0.56 (0.46; 0.68)	0.68 (0.54; 0.86)	0.60 (0.44; 0.82)	0.82 (0.67; 1.02)						1.59 (1.36; 1.88)
PIO	1.18 (0.95; 1.48)	0.99 (0.81; 1.23)	0.79 (0.64; 0.97)	0.76 (0.62; 0.94)	0.92 (0.72; 1.18)	0.82 (0.59; 1.13)	1.11 (0.89; 1.40)	1.36 (1.06; 1.73)					1.18 (0.98; 1.41)
SEMAi	0.72 (0.55; 0.93)	0.60 (0.47; 0.77)	0.47 (0.37; 0.61)	0.46 (0.36; 0.59)	0.56 (0.42; 0.73)	0.49 (0.35; 0.70)	0.67 (0.52; 0.87)	0.82 (0.62; 1.08)	0.60 (0.45; 0.80)				1.95 (1.56; 2.42)
SEMAo	0.78 (0.60; 1.02)	0.66 (0.51; 0.85)	0.52 (0.40; 0.67)	0.50 (0.39; 0.65)	0.61 (0.46; 0.81)	0.54 (0.38; 0.77)	0.74 (0.56; 0.96)	0.90 (0.68; 1.19)	0.66 (0.49; 0.88)	1.09 (0.80; 1.50)			1.78 (1.41; 2.24)
SU	1.39 (1.12; 1.71)	1.16 (0.96; 1.41)	0.92 (0.81; 1.04)	0.89 (0.73; 1.08)	1.08 (0.86; 1.36)	0.95 (0.70; 1.30)	1.30 (1.06; 1.61)	1.59 (1.26; 1.99)	1.17 (0.92; 1.49)	1.94 (1.48; 2.54)	1.77 (1.34; 2.35)		
PLAC	1.39 (1.22; 1.59)	1.17 (1.05; 1.30)	0.92 (0.83; 1.02)	0.89 (0.81; 0.99)	1.08 (0.92; 1.28)	0.96 (0.73; 1.25)	1.31 (1.14; 1.50)	1.59 (1.36; 1.88)	1.18 (0.98; 1.41)	1.95 (1.56; 2.42)	1.78 (1.41; 2.24)	1.00 (0.86; 1.18)	

Probability ranking for discontinuation due to adverse events

Table 28 Probability that each intervention is one of the best treatments. Higher probabilities indicate that the intervention would be ranked as more effective.

Treatment	P-score (fixed effects)
EMPA	0.9335
DPP-4	0.8913
EXEN	0.7916
PLAC	0.7313
SU	0.7203
ERTU	0.5995
DAPA	0.4812
PIO	0.4794
LIRA	0.3354
CANA	0.2693
LIXI	0.1541
SEMAo	0.0820
SEMAi	0.0311

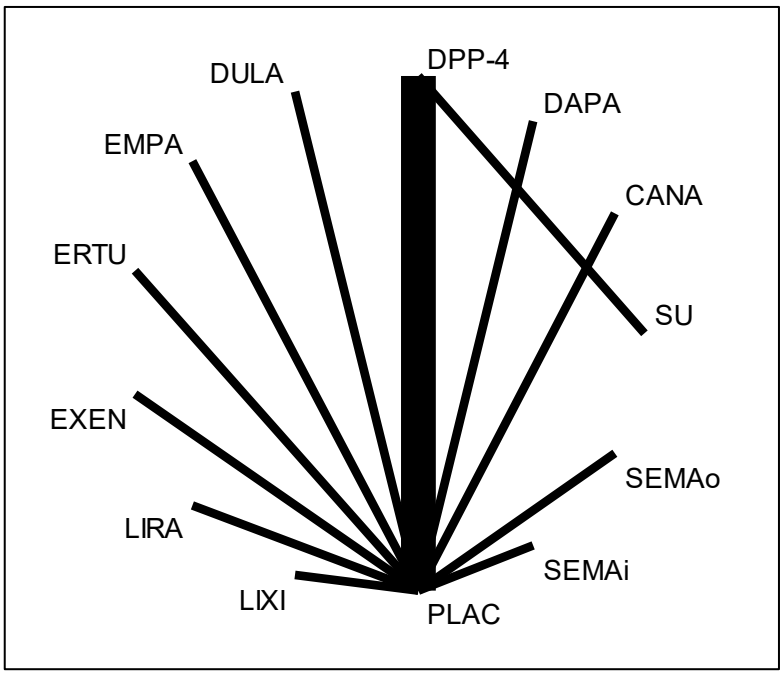
Hospitalisation for heart failure

The random effects model for hospitalised for heart failure generated a network diagram (see Figure 10). Data for this outcome was included from 15 RCTs. As specified by the committee, both the sulfonylureas and DPP-4 drugs were analysed at the class level, assuming the treatments within the class have the same effectiveness. Five trials included DPP-4 interventions, whilst the sulfonylurea class consisted of a single treatment (glimepiride). Other drugs were analysed at the individual level.

Abbreviations used in figures and tables: PLAC, Placebo; PIO, Pioglitazone; LIXI, Lixisenatide; LIRA, Liraglutide; EXEN, Exenatide; ERTU, Ertugliflozin; EMPA, Empagliflozin; DULA, Dulaglutide; DPP-4, Dipeptidyl peptidase-4 inhibitors; DAPA, Dapagliflozin; CANA, Canagliflozin; SU, Sulphonylurea; SEMAo, Oral semaglutide; SEMAi, Injected semaglutide.

Network diagram for hospitalised due to heart failure

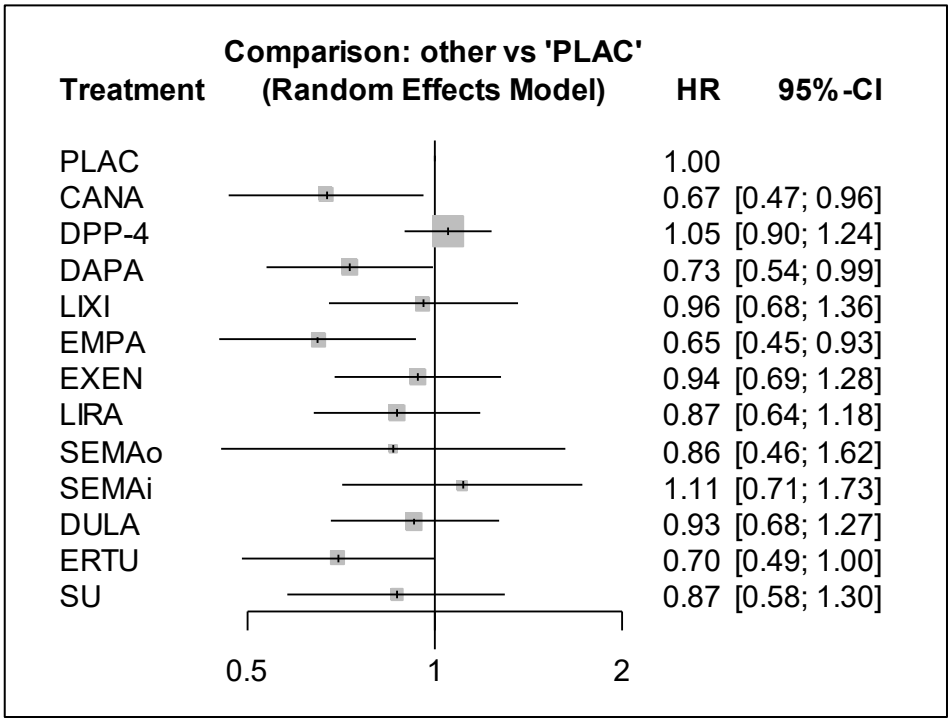
Figure 10 Network diagram for hospitalisation for heart failure[1]



[1] Line width is proportional to the number of trials comparing every pair of treatments.

Caterpillar plot for hospitalisation for heart failure

Figure 11 Relative effectiveness of all options versus placebo. (Hazard ratios with 95% confidence intervals and line of no effect as the vertical line at 1).



Relative effectiveness chart for hospitalisation for heart failure

Table 29 Relative effectiveness of all pairwise combinations for hospitalisation for heart failure. Upper diagonal: hazard ratios (HR) with 95% confidence intervals from the pair-wise meta-analysis. HR less than 1 favour the row defining treatment. HRs greater than 1 favour the column defining treatment.) Lower diagonal: HR with 95% confidence intervals from the from the NMA results. HRs greater than 1 favour the row defining treatment, HRs less than 1 favour the column defining treatment.

	CANA	DAPA	DPP-4	DULA	EMPA	ERTU	EXEN	LIRA	LIXI	SEMAi	SEMAo	SU	PLAC
CANA													0.67 (0.47; 0.96)
DAPA	0.92 (0.57; 1.47)												0.73 (0.54; 0.99)
DPP-4	0.64 (0.43; 0.94)	0.69 (0.49; 0.98)										1.21 (0.84; 1.75)	1.05 (0.90; 1.24)
DULA	0.72 (0.45; 1.16)	0.78 (0.51; 1.22)	1.13 (0.80; 1.61)										0.93 (0.68; 1.27)
EMPA	1.03 (0.62; 1.72)	1.12 (0.70; 1.81)	1.62 (1.09; 2.41)	1.43 (0.89; 2.31)									0.65 (0.45; 0.93)
ERTU	0.96 (0.58; 1.58)	1.04 (0.65; 1.67)	1.50 (1.02; 2.22)	1.33 (0.83; 2.13)	0.93 (0.56; 1.54)								0.70 (0.49; 1.00)
EXEN	0.71 (0.44; 1.14)	0.78 (0.50; 1.20)	1.12 (0.79; 1.59)	0.99 (0.64; 1.53)	0.69 (0.43; 1.11)	0.74 (0.46; 1.19)							0.94 (0.69; 1.28)
LIRA	0.77 (0.48; 1.23)	0.84 (0.54; 1.30)	1.21 (0.86; 1.71)	1.07 (0.69; 1.65)	0.75 (0.46; 1.20)	0.80 (0.50; 1.29)	1.08 (0.70; 1.67)						0.87 (0.64; 1.18)
LIXI	0.70 (0.42; 1.15)	0.76 (0.48; 1.21)	1.10 (0.75; 1.61)	0.97 (0.61; 1.55)	0.68 (0.41; 1.12)	0.73 (0.44; 1.20)	0.98 (0.61; 1.56)	0.91 (0.57; 1.44)					0.96 (0.68; 1.36)
SEMAi	0.60 (0.34; 1.07)	0.66 (0.38; 1.13)	0.95 (0.59; 1.52)	0.84 (0.49; 1.44)	0.59 (0.33; 1.04)	0.63 (0.36; 1.11)	0.85 (0.49; 1.46)	0.78 (0.46; 1.35)	0.86 (0.49; 1.52)				1.11 (0.71; 1.73)
SEMAo	0.78 (0.38; 1.62)	0.85 (0.42; 1.72)	1.22 (0.64; 2.36)	1.08 (0.53; 2.20)	0.76 (0.36; 1.57)	0.81 (0.39; 1.69)	1.09 (0.54; 2.22)	1.01 (0.50; 2.05)	1.12 (0.54; 2.31)	1.29 (0.59; 2.80)			0.86 (0.46; 1.62)
SU	0.77 (0.45; 1.32)	0.84 (0.51; 1.39)	1.21 (0.84; 1.75)	1.07 (0.64; 1.78)	0.75 (0.43; 1.28)	0.80 (0.47; 1.38)	1.08 (0.65; 1.80)	1.00 (0.60; 1.66)	1.10 (0.65; 1.88)	1.28 (0.70; 2.32)	0.99 (0.47; 2.10)		
PLAC	0.67 (0.47; 0.96)	0.73 (0.54; 0.99)	1.05 (0.90; 1.24)	0.93 (0.68; 1.27)	0.65 (0.45; 0.93)	0.70 (0.49; 1.00)	0.94 (0.69; 1.28)	0.87 (0.64; 1.18)	0.96 (0.68; 1.36)	1.11 (0.71; 1.73)	0.86 (0.46; 1.62)	0.87 (0.58; 1.30)	

Probability ranking for hospitalisation for heart failure

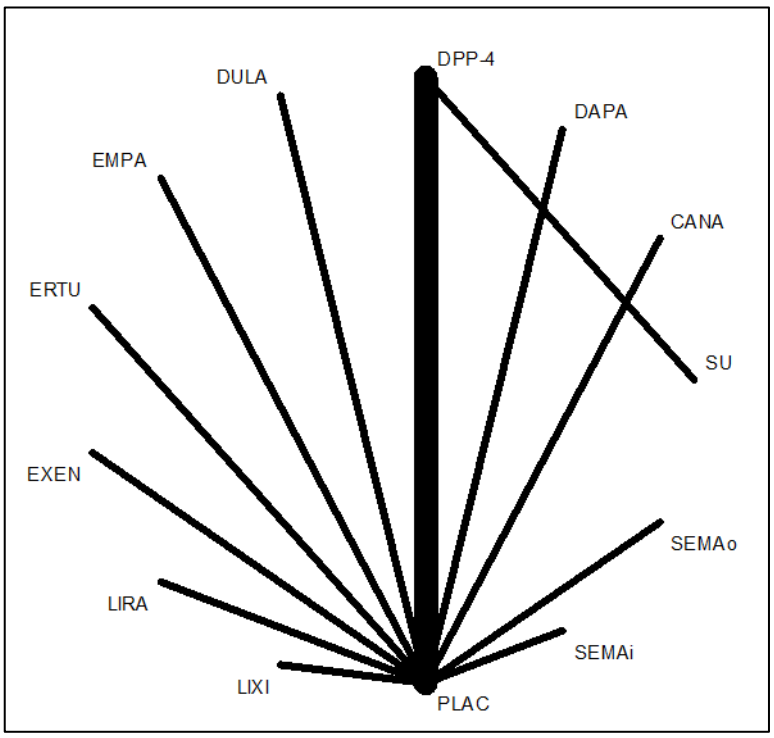
Table 30 Probability that each intervention is one of the best treatments. Higher probabilities indicate that the intervention would be ranked as more effective.

Treatment	P-score (random effects)
EMPA	0.8418
CANA	0.8155
ERTU	0.7721
DAPA	0.7351
SEMAo	0.5054
LIRA	0.5030
SU	0.5004
DULA	0.4047
EXEN	0.3889
LIXI	0.3612
PLAC	0.2768
SEMAi	0.2030
DPP-4	0.1921

Sensitivity analysis: hospitalisation for heart failure (minus SAVOR-TIMI 53 [saxagliptin versus placebo] and using fixed effects model)

Network diagram for hospitalised due to heart failure

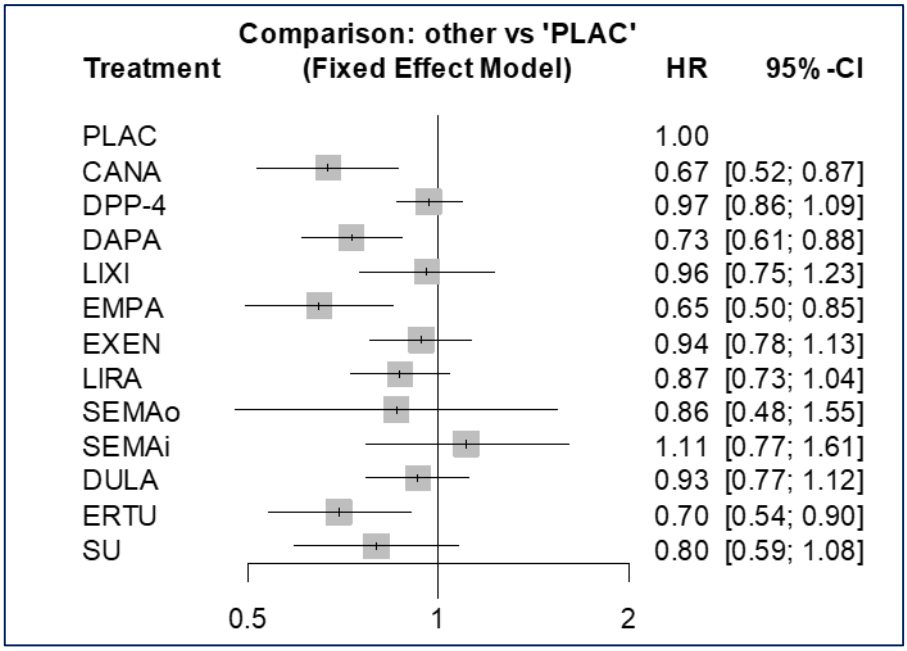
Figure 12 Network diagram for hospitalisation for heart failure[1]



[1] Line width is proportional to the number of trials comparing every pair of treatments.

