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Dipeptidyl peptidase-4 inhibitors, glucagon-like peptide 1 receptor agonists and sodium-glucose co-transporter-2 inhibitors for people with cardiovascular disease: a network meta-analysis (Review)

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[Intervention Review]

Dipeptidyl peptidase-4 inhibitors, glucagon-like peptide 1 receptor agonists and sodium-glucose co-transporter-2 inhibitors for people with cardiovascular disease: a network meta-analysis

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ABSTRACT

Background

Cardiovascular disease (CVD) is a leading cause of death globally. Recently, dipeptidyl peptidase-4 inhibitors (DPP4i), glucagon-like peptide-1 receptor agonists (GLP-1RA) and sodium-glucose co-transporter-2 inhibitors (SGLT2i) were approved for treating people with type 2 diabetes mellitus. Although metformin remains the first-line pharmacotherapy for people with type 2 diabetes mellitus, a body of evidence has recently emerged indicating that DPP4i, GLP-1RA and SGLT2i may exert positive effects on patients with known CVD.

Objectives

To systematically review the available evidence on the benefits and harms of DPP4i, GLP-1RA, and SGLT2i in people with established CVD, using network meta-analysis.

Search methods

We searched CENTRAL, MEDLINE, Embase, and the Conference Proceedings Citation Index on 16 July 2020. We also searched clinical trials registers on 22 August 2020. We did not restrict by language or publication status.

Selection criteria

We searched for randomised controlled trials (RCTs) investigating DPP4i, GLP-1RA, or SGLT2i that included participants with established CVD. Outcome measures of interest were CVD mortality, fatal and non-fatal myocardial infarction, fatal and non-fatal stroke, all-cause mortality, hospitalisation for heart failure (HF), and safety outcomes.

Data collection and analysis

Three review authors independently screened the results of searches to identify eligible studies and extracted study data. We used the GRADE approach to assess the certainty of the evidence. We conducted standard pairwise meta-analyses and network meta-analyses by pooling studies that we assessed to be of substantial homogeneity; subgroup and sensitivity analyses were also pursued to explore how study characteristics and potential effect modifiers could affect the robustness of our review findings. We analysed study data using the odds ratios (ORs) and log odds ratios (LORs) with their respective 95% confidence intervals (CIs) and credible intervals (CrIs), where appropriate. We also performed narrative synthesis for included studies that were of substantial heterogeneity and that did not report quantitative data in a usable format, in order to discuss their individual findings and relevance to our review scope.

Main results

We included 31 studies (287 records), of which we pooled data from 20 studies (129,465 participants) for our meta-analysis. The majority of the included studies were at low risk of bias, using Cochrane's tool for assessing risk of bias. Among the 20 pooled studies, six investigated DPP4i, seven studied GLP-1RA, and the remaining seven trials evaluated SGLT2i. All outcome data described below were reported at the longest follow-up duration.

1. DPP4i versus placebo

Our review suggests that DPP4i do not reduce any risk of efficacy outcomes: CVD mortality (OR 1.00, 95% CI 0.91 to 1.09; high-certainty evidence), myocardial infarction (OR 0.97, 95% CI 0.88 to 1.08; high-certainty evidence), stroke (OR 1.00, 95% CI 0.87 to 1.14; high-certainty evidence), and all-cause mortality (OR 1.03, 95% CI 0.96 to 1.11; high-certainty evidence). DPP4i probably do not reduce hospitalisation for HF (OR 0.99, 95% CI 0.80 to 1.23; moderate-certainty evidence). DPP4i may not increase the likelihood of worsening renal function (OR 1.08, 95% CI 0.88 to 1.33; low-certainty evidence) and probably do not increase the risk of bone fracture (OR 1.00, 95% CI 0.83 to 1.19; moderate-certainty evidence) or hypoglycaemia (OR 1.11, 95% CI 0.95 to 1.29; moderate-certainty evidence). They are likely to increase the risk of pancreatitis (OR 1.63, 95% CI 1.12 to 2.37; moderate-certainty evidence).

2. GLP-1RA versus placebo

Our findings indicate that GLP-1RA reduce the risk of CV mortality (OR 0.87, 95% CI 0.79 to 0.95; high-certainty evidence), all-cause mortality (OR 0.88, 95% CI 0.82 to 0.95; high-certainty evidence), and stroke (OR 0.87, 95% CI 0.77 to 0.98; high-certainty evidence). GLP-1RA probably do not reduce the risk of myocardial infarction (OR 0.89, 95% CI 0.78 to 1.01; moderate-certainty evidence), and hospitalisation for HF (OR 0.95, 95% CI 0.85 to 1.06; high-certainty evidence). GLP-1RA may reduce the risk of worsening renal function (OR 0.61, 95% CI 0.44 to 0.84; low-certainty evidence), but may have no impact on pancreatitis (OR 0.96, 95% CI 0.68 to 1.35; low-certainty evidence). We are uncertain about the effect of GLP-1RA on hypoglycaemia and bone fractures.

3. SGLT2i versus placebo

This review shows that SGLT2i probably reduce the risk of CV mortality (OR 0.82, 95% CI 0.70 to 0.95; moderate-certainty evidence), all-cause mortality (OR 0.84, 95% CI 0.74 to 0.96; moderate-certainty evidence), and reduce the risk of HF hospitalisation (OR 0.65, 95% CI 0.59 to 0.71; high-certainty evidence); they do not reduce the risk of myocardial infarction (OR 0.97, 95% CI 0.84 to 1.12; high-certainty evidence) and probably do not reduce the risk of stroke (OR 1.12, 95% CI 0.92 to 1.36; moderate-certainty evidence). In terms of treatment safety, SGLT2i probably reduce the incidence of worsening renal function (OR 0.59, 95% CI 0.43 to 0.82; moderate-certainty evidence), and probably have no effect on hypoglycaemia (OR 0.90, 95% CI 0.75 to 1.07; moderate-certainty evidence) or bone fracture (OR 1.02, 95% CI 0.88 to 1.18; high-certainty evidence), and may have no impact on pancreatitis (OR 0.85, 95% CI 0.39 to 1.86; low-certainty evidence).

4. Network meta-analysis

Because we failed to identify direct comparisons between each class of the agents, findings from our network meta-analysis provided limited novel insights. Almost all findings from our network meta-analysis agree with those from the standard meta-analysis. GLP-1RA may not reduce the risk of stroke compared with placebo (OR 0.87, 95% CrI 0.75 to 1.0; moderate-certainty evidence), which showed similar odds estimates and wider 95% CrI compared with standard pairwise meta-analysis. Indirect estimates also supported comparison across all three classes. SGLT2i was ranked the best for CVD and all-cause mortality.

Authors' conclusions

Findings from both standard and network meta-analyses of moderate- to high-certainty evidence suggest that GLP-1RA and SGLT2i are likely to reduce the risk of CVD mortality and all-cause mortality in people with established CVD; high-certainty evidence demonstrates that treatment with SGLT2i reduce the risk of hospitalisation for HF, while moderate-certainty evidence likely supports the use of GLP-1RA

to reduce fatal and non-fatal stroke. Future studies conducted in the non-diabetic CVD population will reveal the mechanisms behind how these agents improve clinical outcomes irrespective of their glucose-lowering effects.

PLAIN LANGUAGE SUMMARY

The effects of DPP-4 inhibitors, GLP-1 receptor agonists and SGLT-2 inhibitors for people with cardiovascular disease

Key messages

- GLP-1RA and SGLT2i (two new diabetes medicines) are likely to reduce the risk of death from cardiovascular disease and death from any cause in people with both diabetes and established cardiovascular disease (diseases of the heart and blood vessels).

- SGLT2i medicines are likely to reduce the risk of hospitalisation for heart failure and GLP-1RA medicines may reduce fatal and non-fatal stroke.

- We need further studies to find out if these medicines also have a positive effect on cardiovascular health in people without diabetes or if the effects seen in people with diabetes are due only to these medicines' ability to control blood sugar.

What is cardiovascular disease?

Cardiovascular disease is a general term for conditions that affect the heart and blood vessels. It is one of the leading causes of death worldwide. Fatty substances in the blood can build up and block blood vessels, leading to problems such as heart failure – when the heart cannot pump blood around the body properly – stroke and heart attacks. People who are inactive or overweight, or have high blood pressure, high cholesterol or diabetes are at risk of cardiovascular disease.

Some new types of diabetes medicines, DPP4i, GLP-1RA and SGLT2i, have been designed to control blood sugar. They may also prevent cardiovascular complications in people with diabetes who also have cardiovascular disease.

What did we want to find out?

We wanted to know if DPP4i, GLP-1RA and SGLT2i medicines are effective treatments for cardiovascular disease in people with established cardiovascular disease, both with and without diabetes. We also wanted to know whether these medicines cause unwanted effects.

We were interested in whether people taking these medicines were at higher or lower risk of: dying from cardiovascular disease; having a fatal or non-fatal heart attack; having a fatal or non-fatal stroke; dying from any cause; being hospitalised due to heart failure; and experiencing unwanted effects, such as worsening kidney function, low blood sugar, bone fracture, and inflammation of the pancreas (pancreatitis).

What did we do?
We searched for studies that investigated DPP4i, GLP-1RA and SGLT2i medicines compared with each other or with placebo (a medicine that looks like the real medicine but that has no active ingredient).

We compared and summarised the results of the studies and rated our confidence in the evidence, based on factors such as study methods and sizes.

What did we find?

We found 31 studies. We were able to combine and analyse the evidence from 20 studies, with 129,465 participants. Six of the 20 studies investigated DPP4i, 7 studied GLP-1RA and 7 investigated SGLT2i medicines, all compared with placebo. People in the studies were aged between 60 and 71 years and most people had diabetes.

Main results

DPP4i medicines compared to placebo:

- do not reduce the risk of death from cardiovascular disease or from any cause, or risk of heart attack or stroke;

- probably do not reduce the risk of hospitalisation due to heart failure;

- may not increase the risk of worsening kidney function or bone fracture and probably do not increase the risk of low blood sugar;

- are likely to increase the risk of pancreatitis.

GLP-1RA medicines compared to placebo:

- reduce the risk of death due to cardiovascular disease and from any cause slightly, and reduce the risk of stroke slightly;

- probably do not reduce the risk of heart attack;

- do not reduce the risk of hospitalisation due to heart failure;

- may reduce the risk of worsening kidney function but may have no impact on pancreatitis;

- uncertainty about effects on low blood sugar and bone fracture.

SGLT2i medicines compared to placebo:

- probably reduce the risk of death from cardiovascular disease and from any cause slightly;

- reduce the risk of hospitalisation due to heart failure;

- do not reduce the risk of heart attack and probably do not reduce the risk of stroke;

- probably reduce the risk of worsening kidney function;

- may have no impact on pancreatitis and they have no effect on bone fracture.

Although none of the studies compared one medicine directly with another, we used a statistical technique called network meta-analysis that allowed us to compare one against another. The results were similar to those above.

What are the limitations of the evidence?

We are confident or moderately confident in the evidence for deaths from cardiovascular disease or any cause, heart attack, stroke and hospitalisation due to heart failure. We are less confident in the evidence for unwanted effects because few studies provided information on unwanted effects and they did not report many. Most studies included people with diabetes only so these results could be due to better control of their diabetes, rather than the medicines' effect on cardiovascular disease.

How up-to-date is this evidence?

The evidence is current to 16 July 2020.

SUMMARY OF FINDINGS

Summary of findings 1. DPP4i compared to placebo in people with CVD: efficacy outcomes

DPP4i compared to placebo in people with CVD

Patient or population: CVD (ASCVD, HF, or both)
Setting: outpatient
Intervention: DPP4i (linagliptin, alogliptin, saxagliptin, sitagliptin, vildagliptin, omarigliptin)
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with DPP4i				
Cardiovascular mortality Follow-up duration: range 1.0 to 3.0 years	42 per 1,000	42 per 1,000 (38 to 45)	OR 1.00 (0.91 to 1.09)	47968 (6 RCTs)	⊕⊕⊕⊕ HIGH	
Myocardial infarction (fatal or non-fatal) Follow-up duration: range 1.7 to 3.0 years	38 per 1,000	37 per 1,000 (33 to 41)	OR 0.97 (0.88 to 1.08)	42334 (4 RCTs)	⊕⊕⊕⊕ HIGH	
Stroke (fatal or non-fatal) Follow-up duration: range 1.0 to 3.0 years	21 per 1,000	21 per 1,000 (18 to 24)	OR 1.00 (0.87 to 1.14)	42588 (5 RCTs)	⊕⊕⊕⊕ HIGH	The VIVID trial (McMurray 2018) only showed wide range of 95% CI with small sample size (total 254 participants).
All-cause mortality Follow-up duration: range 1.0 to 3.0 years	63 per 1,000	65 per 1,000 (61 to 70)	OR 1.03 (0.96 to 1.11)	47968 (6 RCTs)	⊕⊕⊕⊕ HIGH	
Hospitalisation for HF Follow-up duration: range 1.7 to 3.0 years	34 per 1,000	34 per 1,000 (27 to 41)	OR 0.99 (0.80 to 1.23)	42334 (4 RCTs)	⊕⊕⊕⊖ MODERATE [1]	The results between them showed significant heterogeneity (I^2 = 71%, P = 0.02)

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1]Graded down for inconsistency: substantial heterogeneity in effect. (-1)
ASCVD: atherosclerotic cardiovascular disease, CI: confidence interval, CVD; cardiovascular disease, DPP4i: dipeptidyl peptidase 4 inhibitor, HF: heart failure, OR: odds ratio, RCT: randomized controlled trial

Summary of findings 2. DPP4i compared to placebo in people with CVD: safety outcomes

DPP4i compared to placebo in people with CVD

Patient or population: CVD (ASCVD, HF, or both)
Setting: outpatient
Intervention: DPP4i (linagliptin, alogliptin, saxagliptin, sitagliptin, vildagliptin, omarigliptin)
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with DPP4i				
Worsening renal function Follow-up duration: median 2.1 years	22 per 1,000	23 per 1,000 (19 to 29)	OR 1.08 (0.88 to 1.33)	16492 (1 RCT)	⊕⊕⊖⊖ LOW [1,2]	
Hypoglycaemia Follow-up duration: range 1.7 to 3.0 years	27 per 1,000	30 per 1,000 (26 to 35)	OR 1.11 (0.95 to 1.29)	25842 (3 RCTs)	⊕⊕⊕⊖ MODERATE [1]	
Pancreatitis Follow-up duration: range 1.5 to 3.0 years	3 per 1,000	5 per 1,000 (3 to 7)	OR 1.63 (1.12 to 2.37)	47684 (5 RCTs)	⊕⊕⊕⊖ MODERATE [3]	
Fracture Follow-up duration: median 2.1 years	29 per 1,000	29 per 1,000 (24 to 34)	OR 1.00 (0.83 to 1.19)	16492 (1 RCT)	⊕⊕⊕⊖ MODERATE [2]	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1]Graded down for imprecision: The 95% CI includes no effect and includes default values for appreciable harm (i.e. CI > 1.25),appreciable benefit (i.e. CI < 0.75), or both. (-1)
[2]Graded down for imprecision: Only 1 RCT was included for this outcome. (-1)
[3]Graded down for imprecision: The number of accrued outcome events was small. (-1)
ASCVD: atherosclerotic cardiovascular disease, CI: confidence interval, CVD; cardiovascular disease, DPP4i: dipeptidyl peptidase 4 inhibitor, HF: heart failure, OR: odds ratio, RCT: randomized controlled trial

Summary of findings 3. GLP-1RA compared to placebo in people with CVD: efficacy outcomes

GLP-1RA compared to placebo in people with CVD

Patient or population: CVD (ASCVD, HF, or both)
Setting: outpatient
Intervention: GLP-1RA (lixisenatide, exenatide, albiglutide, liraglutide, semaglutide)
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with GLP-1RA				
Cardiovascular mortality Follow-up duration: range 1.3 to 3.8 years	44 per 1,000	39 per 1,000 (35 to 42)	OR 0.87 (0.79 to 0.95)	46093 (6 RCTs)	⊕⊕⊕⊕ HIGH	I^2 showed low heterogeneity of 20%. All effect sizes were around 0.87 except PIONEER 6 trial (Husain 2019) with 0.50 and SUSTAIN trial (Marso 2016b) with 0.96. These studies showed wider 95% CIs due to lower event rates and smaller sample sizes when compared with the other 4 trials. PIONEER 6 trial (Husain 2019) showed 15 (0.9%) /1591 in intervention arm and 30 (1.9%) / 1592 in placebo arm. SUSTAIN 6 (Marso 2016b) revealed 44 (2.7%) / 1648 in intervention arm and 46 (2.8%) / 1679 in placebo arm. Other 4 trials showed 156 (5.1%) / 3034 vs 158 (5.2%) / 3024 in ELIXA (Pfeffer 2015), 340 (4.6%) / 7356 vs 383 (5.2%) / 7396 in EXSCEL (Holman 2017), 122 (3%) / 4731 vs 130 (3%) / 4732 in Harmony Outcomes (Hernandez 2018), and 219 (4.7%) / 4668 vs 278 (6.0%) / 4672 in LEADER trials (Marso 2016a).