Caterpillar plot for hospitalisation for heart failure

Figure 13 Relative effectiveness of all options minus saxagliptin versus placebo. (Risk ratios with 95% confidence intervals and line of no effect as the vertical line at 1).



Relative effectiveness chart for hospitalisation for heart failure (sensitivity analysis using fixed effects model)

Table 31 Relative effectiveness of all pairwise combinations for nonfatal stroke. Upper diagonal: risk ratios (RR) with 95% confidence intervals from the pair-wise meta-analysis. RR less than 1 favour the row defining treatment. RRs greater than 1 favour the column defining treatment.) Lower diagonal: RR with 95% confidence intervals from the from the NMA results. RRs greater than 1 favour the row defining treatment, RRs less than 1 favour the column defining treatment.

	CANA	DPP-4	DAPA	LIXI	EMPA	EXEN	LIRA	SEMAo	SEMAi	DULA	ERTU	SU	PLAC
CANA													0.67 (0.52; 0.87)
DPP-4	0.69 (0.52; 0.92)											1.21 (0.92; 1.59)	0.97 (0.86; 1.09)
DAPA	0.92 (0.67; 1.26)	1.33 (1.06; 1.65)											0.73 (0.61; 0.88)
LIXI	0.70 (0.49; 1.00)	1.01 (0.77; 1.33)	0.76 (0.56; 1.03)										0.96 (0.75; 1.23)
EMPA	1.03 (0.71; 1.49)	1.49 (1.11; 1.99)	1.12 (0.81; 1.55)	1.48 (1.03; 2.12)									0.65 (0.50; 0.85)
EXEN	0.71 (0.52; 0.98)	1.03 (0.82; 1.28)	0.78 (0.60; 1.01)	1.02 (0.75; 1.39)	0.69 (0.50; 0.96)								0.94 (0.78; 1.13)
LIRA	0.77 (0.56; 1.06)	1.11 (0.89; 1.38)	0.84 (0.65; 1.09)	1.10 (0.81; 1.50)	0.75 (0.54; 1.03)	1.08 (0.83; 1.40)							0.87 (0.73; 1.04)
SEMAo	0.78 (0.41; 1.48)	1.13 (0.62; 2.05)	0.85 (0.46; 1.57)	1.12 (0.59; 2.11)	0.76 (0.40; 1.44)	1.09 (0.59; 2.02)	1.01 (0.55; 1.87)						0.86 (0.48; 1.55)
SEMAi	0.60 (0.38; 0.95)	0.87 (0.59; 1.29)	0.66 (0.44; 0.99)	0.86 (0.55; 1.35)	0.59 (0.37; 0.92)	0.85 (0.56; 1.28)	0.78 (0.52; 1.18)	0.77 (0.39; 1.55)					1.11 (0.77; 1.61)
DULA	0.72 (0.52; 0.99)	1.04 (0.83; 1.30)	0.78 (0.60; 1.02)	1.03 (0.76; 1.41)	0.70 (0.51; 0.97)	1.01 (0.78; 1.32)	0.94 (0.72; 1.21)	0.92 (0.50; 1.71)	1.19 (0.79; 1.81)				0.93 (0.77; 1.12)
ERTU	0.96 (0.67; 1.38)	1.38 (1.04; 1.83)	1.04 (0.76; 1.43)	1.37 (0.96; 1.96)	0.93 (0.64; 1.34)	1.34 (0.98; 1.84)	1.24 (0.91; 1.70)	1.23 (0.65; 2.33)	1.59 (1.01; 2.48)	1.33 (0.97; 1.82)			0.70 (0.54; 0.90)
SU	0.84 (0.56; 1.24)	1.21 (0.92; 1.59)	0.91 (0.64; 1.30)	1.20 (0.81; 1.77)	0.81 (0.54; 1.21)	1.18 (0.83; 1.67)	1.09 (0.77; 1.54)	1.08 (0.56; 2.08)	1.39 (0.86; 2.23)	1.16 (0.82; 1.66)	0.88 (0.59; 1.30)		
PLAC	0.67 (0.52; 0.87)	0.97 (0.86; 1.09)	0.73 (0.61; 0.88)	0.96 (0.75; 1.23)	0.65 (0.50; 0.85)	0.94 (0.78; 1.13)	0.87 (0.73; 1.04)	0.86 (0.48; 1.55)	1.11 (0.77; 1.61)	0.93 (0.77; 1.12)	0.70 (0.54; 0.90)	0.80 (0.59; 1.08)	

Probability ranking for hospitalisation for heart failure (sensitivity analysis using fixed effects model)

Table 32 Probability that each intervention is one of the best treatments. Higher probabilities indicate that the intervention would be ranked as more effective.

Treatment	P-score (fixed effects)
EMPA	0.8772
CANA	0.8486
ERTU	0.8001
DAPA	0.7587
SU	0.6134
SEMAo	0.4887
LIRA	0.4884
DULA	0.3621
EXEN	0.3414
LIXI	0.3075
DPP-4	0.2775
PLAC	0.1927
SEMAi	0.1438

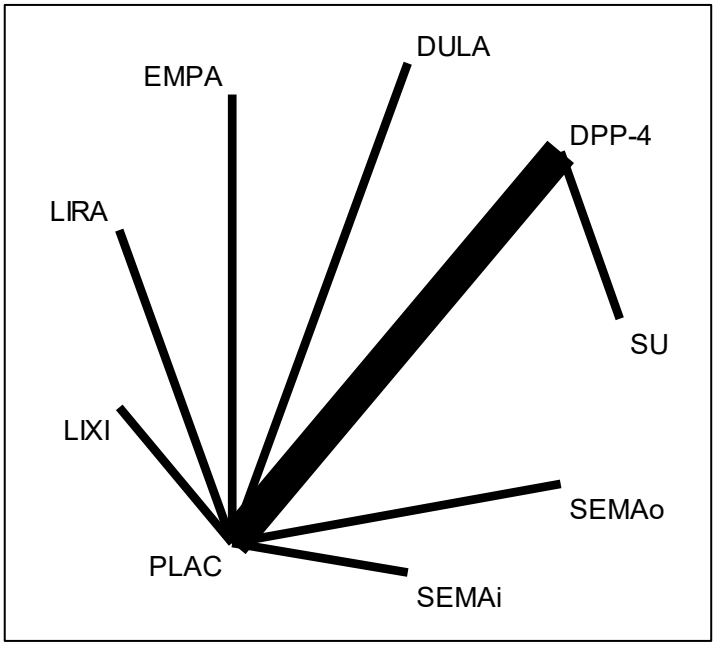
Hospitalisation for unstable angina

The fixed effects model for hospitalised for unstable angina generated a network diagram (see Figure 14). Data for this outcome was included from 11 RCTs. As specified by the committee, both the sulfonylureas and DPP-4 drugs were analysed at the class level, assuming the treatments within the class have the same effectiveness. Five trials included DPP-4 interventions, whilst the sulfonylurea class consisted of a single treatment (glimepiride). Other drugs were analysed at the individual level.

Abbreviations used in figures and tables: PLAC, Placebo; PIO, Pioglitazone; LIXI, Lixisenatide; LIRA, Liraglutide; EXEN, Exenatide; ERTU, Ertugliflozin; EMPA, Empagliflozin; DULA, Dulaglutide; DPP-4, Dipeptidyl peptidase-4 inhibitors; DAPA, Dapagliflozin; CANA, Canagliflozin; SU, Sulphonylurea; SEMAo, Oral semaglutide; SEMAi, Injected semaglutide.

Network diagram for hospitalisation for unstable angina

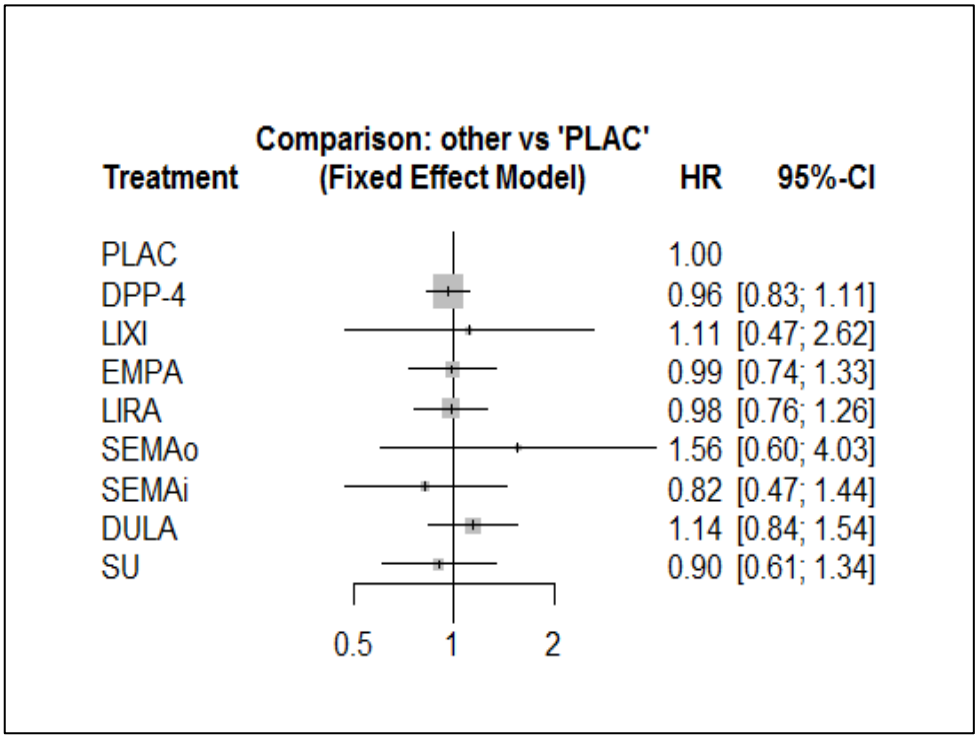
Figure 14 Network diagram for hospitalisation for unstable angina[1]



[1] Line width is proportional to the number of trials comparing every pair of treatments.

Caterpillar plot for hospitalisation for unstable angina

Figure 15 Relative effectiveness of all options versus placebo. (Hazard ratios with 95% confidence intervals and line of no effect as the vertical line at 1).



Relative effectiveness chart for hospitalisation for unstable angina

Table 33 Relative effectiveness of all pairwise combinations for hospitalisation for unstable angina. Upper diagonal: hazard ratios (HR) with 95% confidence intervals from the pair-wise meta-analysis. HR less than 1 favour the row defining treatment. HRs greater than 1 favour the column defining treatment.) Lower diagonal: HR with 95% confidence intervals from the from the NMA results. HRs greater than 1 favour the row defining treatment, HRs less than 1 favour the column defining treatment.

	DPP-4	DULA	EMPA	LIRA	LIXI	SEMAi	SEMAo	SU	Placebo
DPP-4								1.07 (0.74; 1.54)	0.96 (0.83; 1.11)
DULA	0.84 (0.60; 1.18)								1.14 (0.84; 1.54)
EMPA	0.97 (0.70; 1.35)	1.15 (0.75; 1.76)							0.99 (0.74; 1.33)
LIRA	0.98 (0.73; 1.32)	1.16 (0.78; 1.73)	1.01 (0.68; 1.49)						0.98 (0.76; 1.26)
LIXI	0.87 (0.36; 2.07)	1.03 (0.41; 2.55)	0.89 (0.36; 2.21)	0.88 (0.36; 2.16)					1.11 (0.47; 2.62)
SEMAi	1.17 (0.66; 2.09)	1.39 (0.74; 2.63)	1.21 (0.64; 2.28)	1.20 (0.65; 2.21)	1.35 (0.49; 3.77)				0.82 (0.47; 1.44)
SEMAo	0.62 (0.24; 1.61)	0.73 (0.27; 1.98)	0.63 (0.23; 1.72)	0.63 (0.24; 1.68)	0.71 (0.20; 2.56)	0.53 (0.17; 1.58)			1.56 (0.60; 4.03)
SU	1.07 (0.74; 1.54)	1.27 (0.77; 2.08)	1.10 (0.67; 1.80)	1.09 (0.68; 1.74)	1.23 (0.48; 3.17)	0.91 (0.46; 1.81)	1.73 (0.62; 4.85)		
Placebo	0.96 (0.83; 1.11)	1.14 (0.84; 1.54)	0.99 (0.74; 1.33)	0.98 (0.76; 1.26)	1.11 (0.47; 2.62)	0.82 (0.47; 1.44)	1.56 (0.60; 4.03)	0.90 (0.61; 1.34)	

Probability ranking for hospitalisation for unstable angina

Table 34 Probability that each intervention is one of the best treatments. Higher probabilities indicate that the intervention would be ranked as more effective.

Treatment	P-score (fixed effects)
SEMAi	0.7426
SU	0.6708
DPP-4	0.5944
LIRA	0.5483
EMPA	0.5287
PLAC	0.4973
LIXI	0.4264
DULA	0.2980
SEMAo	0.1935

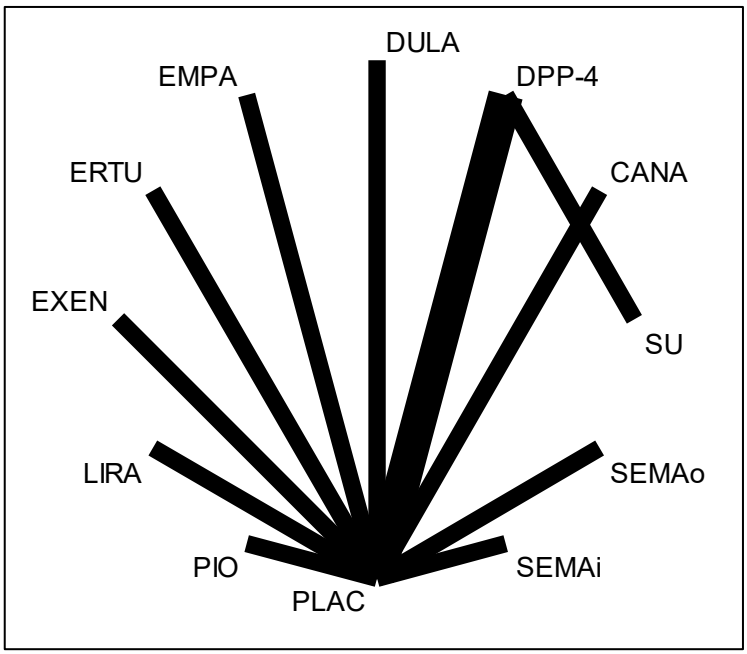
Nonfatal myocardial infarction

The fixed effects model for nonfatal myocardial infarction (MI) generated a network diagram (see Figure 16). Data for this outcome was included from 12 RCTs. As specified by the committee, both the sulfonylureas and DPP-4 drugs were analysed at the class level, assuming the treatments within the class have the same effectiveness. Three trials included DPP-4 interventions, whilst the sulfonylurea class consisted of a single treatment (glimepiride). Other drugs were analysed at the individual level.

Abbreviations used in figures and tables: PLAC, Placebo; PIO, Pioglitazone; LIXI, Lixisenatide; LIRA, Liraglutide; EXEN, Exenatide; ERTU, Ertugliflozin; EMPA, Empagliflozin; DULA, Dulaglutide; DPP-4, Dipeptidyl peptidase-4 inhibitors; DAPA, Dapagliflozin; CANA, Canagliflozin; SU, Sulphonylurea; SEMAo, Oral semaglutide; SEMAi, Injected semaglutide.