Myocardial infarction (fatal or non-fatal) Follow-up duration: range 1.6 to 3.8 years	65 per 1,000	58 per 1,000 (51 to 66)	OR 0.89 (0.78 to 1.01)	42910 (5 RCTs)	⊕⊕⊕⊖ MODERATE [1]	These 5 trials showed moderate heterogeneity (I^2 = 57%). Harmony outcome (Hernandez 2018) only revealed that GLP-1RA reduced the rate of myocardial infarction in intervention arm (3.8% vs 5.0%). This could induce significant heterogeneity among these 5 trials. Other 4 trials showed GLP-1RA did not reduce the rate of myocardial infarction.
Stroke (fatal or non-fatal) Follow-up duration: range 1.6 to 3.8 years	29 per 1,000	26 per 1,000 (23 to 29)	OR 0.87 (0.77 to 0.98)	42910 (5 RCTs)	⊕⊕⊕⊕ HIGH	Small heterogeneity (I^2 = 1%). Apart from SUSTAIN 6 (Marso 2016b) (OR 0.61, 95% CI 0.37-0.99), other 4 trials did not show GLP-1RA reduced the rate of stroke. Outcome of each trial were as follows: -ELIXA (Pfeffer 2015) 2.2% vs 2.0% -EXSCEL (Holman 2017) 2.5% vs 2.9% -Harmony Outcomes (Hernandez 2018) 2%vs 2% -LEADER (Marso 2016a) 3.7% vs 4.3% -SUSTAIN 6 (Marso 2016b) 1.6% vs 2.7% Considering these, the outcome could be smaller to detect in each individual trial.
All-cause mortality Follow-up duration: range 0.5 to 3.8 years	68 per 1,000	60 per 1,000 (57 to 65)	OR 0.88 (0.82 to 0.95)	46393 (7 RCTs)	⊕⊕⊕⊕ HIGH	I^2 was 20%. Two relatively small studies (SUSTAIN 6 :Marso 2016b and FIGHT trial :Margulies 2016 revealed that their odds ratios slightly crossed 1.0 (no effects) and were not statistically significant (OR 1.04, 95% CI 0.72-1.49; OR 1.14, 95% CI 0.56-2.32, respectively).
Hospitalisation for HF Follow-up duration: range 0.5 to 3.8 years	40 per 1,000	38 per 1,000 (34 to 42)	OR 0.95 (0.85 to 1.06)	36930 (6 RCTs)	⊕⊕⊕⊕ HIGH	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1]Graded down for inconsistency: moderate to substantial heterogeneity in effect. (-1)

ASCVD: atherosclerotic cardiovascular disease, CI: confidence interval, CVD; cardiovascular disease, GLP-1RA: glucagon-like peptide-1 receptor agonist, HF: heart failure, OR: odds ratio, RCT: randomized controlled trial

Summary of findings 4. GLP-1RA compared to placebo in people with CVD: safety outcomes

GLP-1RA compared to placebo in people with CVD

Patient or population: CVD (ASCVD, HF, or both)
Setting: outpatient
Intervention: GLP-1RA (lixisenatide, exenatide, albiglutide, liraglutide, semaglutide)
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with GLP-1RA				
Worsening renal function Follow-up duration: median 2.1 years	61 per 1,000	38 per 1,000 (28 to 51)	OR 0.61 (0.44 to 0.84)	3297 (1 RCT)	⊕⊕⊖⊖ LOW [1,2]	
Hypoglycaemia	We did not pool the study results because of the significant heterogeneity (I^2 = 76%, P = 0.002).			37038 (5 RCTs)	⊕⊕⊖⊖ LOW [3,4]	
Pancreatitis Follow-up duration: range 1.3 to 3.8 years)	3 per 1,000	3 per 1,000 (2 to 4)	OR 0.96 (0.68 to 1.35)	40035 (5 RCTs)	⊕⊕⊖⊖ LOW [2,4]	
Fracture	None of the included studies reported this outcome					

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1]Graded down for imprecision: Only 1 RCT was included for this outcome. (-1)
[2]Graded down for imprecision: The number of accrued outcome events was small. (-1)

[3]Graded down for inconsistency: substantial heterogeneity in effect. (-1)
[4]Graded down for imprecision: The 95% CI includes no effect and includes default values for appreciable harm (i.e. CI > 1.25), appreciable benefit (i.e. CI < 0.75), or both. (-1)
ASCVD: atherosclerotic cardiovascular disease, CI: confidence interval, CVD; cardiovascular disease, GLP-1RA: glucagon-like peptide-1 receptor agonist, HF: heart failure, OR: odds ratio, RCT: randomized controlled trial

Summary of findings 5. SGLT2i compared to placebo in people with CVD: efficacy outcomes

SGLT2i compared to placebo in people with CVD

Patient or population: CVD (ASCVD, HF, or both)
Setting: outpatient
Intervention: SGLT2i (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, sotagliflozin)
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with SGLT2i				
Cardiovascular mortality Follow-up duration: range 0.8 to 3.5 years	86 per 1,000	72 per 1,000 (62 to 82)	OR 0.82 (0.70 to 0.95)	24962 (5 RCTs)	⊕⊕⊕⊖ MODERATE [1]	Although the I^2 statistic was 67%, SGLT2i reduced cardiovascular mortality. The heterogeneity might be derived from the differences in odds ratios (estimates).
Myocardial infarction (fatal or non-fatal) Follow-up duration: range 3.1 to 3.5 years	56 per 1,000	54 per 1,000 (47 to 62)	OR 0.97 (0.84 to 1.12)	15266 (2 RCTs)	⊕⊕⊕⊕ HIGH	
Stroke (fatal or non-fatal) Follow-up duration: range 3.1 to 3.5 years	31 per 1,000	34 per 1,000 (28 to 41)	OR 1.12 (0.92 to 1.36)	15266 (2 RCTs)	⊕⊕⊕⊖ MODERATE [2]	
All-cause mortality Follow-up duration: range 0.8 to 3.5 years	113 per 1,000	96 per 1,000 (86 to 109)	OR 0.84 (0.74 to 0.96)	24962 (5 RCTs)	⊕⊕⊕⊖ MODERATE [1]	Despite heterogeneity of I^2 = 56%, the results seemed to be consistent.
Hospitalisation for HF	116 per 1,000	78 per 1,000 (72 to 85)	OR 0.65 (0.59 to 0.71)	24962 (5 RCTs)	⊕⊕⊕⊕ HIGH	Because the estimate of these 5 trials were quite similar, heterogeneity was low: I^2 = 33%.

Follow-up duration: range 0.8 to 3.5 years	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1]Graded down for inconsistency: Moderate to substantial heterogeneity in effect. (-1)
[2]Graded down for imprecision: The 95% CI includes no effect and includes default values for appreciable harm (i.e. CI > 1.25), appreciable benefit (i.e. CI < 0.75), or both. (-1)
ASCVD: atherosclerotic cardiovascular disease, CI: confidence interval, CVD; cardiovascular disease, HF: heart failure, OR: odds ratio, RCT: randomized controlled trial, SGLT2i: sodium-glucose co-transporter-2 inhibitor

Summary of findings 6. SGLT2i compared to placebo in people with CVD: safety outcomes

SGLT2i compared to placebo in people with CVD

Patient or population: CVD (ASCVD, HF, or both)
Setting: outpatient
Intervention: SGLT2i (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, sotagliflozin)
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with SGLT2i				
Worsening renal function Follow-up duration: range 1.3 to 1.5 years	23 per 1,000	14 per 1,000 (10 to 19)	OR 0.59 (0.43 to 0.82)	8474 (2 RCTs)	⊕⊕⊕⊖ MODERATE [2]	
Hypoglycaemia Follow-up duration: range 0.8 to 3.5 years	27 per 1,000	25 per 1,000 (21 to 29)	OR 0.90 (0.75 to 1.07)	21232 (4 RCTs)	⊕⊕⊕⊖ MODERATE [1]	
Pancreatitis Follow-up duration: median 3.5 years	3 per 1,000	3 per 1,000 (1 to 6)	OR 0.85 (0.39 to 1.86)	8246 (1 RCT)	⊕⊕⊖⊖ LOW [3]	

Fracture Follow-up duration: range 0.8 to 3.5 years	32 per 1,000	33 per 1,000 (29 to 38)	OR 1.02 (0.88 to 1.18)	24962 (5 RCTs)	⊕⊕⊕⊕ HIGH

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1]Graded down for imprecision: The 95% CI includes no effect and includes default values for appreciable harm (i.e. CI > 1.25), appreciable benefit (i.e. CI < 0.75), or both. (-1)
[2]Graded down for imprecision: The number of accrued outcome events was small. (-1)
[3]Graded down for imprecision: Only 1 RCT was included for this outcome, the 95% CI includes no effect and includes default values for appreciable harm (i.e. CI > 1.25) and appreciable benefit (i.e. CI < 0.75), and the number of accrued outcome events was small. (-2)
ASCVD: atherosclerotic cardiovascular disease, CI: confidence interval, CVD; cardiovascular disease, HF: heart failure, OR: odds ratio, RCT: randomized controlled trial, SGLT2i: sodium-glucose co-transporter-2 inhibitor

BACKGROUND

Description of the condition

Cardiovascular disease (CVD) is one of the most common causes of death, leading to an estimated 17.3 million deaths annually worldwide (Roth 2015a). As the world's population increases and ages, so does the prevalence of CVD (Roth 2015b). The prevalence of heart failure (HF) in the USA alone has been projected to rise steadily over the next four decades, with an estimated 772,000 new cases projected by 2040 (Owan 2005; Ponikowski 2014), and a similar trend has also been shown for Asian and European countries (Conrad 2018; Maggioni 2015; Sato 2015).

To effectively tackle this global issue, a wide array of CVD risk factors should be considered, and of these, hypertension, dyslipidaemia and diabetes mellitus are probably the most widely-discussed management goals because of their corresponding prevalence and mortality rates (Joseph 2017; Mensah 2017). Theoretically, effective blood glycaemic control in people with diabetes mellitus is beneficial to reduce the rate of CVD (IDF 2019); however, findings from several large-scale clinical trials indicated that an improved glycaemic control profile in diabetics only reduces the risk of microvascular complications such as retinopathy, but not the risk of macro-vascular complications such as cardiovascular events and overall mortality (Selvin 2004). In light of the current challenges, three new classes of glucose-lowering interventions, namely dipeptidyl peptidase-4 inhibitors (DPP4i), glucagon-like peptide 1 receptor agonists (GLP-1RA) and sodium-glucose co-transporter-2 inhibitors (SGLT2i), have been proposed as potential new pharmacological agents for modifying cardiovascular risks in people with or without diabetes mellitus (Marso 2016a; McMurray 2019; Zinman 2015).

Description of the intervention

Glucose-lowering interventions were developed in the early 1900s and remain as standard treatment options for people with diabetes mellitus for the management of hyperglycaemia (White 2014). Historically, subcutaneous or bolus insulin infusion, sulphonylureas, metformin were first developed. Insulin, sulphonylureas and other insulin secretagogues were not currently considered as the first-line therapy due to lack of long-term efficacy and side effects like hypoglycaemia. Metformin is currently the preferred initial oral glucose-lowering agent for the treatment of type 2 diabetes mellitus (ADA 2019). The major mechanism of action illustrated by metformin is the ability to decrease hepatic glucose output by inhibiting gluconeogenesis (Rena 2017). Metformin also improves insulin sensitivity and increases insulin-mediated glucose utilisation in muscle and liver (Mclntyre 1991). Although metformin could improve vascular function and decrease myocardial ischaemia even in people without diabetes (Jadhav 2006), this effect remains to be confirmed (Luo 2019). From a clinical perspective, treatment with metformin has been linked to a reduction in cardiovascular events in certain subpopulations, including the obese and people with co-existing coronary heart disease (DPP Research Group 2012; Hong 2013; Tanabe 2015; UKPDS 1998). However, metformin also has some points to be concerned about. Recognised adverse effects associated with metformin other than hypoglycaemia are lactic acidosis and gastrointestinal symptoms (diarrhoea and nausea). Metformin is contraindicated for patients or elderly people with low estimated glomerular filtration rate (eGFR).

Recently, DPP4i, GLP-1RA and SGLT2i were approved for treating people with type 2 diabetes mellitus (ADA 2018). Two large-scale randomised trials showed that adding SGLT2i to existing glucose-lowering medications in people with type 2 diabetes mellitus and established CVD led to a reduced risk of major adverse cardiovascular events (MACE), defined as a composite of nonfatal myocardial infarction, nonfatal stroke, and cardiovascular death (Zinman 2015; Neal 2017). Although the class effect of SGLT2i is currently unclear (Wiviott 2019), a recent systematic review reported that treatment with SGLT2i was effective in minimising the rates of heart failure (HF)-related hospitalisation, as well as renal disease progression, in people with type 2 diabetes mellitus (Zelniker 2019). Furthermore, a recent study revealed these effects could be found, regardless of the presence or absence of diabetes (Packer 2020).

Two studies have also shown that add-on treatment with GLP-1RA (liraglutide and semaglutide) among people with type 2 diabetes mellitus and CVD decreased their cardiovascular risk, compared with placebo (Marso 2016a; Marso 2016b). However, it is worth noting that other GLP-1RA (exenatide and lixisenatide) showed no effects against cardiovascular outcomes (Holman 2017; Pfeffer 2015); similarly, treatment with DPP4i did not lead to a reduction in cardiovascular risk (Green 2015; Rosenstock 2019; Scirica 2013; White 2013).

It is therefore clear that, despite increased global usage of DPP4i, GLP-1RA, and SGLT2i (Kim 2019), their precise effects on reducing cardiovascular events in people with high cardiovascular risks with or without diabetes mellitus are yet to be fully evaluated.

How the intervention might work

Evidence has recently emerged that DPP4i, GLP-1RA and SGLT2i are viable pharmacological treatment options for people with diabetes who are at risk of CVD and in whom metformin monotherapy has failed or is inadequate, giving demonstrable evidence of cardiovascular risk reduction (Marso 2016a; Marso 2016b; Zinman 2015). In 2018, the American Diabetes Association's (ADA's) *Standards of Medical Care in Diabetes* introduced new recommendations for the use of anti-diabetic drugs with proven cardiovascular benefits in people with type 2 diabetes mellitus (ADA 2018). The detailed mechanisms of how these three pharmacological agents (DPP4i, GLP-1RA, and SGLT2i) could work are as follows:

DPP4i and GLP-1RA

Considering their biological mechanisms of action, both DPP4i and GLP-1RA are classified as 'GLP-1-based therapies', referring to their actions on glycaemic control through enhancement of glucose-dependent insulin secretion. Glucose homeostasis is dependent upon a complex interplay of multiple hormones. As one of the gastrointestinal peptides, GLP-1 is produced from the small intestine and secreted in response to nutrients, stimulating insulin synthesis and insulin secretion (Koliaki 2011). In people with type 2 diabetes mellitus, the insulin response to GLP-1 becomes lower, possibly related to a reduction in postprandial GLP-1 secretion (Vilsbøll 2001). Due to N-terminal degradation by the DPP-4 enzyme, GLP-1 exhibits a short half-life. GLP-1-based agents are therefore resistant to DPP-4 degradation and are thus able to influence blood glucose control.