Network diagram for nonfatal MI

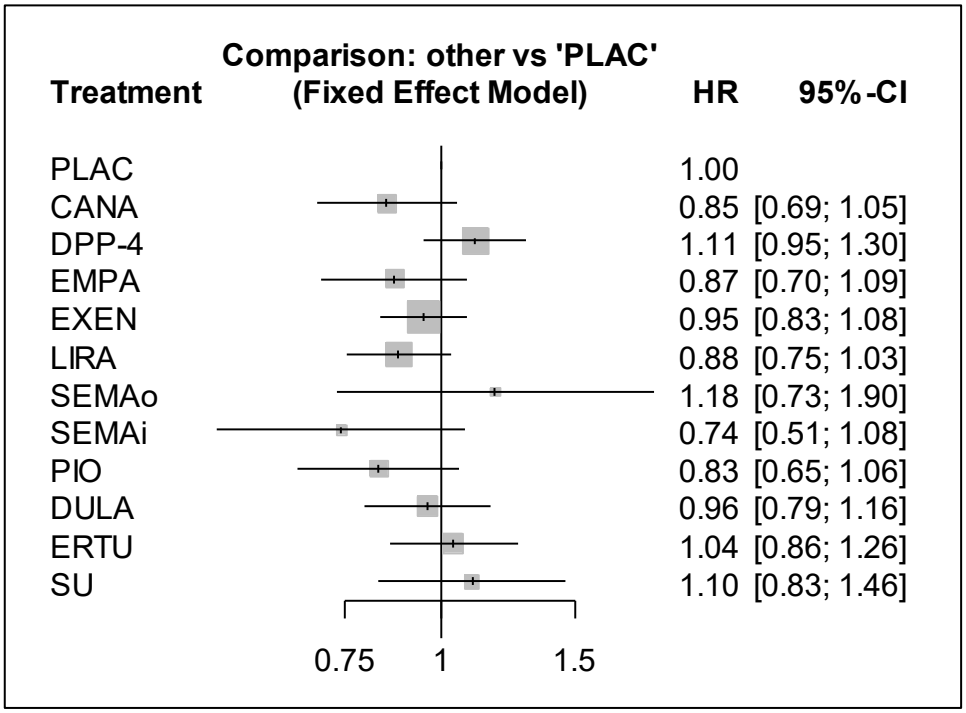
Figure 16 Network diagram for nonfatal MI[1]



[1] Line width is proportional to the number of trials comparing every pair of treatments.

Caterpillar plot for nonfatal myocardial infarction

Figure 17 Relative effectiveness of all options versus placebo. (Hazard ratios with 95% confidence intervals and line of no effect as the vertical line at 1).



Relative effectiveness chart for nonfatal myocardial infarction

Table 35 Relative effectiveness of all pairwise combinations for nonfatal myocardial infarction. Upper diagonal: hazard ratios (HR) with 95% confidence intervals from the pair-wise meta-analysis. HR less than 1 favour the row defining treatment. HRs greater than 1 favour the column defining treatment.) Lower diagonal: HR with 95% confidence intervals from the from the NMA results. HRs greater than 1 favour the row defining treatment, HRs less than 1 favour the column defining treatment.

	CANA	DPP-4	DULA	EMPA	ERTU	EXEN	LIRA	PIO	SEMAi	SEMAo	SU	Placebo
CANA												0.85 (0.69; 1.05)
DPP-4	0.77 (0.59; 0.99)										1.01 (0.80; 1.28)	1.11 (0.95; 1.30)
DULA	0.89 (0.67; 1.18)	1.16 (0.90; 1.48)										0.96 (0.79; 1.16)
EMPA	0.98 (0.72; 1.33)	1.28 (0.97; 1.67)	1.10 (0.82; 1.48)									0.87 (0.70; 1.09)
ERTU	0.82 (0.61; 1.09)	1.07 (0.83; 1.37)	0.92 (0.70; 1.21)	0.84 (0.62; 1.12)								1.04 (0.86; 1.26)
EXEN	0.89 (0.70; 1.15)	1.17 (0.95; 1.43)	1.01 (0.80; 1.27)	0.92 (0.71; 1.18)	1.09 (0.87; 1.38)							0.95 (0.83; 1.08)
LIRA	0.97 (0.74; 1.26)	1.26 (1.01; 1.57)	1.09 (0.85; 1.40)	0.99 (0.75; 1.30)	1.18 (0.92; 1.52)	1.08 (0.88; 1.33)						0.88 (0.75; 1.03)
PIO	1.02 (0.74; 1.41)	1.34 (1.00; 1.79)	1.16 (0.85; 1.58)	1.05 (0.75; 1.46)	1.25 (0.92; 1.71)	1.14 (0.87; 1.51)	1.06 (0.79; 1.42)					0.83 (0.65; 1.06)
SEMAi	1.15 (0.75; 1.77)	1.50 (1.00; 2.25)	1.30 (0.85; 1.98)	1.18 (0.76; 1.82)	1.41 (0.92; 2.14)	1.28 (0.86; 1.91)	1.19 (0.79; 1.79)	1.12 (0.72; 1.76)				0.74 (0.51; 1.08)
SEMAo	0.72 (0.43; 1.21)	0.94 (0.57; 1.56)	0.81 (0.49; 1.36)	0.74 (0.44; 1.25)	0.88 (0.53; 1.48)	0.81 (0.49; 1.32)	0.75 (0.45; 1.23)	0.70 (0.41; 1.20)	0.63 (0.34; 1.15)			1.18 (0.73; 1.90)
SU	0.77 (0.54; 1.10)	1.01 (0.80; 1.28)	0.87 (0.62; 1.23)	0.79 (0.55; 1.13)	0.95 (0.67; 1.33)	0.86 (0.63; 1.18)	0.80 (0.58; 1.11)	0.76 (0.52; 1.10)	0.67 (0.42; 1.08)	1.07 (0.62; 1.87)		
Placebo	0.85 (0.69; 1.05)	1.11 (0.95; 1.30)	0.96 (0.79; 1.16)	0.87 (0.70; 1.09)	1.04 (0.86; 1.26)	0.95 (0.83; 1.08)	0.88 (0.75; 1.03)	0.83 (0.65; 1.06)	0.74 (0.51; 1.08)	1.18 (0.73; 1.90)	1.10 (0.83; 1.46)	

Probability ranking for nonfatal MI

Table 36 Probability that each intervention is one of the best treatments. Higher probabilities indicate that the intervention would be ranked as more effective.

Treatment	P-score (fixed effects)
SEMAi	0.8651
PIO	0.7672
CANA	0.7384
EMPA	0.6906
LIRA	0.6861
EXEN	0.5093
DULA	0.4801
PLAC	0.3611
ERTU	0.2994
SU	0.2310
SEMAo	0.2104
DPP-4	0.1614

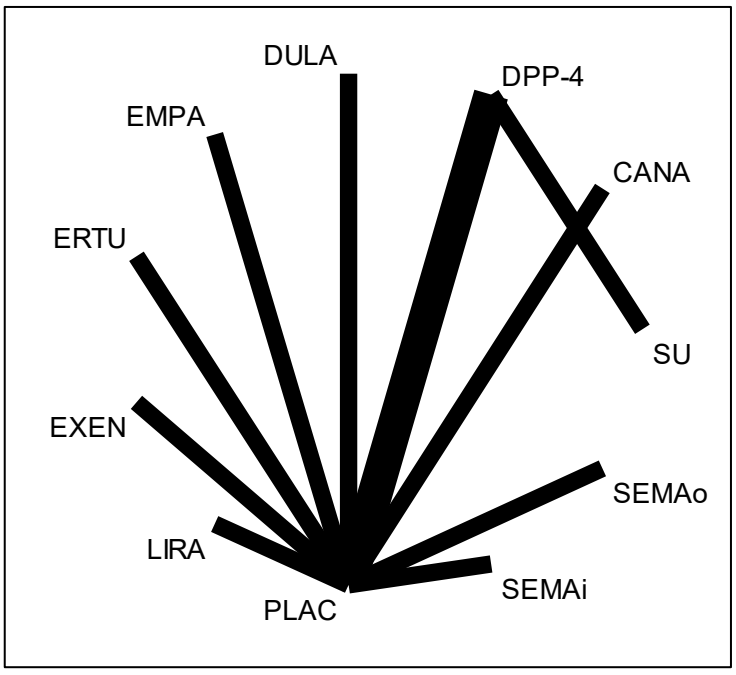
Nonfatal stroke

The fixed effects model for nonfatal stroke generated a network diagram (see Figure 18). Data for this outcome was included from 11 RCTs. As specified by the committee, both the sulfonylureas and DPP-4 drugs were analysed at the class level, assuming the treatments within the class have the same effectiveness. Three trials included DPP-4 interventions, whilst the sulfonylurea class consisted of a single treatment (glimepiride). Other drugs were analysed at the individual level.

Abbreviations used in figures and tables: PLAC, Placebo; PIO, Pioglitazone; LIXI, Lixisenatide; LIRA, Liraglutide; EXEN, Exenatide; ERTU, Ertugliflozin; EMPA, Empagliflozin; DULA, Dulaglutide; DPP-4, Dipeptidyl peptidase-4 inhibitors; DAPA, Dapagliflozin; CANA, Canagliflozin; SU, Sulphonylurea; SEMAo, Oral semaglutide; SEMAi, Injected semaglutide.

Network diagram for nonfatal stroke

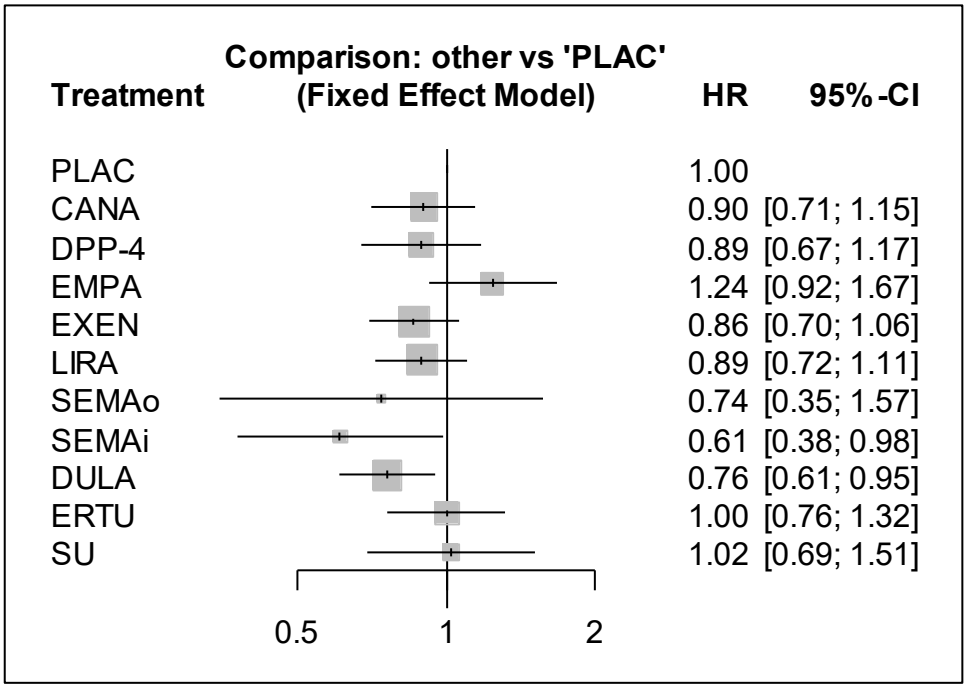
Figure 18 Network diagram for nonfatal stroke[1]



[1] Line width is proportional to the number of trials comparing every pair of treatments.

Caterpillar plot for nonfatal stroke

Figure 19 Relative effectiveness of all options versus placebo. (Hazard ratios with 95% confidence intervals and line of no effect as the vertical line at 1).



Relative effectiveness chart for nonfatal stroke

Table 37 Relative effectiveness of all pairwise combinations for nonfatal stroke. Upper diagonal: hazard ratios (HR) with 95% confidence intervals from the pair-wise meta-analysis. HR less than 1 favour the row defining treatment. HRs greater than 1 favour the column defining treatment.) Lower diagonal: HR with 95% confidence intervals from the from the NMA results. HRs greater than 1 favour the row defining treatment, HRs less than 1 favour the column defining treatment.

	CANA	DPP-4	DULA	EMPA	ERTU	EXEN	LIRA	SEMAi	SEMAo	SU	Placebo
CANA											0.90 (0.71; 1.15)
DPP-4	1.01 (0.70; 1.46)									0.87 (0.66; 1.15)	0.89 (0.67; 1.17)
DULA	1.18 (0.85; 1.64)	1.17 (0.82; 1.67)									0.76 (0.61; 0.95)
EMPA	0.73 (0.49; 1.06)	0.72 (0.48; 1.08)	0.61 (0.42; 0.89)								1.24 (0.92; 1.67)
ERTU	0.90 (0.62; 1.30)	0.89 (0.60; 1.32)	0.76 (0.53; 1.08)	1.24 (0.83; 1.86)							1.00 (0.76; 1.32)
EXEN	1.05 (0.76; 1.44)	1.03 (0.73; 1.47)	0.88 (0.65; 1.20)	1.44 (1.00; 2.08)	1.16 (0.82; 1.65)						0.86 (0.70; 1.06)
LIRA	1.01 (0.73; 1.40)	1.00 (0.70; 1.42)	0.85 (0.63; 1.16)	1.39 (0.96; 2.01)	1.12 (0.79; 1.60)	0.97 (0.71; 1.31)					0.89 (0.72; 1.11)
SEMAi	1.48 (0.86; 2.52)	1.46 (0.84; 2.54)	1.25 (0.74; 2.11)	2.03 (1.16; 3.57)	1.64 (0.94; 2.85)	1.41 (0.84; 2.38)	1.46 (0.86; 2.47)				0.61 (0.38; 0.98)
SEMAo	1.22 (0.55; 2.68)	1.20 (0.54; 2.68)	1.03 (0.47; 2.25)	1.68 (0.75; 3.76)	1.35 (0.61; 3.01)	1.16 (0.53; 2.53)	1.20 (0.55; 2.63)	0.82 (0.34; 2.01)			0.74 (0.35; 1.57)
SU	0.88 (0.56; 1.40)	0.87 (0.66; 1.15)	0.74 (0.47; 1.17)	1.21 (0.74; 1.99)	0.98 (0.61; 1.58)	0.84 (0.54; 1.32)	0.87 (0.56; 1.36)	0.60 (0.32; 1.11)	0.72 (0.31; 1.69)		
Placebo	0.90 (0.71; 1.15)	0.89 (0.67; 1.17)	0.76 (0.61; 0.95)	1.24 (0.92; 1.67)	1.00 (0.76; 1.32)	0.86 (0.70; 1.06)	0.89 (0.72; 1.11)	0.61 (0.38; 0.98)	0.74 (0.35; 1.57)	1.02 (0.69; 1.51)	

Probability ranking for nonfatal stroke

Table 38 Probability that each intervention is one of the best treatments. Higher probabilities indicate that the intervention would be ranked as more effective.