As well as glucose-lowering effects, several direct effects of these agents on cardiovascular systems have also been reported. In people without diabetes mellitus, GLP-1-based therapies have been shown to simultaneously exert an incretin effect on insulin secretion, illustrating a protective effect on endothelial function (Ceriello 2011). In addition, GLP-1-based agents could also reduce arrhythmias and improve cardiac functions, such as left ventricular ejection fraction (LVEF) in HF (Sheikh 2013). The mechanisms of these effects remain to be fully explored, but attenuated insulin resistance has been proposed as a possible explanation (Ingelsson 2005).

SGLT2i

The SGLT2 receptors are expressed in the proximal tubule, and mediate reabsorption of approximately 90% of the filtered glucose load. The effects of SGLT2i in people with diabetes are not only reducing blood glucose levels but also lowering blood pressure and body weight (Clar 2012). Studies of SGLT2i have also demonstrated that blocking endothelial SGLT2 led to improved endothelial function, which could be beneficial for non-diabetic populations (Bairey Merz 2019; Pulakazhi 2019). A recent study revealed that SGLT2i would be beneficial in people with heart failure and without diabetes mellitus (McMurray 2019), the mechanisms of which could be explained by effective weight reduction. It is worth highlighting that the rationale of using SGLT2i in people without diabetes mellitus focuses on the observation that, while these agents were shown to reduce cardiac events in people with diabetes mellitus, the achieved glycaemic control was no better than what was achieved with standard glucose-lowering agents. For example, canagliflozin was found to slow the progression of renal disease over two years in people with type 2 diabetes mellitus and the illustrated renoprotection was independent of glycaemic control (Heerspink 2017). The hypothesis that SGLT2i could be of interest to populations with cardiovascular disease, namely heart failure, prompted further clinical research. However, it is currently unclear whether these novel antidiabetic agents truly reduce cardiovascular events; comprehensive and methodologically-sound systematic reviews assessing all these three drug classes are lacking.

Why it is important to do this review

It is well recognised that CVD remains one of the most common causes of death all over the world. Among many subtypes of CVD, the rapidly-increasing number of people with HF, sometimes referred to as the "heart failure pandemic", should be emphasised (Ambrosy 2014; Shimokawa 2015). Considering that diabetes mellitus is a leading cause and associated comorbidity of CVD, effective blood glycaemic control for people with or without CVD has been focussed as a global management target for both prevention and treatment of CVD. Evidence for the beneficial effects of the new glucose-lowering agents (DPP4i, GLP-1RA, and SGLT2i) in people with CVD appeared to be promising. Comprehensive and systematic assessment of available study findings is warranted, due to the rapidly-evolving evidence base.

Among these three new glucose-lowering interventions (DPP4i, GLP-1RA, and SGLT2i), SGLT2i has received considerable attention recently due to its class effect on cardiovascular outcomes, even in non-diabetic populations. As highlighted in a previous meta-analysis (Zelniker 2019), the effectiveness of SGLT2i could vary by baseline patient characteristics; they were shown to reduce MACE (myocardial infarction, stroke, or cardiovascular death), with benefits only seen in people with established atherosclerotic cardiovascular disease and not in the at-risk subgroup. A precise review of clinical treatment effects and a better understanding of appropriate target populations for these new pharmacological agents are important for optimal treatment pathways.

It is worth noting that these novel glucose-lowering agents could be provided as a monotherapy or as a combination with classical treatments for diabetes. Quantitative comparisons between numerous groups of treatment modalities pose quite a challenge since head-to-head comparisons assessed by randomised pivotal trials are not always available. Therefore, we planned to conduct this Cochrane Review with a network meta-analysis to investigate the effectiveness of these agents, with both direct and indirect comparisons.

OBJECTIVES

To systematically review the available evidence on the effects (benefits and harms) of DPP4i, GLP-1RA, and SGLT2i in people with established CVD, using network meta-analysis.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs), randomised at the individual participant level as well as at the cluster level. We also included cross-over trials by incorporating data from the first phase only, i.e. before participants crossed over. We included trials reported as full-text, those published as abstract only, and unpublished data. We included trials irrespective of publication type, date, or language. Given the nature of the moderate- to long-term outcome measures (Types of outcome measures), we only included trials with a treatment duration of 24 weeks or longer.

Types of participants

We considered all participants aged 18 years or older with the following subtypes of CVD, with or without established type 2 diabetes mellitus.

- People with atherosclerotic cardiovascular disease (ASCVD), i.e. a history of acute coronary syndrome or other coronary heart diseases with or without revascularisation, other arterial revascularisation, stroke, or peripheral artery disease assumed to be atherosclerotic in origin, as defined by the American College of Cardiology (ACC) and American Diabetes Association (ADA) guidelines).
- People with HF: HF with preserved ejection fraction (HFpEF) or HF with reduced ejection fraction (HFrEF), as defined by the European Society of Cardiology (ESC) guidelines (Subgroup analysis and investigation of heterogeneity).

For trials consisting of mixed populations (e.g. ASCVD and other healthy population in primary prevention studies), we extracted only data from desired participant subgroups. If the subgroup data required were not available, we contacted corresponding authors of the trial to request this information; failing that we excluded the whole trial if fewer than 80% of participants met the inclusion criteria.

Types of interventions

We included RCTs comparing one or more of the following interventions:

- DPP4i;
- GLP-1RA;
- SGLT2i.

We included trials using any combination of the above drugs. We did not exclude trials on the basis of the route, dose, timing, or frequency of drug administration. The comparison groups were as defined by the trial, which could be placebo, a lifestyle/behavioural interventions (e.g. diet, exercise, diet + exercise), or another glucose-lowering pharmacological intervention. We combined trials which used placebo, lifestyle/behavioural interventions or another glucose-lowering pharmacological intervention as a single comparator for the direct comparison. Theoretically, the combination of DPP4i and GLP-1RA is usually not recommended in clinical practice but for the purpose of this Cochrane Review, this combination regimen was eligible for inclusion.

Our comparisons were based on the aforementioned three types of interventions, with each drug type corresponding to one node in our network meta-analysis. We assumed the concept of 'jointly randomisable' might be applied to all treatment arms included in the network comprising these interventions and comparators.

Types of outcome measures

We originally aimed to analyse outcome data reported at 30 days, at one year, as well as analyse any data available at the longest follow-up duration reported by the study investigators. Because none of our included studies reported primary/secondary outcome data measured at these pre-specified time points, we eventually decided to analyse outcome data measured at the longest follow-up duration, as defined by individual studies.

Reporting one or more of the outcomes listed here was not a trial inclusion criterion for the review. Where a published trial did not report one of these outcomes, we attempted to retrieve and assess the trial protocol for further information or, where necessary, contacted the trial authors, to ascertain whether the outcomes were actually measured (as pre-specified outcomes) but were not reported. Relevant trials which measured these outcomes but did not report the data at all, or not in a usable format, were eligible for inclusion and we planned to describe their findings and implications as part of a narrative synthesis.

Primary outcomes

- Cardiovascular mortality
- Fatal or non-fatal myocardial infarction
- Fatal or non-fatal stroke

Secondary outcomes

- All-cause mortality
- Hospitalisation for HF
- Safety outcomes
  - Worsening renal function (e.g. reduction of 40% or more in the eGFR, doubling of the serum creatinine level, end-stage kidney disease (glomerular filtration rate (GFR) < 15), initiation of renal-replacement therapy)
  - Hypoglycaemia
  - Pancreatitis
  - Fractures
  - Any reported adverse effects

We used and defined all outcomes as reported by trial investigators. It is worth noting that at the protocol stage, we initially considered 'end-stage kidney disease' and 'initiation of renal replacement therapy' as renal efficacy measures; however, during the study selection and data extraction process, we noticed that many trial investigators defined these as renal safety outcomes and thus we decided to categorise these as safety outcomes.

Search methods for identification of studies

Electronic searches

We performed systematic searches of the following bibliographic databases on 16 July 2020:

- Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library (Issue 7 of 12, 2020);
- Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE Daily and MEDLINE (Ovid, 1946 to 14 July 2020);
- Embase (Ovid, 1980 to 2020 week 28);
- Conference Proceedings Citation Index-Science (CPCI-S) Web of Science (Clarivate Analytics, 1990 to 16 July 2020).

We adapted the search strategy for MEDLINE (Ovid) as illustrated in Appendix 1 for use in the other databases. We applied the Cochrane sensitivity and precision-maximising RCT filter (Lefebvre 2020) to MEDLINE (Ovid) and adaptations of it to the other databases, except for CENTRAL.

We also conducted a search of ClinicalTrials.gov (www.clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) Search Portal (apps.who.int/trialsearch) for ongoing or unpublished trials on 22 August 2020, using the search terms as indicated in Appendix 1.

No restrictions by language of publication or publication status were imposed.

We did not perform a separate search for adverse effects but instead considered any adverse effects as described in the included studies.

Searching other resources

We checked reference lists of all included trials and any relevant systematic reviews identified for additional references to trials. We also examined any relevant retraction statements and errata for included studies.

Data collection and analysis

Selection of studies

Three review authors (TY, TS, TK) independently screened titles and abstracts for inclusion of all the potential studies we identify as a result of the search, and coded them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve' (clearly irrelevant). If there are any disagreements, they asked another review author (AM) to arbitrate. We retrieved the full-text study reports/publication, and the three authors (TY, TS, TK) independently

screen the full text and identify trials for inclusion, recording reasons for exclusion of the ineligible studies. We resolved any disagreement through discussion, when required, we consulted another author (AM, JSWK). We identified and excluded duplicates and collated multiple reports of the same study so that each study rather than each report was the unit of interest in the review. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram and a 'Characteristics of excluded studies' table (Liberati 2009).

Data extraction and management

We used a data collection form for study characteristics and outcome data which has been piloted on at least one study in the review. Two review authors (TY, TS) extracted study characteristics from included studies. We extracted the following study characteristics.

1. Methods: study design, total duration of study, details of any 'run-in' period, number of study centres and location, study setting, and date of study.
2. Participants: N randomised, N lost to follow-up/withdrawn, N analysed, mean age, age range, gender, weight, body mass index (BMI), cardiovascular disease categories, severity of condition (such as the commonly-used classification system, New York Heart Association (NYHA) classification or the ACC/American Heart Association (AHA) stages of heart failure), left ventricular ejection fraction, baseline diabetes condition including HbA1c, smoking history, trial inclusion and exclusion criteria.
3. Interventions: intervention, comparison, concomitant medications, and excluded medications.
4. Outcomes: primary and secondary outcomes specified and collected, and time points reported.
5. Notes: funding for trial, and notable conflicts of interest of trial authors.

All included studies used very similar inclusion criteria and find comparable baseline characteristics. From each study, we extracted the following characteristics that may have acted as effect modifiers: age, gender, BMI, and comorbidities.

Two review authors (TK, AM) independently extracted outcome data from included studies. We resolved disagreements by consensus or by involving a third review author (JSWK). One review author (TK) entered data into Review Manager 5 (Review Manager 2020), and performed double-checking to ensure that data were entered correctly, by comparing the data presented in the review with the completed data extraction form. A second author (AM) also performed spot-checking of included study characteristics for accuracy.

Assessment of risk of bias in included studies

Three review authors (YT, TS, TK) independently assessed risks of bias for each study, using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any disagreements by discussion or by involving another author (JSWK). We assessed the risks of bias according to the following domains.

- Random sequence generation;
- Allocation concealment;
- Blinding of participants and personnel;
- Blinding of outcome assessment;
- Incomplete outcome data;
- Selective outcome reporting;
- Other potential bias.

We graded each potential source of bias as high, low or unclear, and provided a quote from the trial report together with a justification for our judgement in the 'Risk of bias' table. We summarised the 'Risk of bias' judgements across different trials for each of the domains listed. Where information on risk of bias relates to unpublished data or correspondence with the trialists, we noted this in the 'Risk of bias' table.

When considering treatment effects, we planed to take into account the risk of bias for the trials that contribute to that outcome.

Measures of treatment effect

We analysed our a priori primary and secondary outcome measures (all dichotomous outcomes) using odds ratios (ORs) with 95% confidence intervals (CIs). For efficacy, an OR greater than 1.0 favoured the intervention (as opposed to the comparator); when we addressed safety outcomes, an OR greater than 1.0 favoured the comparator.

Unit of analysis issues

All of our included trials were RCTs at the individual-participant level. As we previously assumed in the review protocol, our types of interventions of interest were less likely to be evaluated in a cluster-randomisation setting.

For trials that measured outcomes at different time points, we focussed only in effects of the interventions from the longest follow-up duration as previously addressed in the protocol. Network meta-analysis is considered to be particularly helpful in taking account of the comparison of multiple interventions; however we could not identify any head-to-head comparative studies and or eligible studies involving multiple arms for meta-analysis. For future updates, if we identify eligible multi-arm studies, we will incorporate the correlation between the multiple arms by revising the within-study covariance matrix.

Dealing with missing data

We contacted the investigators/authors of the included trials to request any missing data. Our default approach was to analyse data by following intention-to-treat principles. To explore the impact of missing data, we conducted sensitivity analysis by including trials that reported data using an intention-to-treat approach, and compare the results with those from the overall analysis that includes trials following either an intention-to-treat or a per-protocol approach (Sensitivity analysis).

Assessment of heterogeneity

We inspected forest plots to identify signs of heterogeneity for each direct comparison. We assessed the presence of statistical heterogeneity and quantify it using the Chi^2 test (threshold $P < 0.10$), and the I^2 statistic, respectively. The importance of the observed value of I^2 depends on both the magnitude and the direction of effects and strength of evidence for heterogeneity. Uncertainty in the value of I^2 is substantial when the number of trials is small. We followed the recommendations for thresholds

in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2020):

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

We reported important sources of heterogeneity and explored possible causes by pre-specified subgroup analysis and meta-regression (Subgroup analysis and investigation of heterogeneity).

Assessment of reporting biases

We planned to create a funnel plot to visually explore possible small-study biases for the primary outcomes and to use Egger's test to statistically examine the risk of reporting bias (Egger 1997), However, due to limited data identified for each a priori primary outcome measure (fewer than 10 trials), we did not pursue this for the pairwise and network meta-analyses.

Data synthesis

Direct comparison

We conducted direct pairwise meta-analysis using Review Manager 5 (Review Manager 2020) and R software, version 3.4.2 (R 2017), with the meta and metafor packages. We calculated ORs with their respective 95% CIs for dichotomous outcomes. Our considerations on whether to perform pooling of the results depended on the level of statistical heterogeneity among the trials as assessed and quantified by the Chi^2 test and the I^2 statistics, respectively (Assessment of heterogeneity). We used both fixed-effect and random-effects (DerSimonian and Laird method) analytical models for direct comparison meta-analysis based on the degree of heterogeneity. If we assessed the level of heterogeneity considerable ($I^2 \geq 75\%$), we planned not to pool the results but instead performed a narrative synthesis. We also performed subgroup analyses to detect any potential sources of important heterogeneity between studies (Subgroup analysis and investigation of heterogeneity).

Network meta-analysis

For indirect and mixed comparisons, we planned to use network meta-analysis to obtain estimates for the outcomes, and presented these estimates as risk ratios (RRs) with 95% confidence intervals (CI). In the review process, we became aware that the OR was a relatively more popular effect measure in this field to estimate the effectiveness of pharmacological interventions and thus we decided to use the OR with 95% credible interval (CrIs) instead of the RR to assure comparability of the pooled results with other published systematic reviews.

We performed our network meta-analysis within a Bayesian framework, assuming an equal heterogeneity parameter across all comparisons, and then created network diagrams to visually check the direct or indirect comparisons. For Bayesian analysis, we used the Markov Chain Monte Carlo method for the estimation with 10,000 iterations including a 5000 iteration burn-in period and 10 iteration thinning interval. To estimate the relative ranking probability of an intervention being among the best options, we calculated for all outcomes the surface under the cumulative ranking (SUCRA) curve. Smaller SUCRA scores meant a more effective or safer intervention. To check for the presence of inconsistency in the estimated diagram, we planned to use the loop-specific approach to analyse the statistical difference between direct and indirect estimates for a certain comparison in a loop. However, as we mentioned, the direct estimates could not be obtained in this review.