Treatment	P-score (fixed effects)
SEMAi	0.8991
DULA	0.7782
SEMAo	0.6769
EXEN	0.5909
DPP-4	0.5365
LIRA	0.5282
CANA	0.5057
ERTU	0.3240
SU	0.3033
PLAC	0.2837
EMPA	0.0736

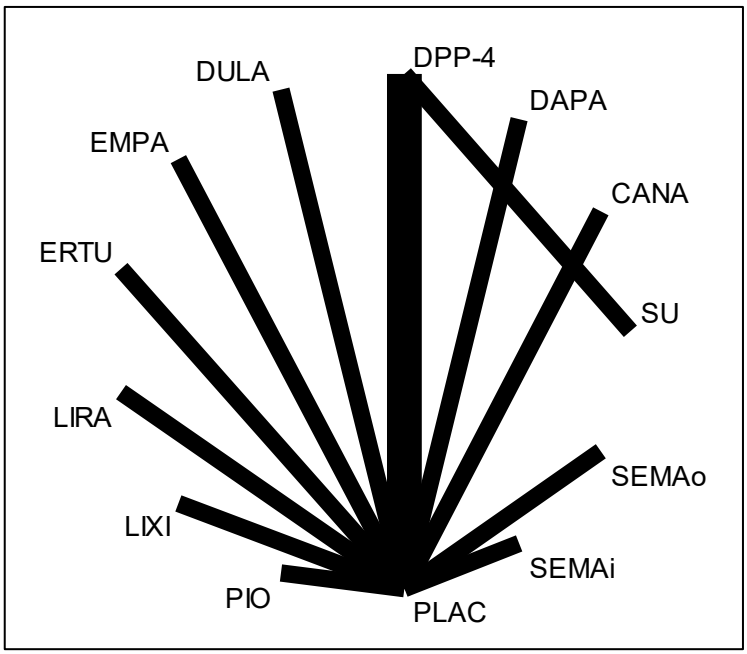
Severe hypoglycaemia

The fixed effects model for severe hypoglycaemia generated a network diagram (see Figure 20). Data for this outcome was included from 13 RCTs. As specified by the committee, both the sulfonylureas and DPP-4 drugs were analysed at the class level, assuming the treatments within the class have the same effectiveness. Three trials included DPP-4 interventions, whilst the sulfonylurea class consisted of a single treatment (glimepiride). Other drugs were analysed at the individual level. The committee reviewed the definitions of severe hypoglycaemic events used in the trials. They decided that the definition was sufficiently similar in 13 trials to compare the results in network meta-analysis. The 3 remaining trials which differed by specifying that medical intervention (for example hospitalisation) were analysed in a pairwise manner (see section 1.1.6).

Abbreviations used in figures and tables: PLAC, Placebo; PIO, Pioglitazone; LIXI, Lixisenatide; LIRA, Liraglutide; EXEN, Exenatide; ERTU, Ertugliflozin; EMPA, Empagliflozin; DULA, Dulaglutide; DPP-4, Dipeptidyl peptidase-4 inhibitors; DAPA, Dapagliflozin; CANA, Canagliflozin; SU, Sulphonylurea; SEMAo, Oral semaglutide; SEMAi, Injected semaglutide.

Network diagram for severe hypoglycaemia

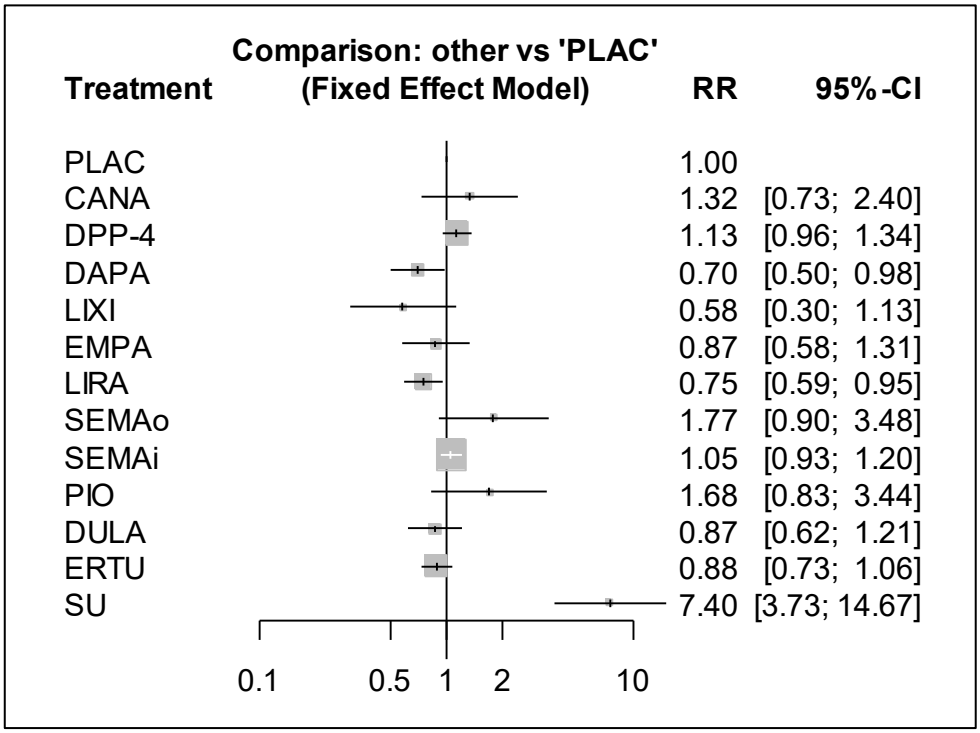
Figure 20 Network diagram for severe hypoglycaemia[1]



[1] Line width is proportional to the number of trials comparing every pair of treatments.

Caterpillar plot for severe hypoglycaemia

Figure 21 Relative effectiveness of all options versus placebo. (Risk ratios with 95% confidence intervals and line of no effect as the vertical line at 1).



Relative effectiveness chart for severe hypoglycaemia

Table 39 Relative effectiveness of all pairwise combinations for nonfatal stroke. Upper diagonal: risk ratios (RR) with 95% confidence intervals from the pair-wise meta-analysis. RR less than 1 favour the row defining treatment. RRs greater than 1 favour the column defining treatment.) Lower diagonal: RR with 95% confidence intervals from the from the NMA results. RRs greater than 1 favour the row defining treatment, RRs less than 1 favour the column defining treatment.

	CANA	DAPA	DPP-4	DULA	EMPA	ERTU	LIRA	LIXI	PIO	SEMAi	SEMAo	SU	Placebo
CANA													1.32 (0.73; 2.40)
DAPA	1.90 (0.96; 3.75)												0.70 (0.50; 0.98)
DPP-4	1.17 (0.63; 2.17)	0.62 (0.42; 0.90)										0.15 (0.08; 0.30)	1.13 (0.96; 1.34)
DULA	1.53 (0.77; 3.02)	0.81 (0.50; 1.29)	1.31 (0.90; 1.90)										0.87 (0.62; 1.21)
EMPA	1.52 (0.74; 3.12)	0.80 (0.47; 1.36)	1.30 (0.84; 2.02)	0.99 (0.59; 1.68)									0.87 (0.58; 1.31)
ERTU	1.51 (0.81; 2.82)	0.80 (0.54; 1.17)	1.29 (1.01; 1.66)	0.99 (0.67; 1.45)	0.99 (0.64; 1.56)								0.88 (0.73; 1.06)
LIRA	1.78 (0.94; 3.37)	0.94 (0.62; 1.41)	1.52 (1.13; 2.04)	1.16 (0.77; 1.75)	1.17 (0.73; 1.87)	1.17 (0.87; 1.59)							0.75 (0.59; 0.95)
LIXI	2.27 (0.94; 5.50)	1.20 (0.57; 2.50)	1.94 (0.99; 3.83)	1.48 (0.71; 3.10)	1.49 (0.69; 3.23)	1.50 (0.76; 2.97)	1.28 (0.64; 2.57)						0.58 (0.30; 1.13)
PIO	0.79 (0.31; 1.99)	0.41 (0.19; 0.91)	0.67 (0.32; 1.40)	0.51 (0.23; 1.13)	0.52 (0.23; 1.18)	0.52 (0.25; 1.09)	0.44 (0.21; 0.94)	0.35 (0.13; 0.91)					1.68 (0.83; 3.44)
SEMAi	1.26 (0.68; 2.30)	0.66 (0.46; 0.95)	1.07 (0.87; 1.33)	0.82 (0.57; 1.17)	0.83 (0.54; 1.26)	0.83 (0.66; 1.04)	0.71 (0.54; 0.93)	0.55 (0.28; 1.08)	1.60 (0.77; 3.30)				1.05 (0.93; 1.20)
SEMAo	0.75 (0.30; 1.84)	0.39 (0.19; 0.84)	0.64 (0.32; 1.29)	0.49 (0.23; 1.04)	0.49 (0.22; 1.08)	0.49 (0.25; 1.00)	0.42 (0.21; 0.86)	0.33 (0.13; 0.85)	0.95 (0.36; 2.54)	0.60 (0.30; 1.19)			1.77 (0.90; 3.48)
SU	0.18 (0.07; 0.44)	0.09 (0.04; 0.20)	0.15 (0.08; 0.30)	0.12 (0.05; 0.25)	0.12 (0.05; 0.26)	0.12 (0.06; 0.24)	0.10 (0.05; 0.21)	0.08 (0.03; 0.20)	0.23 (0.08; 0.61)	0.14 (0.07; 0.29)	0.24 (0.09; 0.63)		
Placebo	1.32 (0.73; 2.40)	0.70 (0.50; 0.98)	1.13 (0.96; 1.34)	0.87 (0.62; 1.21)	0.87 (0.58; 1.31)	0.88 (0.73; 1.06)	0.75 (0.59; 0.95)	0.58 (0.30; 1.13)	1.68 (0.83; 3.44)	1.05 (0.93; 1.20)	1.77 (0.90; 3.48)	7.40 (3.73; 14.67)	

Probability ranking for severe hypoglycaemia

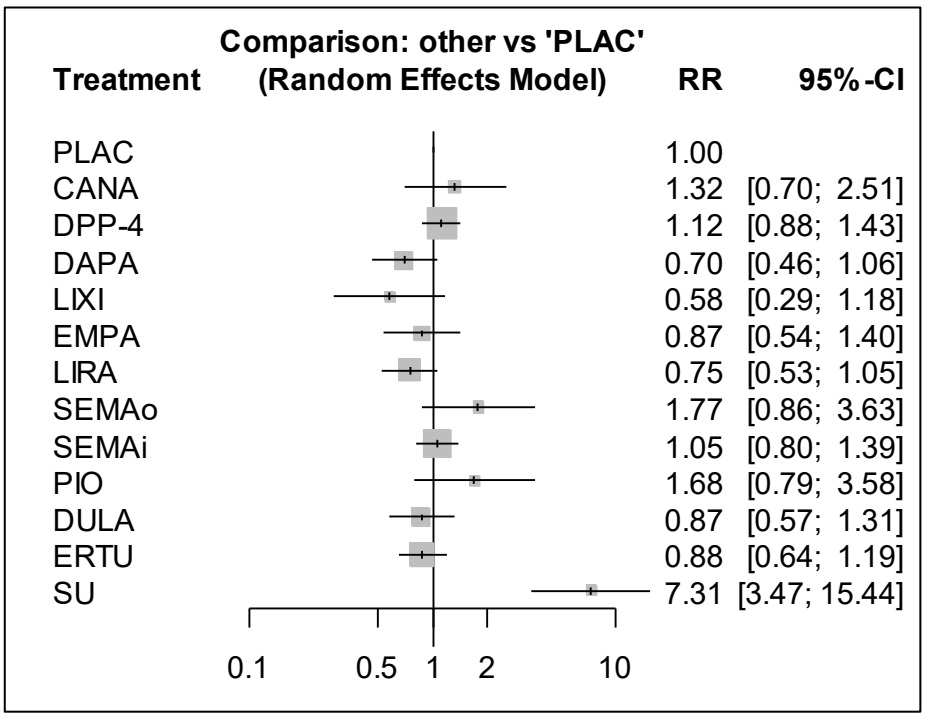
Table 40 Probability that each intervention is one of the best treatments. Higher probabilities indicate that the intervention would be ranked as more effective.

Treatment	P-score (fixed effects)
LIXI	0.9024
DAPA	0.8612
LIRA	0.8245
DULA	0.6669
ERTU	0.6696
EMPA	0.6527
PLAC	0.5024
SEMAi	0.4159
DPP-4	0.3355
CANA	0.2993
PIO	0.1968
SEMAo	0.1724
SU	0.0003

Sensitivity analysis: severe hypoglycaemia (using random effects model)

Caterpillar plot for severe hypoglycaemia

Figure 22 Relative effectiveness of all options versus placebo. (Risk ratios with 95% confidence intervals and line of no effect as the vertical line at 1).



Relative effectiveness chart for severe hypoglycaemia (sensitivity analysis using random effects model)

Table 41 Relative effectiveness of all pairwise combinations for nonfatal stroke. Upper diagonal: risk ratios (RR) with 95% confidence intervals from the pair-wise meta-analysis. RR less than 1 favour the row defining treatment. RRs greater than 1 favour the column defining treatment.) Lower diagonal: RR with 95% confidence intervals from the from the NMA results. RRs greater than 1 favour the row defining treatment, RRs less than 1 favour the column defining treatment.

	CANA	DAPA	DPP-4	DULA	EMPA	ERTU	LIRA	LIXI	PIO	SEMAi	SEMAo	SU	PLAC
CANA													1.32 (0.70; 2.51)
DAPA	1.90 (0.88; 4.06)												0.70 (0.46; 1.06)
DPP-4	1.18 (0.60; 2.34)	0.62 (0.39; 1.01)										0.15 (0.08; 0.31)	1.12 (0.88; 1.43)
DULA	1.53 (0.71; 3.28)	0.81 (0.45; 1.45)	1.29 (0.80; 2.09)										0.87 (0.57; 1.31)
EMPA	1.52 (0.68; 3.37)	0.80 (0.43; 1.50)	1.29 (0.76; 2.19)	0.99 (0.53; 1.86)									0.87 (0.54; 1.40)
ERTU	1.51 (0.74; 3.08)	0.80 (0.48; 1.33)	1.28 (0.87; 1.89)	0.99 (0.59; 1.65)	0.99 (0.57; 1.75)								0.88 (0.64; 1.19)
LIRA	1.78 (0.86; 3.67)	0.94 (0.55; 1.60)	1.50 (0.99; 2.28)	1.16 (0.68; 1.98)	1.17 (0.65; 2.09)	1.17 (0.74; 1.86)							0.75 (0.53; 1.05)
LIXI	2.27 (0.88; 5.87)	1.20 (0.53; 2.70)	1.92 (0.92; 4.03)	1.48 (0.66; 3.34)	1.49 (0.64; 3.48)	1.50 (0.70; 3.23)	1.28 (0.59; 2.78)						0.58 (0.29; 1.18)
PIO	0.79 (0.29; 2.11)	0.41 (0.18; 0.98)	0.67 (0.30; 1.47)	0.51 (0.22; 1.21)	0.52 (0.21; 1.26)	0.52 (0.23; 1.17)	0.44 (0.19; 1.01)	0.35 (0.12; 0.97)					1.68 (0.79; 3.58)
SEMAi	1.26 (0.62; 2.52)	0.66 (0.40; 1.09)	1.06 (0.74; 1.53)	0.82 (0.50; 1.35)	0.83 (0.48; 1.43)	0.83 (0.55; 1.25)	0.71 (0.46; 1.09)	0.55 (0.26; 1.17)	1.60 (0.72; 3.56)				1.05 (0.80; 1.39)
SEMAo	0.75 (0.29; 1.96)	0.39 (0.17; 0.90)	0.63 (0.30; 1.35)	0.49 (0.21; 1.12)	0.49 (0.21; 1.16)	0.49 (0.23; 1.08)	0.42 (0.19; 0.93)	0.33 (0.12; 0.90)	0.95 (0.34; 2.70)	0.60 (0.28; 1.29)			1.77 (0.86; 3.63)
SU	0.18 (0.07; 0.48)	0.10 (0.04; 0.22)	0.15 (0.08; 0.31)	0.12 (0.05; 0.28)	0.12 (0.05; 0.29)	0.12 (0.05; 0.27)	0.10 (0.04; 0.23)	0.08 (0.03; 0.22)	0.23 (0.08; 0.67)	0.14 (0.07; 0.32)	0.24 (0.09; 0.68)		
PLAC	1.32 (0.70; 2.51)	0.70 (0.46; 1.06)	1.12 (0.88; 1.43)	0.87 (0.57; 1.31)	0.87 (0.54; 1.40)	0.88 (0.64; 1.19)	0.75 (0.53; 1.05)	0.58 (0.29; 1.18)	1.68 (0.79; 3.58)	1.05 (0.80; 1.39)	1.77 (0.86; 3.63)	7.31 (3.47; 15.44)	

Probability ranking for severe hypoglycaemia (sensitivity analysis using random effects model)

Table 42 Probability that each intervention is one of the best treatments. Higher probabilities indicate that the intervention would be ranked as more effective.

Treatment	P-score (fixed effects)
LIXI	0.8876
DAPA	0.8371
LIRA	0.7998
DULA	0.6561
ERTU	0.6535
EMPA	0.6448
PLAC	0.5010
SEMAi	0.4434
DPP-4	0.3738
CANA	0.3126
PIO	0.2072
SEMAo	0.1826
SU	0.0006

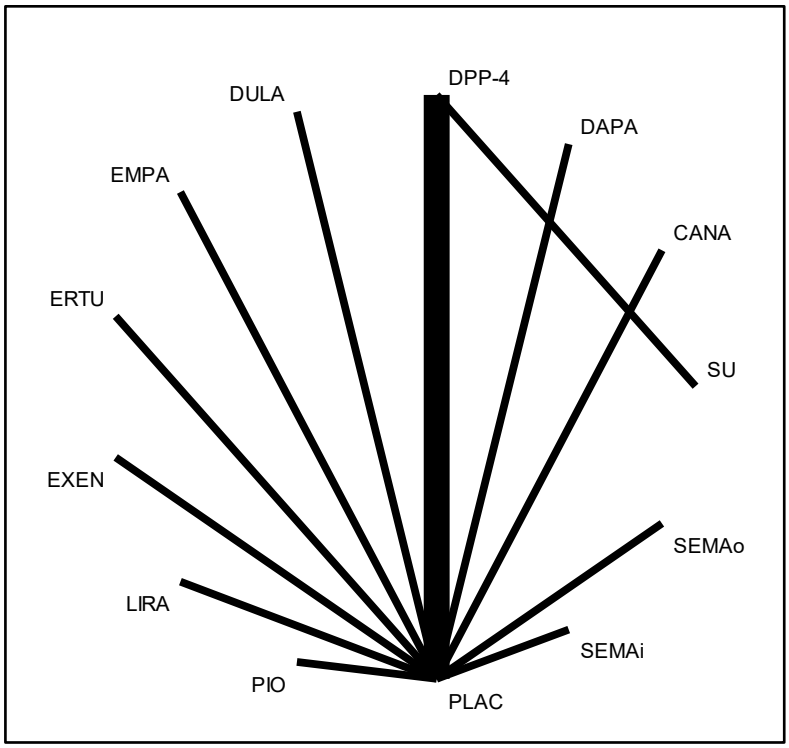
3-point MACE

The fixed effects model for 3-point MACE (major adverse cardiovascular events, comprising cardiovascular death, nonfatal MI and nonfatal stroke) generated a network diagram (See Figure 23). Data for this outcome was included from 14 RCTs. As specified by the committee, both the sulfonylureas and DPP-4 drugs were analysed at the class level, assuming the treatments within the class have the same effectiveness. Three trials included DPP-4 interventions, whilst the sulfonylurea class consisted of a single treatment (glimepiride). Other drugs were analysed at the individual level.

Abbreviations used in figures and tables: PLAC, Placebo; PIO, Pioglitazone; LIXI, Lixisenatide; LIRA, Liraglutide; EXEN, Exenatide; ERTU, Ertugliflozin; EMPA, Empagliflozin; DULA, Dulaglutide; DPP-4, Dipeptidyl peptidase-4 inhibitors; DAPA, Dapagliflozin; CANA, Canagliflozin; SU, Sulphonylurea; SEMAo, Oral semaglutide; SEMAi, Injected semaglutide.

Network diagram for 3-point MACE

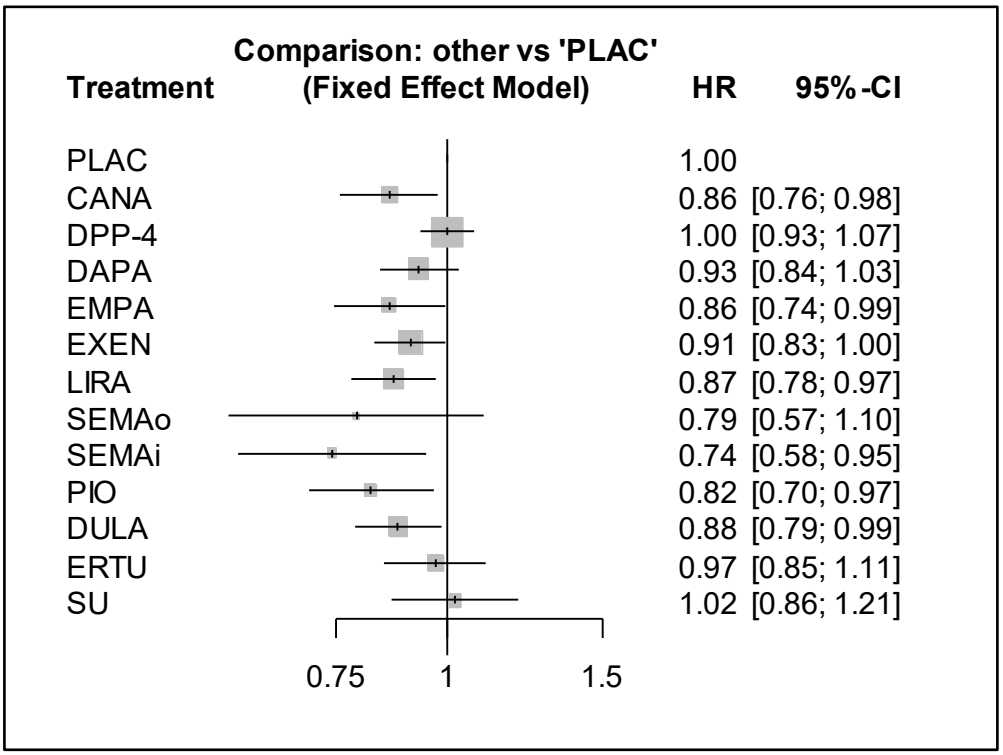
Figure 23 Network diagram for 3-point MACE[1]



[1] Line width is proportional to the number of trials comparing every pair of treatments

Caterpillar plot for 3-point MACE

Figure 24 Relative effectiveness of all options versus placebo. (Hazard ratios with 95% confidence intervals and line of no effect as the vertical line at 1).



Relative effectiveness chart for 3-point MACE

Table 43 Relative effectiveness of all pairwise combinations for 3-point MACE. Upper diagonal: hazard ratios (HR) with 95% confidence intervals from the pair-wise meta-analysis. HR less than 1 favour the row defining treatment. HRs greater than 1 favour the column defining treatment.) Lower diagonal: HR with 95% confidence intervals from the from the NMA results. HRs greater than 1 favour the row defining treatment, HRs less than 1 favour the column defining treatment. (Results highlighted red indicate statistically significant differences).

	CANA	DPP-4	DAPA	EMPA	EXEN	LIRA	SEMAo	SEMAi	PIO	DULA	ERTU	SU	Placebo
CANA													0.86 (0.76; 0.98)
DPP-4	0.86 (0.74; 0.99)											0.98 (0.84; 1.14)	1.00 (0.93; 1.07)
DAPA	0.92 (0.78; 1.09)	1.08 (0.95; 1.22)											0.93 (0.84; 1.03)
EMPA	1.00 (0.82; 1.21)	1.16 (0.99; 1.37)	1.08 (0.91; 1.29)										0.86 (0.74; 0.99)
EXEN	0.95 (0.81; 1.11)	1.10 (0.98; 1.24)	1.02 (0.89; 1.17)	0.95 (0.80; 1.12)									0.91 (0.83; 1.00)
LIRA	0.99 (0.84; 1.17)	1.15 (1.01; 1.31)	1.07 (0.92; 1.24)	0.99 (0.82; 1.19)	1.05 (0.91; 1.21)								0.87 (0.78; 0.97)
SEMAo	1.09 (0.76; 1.56)	1.27 (0.90; 1.78)	1.18 (0.83; 1.67)	1.09 (0.76; 1.57)	1.15 (0.81; 1.63)	1.10 (0.78; 1.56)							0.79 (0.57; 1.10)
SEMAi	1.16 (0.88; 1.53)	1.35 (1.05; 1.75)	1.26 (0.96; 1.64)	1.16 (0.87; 1.55)	1.23 (0.94; 1.60)	1.18 (0.90; 1.54)	1.07 (0.71; 1.62)						0.74 (0.58; 0.95)
PIO	1.05 (0.85; 1.29)	1.22 (1.02; 1.46)	1.13 (0.94; 1.37)	1.05 (0.84; 1.31)	1.11 (0.92; 1.34)	1.06 (0.87; 1.29)	0.96 (0.66; 1.40)	0.90 (0.67; 1.21)					0.82 (0.70; 0.97)
DULA	0.98 (0.82; 1.16)	1.14 (1.00; 1.30)	1.06 (0.91; 1.23)	0.98 (0.81; 1.17)	1.03 (0.89; 1.20)	0.99 (0.85; 1.16)	0.90 (0.63; 1.28)	0.84 (0.64; 1.10)	0.93 (0.76; 1.14)				0.88 (0.79; 0.99)
ERTU	0.89 (0.74; 1.07)	1.03 (0.89; 1.20)	0.96 (0.81; 1.13)	0.89 (0.73; 1.08)	0.94 (0.80; 1.10)	0.90 (0.75; 1.07)	0.81 (0.57; 1.17)	0.76 (0.58; 1.01)	0.85 (0.68; 1.04)	0.91 (0.76; 1.08)			0.97 (0.85; 1.11)
SU	0.84 (0.68; 1.04)	0.98 (0.84; 1.14)	0.91 (0.75; 1.11)	0.84 (0.67; 1.05)	0.89 (0.74; 1.08)	0.85 (0.70; 1.04)	0.77 (0.53; 1.12)	0.72 (0.54; 0.98)	0.80 (0.64; 1.01)	0.86 (0.70; 1.05)	0.95 (0.77; 1.18)		
PLAC	0.86 (0.76; 0.98)	1.00 (0.93; 1.07)	0.93 (0.84; 1.03)	0.86 (0.74; 0.99)	0.91 (0.83; 1.00)	0.87 (0.78; 0.97)	0.79 (0.57; 1.10)	0.74 (0.58; 0.95)	0.82 (0.70; 0.97)	0.88 (0.79; 0.99)	0.97 (0.85; 1.11)	1.02 (0.86; 1.21)	

Probability ranking for 3-point MACE

Table 44 Probability that each intervention is one of the best treatments. Higher probabilities indicate that the intervention would be ranked as more effective.

Treatment	P-score (fixed effects)
SEMAi	0.8898
PIO	0.7614
SEMAo	0.7470
CANA	0.6536
EMPA	0.6473
LIRA	0.6248
DULA	0.5873
EXEN	0.4764
DAPA	0.4013
ERTU	0.2691
DPP-4	0.1509
SU	0.1499
PLAC	0.1412

Appendix H - NMA summary tables

Table 45 Summary of NMA results showing where treatments are better than another treatment based on an MID.

The following outcomes use the default MIDs of 0.8, 1.25. The columns list the treatments, and the rows list the outcomes. Within each box, the treatments listed represent results where there was an improvement in that outcome (the text in **bold** represents situations where the 95% CI does not cross the line of no effect **and** the effect treatment point estimate meets or exceeds the MID; the text which is not bold represents situations where the 95% CI does not cross the line of no effect **and** the effect point estimate treatment is less than the MID). Results have been reversed where necessary to ensure that they are presented as improvements. Boxes with dashes represent cases where the NMA could not differentiate between treatments (the 95% CI crosses the line of no effect, and it is not completely within the MID) or in cases where the difference was not meaningful (the 95% CI is completely within the MID).

Abbreviations are as follows: PLAC, Placebo; PIO, Pioglitazone; LIXI, Lixisenatide; LIRA, Liraglutide; EXEN, Exenatide; ERTU, Ertugliflozin; EMPA, Empagliflozin; DULA, Dulaglutide; DPP-4, Dipeptidyl peptidase-4 inhibitors; DAPA, Dapagliflozin; CANA, Canagliflozin; SU, Sulphonylurea; SEMAo, Oral semaglutide; SEMAi, Injected semaglutide. N/A is used when the treatment was not represented in the NMA. See section 1.1.3 for more details on the interpretation of results.

TREATMENTS														
OUTCOME	**PLAC**	**CANA**	**DPP-4**	**DAPA**	**LIXI**	**EMPA**	**EXEN**	**LIRA**	**SEMAo**	**SEMAi**	**PIO**	**DULA**	**ERTU**	**SU**
IMPROVEMENTS COMPARED TO:														
All-cause mortality	-	**SU**	-	-	-	**SU DPP-4 PLAC CANA DAPA DULA ERTU EXEN LIXI**	**SU** DPP-4 PLAC	**SU** DPP-4 PLAC	**SU DPP-4 PLAC CANA DAPA DULA ERTU EXEN LIXI**	-	-	SU	-	-

TREATMENTS														
OUTCOME	**PLAC**	**CANA**	**DPP-4**	**DAPA**	**LIXI**	**EMPA**	**EXEN**	**LIRA**	**SEMAo**	**SEMAi**	**PIO**	**DULA**	**ERTU**	**SU**
						PIO SEMAi			**PIO SEMAi**					
Cardiovascular mortality	-	**-**	-	-	-	**SU DPP-4 PLAC CANA DAPA LIXI DULA ERTU EXEN PIO**	-	**DPP-4 PLAC**	**SU DPP-4 PLAC DAPA LIXI**	-	-	-	-	-
Any discontinuation	**SEMAo**	**SEMAo** LIXI	**SEMAo** SEMAi **LIXI**	**SEMAo SEMAi LIXI** CANA PIO	**SEMAo** SU	**SEMAo SEMAi LIXI** CANA PIO DULA EXEN SU **PLAC**	**SEMAo** SEMAi LIXI	N/A	-	**SEMAo**	**SEMAo**	**SEMAo** SEMAi LIXI	**SEMAo SEMAi LIXI** CANA PIO SU PLAC	**SEMAo** SEMAi LIXI
Discontinuation due to adverse events	**SEMAo SEMAi LIXI CANA** DAPA **LIRA**	**SEMAi**	**SEMAo SEMAi LIXI CANA DAPA LIRA PIO**	**SEMAo SEMAi LIXI**	**-**	**SEMAo SEMAi LIXI CANA DAPA LIRA PIO**	**SEMAo SEMAi LIXI CANA LIRA**	**SEMAo SEMAi**	-	-	**SEMAo SEMAi LIXI**	N/A	**SEMAo SEMAi LIXI CANA**	**SEMAo SEMAi LIXI CANA LIRA**

TREATMENTS														
OUTCOME	**PLAC**	**CANA**	**DPP-4**	**DAPA**	**LIXI**	**EMPA**	**EXEN**	**LIRA**	**SEMAo**	**SEMAi**	**PIO**	**DULA**	**ERTU**	**SU**
Hospitalisation for heart failure	**-**	**DPP-4 PLAC**	**-**	**DPP-4 PLAC**	**-**	**DPP-4 PLAC**	**-**	**-**	-	-	N/A	-	**DPP-4**	**-**
Hospitalisation for unstable angina	**-**	N/A	-	N/A	-	-	N/A	-	-	-	N/A	-	N/A	-
Nonfatal MI	**-**	**DPP-4**	-	N/A	N/A	-	-	**DPP-4**	-	-	-	-	-	-
Nonfatal stroke	**-**	-	-	N/A	N/A	-	-	-	-	**EMPA PLAC**	N/A	**EMPA PLAC**	-	-
Severe hypoglycaemia	**SU**	**SU**	**SU**	**SU PLAC DPP-4 PIO SEMAi SEMAo**	**SU PIO SEMAo**	**SU**	N/A	**SU PLAC DPP-4 PIO SEMAi SEMAo**	**SU**	**SU**	**SU**	**SU**	**SU DPP-4**	-
3-POINT mace	**-**	DPP-4 PLAC	**-**	**-**	N/A	PLAC	-	DPP-4 PLAC	**-**	**DPP-4 PLAC SU**	DPP-4 PLAC	PLAC	**-**	-

Appendix I – GRADE tables

Network meta-analysis

No. of studies	Study design	Sample size	Effect estimates	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
All-cause mortality								
16 studies	RCT	146,500	See appendix G	Not serious	Not serious	Not serious	Not serious	High
Cardiovascular mortality								
16 studies	RCT	146,500	See appendix G	Not serious	Not serious	Not serious	Not serious	High
Any discontinuation								
15 studies	RCT	134,523	See appendix G	Not serious	Not serious	Not serious	Not serious	High
Discontinuation due to adverse events								
13 studies	RCT	102,756	See appendix G	Not serious	Not serious	Not serious	Not serious	High
Hospitalisation for heart failure								
15 studies	RCT	141,262	See appendix G	Not serious	Not serious	Serious[1]	Not serious	Moderate
Hospitalisation for unstable angina								
11 studies	RCT	88,216	See appendix G	Not serious	Not serious	Not serious	Serious[2]	Moderate
Nonfatal myocardial infarction								
12 studies	RCT	92,257	See appendix G	Not serious	Not serious	Not serious	Not serious	High
Nonfatal stroke								
11 studies	RCT	87,019	See appendix G	Not serious	Not serious	Not serious	Not serious	High
Severe hypoglycaemia								
13 studies	RCT	109,061	See appendix G	Not serious	Not serious	Not serious	Not serious	High
3-point major adverse cardiovascular events (MACE) composite outcome								
14 studies	RCT	132,298	See appendix G	Not serious	Not serious	Not serious	Not serious	High
Sensitivity analyses								
Any discontinuation (using random effects model)								
15 studies	RCT	134,523	See appendix G	Not serious	Not serious	Not serious	Not serious	High

Severe hypoglycaemia (using random effects model)								
13 studies	RCT	109,061	See appendix G	Not serious	Not serious	Not serious	Not serious	High
Hospitalisation for heart failure (using fixed effects model and omitting the SAVOR-TIMI 53 [saxagliptin] study)								
14 studies	RCT	122,024	See appendix G	Not serious	Not serious	Not serious	Not serious	High

1. The network was downgraded one level as the I^2 was greater than 50%.
2. It was not possible to differentiate between any meaningfully distinct treatments options in the network (based on of the 95% confidence intervals for all the comparison crossing the line of no effect). The sample size was sufficiently large that difference could plausibly have been detected so this outcome was only downgraded once.