We performed the analysis using 'R' software, version 3.4.2 (R 2017) with 'netmeta' and 'gemtc' packages. The detailed description of the methodology could be found in 'netmeta' and 'gemtc'.

Subgroup analysis and investigation of heterogeneity

We investigated possible sources of heterogeneity through subgroup analyses in both the direct and the network meta-analyses. This approach was based on the presence of statistical heterogeneity considered to be important ($I^2 > 40\%$, as calculated by Review Manager 5) in the standard direct-comparison meta-analysis, together with underlying clinical heterogeneity in baseline participant characteristics.

We considered the following subgroups.

- Type of baseline CVD:
  - participants with clinically-diagnosed ASCVD (further stratified by the type of ASCVD, e.g. acute coronary syndrome, coronary heart disease with or without revascularisation);
  - participants with clinically-confirmed HF (further stratified by left ventricular ejection fraction (LVEF) status, where normal LVEF (heart failure with preserved EF, HFpEF) is typically considered as EF of ≥ 50% and reduced LVEF (heart failure with reduced EF, HFrEF) is defined as EF < 40%) (Ponikowski 2016).
- Background comorbidities (diabetes mellitus, chronic kidney disease (CKD)).
- Type of active treatment (individual DPP4i, GLP-1RA, and SGLT2i).
- Type of control (placebo, lifestyle/behavioural intervention, another glucose-lowering pharmacological intervention).
- Duration of study (≤ 52 weeks versus > 52 weeks).
- Mode of therapy (monotherapy or combination therapy).

Our *a priori* outcome measures for the above subgroup analyses were:

- cardiovascular mortality;
- fatal or non-fatal myocardial infarction;
- fatal or non-fatal stroke;
- all-cause mortality.

We used the formal test for subgroup differences in Review Manager 5 (Review Manager 2020), and base our interpretation on this.

However, due to limited data, we were only able to pursue the following subgroup analyses (Effects of interventions):

- type of baseline CVD (ASCVD or HF);
- background comorbidity - diabetes mellitus.

For future review updates, we anticipate a larger body of evidence will facilitate analyses of the other pre-specified subgroups as indicated above.

Sensitivity analysis

We planned to carry out sensitivity analysis to test whether key methodological factors or decisions may have affected the main results of our direct-comparison meta-analysis. We planned the following sensitivity analyses by only including:

- trials assessed at low risk of bias (i.e. for which we rate all domains at low risk);
- trials adopting an intention-to-treat approach for data analysis;
- trials published as full-text articles.

Our outcome measures for these sensitivity analyses were:

- cardiovascular mortality;
- fatal or non-fatal myocardial infarction;
- fatal or non-fatal stroke;
- all-cause mortality.

However, due to limited data, we limited our sensitivity analysis by exploring the impact of trial quality/risk of bias on the overall review findings by including only trials assessed at low risk of bias. We anticipate a large body of evidence included in future review updates will facilitate sensitivity analysis as mentioned above.

Summary of findings and assessment of the certainty of the evidence

We created 'Summary of findings' tables for the following efficacy and safety outcomes (Types of outcome measures).

I) Efficacy outcomes:

1. cardiovascular mortality;
2. fatal or non-fatal myocardial infarction;
3. fatal or non-fatal stroke;
4. all-cause mortality;
5. hospitalisation for HF.

II) Safety outcomes:

1. worsening renal function;
2. hypoglycaemia;
3. pancreatitis;
4. bone fracture.

We used the five Grading of Recommendations Assessment, Development and Evaluation (GRADE) considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the certainty of a body of evidence as it relates to the studies which contribute data to the meta-analyses for the pre-specified outcomes. We applied the GRADE methods and recommendations described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2020), and used the GRADEpro software (GRADEpro GDT).

We planned to produce a 'Summary of findings' table for the following comparisons (Types of interventions):

- active monotherapy treatment group versus a combined control group (placebo or lifestyle/behavioral interventions or another active treatment);
- active combination therapy group versus a combined control group.

However, as mentioned previously, we found only RCTs that compared active monotherapy with placebo. Therefore, we created 'Summary of findings' tables regarding this particular comparison, and further divided the tables into 'efficacy outcomes' and 'safety outcomes'.

We justified all decisions to downgrade the quality of studies using footnotes and made comments to aid readers' understanding of the review where necessary. Judgements about evidence quality were made by two review authors (TK and AM*)* working independently, with disagreements resolved by discussion or involving a third review author (JSWK). Judgements were justified, documented, and incorporated into reporting of results for each outcome.

We planned to use the Confidence in Network Meta-Analysis (CINeMA) approach to calculate and visualise the percentage contribution of each direct contrast to each network estimate (Nikolakopoulou 2020), but our review did not identify any direct comparison between each drug. For rating of evidence studies compared with placebo in a network meta-analysis, we followed the GRADE Working Group's approach (Puhan 2014). Because network analysis did not add much information, due to the lack of closing loops, we could not use most GRADE criteria (study limitations, indirectness, and publication bias) to downgrade or upgrade evidence certainty in network analysis results. We only downgrade certainty of evidence in network meta-analysis results due to imprecision, especially CrI including no effect and including default values for appreciable harm (i.e. CrI > 1.25), appreciable benefit (i.e. CrI < 0.75), or both.

Finally, for standard pairwise meta-analysis, we extracted study data and presented them in the 'Summary of findings' tables. We also included a separate table to illustrate results from our network meta-analysis as per the recent guidance from Yepes-Nuñez 2019.

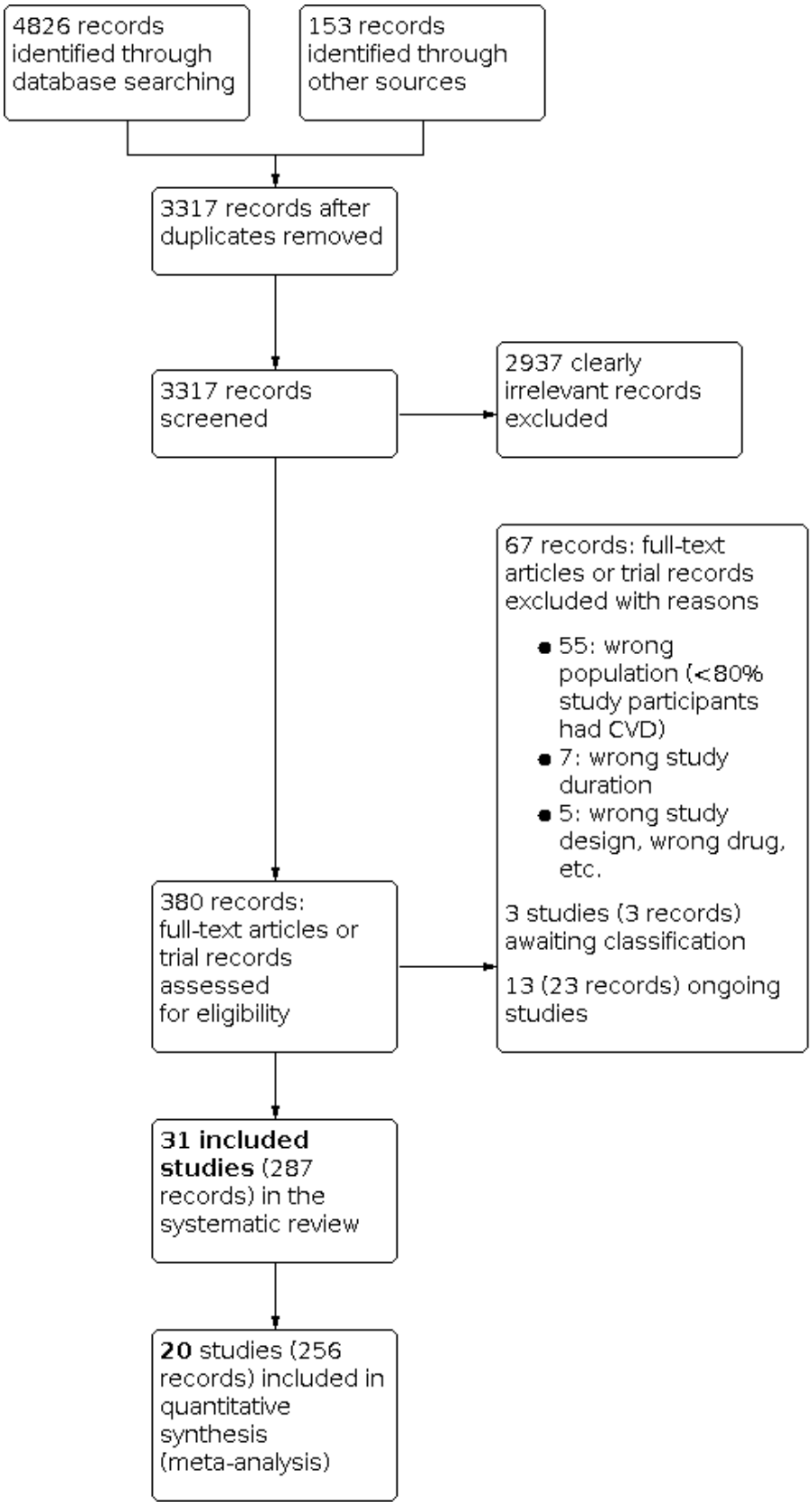
RESULTS

Description of studies

Results of the search

Our study selection process is illustrated in Figure 1. Our comprehensive searches yielded a total of 4826 records; 153 records were identified from other sources (e.g. clinical trials registers). After de-duplication, 3317 records remained. Upon first-level screening by reviewing titles and abstracts, we excluded 2937 clearly irrelevant records (2247 records were excluded as they were duplicates or of the wrong study design, and 690 records were excluded as studies were of the wrong population). Full-text reports and trial records of the remaining 380 records were retrieved for further assessment. We excluded 55 records that enrolled < 80% participants with any CVD (i.e. wrong population). Seven records were excluded due to short study duration (< 24 weeks), and we excluded a further five due to the wrong study design or drug. We identified 13 ongoing studies (23 records), and three studies (three records) were recorded as 'Studies awaiting classification' (details in Characteristics of studies awaiting classification).

Figure 1. PRISMA study flow diagram



Overall, we included 31 studies (287 records) for qualitative synthesis as included studies (Included studies), of which we included 20 studies (256 records) in our meta-analysis for quantitative analysis (Figure 1).

Included studies

As described above, we included 31 studies (287 records) in our qualitative analysis and 20 studies (256 records) were pooled in our meta-analysis. All included studies were designed as RCTs. We described each study details in 'Characteristics of included studies'.

Of these 31 studies, six examined DPP4i compared with placebo (Gantz 2017; Green 2015; McMurray 2018; Rosenstock 2019; Scirica 2013; White 2013), eight examined GLP-1RA compared with placebo (Hernandez 2018; Holman 2017; Husain 2019; Jorsal 2017; Margulies 2016; Marso 2016a; Marso 2016b; Pfeffer 2015), and twelve examined SGLT2i compared with placebo (Bhatt 2021; Cannon 2020; Cefalu 2015; Leiter 2014; McMurray 2019; Neal 2017a; Neal 2017b; Packer 2020; Shimizu 2020; Tanaka 2019; Verma 2019; Zinman 2015). Four studies were not placebo-controlled trials (Phrommintikul 2019: SGLT2i versus DPP4i; Wang 2020: DPP4i versus GLP1-RA; Tanaka 2020: SGLT2i versus sulphonylurea; Kato 2017: DPP4i versus no DPP4i). One study utilised a three-arm design (Arturi 2017: GLP-1RA versus DPP4i versus insulin glargine).

Sample sizes across the included studies ranged from 32 to 16,492 (mean N = 4268). The range of average age and gender (i.e. percentage female) of the study participants were 60 to 71 years and 7% to 48%, respectively. As for their baseline conditions, all participants had ASCVD in 15 of 31 studies (Arturi 2017; Cannon 2020; Cefalu 2015; Gantz 2017; Hernandez 2018; Kato 2017; Leiter 2014; Pfeffer 2015; Phrommintikul 2019; Shimizu 2020; Tanaka 2019; Verma 2019; Wang 2020; White 2013; Zinman 2015). In eight of 31 studies, all participants had heart failure (Arturi 2017; Bhatt 2021; Jorsal 2017; Margulies 2016; McMurray 2018; McMurray 2019; Packer 2020; Tanaka 2020). In 27 studies, all participants had diabetes. In four studies (Jorsal 2017; Margulies 2016; McMurray 2019; Packer 2020), only some participants had diabetes (range across intervention groups: 30.7% to 59.3%; proportions in the respective control groups of each trial were similar). Four studies enrolled at least 40% of participants with CKD, defined as eGFR of less than 60 mL/min/1.73 m^2 (Bhatt 2021; McMurray 2019; Packer 2020; Rosenstock 2019); however, none of our included studies investigated the effects of the study interventions in people with CKD only.

As for funding sources, a total of 26 studies (83.9%) were funded by industry, three studies (9.7%) were funded by non-industrial resources, and the remaining two studies (6.5%) did not report funding sources. The study duration of 11 studies (35.5%) was within one year (Bhatt 2021; Cefalu 2015; Jorsal 2017; Kato 2017; Margulies 2016; Phrommintikul 2019; Shimizu 2020; Tanaka 2019; Tanaka 2020; Verma 2019; Wang 2020).

Studies on DDP4i

Ten studies evaluated DPP4i (Arturi 2017; Gantz 2017; Green 2015; Kato 2017; McMurray 2018; Phrommintikul 2019; Rosenstock 2019; Scirica 2013; Wang 2020; White 2013). The types of DPP4i investigated included alogliptin, linagliptin, omarigliptin, saxagliptin, sitagliptin, and vildagliptin. Regarding the type of baseline CVD, in six of 10 studies all participants had ASCVD (Arturi 2017; Gantz 2017; Kato 2017; Phrommintikul 2019; Wang 2020; White 2013), and in two studies all the study participants had HF (Arturi 2017; McMurray 2018). All participants receiving DPP4i were diagnosed with diabetes mellitus.

Studies on GLP-1RA

Ten studies investigated GLP-1RA (Arturi 2017; Hernandez 2018; Holman 2017; Husain 2019; Jorsal 2017; Margulies 2016; Marso 2016a; Marso 2016b; Pfeffer 2015; Wang 2020); the types of agents included albiglutide, exenatide, liraglutide, lixisenatide, and semaglutide. Of these 10 included studies, four involved participants with ASCVD (Arturi 2017; Hernandez 2018; Pfeffer 2015; Wang 2020), three included participants with HF (Arturi 2017; Jorsal 2017; Margulies 2016). In 8 studies, all participants had diabetes. In the remaining two studies (Jorsal 2017; Margulies 2016), only some participants had diabetes.

Studies on SGLT2i

Fourteen studies explored the effects of SGLT2i (Bhatt 2021; Cannon 2020; Cefalu 2015; Leiter 2014; McMurray 2019; Neal 2017a; Neal 2017b; Packer 2020; Phrommintikul 2019; Shimizu 2020; Tanaka 2019; Tanaka 2020; Verma 2019; Zinman 2015). Study interventions included canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, and sotagliflosin. As for the baseline cardiac conditions amongst the included participants, eight of the 14 studies randomised participants with ASCVD (Cannon 2020; Cefalu 2015; Leiter 2014; Phrommintikul 2019; Shimizu 2020; Tanaka 2019; Verma 2019; Zinman 2015); four studies included participants with HF (Bhatt 2021; McMurray 2019; Packer 2020; Tanaka 2020). In 12 studies, all participants had diabetes. In the remaining two studies (McMurray 2019; Packer 2020), only some participants had diabetes.

Excluded studies

Sixty-seven records were excluded after assessing the full-text articles. The most common reason for exclusion was that studies had the wrong type of study participants, and enrolled less than 80% of participants with CVDs (Excluded studies).