6

Pairwise meta-analysis

These tables only show the pairwise results for treatments that could not be included in the relevant NMA.

Dapagliflozin versus placebo

Table 46 GRADE table for Dapagliflozin versus placebo

No. of studies	Study design	Sample size	Effect size* (95% CI)	Absolute risk: control	Absolute risk intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Myocardial infarction (unclear if fatal or nonfatal) (HR<1 favour dapagliflozin)										
1 (Wiviott et al 2019)	RCT	17,160	HR 0.89 (0.78 to 1.02)	51 per 1000	45 per 1000 (40 to 52)	Not serious	Not serious	N/A	Serious[1]	Moderate
Ischaemic stroke (unclear if fatal or nonfatal) (HR<1 favour dapagliflozin)										
1 (Wiviott et al 2019)	RCT	17,160	HR 1.01 (0.84 to 1.21)	27 per 1000	27 per 1000 (23 to 33)	Not serious	Not serious	N/A	Not serious	High

1. Downgraded once for imprecision: the 95% confidence interval for the effect size crossed the lower MID line (0.80)

Saxagliptin versus placebo

Table 47 GRADE table for Saxagliptin versus placebo

No. of studies	Study design	Sample size	Effect size* (95% CI)	Absolute risk: control	Absolute risk intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Myocardial infarction (unclear if fatal or nonfatal) (HR<1 favours saxagliptin)										
1 (Scirica et al 2013)	RCT	16,492	HR 0.95	34 per 1000	32 per 1000 (27 to 38)	Not serious	Not serious	N/A	Serious[1]	Moderate

No. of studies	Study design	Sample size	Effect size* (95% CI)	Absolute risk: control	Absolute risk intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
			(0.80 to 1.12)							
Ischaemic stroke (unclear if fatal or nonfatal) (HR<1 favours saxagliptin)										
1 (Scirica et al 2013)	RCT	16,492	HR 1.11 (0.88 to 1.40)	17 per 1000	19 per 1000 (15 to 24)	Not serious	Not serious	N/A	Serious[2]	Moderate

1. Downgraded once for imprecision: the 95% confidence interval for the effect size crossed the lower MID line (0.80)
2. Downgraded once for imprecision: the 95% confidence interval for the effect size crossed the upper MID line (1.25)

1 Lixisenatide versus placebo

2 Table 48 GRADE table for Lixisenatide versus placebo

No. of studies	Study design	Sample size	Effect size* (95% CI)	Absolute risk: control	Absolute risk intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Myocardial infarction (fatal and nonfatal) (HR<1 favours lixisenatide)										
1 (Pfeffer et al 2013)	RCT	6,068	HR 1.03 (0.87 to 1.22)	86 per 1000	89 per 1000 (75 to 105)	Not serious	Not serious	N/A	Not serious	High
Stroke (fatal and nonfatal) (HR<1 favours lixisenatide)										
1 (Pfeffer et al 2013)	RCT	6,068	HR 1.12 (0.79 to 1.58)	20 per 1000	22 per 1000 (16 to 32)	Not serious	Not serious	N/A	Very serious[1]	Low

1. Downgraded twice for imprecision: the 95% confidence interval for the effect size crossed both sides of MID (0.8, 1.25)

DPP-4 versus placebo

Table 49 GRADE table for DPP-4 versus placebo

No. of studies	Study design	Sample size	Effect size* (95% CI)	Absolute risk: control	Absolute risk intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Sitagliptin										
Myocardial infarction (fatal and nonfatal) (HR<1 favours sitagliptin)										
1 (Green et al 2013)	RCT	14,671	HR 0.95 (0.81 to 1.11)	43 per 1000	41 per 1000 (35 to 48)	Not serious	Not serious	N/A	Not serious	High
Stroke (fatal and nonfatal) (HR<1 favours sitagliptin)										
1 (Green et al 2013)	RCT	14,671	HR 0.97 (0.79 to 1.19)	25 per 1000	24 per 1000 (20 to 30)	Not serious	Not serious	N/A	Serious[1]	Moderate
Sitagliptin and Alogliptin										
Severe hypoglycaemia (RR<1 favours DPP-4)										
2 (Green et al 2013; White et al 2013)	RCTs	19,903	RR 1.15 (0.92 to 1.44)	14 per 1000	16 per 1000 (13 to 20)	Not serious	Not serious	Not serious	Serious[1]	Moderate

1. Downgraded once for imprecision: the upper or lower bound of the 95% confidence interval for the effect size crossed the line of minimal important difference once (0.80 or 1.25)

Pioglitazone versus placebo

Table 50 GRADE table for Pioglitazone versus placebo

No. of studies	Study design	Sample size	Effect size* (95% CI)	Absolute risk: control	Absolute risk intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Stroke (not further defined) (HR<1 favours pioglitazone)										

No. of studies	Study design	Sample size	Effect size* (95% CI)	Absolute risk: control	Absolute risk intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
1 (Wilcox et al 2008)	RCT	5,238	HR 0.81 (0.61 to 1.07)	41 per 1000	33 per 1000 (25 to 44)	Not serious	Not serious	N/A	Serious[1]	Moderate
1. Downgraded once for imprecision: the 95% confidence interval for the effect size crossed the lower MID line (0.80)										

Exenatide versus placebo

Table 51 GRADE table for Exenatide versus placebo

No. of studies	Study design	Sample size	Effect size* (95% CI)	Absolute risk: control	Absolute risk intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Severe hypoglycaemia (RR<1 favours exenatide)										
1 (Holman et al 2017)	RCT	14,716	RR 1.13 (0.95 to 1.35)	30 per 1000	34 per 1000 (29 to 41)	Not serious	Not serious	N/A	Serious[1]	Moderate
1. Downgraded once for imprecision: the 95% confidence interval for the effect size crossed the upper MID line (1.25)										

Appendix J – Economic evidence study selection

Following the approach outlined in Section 1.1.7, no economic studies were identified that matched the criteria specified in the review.

Appendix K – Economic evidence tables

Following the approach outlined in Section 1.1.7, no economic studies were identified that matched the criteria specified in the review.

Appendix L – Health economic model

Details of the health economic model can be found in the separate health economic model report.

1 Appendix M– Excluded studies

M.1.121 Clincal

Study	Reason
Ahren, Bo, Johnson Susan, L, Stewart, Murray et al. (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. Diabetes care 37(8): 2141-8	Study does not contain a relevant intervention: *Albiglutide a GLP-1 agonist that is not available in the UK.*
Anholm, Christian, Kumarathurai, Preman, Pedersen Lene, R et al. (2017) Liraglutide effects on beta-cell, insulin sensitivity and glucose effectiveness in patients with stable coronary artery disease and newly diagnosed type 2 diabetes. Diabetes, obesity & metabolism 19(6): 850-857	Study did not meet the review protocol: *The intervention was not against mixed treatment background. The washout period in the crossover was not the 4-6 weeks detailed in the protocol. The outcomes were also not CVOT and no time to event data was presented.*
Berg David, D, Wiviott Stephen, D, Scirica Benjamin, M et al. (2019) Heart Failure Risk Stratification and Efficacy of Sodium-Glucose Cotransporter-2 Inhibitors in Patients With Type 2 Diabetes Mellitus. Circulation 140(19): 1569-1577	Secondary publication of an included study that does not provide any additional relevant information: *Not time-to-event CV outcome data.*
Bilal, Anika and Pratley Richard, E (2018) Cardiovascular Outcomes Trials Update: Insights from the DEVOTE Trial. Current diabetes reports 18(11): 102	Study does not contain a relevant intervention: *Insulin versus insulin.*
Brown A, J.M, Gandy, S, McCrimmon, R et al. (2020) A randomized controlled trial of dapagliflozin on left ventricular hypertrophy in people with type two diabetes: the DAPA-LVH trial. European heart journal 41(36): 3421-3432	Excluded on outcomes: *Outcomes not reported as time-to-event (HR/K-M curve). Primary outcome (Left ventricular mass - MRI assessed) and secondary outcomes not specified in protocol.*
Carbone, S, Billingsley H, E, Canada J, M et al. (2020) The effects of canagliflozin compared to sitagliptin on cardiorespiratory fitness in type 2 diabetes mellitus and heart failure with reduced ejection fraction: The CANA-HF study. Diabetes/Metabolism Research and Reviews 36(8): e3335	Duplicate reference (see below).
Carbone, S, Billingsley H, E, Canada J, M et al. (2020) The Effects of Canagliflozin compared to Sitagliptin on Cardiorespiratory Fitness in Type 2 Diabetes Mellitus and Heart Failure with Reduced Ejection Fraction: Results of the CANA-HF Study.	Excluded on outcome and follow-up period: *Not time-to-even data, and follow-up at 12 weeks.*

Study	Reason
Diabetes/metabolism research and reviews: e3335	
de Boer R, A, Nunez, J, Kozlovski, P et al. (2020) Effects of the dual sodium-glucose linked transporter inhibitor, licogliflozin vs placebo or empagliflozin in patients with type 2 diabetes and heart failure. British Journal of Clinical Pharmacology 86(7): 1346-1356	Excluded as not a relevant study design: *Inadequate length of study follow-up.*
Fuchigami, Ayako, Shigiyama, Fumika, Kitazawa, Toru et al. (2020) Efficacy of dapagliflozin versus sitagliptin on cardiometabolic risk factors in Japanese patients with type 2 diabetes: a prospective, randomized study (DIVERSITY-CVR). Cardiovascular diabetology 19(1): 1	Excluded on outcomes: *No time-to-event CV outcomes.*
Hiramatsu, Takeyuki, Asano, Yuko, Mabuchi, Masatsuna et al. (2018) Liraglutide relieves cardiac dilated function than DPP-4 inhibitors. European journal of clinical investigation 48(10): e13007	Excluded as not a relevant study design: *longitudinal observational study.*
Home P, D, Shamanna, P, Stewart, M et al. (2015) Efficacy and tolerability of albiglutide versus placebo or pioglitazone over 1 year in people with type 2 diabetes currently taking metformin and glimepiride: HARMONY 5. Diabetes, obesity & metabolism 17(2): 179-87	Excluded on intervention: *Albiglutide a GLP-1 agonist that is not available in the UK.*
Hong, Jie, Zhang, Yifei, Lai, Shenghan et al. (2013) Effects of metformin versus glipizide on cardiovascular outcomes in patients with type 2 diabetes and coronary artery disease. Diabetes care 36(5): 1304-11	Excluded as not a relevant study design: *The intervention was not against mixed treatment background.*
Hughes Alun, David, Park, Chloe, March, Katherine et al. (2013) A randomized placebo controlled double blind crossover study of pioglitazone on left ventricular diastolic function in type 2 diabetes. International journal of cardiology 167(4): 1329-32	Excluded as not a relevant study design: *Washout period for cross over was shorter than specified in the protocol, no time-to-event CV data.*
Husain, M, Bain S, C, Jeppesen O, K et al. (2020) Semaglutide (SUSTAIN and PIONEER) reduces cardiovascular events in type 2 diabetes across varying cardiovascular risk. Diabetes, Obesity and Metabolism 22(3): 442-451	Excluded as not a primary study: *Systematic review used as source of primary studies.*

Study	Reason
Iacobellis, Gianluca and Gra-Menendez, Silvia (2020) Effects of Dapagliflozin on Epicardial Fat Thickness in Patients with Type 2 Diabetes and Obesity. Obesity (Silver Spring, Md.) 28(6): 1068-1074	Excluded as outcome was not in scope: *Outcome (epicardial fat thickness) not in protocol.*
Ishikawa, Shinji, Shimano, Masayuki, Watarai, Masato et al. (2014) Impact of sitagliptin on carotid intima-media thickness in patients with coronary artery disease and impaired glucose tolerance or mild diabetes mellitus. The American journal of cardiology 114(3): 384-8	Excluded as outcome was not in scope: *Outcome (carotid intima thickness) not in protocol.*
Januzzi James L, Jr, Butler, Javed, Jarolim, Petr et al. (2017) Effects of Canagliflozin on Cardiovascular Biomarkers in Older Adults With Type 2 Diabetes. Journal of the American College of Cardiology 70(6): 704-712	Excluded as outcome was not in scope: *Outcome (cardiovascular biomarkers) not in protocol.*
Jensen, Jesper, Omar, Massar, Kistorp, Caroline et al. (2019) Empagliflozin in heart failure patients with reduced ejection fraction: a randomized clinical trial (Empire HF). Trials 20(1): 374	Excluded as not a relevant study design: *Trial protocol only.*
Jhund P, S, Solomon S, D, Docherty K, F et al. (2020) Efficacy of Dapagliflozin on Renal Function and Outcomes in Patients with Heart Failure with Reduced Ejection Fraction: Results of DAPA-HF. Circulation	Excluded as does not contain a population of people with T2D: *Population with T2D <85% specified in the protocol.*
Kaku, Kohei, Daida, Hiroyuki, Kashiwagi, Atsunori et al. (2009) Long-term effects of pioglitazone in Japanese patients with type 2 diabetes without a recent history of macrovascular morbidity. Current medical research and opinion 25(12): 2925-32	Excluded as the comparator in study does not match that specified in protocol: *No active control arm.*
Kosiborod, Mikhail, Gause-Nilsson, Ingrid, Xu, John et al. (2017) Efficacy and safety of dapagliflozin in patients with type 2 diabetes and concomitant heart failure. Journal of diabetes and its complications 31(7): 1215-1221	Excluded as not a primary study: *Systematic review used as source of primary studies.*
Kumarathurai, Preman, Anholm, Christian, Fabricius-Bjerre, Andreas et al. (2017) Effects of the glucagon-like peptide-1 receptor agonist liraglutide on 24-h ambulatory blood pressure in patients with type 2 diabetes and stable coronary artery disease: a randomized, double-blind,	Excluded as outcome was not in scope: *Outcome (ambulatory blood pressure) not in protocol.*

Study	Reason
placebo-controlled, crossover study. Journal of hypertension 35(5): 1070-1078	
Kumarathurai, Preman, Anholm, Christian, Nielsen Olav, W et al. (2016) Effects of the glucagon-like peptide-1 receptor agonist liraglutide on systolic function in patients with coronary artery disease and type 2 diabetes: a randomized double-blind placebo-controlled crossover study. Cardiovascular diabetology 15(1): 105	Excluded as outcome was not in scope: *Outcome (systolic function) not in protocol.*
Li, B, Luo Y, R, Tian, F et al. (2020) Sitagliptin attenuates the progression of coronary atherosclerosis in patients with coronary disease and type 2 diabetes. Atherosclerosis 300: 10-18	Exclude as comparator in study does not match that specified in protocol: *Control is Acarbose (excluded as intervention / comparator in protocol)*
Lincoff, A Michael, Wolski, Kathy, Nicholls, Stephen J et al. (2007) Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials. JAMA 298(10): 1180-8	Excluded as not a primary study: *Systematic review used as source of primary studies.*
Maruhashi, Tatsuya, Higashi, Yukihito, Kihara, Yasuki et al. (2016) Long-term effect of sitagliptin on endothelial function in type 2 diabetes: a sub-analysis of the PROLOGUE study. Cardiovascular diabetology 15(1): 134	Excluded as outcome was not in scope: *Outcome (HbA1c) not in protocol.*
McMurray John J, V, Ponikowski, Piotr, Bolli Geremia, B et al. (2018) Effects of Vildagliptin on Ventricular Function in Patients With Type 2 Diabetes Mellitus and Heart Failure: A Randomized Placebo-Controlled Trial. JACC. Heart failure 6(1): 8-17	Excluded as not a relevant study design: *Inadequate length of follow-up.*
McMurray John J, V, Solomon Scott, D, Inzucchi Silvio, E et al. (2019) Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. The New England journal of medicine 381(21): 1995-2008	Excluded as does not contain a population of people with T2D: *Rate of people with T2D <85% specified in the protocol.*
Nassif M, E, Windsor, S, Tang, F et al. (2019) Dapagliflozin effects on biomarkers, symptoms, and functional status in patients with heart failure with reduced ejection fraction. Circulation 140(18): 042929	Excluded as duplicate reference (see below).
Nassif Michael, E, Windsor Sheryl, L, Tang, Fengming et al. (2019) Dapagliflozin Effects on Biomarkers, Symptoms, and Functional	Excluded on outcome and study population: *Main paper for define-HF, follow-up was 12 weeks, no hazard ratio for main outcome*

Study	Reason
Status in Patients With Heart Failure With Reduced Ejection Fraction: The DEFINE-HF Trial. Circulation 140(18): 1463-1476	*and odds ratio presented for subgroups of T2D versus no T2D. Population with T2d <65% of sample less than the 85% specified in the protocol.*
Nauck Michael, A, Stewart Murray, W, Perkins, Christopher et al. (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 patients with type 2 diabetes mellitus inadequately controlled with diet and exercise. Diabetologia 59(2): 266-74	Study does not contain a relevant intervention: *Albiglutide a GLP-1 agonist that is not available in the UK.*
Nicholls Stephen, J, Tuzcu E, Murat, Wolski, Kathy et al. (2011) Lowering the triglyceride/high-density lipoprotein cholesterol ratio is associated with the beneficial impact of pioglitazone on progression of coronary atherosclerosis in diabetic patients: insights from the PERISCOPE (Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation) study. Journal of the American College of Cardiology 57(2): 153-9	Excluded on outcomes: *Study does not include survival analysis (time-to-event, hazard ratio) as specified in the protocol.*
Nissen Steven, E, Nicholls Stephen, J, Wolski, Kathy et al. (2008) Comparison of pioglitazone vs glimepiride on progression of coronary atherosclerosis in patients with type 2 diabetes: the PERISCOPE randomized controlled trial. JAMA 299(13): 1561-73	Excluded on outcomes: *Study does not include survival analysis (time-to-event, hazard ratio) as specified in the protocol.*
Nitta, Yoshikazu, Tahara, Nobuhiro, Tahara, Atsuko et al. (2013) Pioglitazone decreases coronary artery inflammation in impaired glucose tolerance and diabetes mellitus: evaluation by FDG-PET/CT imaging. JACC. Cardiovascular imaging 6(11): 1172-82	Excluded as outcome data not reported in an extractable format: *Mixed impaired glucose tolerance and T2D data, results not stratified.*
Njerve Ida, Unhammer, Akra, Sissel, Weiss Thomas, W et al. (2017) A Double-Blinded Randomized Study Investigating a Possible Anti-Inflammatory Effect of Saxagliptin versus Placebo as Add-On Therapy in Patients with Both Type 2 Diabetes And Stable Coronary Artery Disease. Mediators of inflammation 2017: 5380638	Excluded on outcomes: *Study does not include survival analysis (HbA1c as main outcome in study) as specified in the protocol.*

Study	Reason
Nystrom, T, Santos I, P, Hedberg, F et al. (2017) Effects on subclinical heart failure in type 2 diabetic subjects on liraglutide treatment vs. Glimepiride both in combination with metformin: A randomized open parallel-group study. Frontiers in Endocrinology 8(nov): 325	Excluded on outcomes: *Study does not include survival analysis (systolic and diastolic velocities as outcome in study) as specified in the protocol.*
Ogasawara, Daisuke, Shite, Junya, Shinke, Toshiro et al. (2009) Pioglitazone reduces the necrotic-core component in coronary plaque in association with enhanced plasma adiponectin in patients with type 2 diabetes mellitus. Circulation journal: official journal of the Japanese Circulation Society 73(2): 343-51	Excluded as comparator in study does not match that specified in protocol: *No active control arm.*
Ostlund, Papadogeorgos, N, Kuhl, J et al. (2020) Effects of exenatide on microvascular reactivity in patients with type 2 diabetes and coronary artery disease, a randomized controlled study. Microcirculation (New York, N.Y.: 1994): e12670	Excluded as comparator in study does not match that specified in protocol: *No active control arm.*
Packer, Milton, Anker Stefan, D, Butler, Javed et al. (2020) Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. The New England journal of medicine 383(15): 1413-1424	Excluded as does not contain a population of people with T2D: *Population with T2D <85% specified in the protocol.*
Petrie Mark, C, Verma, Subodh, Docherty Kieran, F et al. (2020) Effect of Dapagliflozin on Worsening Heart Failure and Cardiovascular Death in Patients With Heart Failure With and Without Diabetes. JAMA 323(14): 1353-1368	Excluded as does not contain a population of people with T2D: *Population with T2D <85% specified in the protocol.*
Phrommintikul, Arintaya, Wongcharoen, Wanwarang, Kumfu, Sirinart et al. (2019) Effects of dapagliflozin vs vildagliptin on cardiometabolic parameters in diabetic patients with coronary artery disease: a randomised study. British journal of clinical pharmacology 85(6): 1337-1347	Excluded on outcomes: *Study does not include survival analysis (HbA1c as main outcome in study) as specified in the protocol.*
Preiss, David, Lloyd Suzanne, M, Ford, Ian et al. (2014) Metformin for non-diabetic patients with coronary heart disease (the CAMERA study): a randomised controlled trial. The lancet. Diabetes & endocrinology 2(2): 116-24	Excluded as does not contain a population of people with T2D: *Population with T2D <85% specified in the protocol.*

Study	Reason
Reusch, J, Stewart M, W, Perkins C, M et al. (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. Diabetes, obesity & metabolism 16(12): 1257-64	Study does not contain a relevant intervention: *Albiglutide a GLP-1 agonist that is not available in the UK.*
Sacre, J.W.; Magliano, D.J.; Shaw, J.E. (2020) Incidence of Hospitalization for Heart Failure Relative to Major Atherosclerotic Events in Type 2 Diabetes: A Meta-analysis of Cardiovascular Outcomes Trials. Diabetes care 43(10): 2614-2623	Excluded as not a primary study: *Systematic review used as source of primary studies.*
Shimizu, W, Kubota, Y, Hoshika, Y et al. (2020) Effects of empagliflozin versus placebo on cardiac sympathetic activity in acute myocardial infarction patients with type 2 diabetes mellitus: The EMBODY trial. Cardiovascular Diabetology 19(1): 148	Excluded on outcomes: *Study does not include survival analysis (standard deviation of all 5-min mean normal RR intervals as outcome) as specified in the protocol.*
Singh Jagdeep S, S, Mordi Ify, R, Vickneson, Keeran et al. (2020) Dapagliflozin Versus Placebo on Left Ventricular Remodeling in Patients With Diabetes and Heart Failure: The REFORM Trial. Diabetes care 43(6): 1356-1359	Excluded as not a relevant study design: *Inadequate length of follow-up.*
Spinar, J; Spinarova, L; Vitovec, J (2015) The TECOS study - The effect of sitagliptin on cardiovascular events in patients with type 2 diabetes mellitus. Kardiologicka revue 17(3): 257-261	Study not reported in English language.
Tanaka, A, Hisauchi, I, Taguchi, I et al. (2020) Effects of canagliflozin in patients with type 2 diabetes and chronic heart failure: a randomized trial (CANDLE). ESC Heart Failure 7(4): 1585-1594	Excluded as not a relevant study design: *Inadequate length of follow-up.*
Tanaka, Atsushi, Komukai, Sho, Shibata, Yoshisato et al. (2018) Effect of pioglitazone on cardiometabolic profiles and safety in patients with type 2 diabetes undergoing percutaneous coronary artery intervention: a prospective, multicenter, randomized trial. Heart and vessels 33(9): 965-977	Excluded as not a relevant study design and outcomes: *Not CV outcomes trial design, no relevant CV outcomes.*

Study	Reason
Tanaka, Atsushi, Shimabukuro, Michio, Okada, Yosuke et al. (2017) Rationale and design of a multicenter placebo-controlled double-blind randomized trial to evaluate the effect of empagliflozin on endothelial function: the EMBLEM trial. Cardiovascular diabetology 16(1): 48	Excluded as not a relevant study design: *Trial protocol only.*
Verma, Subodh, Mazer C, David, Yan Andrew, T et al. (2019) Effect of Empagliflozin on Left Ventricular Mass in Patients With Type 2 Diabetes Mellitus and Coronary Artery Disease: The EMPA-HEART CardioLink-6 Randomized Clinical Trial. Circulation 140(21): 1693-1702	Excluded as not a relevant study design: *Inadequate length of follow-up.*
Webb D, R, Htike Z, Z, Swarbrick D, J et al. (2020) A randomized, open-label, active comparator trial assessing the effects of 26 weeks of liraglutide or sitagliptin on cardiovascular function in young obese adults with type 2 diabetes. Diabetes, Obesity and Metabolism 22(7): 1187-1196	Excluded as not a relevant study design: *Inadequate length of follow-up.*
Yoshihara, Fumiki, Imazu, Miki, Hamasaki, Toshimitsu et al. (2018) An Exploratory Study of Dapagliflozin for the Attenuation of Albuminuria in Patients with Heart Failure and Type 2 Diabetes Mellitus (DAPPER). Cardiovascular drugs and therapy 32(2): 183-190	Excluded as comparator in study does not match that specified in protocol: *No active control arm.*
You S, H, Kim B, S, Hong S, J et al. (2010) The effects of pioglitazone in reducing atherosclerosis progression and neointima volume in type 2 diabetic patients: Prospective randomized study with volumetric intravascular ultrasonography analysis. Korean Circulation Journal 40(12): 625-631	Excluded on outcomes: *Study does not include survival analysis (atherosclerosis and neointima volume as outcome) as specified in the protocol.*
Younis, A, Eskenazi, D, Goldkorn, R et al. (2017) The addition of vildagliptin to metformin prevents the elevation of interleukin 1? in patients with type 2 diabetes and coronary artery disease: a prospective, randomized, open-label study. Cardiovascular diabetology 16(1): 69	Excluded as comparator in study does not match that specified in protocol: *No active control arm.*
Zainordin N, A, Hatta S, F.W.M, Shah F, Z.M et al. (2020) Effects of dapagliflozin on endothelial dysfunction in type 2 diabetes with established ischemic heart disease	Excluded on outcomes: *Study does not include survival analysis (endothelial dysfunction as outcome) as specified in the protocol.*

Study	Reason
(EDIFIED). Journal of the Endocrine Society 4(1): bvz017	
Zannad, Faiez, Ferreira, Joao Pedro, Pocock, Stuart J et al. (2020) SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials. Lancet (London, England) 396(10254): 819-829	Excluded as not a primary study: *Systematic review used as source of primary studies.*
Zhang, Yifei, Hu, Chunxiu, Hong, Jie et al. (2014) Lipid profiling reveals different therapeutic effects of metformin and glipizide in patients with type 2 diabetes and coronary artery disease. Diabetes care 37(10): 2804-12	Excluded on outcomes: *Study does not include survival analysis (lipid profiling as outcome) as specified in the protocol.*
Zhou, Zien, Lindley Richard, I, Radholm, Karin et al. (2019) Canagliflozin and Stroke in Type 2 Diabetes Mellitus. Stroke 50(2): 396-404	Duplicate reference.

M.1.112 Health economics

References of studies excluded after scanning by full text	Reason
Pollock, Richard F; Valentine, William J; Marso, Steven P; Andersen, Andreas; Gundgaard, Jens; Hallen, Nino; Tutkunkardas, Deniz; Magnuson, Elizabeth A; Buse, John B; DEVOTE study, group. Long-term Cost-effectiveness of Insulin Degludec Versus Insulin Glargine U100 in the UK: Evidence from the Basal-bolus Subgroup of the DEVOTE Trial (DEVOTE 16). Applied health economics and health policy 615-627 doi:10.1007/s40258-019-00494-3	Insulin
Kansal, A; Reifsnider, O S; Proskorovsky, I; Zheng, Y; Pfarr, E; George, J T; Kandaswamy, P; Ruffolo, A. Cost-effectiveness analysis of empagliflozin treatment in people with Type 2 diabetes and established cardiovascular disease in the EMPA-REG OUTCOME trial. Diabetic medicine : a journal of the British Diabetic Association 1494-1502 doi:10.1111/dme.14076	Trial specific CUA, pairwise comparison
McEwan, Phil; Darlington, Oliver; McMurray, John J V; Jhund, Pardeep S; Docherty, Kieran F; Bohm, Michael; Petrie, Mark C; Bergenheim, Klas; Qin, Lei. Cost-effectiveness of dapagliflozin as a treatment for heart failure with reduced ejection fraction: a multinational health-economic analysis of DAPA-HF. European journal of heart failure doi:10.1002/ejhf.1978	Trial specific CUA, pairwise comparison
Ramos, M.; Foos, V.; Ustyugova, A.; Hau, N.; Gandhi, P.; Lamotte, M.. Cost-Effectiveness Analysis of Empagliflozin in Comparison to Sitagliptin and Saxagliptin Based on Cardiovascular Outcome Trials in Patients with Type 2 Diabetes and Established Cardiovascular Disease Diabetes Therapy 2153-2167 doi:10.1007/s13300-019-00701-3	Pairwise comparison only (between two classes)