Studies awaiting classification

We categorised three studies (three records) as 'Studies awaiting classification' (EMPA-HEART2; EXCEED; SUPERIOR). Of these, two studies investigated SGLT2i (EMPA-HEART2; EXCEED), and one investigated DPP4i (SUPERIOR). One study (EMPA-HEART2) has myocardial infarction as an inclusion criterion (minor criteria), but because the study is still recruiting, it is impossible to know what will be the proportion of CVD patients. This study focuses mainly on cardiac remodelling in people without diabetes. The other two studies (EXCEED; SUPERIOR) were eligible for their study populations: participants with chronic heart failure, and participants with coronary artery disease, respectively. However, the duration of the interventions in these studies remains unclear.

Ongoing studies

We categorised 13 studies (23 records) as ongoing studies. Of these, eight studies investigated SGLT2i (CANONICAL; DAPPER; DELIVER; EMMY; EMPA-TROPISM; EMPEROR-Preserved; REFORM; SUGAR-DM-HF). Two studies (Li 2018; MEASURE-HF) assessed the effects of DPP4i, and three studies (LEADPACE; SELECT; STEXAS) assessed the effects of GLP-1RA. The SGLT2i studies focussed on cardiovascular effects; four included people with diabetes (CANONICAL; DAPPER; REFORM; SUGAR-DM-HF), one

enrolled participants without diabetes (EMPA-TROPISM) and three (DELIVER; EMMY; EMPEROR-Preserved) did not consider baseline diabetes status as an inclusion criterion. As for studies on DPP4i, Li 2018 focussed mainly on the effects for the progression of coronary atherosclerosis and MEASURE-HF focussed on the parameters of heart function measured by MRI. Studies on GLP-1RA, namely LEADPACE, SELECT, and STEXAS, focussed mainly on the effects on claudication distance, cardiovascular effects, and the glucose-lowering effects, respectively.

Risk of bias in included studies

All 31 included studies were RCTs, with the majority assessed as having a low risk of bias. Findings of our assessment of risk of bias in the included studies are summarised in Characteristics of included studies, Figure 2 and Figure 3.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

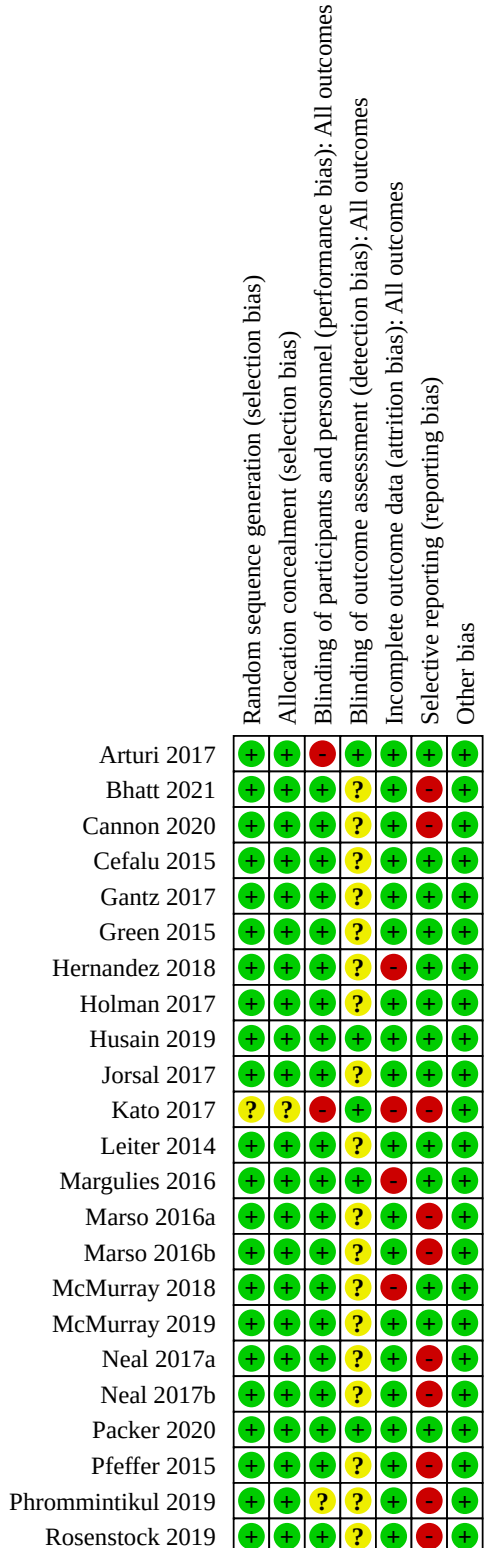


Figure 2. (Continued)

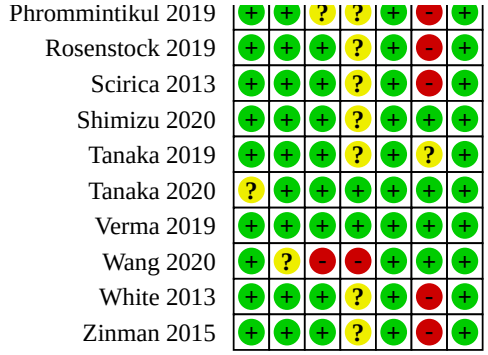
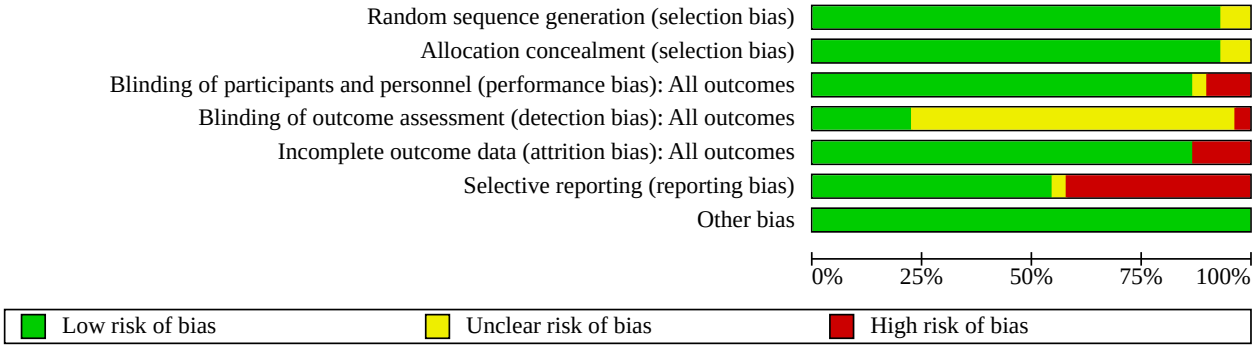


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

Twenty-nine studies (93.5%) reported adequate methods for sequence generation such as random number tables or computer-generated random numbers and were assessed as having low risk of bias. The other two studies (Kato 2017; Tanaka 2020) were assessed as having unclear risk of bias because the process of randomisation was not clearly stated.

Twenty-nine studies (93.5%) were judged to have low risk of bias because allocation concealment was achieved by using central allocation. The remaining studies (Kato 2017; Wang 2020) were assessed to be at unclear risk of bias, because methods for allocation concealment were not clearly mentioned.

Blinding

In 27 of 31 studies (87.1%), it was reported that participants and personnel were well-blinded. We judged them as having a low risk of bias. Three studies were assessed to be at high risk of bias, as they were open-label studies (Arturi 2017; Kato 2017; Wang 2020). One study was assessed to be at unclear risk of bias because although it was double-blinded, this was not clearly declared (Phrommintikul 2019).

In seven of 31 studies (22.6%), it was reported that outcome assessors were well-blinded (Arturi 2017; Husain 2019; Kato 2017; Margulies 2016; Packer 2020; Tanaka 2020; Verma 2019). In one study, they were not blinded, and we judged this study to be at high risk of bias (Wang 2020). In the other 23 studies (74.2%), there was no information or insufficient information on the blinding of outcome assessors, and investigators used such terms as statements such as "blinded study" or "double-blind study." We assessed these studies as having an unclear risk of bias.

Incomplete outcome data

Twenty-seven studies (87.1%) were judged as having a low risk of attrition bias. Four studies (12.9%) had a high risk of attrition bias. In these four studies, more than 20% of participants were lost to follow-up, or discontinued study drugs for some reason (Hernandez 2018; Kato 2017; Margulies 2016; McMurray 2018).

Selective reporting

In all 31 studies, primary outcomes were fully reported in the articles. Some secondary outcomes were available in supplemental files to the main reports, as well as in the ClinicalTrials.gov or WHO ICTRP trials registries. In 13 studies (41.9%), however, some secondary outcomes were not reported in these sources, so we judged them as having high risk of bias (Bhatt 2021; Cannon 2020a; Kato 2017; Marso 2016a; Marso 2016b; Neal 2017a; Neal 2017b; Pfeffer 2015; Phrommintikul 2019; Rosenstock 2019; Scirica 2013; White 2013; Zinman 2015). One study was judged to be at unclear risk of bias because outcomes other than the primary endpoint were not clearly reported (Tanaka 2019).

Other potential sources of bias

There were no other obvious potential sources of bias in the 31 studies.

Effects of interventions

See: **Summary of findings 1** DPP4i compared to placebo in people with CVD: efficacy outcomes; **Summary of findings 2** DPP4i compared to placebo in people with CVD: safety outcomes; **Summary of findings 3** GLP-1RA compared to placebo in people with CVD: efficacy outcomes; **Summary of findings 4** GLP-1RA compared to placebo in people with CVD: safety outcomes; **Summary of findings 5** SGLT2i compared to placebo in people with CVD: efficacy outcomes; **Summary of findings 6** SGLT2i compared to placebo in people with CVD: safety outcomes

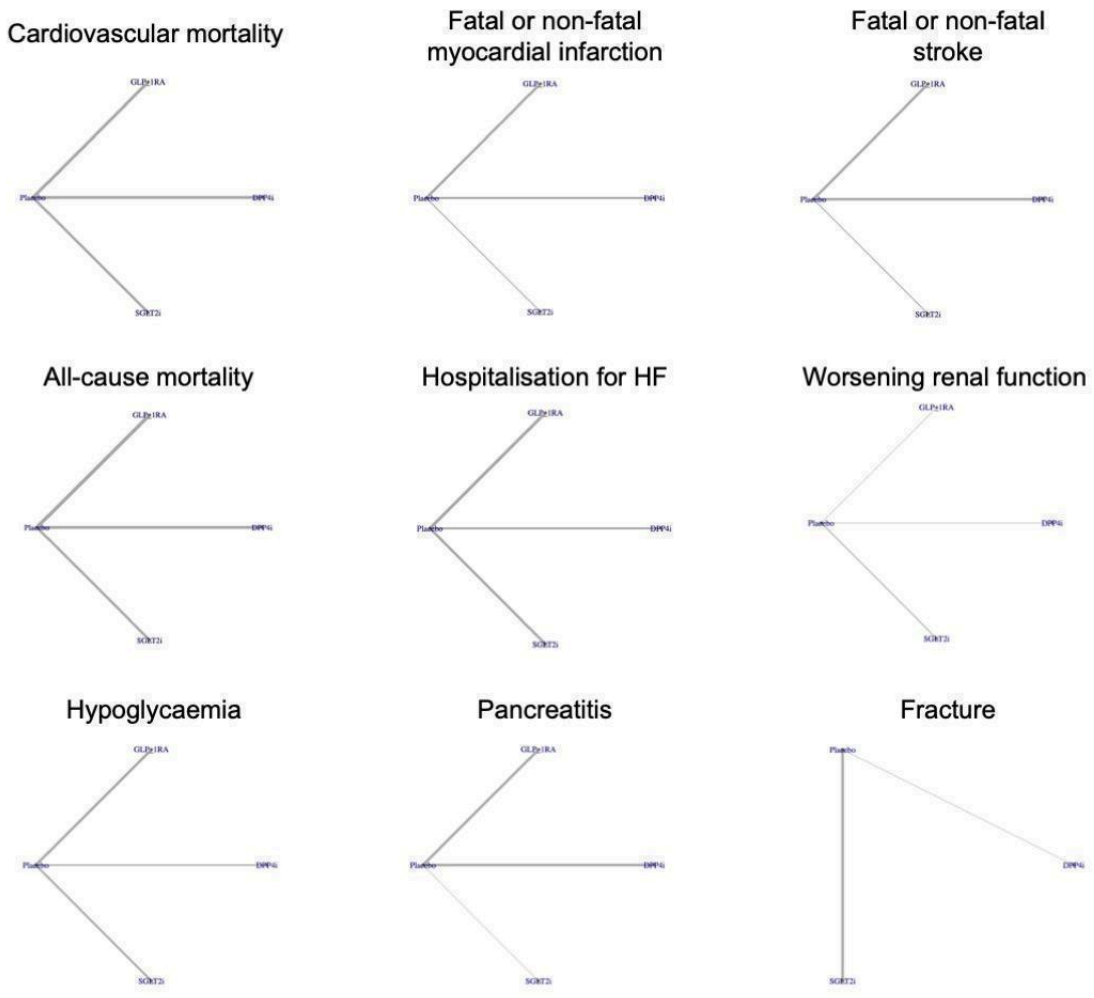
Please see Summary of findings 1; Summary of findings 3; Summary of findings 5; Table 1; Table 2.

As described previously, we performed standard pairwise and network meta-analysis for 20 studies. Findings from the remaining 11 studies were summarised narratively (Included studies). However, we inferred several outcomes such as all-cause mortality in some studies and described them in the section for each outcome.

Pairwise and network meta-analyses

Because we could not find direct head-to-head comparisons of each class of drugs, we conducted direct standard pairwise meta-analysis, and compared results with placebo and network meta-analysis. In the 'Summary of findings' tables, we described the effects of interventions, sorting these tables by each class of drugs (Summary of findings 1; Summary of findings 3; Summary of findings 5). To better present our results, we described them according to the type of outcome measure. We pooled data from reports of each of the three types of drugs to perform network meta-analysis, and we assessed class effects. There were no direct comparisons other than that of target drug versus placebo (Figure 4). We considered that the transitivity assumption was valid because we selected specific populations and indirect estimates in network meta-analysis were only made by using placebo node. We presented our results from the pairwise meta-analysis first, followed by those from the network meta-analysis and then from the indirect network meta-analysis.

Figure 4. Network plot Solid lines represent direct comparisons. Network plot of bone fracture included only three nodes.



Cardiovascular mortality was reported in almost all trials except the FIGHT trial (Margulies 2016), and all-cause mortality was reported in all 20 pooled trials. Thirteen trials reported the rates of fatal or non-fatal myocardial infarction (Cannon 2020; Gantz 2017; Green 2015; Hernandez 2018; Holman 2017; Marso 2016a; Marso 2016b; Neal 2017a; Neal 2017b; Pfeffer 2015; Rosenstock 2019; Scirica 2013; Zinman 2015) and 14 reported the rates of fatal or non-fatal stroke (Cannon 2020; Gantz 2017; Green 2015; Hernandez 2018; Holman 2017; Marso 2016a; Marso 2016b; McMurray 2018; Neal 2017a; Neal 2017b; Pfeffer 2015; Rosenstock 2019; Scirica 2013; Zinman 2015). Seventeen trials reported the rates of hospitalisation for HF (Bhatt 2021; Cannon 2020; Gantz 2017; Green 2015; Holman 2017; Husain 2019; Margulies 2016; Marso 2016a; Marso 2016b; McMurray 2019; Neal 2017a; Neal 2017b; Packer 2020; Pfeffer 2015; Rosenstock 2019; Scirica 2013; Zinman 2015).

Eighteen trials reported at least one of our a priori safety outcomes (Bhatt 2021; Cannon 2020; Gantz 2017; Green 2015; Hernandez 2018; Holman 2017; Husain 2019; Margulies 2016; Marso 2016a; Marso 2016b; McMurray 2019; Neal 2017a; Neal 2017b; Packer 2020; Rosenstock 2019; Scirica 2013; White 2013; Zinman 2015). Six trials reported worsening renal function including end-stage kidney disease (defined as GFR < 15) and/or initiation of renal replacement therapy (Marso 2016b; McMurray 2019; Neal 2017a; Neal 2017b; Packer 2020; Scirica 2013). Although we planned to include initiation of renal replacement therapy as a secondary outcome and renal toxicity as one of the non-cardiac safety outcomes, we could not differentiate these from end-stage renal disease.