References of studies excluded after scanning by full text	Reason
Pollock, R.F.; Valentine, W.J.; Marso, S.P.; Gundgaard, J.; Hallen, N.; Hansen, L.L.; Tutkunkardas, D.; Buse, J.B.. DEVOTE 5: Evaluating the Short-Term Cost-Utility of Insulin Degludec Versus Insulin Glargine U100 in Basal-Bolus Regimens for Type 2 Diabetes in the UK Diabetes Therapy 1217-1232 doi:10.1007/s13300-018-0430-4	Insulin
Ramos, M.; Ustyugova, A.; Hau, N.; Lamotte, M.. Cost-effectiveness of empagliflozin compared with liraglutide based on cardiovascular outcome trials in Type II diabetes Journal of Comparative Effectiveness Research 781-794 doi:10.2217/cer-2020-0071	Pairwise comparison
Johansen, P.; Chubb, B.; Hunt, B.; Malkin, S.J.P.; Sandberg, A.; Capehorn, M.. Evaluating the Long-Term Cost-Effectiveness of Once-Weekly Semaglutide Versus Once-Daily Liraglutide for the Treatment of Type 2 Diabetes in the UK Advances in Therapy 2427-2441 doi:10.1007/s12325-020-01337-7	Pairwise comparison, surrogate biomarkrs only
McEwan, P.; Bennett, H.; Khunti, K.; Wilding, J.; Edmonds, C.; Thuresson, M.; Wittbrodt, E.; Fenici, P.; Kosiborod, M.. Assessing the cost-effectiveness of sodium-glucose cotransporter-2 inhibitors in type 2 diabetes mellitus: A comprehensive economic evaluation using clinical trial and real-world evidence Diabetes, Obesity and Metabolism 2364-2374 doi:10.1111/dom.14162	Single class (SGLT2) only
Reifsnider, O.S.; Kansal, A.R.; Franke, J.; Lee, J.; George, J.T.; Brueckmann, M.; Kaspers, S.; Brand, S.B.; Ustyugova, A.; Linden, S.; Stargardter, M.; Hau, N.. Cost-effectiveness of empagliflozin in the UK in an EMPA-REG OUTCOME subgroup with type 2 diabetes and heart failure ESC Heart Failure doi:10.1002/ehf2.12985	Trial specific CUA, pairwise comparison only
Shyangdan, D.; Cummins, E.; Royle, P.; Waugh, N.. Liraglutide for the treatment of type 2 diabetes Health technology assessment (Winchester, England) 77-86 doi:	ERG summary document
Vega-Hernandez, G.; Wojcik, R.; Schlueter, M.. Cost-Effectiveness of Liraglutide Versus Dapagliflozin for the Treatment of Patients with Type 2 Diabetes Mellitus in the UK Diabetes Therapy 513-530 doi:10.1007/s13300-017-0250-y	Pairwise comparison, surrogate biomarkers only
Viljoen, Adie; Hoxer, Christina S; Johansen, Pierre; Malkin, Samuel; Hunt, Barnaby; Bain, Stephen C. Evaluation of the long-term cost-effectiveness of once-weekly semaglutide versus dulaglutide for treatment of type 2 diabetes mellitus in the UK. Diabetes, obesity & metabolism 611-621 doi:10.1111/dom.13564	Pairwise comparison, surrogate biomarkers only
Gordon, Jason; McEwan, Phil; Evans, Marc; Puelles, Jorge; Sinclair, Alan. Managing glycaemia in older people with type 2 diabetes: A retrospective, primary care-based cohort study, with economic assessment of patient outcomes. Diabetes, obesity & metabolism 644-653 doi:10.1111/dom.12867	Trial specific CUA, surrogate biomarkers
Barnett, Anthony H; Arnoldini, Simon; Hunt, Barnaby; Subramanian, Gowri; Hoxer, Christina Stentoft. Switching from sitagliptin to liraglutide to manage patients with type 2 diabetes in the UK: A long-term cost-effectiveness analysis. Diabetes, obesity & metabolism 1921-1927 doi:10.1111/dom.13318	Pairwise comparison, surrogate biomarkers only

References of studies excluded after scanning by full text	Reason
Hunt, Barnaby; Vega-Hernandez, Gabriela; Valentine, William J; Kragh, Nana. Evaluation of the long-term cost-effectiveness of liraglutide vs lixisenatide for treatment of type 2 diabetes mellitus in the UK setting. Diabetes, obesity & metabolism 842-849 doi:10.1111/dom.12890	Pairwise comparison, surrogate biomarkers only
Charokopou, M; McEwan, P; Lister, S; Callan, L; Bergenheim, K; Tolley, K; Postema, R; Townsend, R; Roudaut, M. The cost-effectiveness of dapagliflozin versus sulfonylurea as an add-on to metformin in the treatment of Type 2 diabetes mellitus. Diabetic medicine : a journal of the British Diabetic Association 890-8 doi:10.1111/dme.12772	Pairwise comparison, surrogate biomarkers only
Chuang, L H; Verheggen, B G; Charokopou, M; Gibson, D; Grandy, S; Kartman, B. 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 NHS perspective. Journal of medical economics 1127-1134 doi:	Pairwise comparison, surrogate biomarkers only
Charokopou, M; McEwan, P; Lister, S; Callan, L; Bergenheim, K; Tolley, K; Postema, R; Townsend, R; Roudaut, M. 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 services research 496 doi:10.1186/s12913-015-1139-y	Pairwise comparison, surrogate biomarkers only
Aguiar-Ibanez, R; Palencia, R; Kandaswamy, P; Li, L. Cost-Effectiveness of Empagliflozin (Jardiance R) 10 Mg And 25 Mg Administered As An Add-on To Metformin Compared To Other Sodium-Glucose Co-Transporter 2 Inhibitors (Sglt2is) for Patients With Type 2 Diabetes Mellitus (T2dm) In The UK. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research a350-1 doi:10.1016/j.jval.2014.08.729	Single class, surrogate bimarkers only
Gordon, J.; McEwan, P.; Hurst, M.; Puelles, J.. The Cost-Effectiveness of Alogliptin Versus Sulfonylurea as Add-on Therapy to Metformin in Patients with Uncontrolled Type 2 Diabetes Mellitus Diabetes Therapy 825-845 doi:10.1007/s13300-016-0206-7	Single class, surrogate biomarkers only
Ramos, M.; Cummings, M.H.; Ustyugova, A.; Raza, S.I.; de Silva, S.U.; Lamotte, M.. Long-Term Cost-Effectiveness Analyses of Empagliflozin Versus Oral Semaglutide, in Addition to Metformin, for the Treatment of Type 2 Diabetes in the UK Diabetes Therapy 2041-2055 doi:10.1007/s13300-020-00883-1	Pairwise comparison, surrogate biomarkers only
Bain, S.C.; Hansen, B.B.; Malkin, S.J.P.; Nuhoho, S.; Valentine, W.J.; Chubb, B.; Hunt, B.; Capehorn, M.. Oral Semaglutide Versus Empagliflozin, Sitagliptin and Liraglutide in the UK: Long-Term Cost-Effectiveness Analyses Based on the PIONEER Clinical Trial Programme Diabetes Therapy 259-277 doi:10.1007/s13300-019-00736-6	surrogate biomarkers only
Evans, M.; Mcewan, P.; O'Shea, R.; George, L.. A retrospective, case-note survey of type 2 diabetes patients prescribed incretin-based therapies in clinical practice Diabetes Therapy 27-40 doi:10.1007/s13300-012-0015-6	Single class, surrogate biomarkers only
Evans, M.; Mehta, R.; Gundgaard, J.; Chubb, B.. Cost-Effectiveness of Insulin Degludec vs. Insulin Glargine U100 in Type 1 and Type 2 Diabetes Mellitus in a UK Setting	Insulin, short-term time horison

References of studies excluded after scanning by full text	Reason
Diabetes Therapy 1919-1930 doi:10.1007/s13300-018-0478-1	
Drummond, Russell; Malkin, Samuel; Du Preez, Michelle; Lee, Xin Ying; Hunt, Barnaby. The management of type 2 diabetes with fixed-ratio combination insulin degludec/liraglutide (IDegLira) versus basal-bolus therapy (insulin glargine U100 plus insulin aspart): A short-term cost-effectiveness analysis in the UK setting. Diabetes, obesity & metabolism 2371-2378 doi:10.1111/dom.13375	Insulin, short-term time horison
Davies, Melanie J; Glah, Divina; Chubb, Barrie; Konidaris, Gerasimos; McEwan, Phil. 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 953-66 doi:10.1007/s40273-016-0433-9	Insulin, surrogate biomarkers only
Evans, M; Wolden, M; Gundgaard, J; Chubb, B; Christensen, T. Cost-effectiveness of insulin degludec compared with insulin glargine for patients with type 2 diabetes treated with basal insulin - from the UK health care cost perspective. Diabetes, obesity & metabolism 366-75 doi:10.1111/dom.12250	Insulin, short-term time horison
Pollock, R.F.; Chubb, B.; Valentine, W.J.; Heller, S.. Evaluating the cost-effectiveness of insulin detemir versus neutral protamine hagedorn insulin in patients with type 1 or type 2 diabetes in the UK using a short-term modeling approach Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy 217-226 doi:10.2147/dmso.s156739	Insulin, short-term time horison
Johnston, Rhona; Uthman, Olalekan; Cummins, Ewen; Clar, Christine; Royle, Pamela; Colquitt, Jill; Tan, Bee Kang; Clegg, Andrew; Shantikumar, Saran; Court, Rachel; O'Hare, J Paul; McGrane, David; Holt, Tim; Waugh, Norman. Canagliflozin, dapagliflozin and empagliflozin monotherapy for treating type 2 diabetes: systematic review and economic evaluation. Health technology assessment (Winchester, England) 1-218 doi:10.3310/hta21020	Systematic review
Schwarz, B.; Gouveia, M.; Chen, J.; Nocea, G.; Jameson, K.; Cook, J.; Krishnarajah, G.; Alemao, E.; Yin, D.; Sintonen, H.. Cost-effectiveness of sitagliptin-based treatment regimens in European patients with type 2 diabetes and haemoglobin A1c above target on metformin monotherapy Diabetes, Obesity and Metabolism 43-55 doi:10.1111/j.1463-1326.2008.00886.x	Rosiglitazone not modelled
Pawaskar, Manjiri; Bilir, S Pinar; Kowal, Stacey; Gonzalez, Claudio; Rajpathak, Swapnil; Davies, Glenn. Cost-effectiveness of intensification with sodium-glucose co-transporter-2 inhibitors in patients with type 2 diabetes on metformin and sitagliptin vs direct intensification with insulin in the United Kingdom. Diabetes, obesity & metabolism 1010-1017 doi:10.1111/dom.13618	Single class, surrogate biomarkers only
Aguiar-Ibanez, R; Palencia, R; Kandaswamy, P; Li, L. Cost-Effectiveness of Empagliflozin (Jardiance R) 10 Mg And 25 Mg Administered As An Add-On To Metformin And Sulfonilurea (Met+Su) Compared To Other Sodium-Glucose Co-Transporter 2 Inhibitors (Sglt2is) in Patients with Type 2 Diabetes Mellitus (T2dm) In The Uk. Value in health : the journal of the International Society for Pharmacoeconomics	Single class, surrogate biomarkers only

References of studies excluded after scanning by full text	Reason
and Outcomes Research a351 doi:10.1016/j.jval.2014.08.732	
Hunt, B.; Ye, Q.; Valentine, W.J.; Ashley, D.. Evaluating the Long-Term Cost-Effectiveness of Daily Administered GLP-1 Receptor Agonists for the Treatment of Type 2 Diabetes in the United Kingdom Diabetes Therapy 129-147 doi:10.1007/s13300-016-0219-2	Single class, surrogate biomarkers only

1
2

Appendix N – NMA code

General code

```
setwd
library("netmeta")
data=read.csv("",header=TRUE)
```

Hazard ratio model code

```
sm="HR"
reference.group="PLAC"
model= netmeta(LogHR, SElogHR, Intervention1, Intervention2, Trial, data = data, sm =
"HR",        n1 = n1, n2 = n2, comb.random=FALSE
model2= netmeta(LogHR, SElogHR, Intervention1, Intervention2, Trial, data = data, sm =
"HR", n1 = n1, n2 = n2, comb.random=FALSE,reference.group=reference.group )
sortvar=c("PLAC","CANA","DPP-4" ,"DAPA" ,"LIXI", "EMPA","EXEN","LIRA", "SEMAo",
"SEMAi", "PIO","DULA","ERTU","SU")
forest(model2,sortvar=sortvar)
seq=c("CANA","DPP-4","DAPA","LIXI","EMPA","EXEN","LIRA","SEMAo", "SEMAi",
"PIO","DULA","ERTU","SU", "PLAC")
netleague <- netleague(model, seq=seq,bracket = "(", digits=2)
write.csv(netleague$fixed, "netleague.csv")
netgraph(model, plastic=FALSE,thickness="number.of.studies",multiarm=FALSE,col="black")
netrank(model,small.values="good")
netsplit(model)
decomp.design(model)
netheat(model)
```

Risk ratio (n/N data analysis) code

```
sm="RR"
reference.group="PLAC"
data2=pairwise(list(Intervention1,Intervention2),n=list(n1,n2),event=list(event1,event2),data=
data,studlab=Trial,sm=sm)
model=netmeta(TE=TE,seTE=seTE,treat1=treat1,treat2=treat2,studlab=data2$studlab,data=
data2,sm=sm,comb.random=FALSE)
```

```
model2=netmeta(TE=TE,seTE=seTE,treat1=treat1,treat2=treat2,studlab=data2$studlab,data
=data2,sm=sm,comb.random=FALSE,reference.group=reference.group)

sortvar=c("PLAC","CANA","DPP-4" ,"DAPA" ,"LIXI", "EMPA","EXEN","LIRA", "SEMAo",
"SEMAi", "PIO","DULA","ERTU","SU ")

forest(model2,sortvar=sortvar)

netleague <- netleague(model, bracket = "(", digits=2)

write.csv(netleague$fixed, "netleague.csv")

netgraph(model, plastic=FALSE,thickness="number.of.studies",multiarm=FALSE,col="black")

netrank(model,small.values="good")

netsplit(model)

decomp.design(model)

netheat(model)
```

Appendix O – Research recommendations – full details

O.1 Research recommendation

What is the effectiveness and cost effectiveness of GLP-1 agonists compared to insulin in adults with type 2 diabetes?

O.2 Why this is important

GLP-1 agonists were not cost effective in the economic model as potential third- and fourth-line treatments for any populations analysed. However, in current practice these drugs are often used in combination with other drugs in place of insulins. Adults with type 2 diabetes may wish to have the GLP-1 drugs for reasons such as weekly rather than daily injections, insulins require blood glucose monitoring, GLP-1s are associated with weight loss and insulin with weight gain, restrictions on activities of daily living with insulin such as driving. It is noted that the GLP-1 drugs have high acquisition cost and common side effects which may lead to frequent discontinuation of use.

The evidence for the cost effectiveness of GLP-1 agonists compared to insulin was not examined in the current update. However, a review on this topic could clarify the place in practice of both insulin and GLP-1s.

O.3 Rationale for research recommendation

Importance to 'patients' or the population	In practice people with type 2 diabetes may perceive benefit (quality of life and CV mortality) from GLP-1 therapy which is not captured or demonstrated by current research evidence.
Relevance to NICE guidance	High - GLP-1 agonist use has been considered both as part of the NG28 [2015 update] and as part of the NG28 [2021 cardiovascular outcomes update]. There is lack of direct comparative evidence with the most appropriate comparator (insulin). The research is essential to inform future updates of key recommendations in the guidance.
Relevance to the NHS	The use of GLP-1 agonists is currently in wider populations than that specified in NG28 [2015 and 2021], but these drugs have not yet demonstrated cost effectiveness for cardiovascular outcomes, or in the wider economic model used in NG28. The NHS is spending a lot of money on these drugs currently.
National priorities	Low
Current evidence base	Minimal long-term data capturing quality of life and cardiovascular benefit compared to insulin therapy.
Equality considerations	None known

O.4 Modified PICO table

Population	Adults with type 2 diabetes for whom a GLP-1 or insulin would ordinarily be considered. Subgroup of interest: people recruited may have established cardiovascular disease or be at high risk of cardiovascular, renal, or peripheral vascular events or outcomes

Intervention	NPH insulin, or similar insulin therapy
Comparator	GLP-1 agonist (for example exenatide, lixisenatide, liraglutide, dulaglutide or semaglutide)
Outcome	Clinical outcomes such as: • total BMI measured at baseline and 12 months • glycaemic control (HbA1c) • cardiovascular, peripheral vascular and renal outcomes • safety and adverse events (severe hypoglycaemia, amputation, and diabetic neuropathy) • discontinuations due to adverse event and total discontinuation (due to any reason) • quality of life
Study design	Systematic review with economic analyses
Timeframe	No time frame for completion of this work, but the sooner it was available it could be used to inform and update the GLP-1 and insulin recommendations in NG28.

1