Furthermore, the definition of renal toxicity/safety outcome differed across studies. Cut-off criteria of creatinine level or eGFR were different as follows.

- Scirica 2013; doubling of creatinine level, or creatinine > 6.0 mg/dL;
- Marso 2016b; doubling of the serum creatinine level and a creatinine clearance of less than 45 mL/min/1.73 m^2;
- McMurray 2019; reduction of 50% or more in the eGFR;
- Neal 2017a; Neal 2017b; 40% reduction in eGFR;
- Packer 2020; reduction of 40% or more in eGFR or a sustained eGFR of less than 15 mL/min/1.73 m^2 in patients with a baseline eGFR of 30 mL/min/1.73 m^2 or more, or a sustained eGFR of less than 10 mL/min/1.73 m^2 in those with a baseline eGFR of less than 30 mL/min/1.73 m^2.

We also identified evidence from 20 studies for three safety outcomes: hypoglycaemia, pancreatitis, and fracture. Hypoglycaemia requiring the assistance of another person was reported in 14 studies (Bhatt 2021; Cannon 2020; Gantz 2017; Green 2015; Hernandez 2018; Holman 2017; Husain 2019; Margulies 2016; Marso 2016a; McMurray 2019; Neal 2017a; Neal 2017b; Rosenstock 2019; Zinman 2015); pancreatitis was reported in 13 of 20 studies (Cannon 2020; Gantz 2017; Green 2015; Hernandez 2018; Holman 2017; Husain 2019; Marso 2016a; Marso 2016b; Neal 2017a; Neal 2017b; Rosenstock 2019; Scirica 2013; White 2013). Fractures were reported in eight studies (Bhatt 2021; Cannon 2020; McMurray 2019; Neal 2017a; Neal 2017b; Packer 2020; Scirica 2013; Zinman 2015).

Since data on hypoglycaemia reported across GLP-1RA studies showed considerable heterogeneity (I^2 = 76%), we opted to report the effects of GLP-1RA on hypoglycaemia narratively, with standard meta-analyses performed for the other two classes of drugs. The CANVAS program (Neal 2017a; Neal 2017b) only reported patient-year outcomes; we did not include these data in our meta-analysis. For further review findings, see Summary of findings 1; Summary of findings 2; Summary of findings 3; Summary of findings 4; Summary of findings 5; Summary of findings 6.

I) Efficacy outcomes

I-i) Cardiovascular mortality

Pairwise meta-analysis

Six RCTs compared DPP4i with placebo (Gantz 2017; Green 2015; McMurray 2018; Rosenstock 2019; Scirica 2013; White 2013). DPP4i did not reduce cardiovascular mortality compared with placebo (fixed-effect model: OR 1.00, 95% CI 0.91 to 1.09; 47,968 participants; 6 studies; high-certainty evidence; Analysis 1.1).

Six RCTs compared GLP-1RA with placebo (Hernandez 2018; Holman 2017; Husain 2019; Marso 2016a; Marso 2016b; Pfeffer 2015). GLP-1RA reduced the risk of cardiovascular mortality compared with placebo (fixed-effect model: OR 0.87, 95% CI 0.79 to 0.95, I^2 = 20%; 46,093 participants, 6 studies; high-certainty evidence; Analysis 2.1).

Five RCTs compared SGLT2i with placebo (Bhatt 2021; Cannon 2020; McMurray 2019; Packer 2020; Zinman 2015). SGLT2i probably reduced the risk of cardiovascular mortality compared with placebo (random-effects model: OR 0.82 , 95% CI 0.70 to 0.95, I^2 = 56%; 24,962 participants, 5 studies; moderate-certainty evidence; Analysis 3.1).

In summary, compared with placebo, GLP-1RA and SGLT2i reduced cardiovascular mortality for people with any CVDs (Analysis 2.1; Analysis 3.1). In contrast, DPP4i did not reduce cardiovascular mortality (Analysis 1.1).

Network meta-analysis

Compared with placebo, GLP-1RA and SGLT2i reduced cardiovascular mortality (OR 0.87, 95% CrI 0.76 to 0.98; high-certainty evidence; and OR 0.82, 95% CrI 0.72 to 0.94; moderate-certainty evidence, respectively), whereas DPP4i did not reduce cardiovascular mortality (OR 0.99, 95% CrI 0.87 to 1.1; high-certainty evidence) (Table 1; Figure 5). Network indirect comparisons revealed that SGLT2i reduced cardiovascular mortality compared with DPP4i (LOR -0.189, 95% CrI -0.374 to -0.005), moderate-certainty evidence) (Table 2). Additionally, we ranked these interventions by the surface under the cumulative ranking curve (SUCRA). According to SUCRA score, SGLT2i was best for cardiovascular mortality (Table 1; Figure 6).

Figure 5. Forrest plot (NMA)

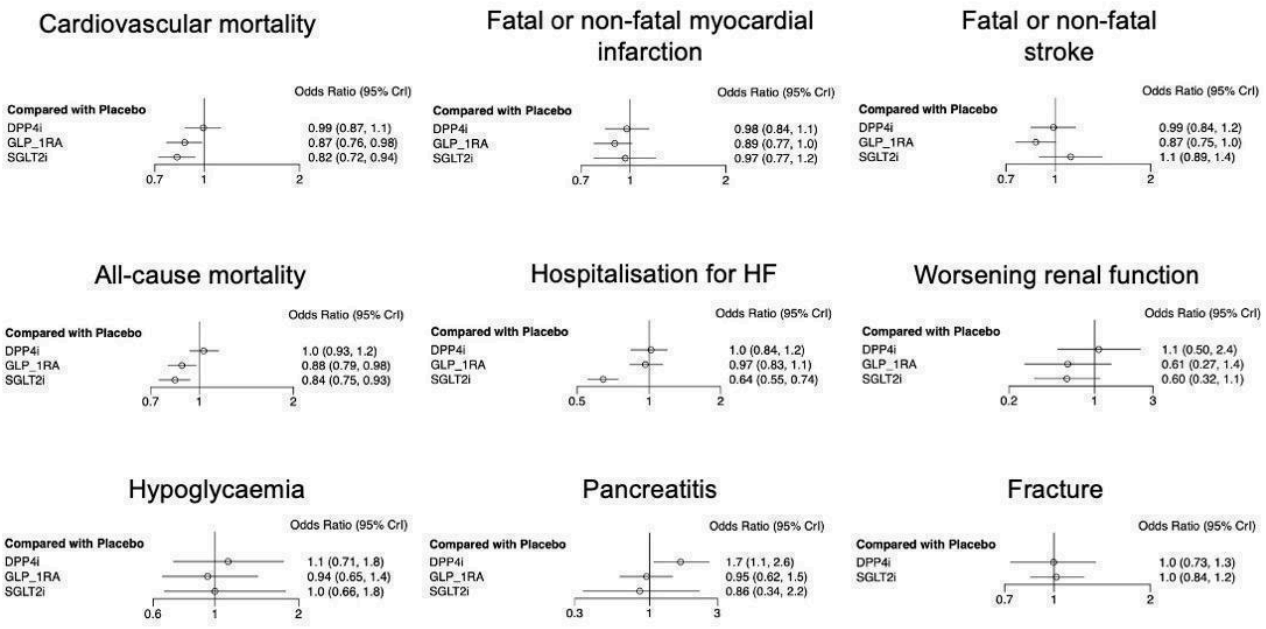
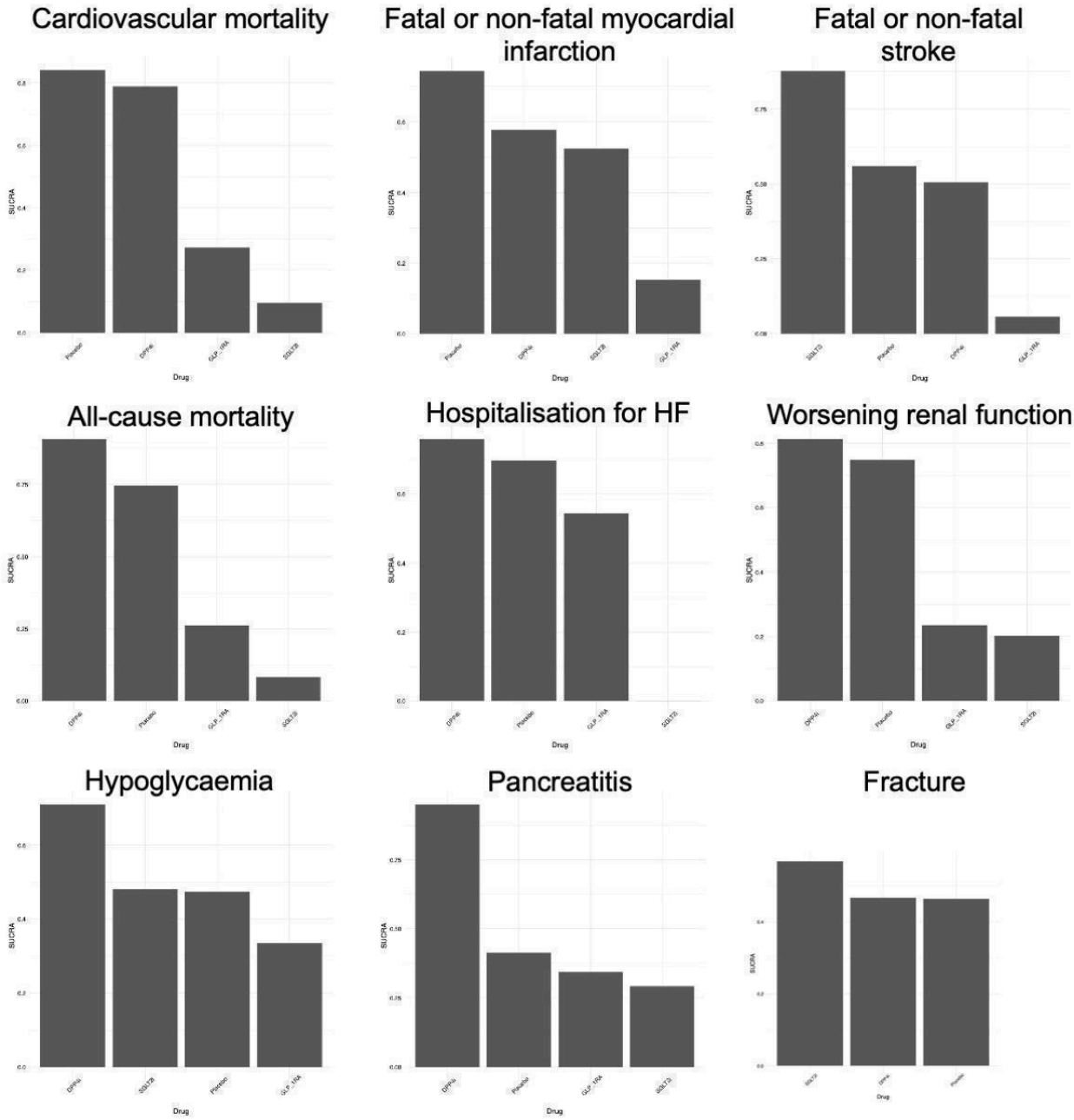


Figure 6. SUCRA ranking



Finally, from a narrative perspective of analysis, Jorsal 2017 reported only one death due to ventricular tachycardia in liraglutide (GLP1-RA) group (1/122, 0.8%) after 24 weeks of intervention.

I-ii) Fatal or non-fatal myocardial infarction

Pairwise meta-analysis

Four RCTs compared DPP4i with placebo (Gantz 2017; Green 2015; Rosenstock 2019; Scirica 2013). DPP4i did not reduce the risk of fatal or non-fatal myocardial infarction(fixed-effect model: OR 0.97, 95% CI 0.88 to 1.08; 42,334 participants, 4 studies; high-certainty evidence; Analysis 1.2).

Five RCTs compared GLP-1RA with placebo (Hernandez 2018; Holman 2017; Marso 2016a; Marso 2016b; Pfeffer 2015). GLP-1RA probably did not reduce the risk of fatal or non-fatal myocardial infarction compared with placebo (random-effects model: OR 0.89, 95% CI 0.78 to 1.01, I^2 = 57%; 42,910 participants, 5 studies; moderate-certainty evidence; Analysis 2.2).

Two RCTs compared SGLT2i with placebo (Cannon 2020; Zinman 2015). SGLT2 did not reduce the risk of fatal or non-fatal myocardial infarction compared with placebo (fixed-effect model: OR 0.97, 95% CI 0.84 to 1.12, I^2 = 28%; 15,266 participants, 2 studies; high-certainty evidence; Analysis 3.2).

All three drugs did not reduce the risk of fatal or non-fatal myocardial infarction (Analysis 1.2; Analysis 2.2; Analysis 3.2).

Network meta-analysis

Compared with placebo, all three type of drugs did not reduce the risk of fatal or non-fatal myocardial infarction (DPP4i: OR 0.98, 95% CrI 0.84 to 1.1; high-certainty evidence, GLP-1RA: OR 0.89, 95% CrI 0.77 to 1.0; moderate-certainty evidence, and SGLT2i: OR 0.97, 95% CrI 0.77 to 1.2; high-certainty evidence, respectively) (Table 1; Figure 5). Indirect network comparison did not show any class of drugs reducing the risk of fatal or non-fatal myocardial infarction, compared with other drugs (Table 2). According to SUCRA score, GLP-1RA ranked first for the outcome of fatal or non-fatal myocardial infarction (Table 1; Figure 6).

I-iii) Fatal or non-fatal stroke

Pairwise meta-analysis

Five RCTs compared DPP4i with placebo (Gantz 2017; Green 2015; McMurray 2018; Rosenstock 2019; Scirica 2013). DPP4i did not reduce the risk of fatal or non-fatal stroke (fixed-effect model: OR 1.00, 95% CI 0.87 to 1.14; 42,588 participants, 5 studies; high-certainty evidence; Analysis 1.3).

Five RCTs compared GLP-1RA with placebo (Hernandez 2018; Holman 2017; Marso 2016a; Marso 2016b; Pfeffer 2015). GLP-1RA reduced the risk of fatal or non-fatal stroke compared with placebo (fixed-effect model: OR 0.87, 95% CI 0.77 to 0.98, I^2 = 1%; 42,910 participants, 5 studies; high-certainty evidence; Analysis 2.3).

Two RCTs compared SGLT2i with placebo (Cannon 2020; Zinman 2015). SGLT2i probably did not reduce the risk of fatal or non-fatal stroke (fixed-effect model: OR 1.12, 95% CI 0.92 to 1.36; 15,266 participants, 2 studies; moderate-certainty evidence; Analysis 3.3).

Compared with placebo, only GLP-1RA reduced stroke (Analysis 2.3). The other drugs did not reduce the risk of fatal or non-fatal stroke (Analysis 1.3; Analysis 3.3).

Network meta-analysis

Compared with placebo, all three type of drugs did not reduce the risk of fatal or non-fatal stroke (DPP4i: OR 0.99, 95% CrI 0.84 to 1.2; high-certainty evidence; GLP-1RA: OR 0.87, 95% CrI 0.75 to 1.0; high-certainty evidence; SGLT2i: OR 1.1, 95% CrI 0.89 to 1.4; moderate-certainty evidence, respectively) (Table 1; Figure 5). Indirect network comparison also did not show that any class of drugs reduced the risk of fatal or non-fatal stroke compared with other drugs (Table 2). According to SUCRA scores, GLP-1RA ranked first for the outcome of fatal or non-fatal stroke (Table 1; Figure 6).

From the perspective view of narrative synthesis, Phrommintikul 2019 reported no stroke events in both dapagliflozin (SGLT2i) and vildagliptin (DPP4i) groups.

I-iv) All-cause mortality

Pairwise meta-analysis

Six RCTs compared DPP4i with placebo (Gantz 2017; Green 2015; McMurray 2018; Rosenstock 2019; Scirica 2013; White 2013). DPP4i did not reduce the risk of all-cause mortality (fixed-effect model: OR 1.03, 95% CI 0.96 to 1.11, I^2 = 37%; 47,968 participants, 6 studies; high-certainty evidence; Analysis 1.4).

Seven RCTs compared GLP-1RA with placebo (Hernandez 2018; Holman 2017; Husain 2019; Margulies 2016; Marso 2016a; Marso 2016b; Pfeffer 2015). GLP-1RA reduced the risk of all-cause mortality compared with placebo (fixed-effect model: OR 0.88, 95% CI 0.82 to 0.95, I^2 = 20%; 46,393 participants, 7 studies; high-certainty evidence; Analysis 2.4).

Five RCTs compared SGLT2i with placebo (Bhatt 2021; Cannon 2020; McMurray 2019; Packer 2020; Zinman 2015). SGLT2i probably reduced the risk of all-cause mortality compared with placebo (random-effects model: OR 0.84, 95% CI 0.74 to 0.96, I^2 = 56%; 24,962 participants, 5 studies; moderate-certainty evidence; Analysis 3.4).

Similar to findings of cardiovascular mortality, compared with placebo, GLP-1RA and SGLT2i reduced all-cause mortality (Analysis 2.4; Analysis 3.4). However, DPP4i did not reduce all-cause mortality (Analysis 1.4).

Network meta-analysis

Compared with placebo, GLP-1RA and SGLT2i decreased all-cause mortality (OR 0.88, 95% CrI 0.79 to 0.98; high-certainty evidence, and OR 0.84, 95% CrI 0.75 to 0.93; moderate-certainty evidence, respectively), whereas DPP4i did not reduce all-cause mortality (OR 1.0, 95% CrI 0.93 to 1.2; moderate-certainty evidence) (Table 1; Figure 5). Indirect network comparison revealed that SGLT2i and GLP-1 reduced all-cause mortality compared with DPP4i (LOR -0.211, 95% CrI -0.372 to -0.061; moderate-certainty evidence, and LOR -0.160, 95% CrI -0.311 to -0.014; high-certainty evidence, respectively) (Table 2). According to SUCRA score, SGLT2i was best for all-cause mortality (Table 1; Figure 6).

Narrative synthesis for all-cause mortality

Four studies (Arturi 2017; Kato 2017; Phrommintikul 2019; Wang 2020) about the effects of DPP4i on all-cause mortality. In Arturi 2017 and Phrommintikul 2019, we could infer there was no mortality at six months (one compared dapagliflozin and vildagliptin, and one compared liraglutide, sitagliptin, and glargine). Because these two trials included fewer than 30 people in each intervention group, sample size could be too small to detect mortality within six months.

Treatment with GLP1-RA was used in three studies (Arturi 2017; Jorsal 2017; Wang 2020). Jorsal 2017 also evaluated the impact of liraglutide compared with placebo and revealed only one death (cardiovascular death due to ventricular tachycardia) in liraglutide group (1/122, 0.8%) after 24 weeks of intervention.

A total of seven studies (Cefalu 2015; Leiter 2014; Phrommintikul 2019; Shimizu 2020; Tanaka 2019; Tanaka 2020; Verma 2019) evaluated SGLT2i. No deaths were reported at six months in the SGLT2-arms in Phrommintikul 2019 (dapagliflozin; n = 25) and in Verma 2019 (empagliflozin; n = 49). The small study sample size potentially hindered the measurement of mortality outcomes by these two studies. Leiter 2014 and Cefalu 2015 evaluated the effects of dapagliflozin in larger groups of study participants (n = 962 and n = 922, respectively). These trials reported all-cause mortality at 52 weeks (4/480, 0.8% in dapagliflozin group versus 5/482, 1.0% in placebo and 7/459, 1.5% in dapagliflozin group versus 2/455, 0.4% in placebo, respectively). Tanaka 2020 compared canagliflozin with glimepiride and reported only two deaths (all-cause) in the control group (2/120, 1.6%).

I-v) Hospitalisation for HF

Pairwise meta-analysis

Four RCTs compared DPP4i with placebo (Gantz 2017; Green 2015; Rosenstock 2019; Scirica 2013). DPP4i probably did not reduce the risk of hospitalisation for HF (random-effects model: OR 0.99, 95% CI 0.80 to 1.23, I^2 = 71%; 42,334 participants, 4 studies; moderate-certainty evidence; Analysis 1.5).

Six RCTs compared GLP-1RA with placebo (Holman 2017; Husain 2019; Margulies 2016; Marso 2016a; Marso 2016b; Pfeffer 2015). GLP-1RA did not reduce the risk of hospitalisation for HF between two groups (fixed-effect model: OR 0.95, 95% CI 0.85 to 1.06; 36,930 participants, 6 studies; high-certainty evidence; Analysis 2.5).

Five RCTs compared SGLT2i with placebo (Bhatt 2021; Cannon 2020; McMurray 2019; Packer 2020; Zinman 2015). SGLT2i reduced the risk of hospitalisation for HF compared with placebo (fixed-effect model: OR 0.65, 95% CI 0.59 to 0.71, I^2 = 33%; 24,962 participants, 5 studies; high-certainty evidence; Analysis 3.5).

In summary, compared with placebo, SGLT2i reduced hospitalisation for HF (Analysis 3.5). The other drugs did not reduce the risk of hospitalisation for HF (Analysis 1.5; Analysis 2.5).

Network meta-analysis

Compared with placebo, SGLT2i reduced hospitalisation for HF (OR 0.64, 95% CrI 0.55 to 0.74; high-certainty evidence), whereas DPP4i and GLP-1RA did not reduce hospitalisation for HF (OR 1.0, 95% CrI 0.84 to 1.2; moderate-certainty evidence; and OR 0.97, 95% CrI 0.83 to 1.1; high-certainty evidence, respectively) (Table 1; Figure 5). Indirect network comparison revealed that only SGLT2i reduced hospitalisation for HF with other drugs (versus DPP4i: LOR -0.461, 95% CrI -0.674 to -0.218); GLP-1RA: LOR -0.405, 95% CrI -0.637 to -0.199) (Table 2). According to SUCRA score, SGLT2i was best in regard to hospitalisation for HF (Table 1; Figure 6).

II) Safety outcomes

Pairwise meta-analysis

Only four included studies assessed the outcome of worsening renal function: one RCT evaluated the effects of DPP4i (Scirica 2013), one RCT about GLP-1RA (Marso 2016b) and two studies about SGLT2i (McMurray 2019; Packer 2020). DPP4i may not increase the risk of worsening renal function (fixed-effect model: OR 1.08, 95% CI 0.88 to 1.33; 16,492 participants, 1 study; low-certainty evidence; Analysis 1.6). Compared with placebo, GLP-1RA may reduce the risk of worsening renal function (fixed-effect model: OR 0.61, 95% CI 0.44 to 0.84; 3,297 participants, 1 study; low-certainty evidence; Analysis 2.6); SGLT2i probably reduced the risk of worsening renal function (fixed-effect model: OR 0.59, 95% CI 0.43 to 0.82; 8,474 participants, 2 studies; moderate-certainty evidence; Analysis 3.6).

Network meta-analysis

Compared with placebo, all three classes of drugs did not increase the risk of worsening renal function (Table 1; Figure 5). Indirect network comparison also revealed that all three classes of drugs did not increase the risk of worsening renal function compared with another class of drugs (Table 2). According to SUCRA score, SGLT2i was best about worsening renal function (Table 1; Figure 6).

II-ii) Hypoglycaemia

Pairwise meta-analysis

Compared with placebo, DPP4i probably did not increase the risk of hypoglycaemia (fixed-effect model: OR 1.11, 95% CI 0.95 to 1.29; 25,842 participants, 3 studies; moderate-certainty evidence. SGLT2i probably exerted no effect on hypoglycaemia (fixed-effect model: OR 0.90, 95% CI 0.75 to 1.07, I^2 = 33%; 21,232 participants, 4 studies; moderate-certainty evidence) (Analysis 1.7; Analysis 3.7; Summary of findings 1; Summary of findings 3; Summary of findings 5).

The risk of hypoglycaemia in studies evaluating GLP-1RA ranged from 0.8% to 3.4% after excluding the FIGHT trial (Margulies 2016), which showed 8.0% in liraglutide group and 6.0% in placebo group. These differences could be derived from the small sample size (n = 154 in liraglutide group and n = 146 in placebo group). The LEADER trial (Marso 2016a) and Harmony Outcomes (Hernandez 2018) showed GLP-1RA reduce the risk of hypoglycaemia (OR 0.75, 95% CI 0.59 to 0.97; and OR 0.56 95% CI 0.36 to 0.87, respectively). The other three studies (Holman 2017; Husain 2019; Margulies 2016) revealed there was no difference between GLP-1RA and placebo.

As described above, results on hypoglycaemia across the GLP-1RA studies showed significant heterogeneity (I^2 = 76%, P = 0.002). Therefore, we did not pool the study results and instead performed only standard pairwise meta-analysis for the other two classes of drugs.

II-iii) Pancreatitis

Pairwise meta-analysis

Compared with placebo, DPP4i were likely to increase the risk of pancreatitis (fixed-effect model: OR 1.63, 95% CI 1.12 to 2.37; 47,684 participants, 5 studies; moderate-certainty evidence), whereas GLP-1RA and SGLT2i may have no impact on this safety outcome (fixed-effect model: OR 0.96, 95% CI 0.68 to 1.35; 40,035 participants, 5 studies; low-certainty evidence for GLP1-RA; OR 0.85, 95% CI 0.39 to 1.86; 8,246 participants, 1 study; low-certainty evidence for SGLT2i) (Analysis 1.8; Analysis 2.7; Analysis 3.8; Summary of findings 1; Summary of findings 3; Summary of findings 5).

In summary, only DPP4i were reported to have increased the risk of pancreatitis when compared with placebo.

Network meta-analysis

As in the standard meta-analysis, only DPP4i increased the risk of pancreatitis (OR 1.7, 95% CrI 1.1 to 2.6; moderate-certainty evidence) (Table 1; Figure 5). Indirect network comparison revealed that any class of drugs increased the risk of pancreatitis compared with other drugs (Table 2). According to SUCRA score, SGLT2i was best for pancreatitis (Table 1).

II-iv) Fracture

Pairwise meta-analysis

None of the GLP-1RA studies reported data on bone fracture. Compared with placebo, DPP4i may not increase the risk of fracture while SGLT2i exerted no effect on this safety outcome (fixed-effect model: OR 1.00, 95% CI 0.83 to 1.19; 16,492 participants, 1 study; moderate-certainty evidence for DPP4i; OR 1.02, 95% CI 0.88 to 1.18; 24,962 participants, 5 studies; high-certainty evidence for SGLT2i)

(Analysis 1.9; Analysis 3.9; Summary of findings 1; Summary of findings 3; Summary of findings 5).

Leiter 2014 reported fracture rates of 1.7% and 1.0% in the placebo and dapagliflozin groups, respectively; the results are consistent with that of the standard pairwise meta-analysis.

Network meta-analysis

Finally, compared with placebo, both DPP4i and SGLT2i did not increase the risk of fracture (DPP4i; OR 1.0, 95% CrI 0.73 to 1.4; low-certainty evidence, SGLT2i; OR 1.0, 95% CI 0.84 to 1.2; high-certainty evidence) (Table 1; Figure 5). Indirect network comparison revealed that SGLT2i did not increase the risk of fracture compared with DPP4i (LOR 0.02 95% CrI -0.333 to 0.385; low-certainty evidence). According to SUCRA score, DPP4i was best for fracture (Table 1).

III) Subgroup analyses

We did not identify any eligible studies involving people with chronic kidney disease (CKD, defined by eGFR < 60 ml/min/1.73 m^2); all the studies included in our quantitative synthesis involved placebo; none of the included studies evaluated combination therapy as a mode of treatment; study duration of all but two studies (Bhatt 2021; Margulies 2016) was over 52 weeks. Therefore, we performed subgroup analyses by type of baseline CVD (ASCVD or HF) and baseline comorbidity (diabetes mellitus)(Table 3). Due to limited data, network meta-analyses for these subgroups were limited to the outcomes of cardiovascular mortality and all-cause mortality only. Furthermore, we collected data on LVEF from a clinician's perspective. The extent or characteristics of LVEF was described only in the studies involving people with HF and not in those enrolling people with ASCVD. Of these HF-population studies, all but one (Bhatt 2021) reported the level of LVEF (EF < 40%). Therefore, due to insufficient information regarding the definition of LVEF in our included studies, our subgroup analysis of HF as a baseline CVD may mainly reflect participants with heart failure and reduced ejection fraction.

Pairwise meta-analysis

Studies on DPP4i

In the six pooled studies investigating DPP4i, two involved people with ASCVD only (Gantz 2017; White 2013), one enrolled people with HF only (McMurray 2018) and all the study participants had diabetes mellitus at baseline. There were no subgroup differences for cardiovascular and all-cause mortality (Analysis 4.1; Analysis 4.2).

Studies on GLP-1RA

Across the seven pooled studies investigating the effects of GLP-1RA, two enrolled people with ASCVD only (Hernandez 2018; Pfeffer 2015), one investigated people with HF only (Margulies 2016), and the study participants in all but one study Margulies 2016 had diabetes mellitus at baseline and thus we did not perform a subgroup analysis for diabetes. In the ASCVD subgroup, GLP-1RA did not reduce cardiovascular mortality (fixed-effect model: OR 0.96, 95% CI 0.81 to 1.14, 15,521 participants (Analysis 5.1), fatal and non-fatal myocardial infarction (random-effects model: OR 0.88, 95% CI 0.64 to 1.21; 15,521 participants (Analysis 5.2); fatal and non-fatal stroke (fixed-effect model: OR 0.96, 95% CI 0.77 to 1.19, 15,521 participants; Analysis 5.3), and all-cause mortality (fixed-effect model: OR 0.95, 95% CI 0.82 to 1.09, 15,521 participants; Analysis 5.4). There were no subgroup differences for these four outcomes (cardiovascular mortality, fatal and non-fatal myocardial infarction, fatal and non-fatal stroke, and all-cause mortality).

Studies on SGLT2i

For the seven pooled studies investigating SGLT2i, two studies enrolled people with ASCVD only (Cannon 2020; Zinman 2015), three studied people with HF only (Bhatt 2021; McMurray 2019; Packer 2020) and five studied only people with diabetes at baseline (Bhatt 2021; Cannon 2020; Neal 2017a; Neal 2017b; Zinman 2015).

In the ASCVD subgroup, SGLT2i did not reduce cardiovascular mortality (random-effects model: OR 0.75, 95% CI 0.50 to 1.13; 15,226 participants; Analysis 6.1) or all-cause mortality (random-effects model: OR 0.79, 95% CI 0.58 to 1.08; 15,226 participants; Analysis 6.3).

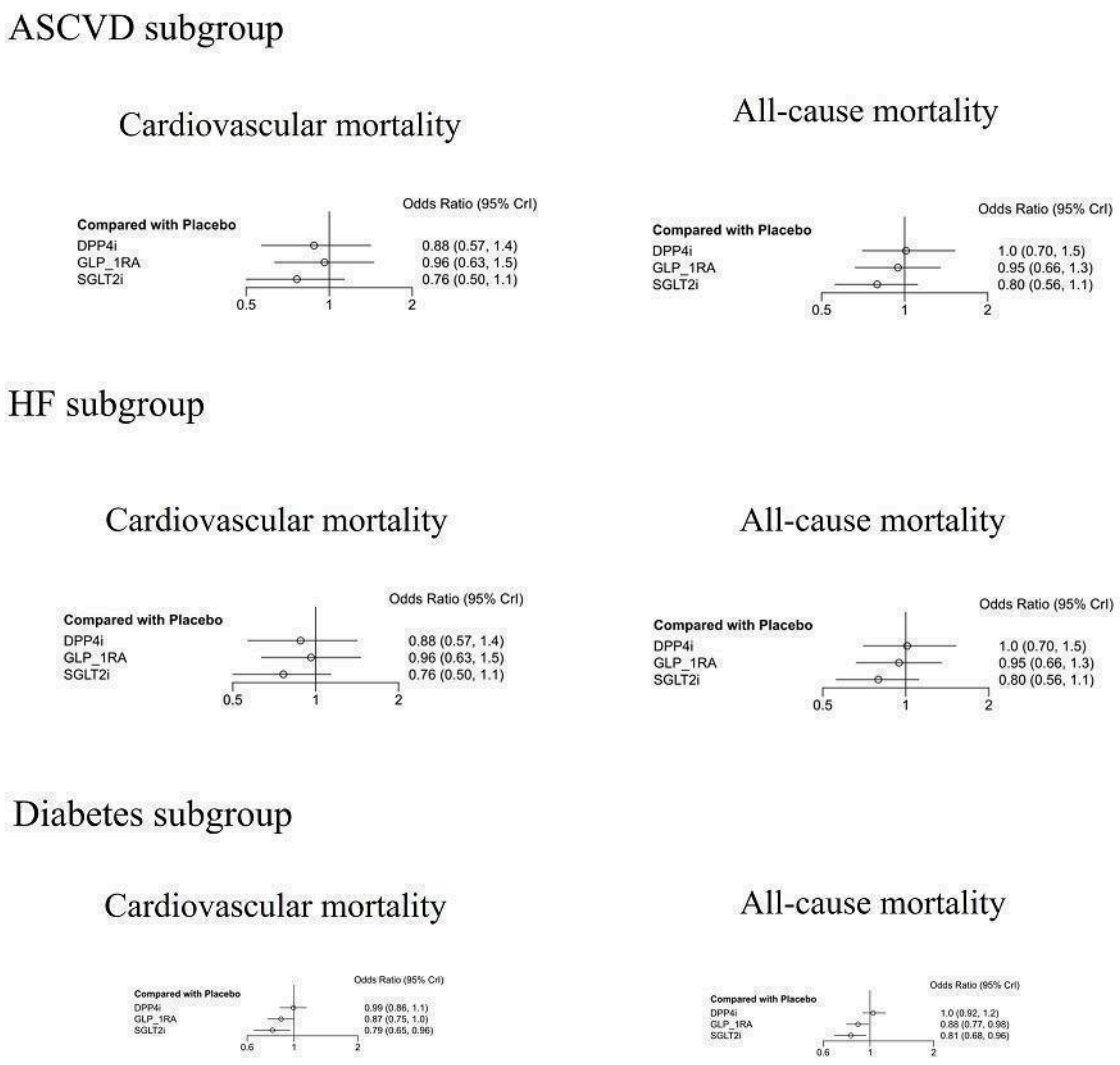
In the HF subgroup, SGLT2i reduced both cardiovascular mortality (random-effects model: OR 0.86, 95% CI 0.75 to 0.98, 9,696 participants; Analysis 6.1) and all-cause mortality (random-effects model: OR 0.88, 95% CI 0.78 to 0.99; 9,696 participants; Analysis 6.3).

Of note, in the 'not all diabetes' subgroup, SGLT2i reduced cardiovascular mortality (random-effects model: OR 0.86, 95% CI 0.75 to 0.99; 8,474 participants; Analysis 6.2). However, there were also no subgroup differences for these two outcomes (cardiovascular mortality and all-cause mortality).

Network meta-analysis

Findings from the ASCVD subgroup and HF subgroup indicated that none of the three classes of interventions impacted on the outcomes of cardiovascular mortality and all-cause mortality as compared to placebo. In the diabetes subgroup, GLP-1RA and SGLT2i reduced all-cause mortality (OR 0.88, 95% CrI 0.77 to 0.98; OR 0.81, 95% CrI 0.68 to 0.96, respectively); treatment with SGLT2i also reduced cardiovascular mortality (OR 0.79, 95% CrI 0.65 to 0.96) (Figure 7).

Figure 7. Subgroup NMA for cardiovascular mortality and all-cause mortality.



IV) Sensitivity analysis

All our trials adopted an intention-to-treat approach and full texts were available for all included studies. Therefore, we performed sensitivity analysis based on the outcome of our assessment of risk of bias in included studies (DPP4i: Figure 8, GLP-1RA: Figure 9, SLGT2i: Figure 10).

Figure 8. Sensitivity analysis with trials assessed at low risk of bias(A: cardiovascular mortality, B: fatal or non-fatal myocardial infarction, C: fatal or non-fatal stroke, D: all-cause mortality); DPP4i

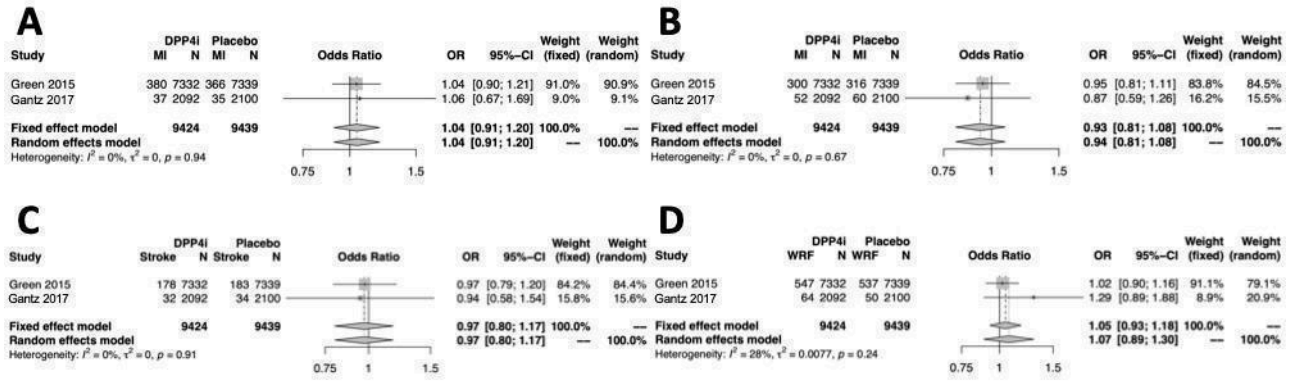


Figure 9. Sensitivity analysis with trials assessed at low risk of bias(A: cardiovascular mortality, B: fatal or non-fatal myocardial infarction, C: fatal or non-fatal stroke, D: all-cause mortality); GLP1-RA

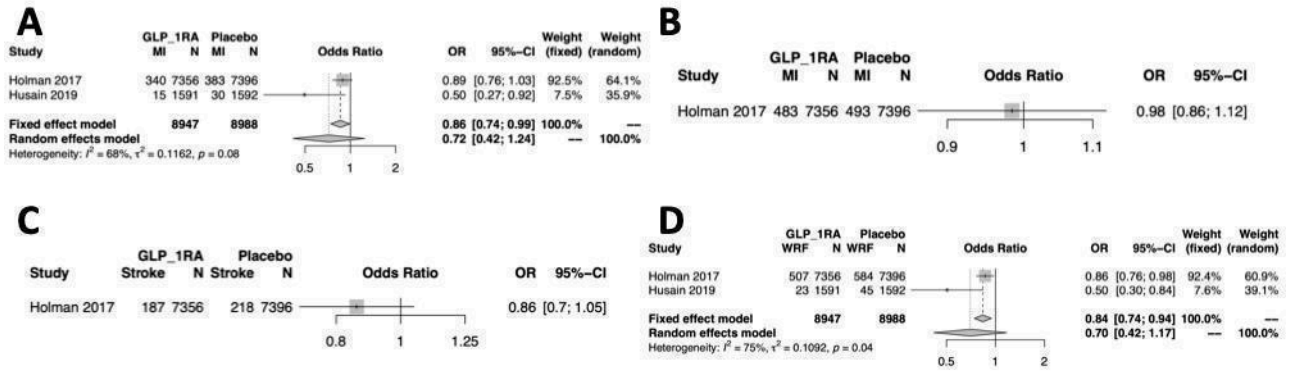
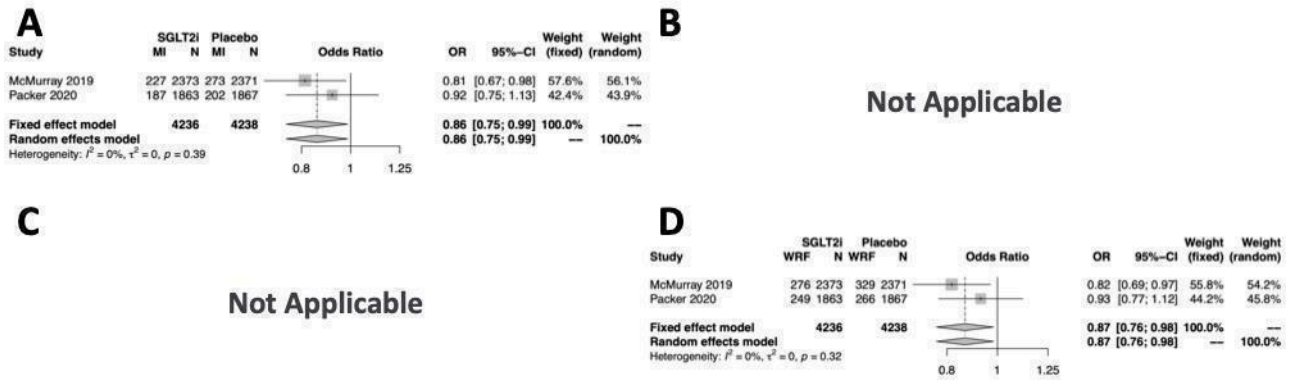


Figure 10. Sensitivity analysis with trials assessed at low risk of bias(A: cardiovascular mortality, B: fatal or non-fatal myocardial infarction, C: fatal or non-fatal stroke, D: all-cause mortality); SGLT2i

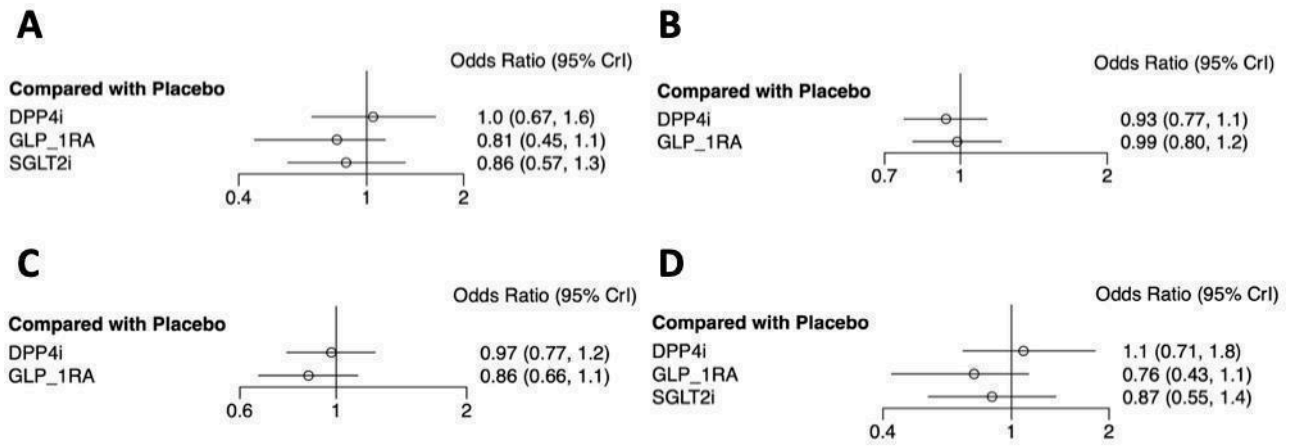


By including trials assessed at low risk of bias (i.e. for which we rated all domains at low risk), DPP4i and GLP-1RA did not lead to any significant changes for any of our a priori outcomes (cardiovascular mortality, fatal or non-fatal myocardial infarction; fatal or non-fatal stroke; and all-cause mortality) (Figure 8; Figure 9). However, treatment with SGLT2i led to reduced cardiovascular mortality and all-cause mortality (fixed-effect model: OR 0.86, 95% CI 0.75 to 0.99; 8,474 participants; OR 0.87, 95% CI 0.76 to 0.98; 8,474 participants, respectively) (Figure 10). All SGLT2i studies reporting the outcomes of fatal/non-fatal myocardial infarction or fatal/non-fatal stroke

were judged to be at unclear or moderate risk of bias and thus were not included in the sensitivity analyses (Analysis 3.2; Analysis 3.3).

Network meta-analysis further revealed that none of the included interventions exerted effects on cardiovascular mortality, fatal or non-fatal myocardial infarction, fatal or non-fatal stroke, and all-cause mortality (Figure 11).

Figure 11. Sensitivity analysis with trials assessed at low risk of bias(A: cardiovascular mortality, B: fatal or non-fatal myocardial infarction, C: fatal or non-fatal stroke, D: all-cause mortality); network meta-analysis



DISCUSSION

Summary of main results

This systematic review with network meta-analysis investigated the efficacy and safety of the three classes of antihyperglycaemic drugs for people with CVD. We included 31 studies (287 records) for qualitative analysis. Twenty studies (256 records) with 129,465 participants were pooled for meta-analysis. We synthesised evidence for the following outcomes: cardiovascular mortality, fatal or non-fatal myocardial infarction, fatal or non-fatal stroke, all-cause mortality, hospitalisation for HF, worsening renal function, hypoglycaemia, pancreatitis, and fractures (Table 4).

DPP4i

DPP4i did not reduce the risk of our a priori efficacy outcomes. However, moderate-certainty evidence indicated that DPP4i were likely to increase the risk of pancreatitis.

GLP-1RA

High-certainty evidence suggested that GLP-1RA reduced both cardiovascular mortality and all-cause mortality. Moderate- to high-certainty evidence suggested that GLP-1RA could reduce the rates of fatal or non-fatal myocardial infarction and fatal or non-fatal stroke. However, network meta-analysis showed a wider range of 95% CrI, which included no effect. In terms of treatment rankings, GLP-1RA was the best for these two outcomes (fatal or non-fatal myocardial infarction/stroke). As for safety outcomes, low-certainty evidence suggested that GLP-1RA may reduce worsening renal function with no impact on pancreatitis.

SGLT2i

We found moderate-certainty evidence that SGLT2i probably reduced both cardiovascular mortality and all-cause mortality. In terms of treatment rankings, SGLT2i was the best for both mortality outcomes. High-certainty evidence suggested that SGLT2i reduced hospitalisation for HF and was the best in terms of treatment rankings. Moderate-certainty evidence indicated that SGLT2i probably reduced the risk of worsening renal function with no impact on other a priori safety outcomes (hypoglycaemia, pancreatitis, and fracture).

Network meta-analysis

Nearly all findings from our network meta-analysis agree with those from the standard meta-analysis. GLP-1RA may not reduce the risk of stroke, which showed similar odds estimates and wider 95% CrI compared with standard pairwise meta-analysis. Indirect estimates also supported comparison across all three classes. SGLT2i was ranked the best for CVD and all-cause mortality.

Finally, all pooled studies except Bhatt 2021 (the SOLOIST-WHF trial) reported baseline diabetic parameters including HbA1c and the changes after interventions. Because the intervention we focussed on was additional treatment, glycaemic control (measured by HbA1c) was improved, as expected, when compared to placebo. Based on current review findings, we are unable to draw robust conclusions on whether these new glucose-lowering agents may improve cardiac outcomes, regardless of diabetes control.

Overall completeness and applicability of evidence

As these three classes of drugs were originally developed as glucose-lowering agents, most of the included studies were focussed only on participants with diabetes. In this review, we focussed on participants with CVDs, to evaluate the efficacy and safety of these three classes of drugs for cardiovascular outcomes; we excluded trials in which the proportion of participants with any CVDs including heart failure was smaller than 80%. Therefore, the findings of this review are applicable especially to people with any CVDs. Although we included people with any CVDs, regardless of diabetes, 17 of 20 pooled studies concerned participants with diabetes only. A large body of evidence on populations with CVDs and without diabetes may be needed. Similarly, six of 20

studies were about ASCVD only and five of 20 pooled studies were about HF only. This evidence base could be too small to draw conclusions about subgroup differences. Furthermore, only one pooled study (Bhatt 2021; SOLOIST-WHF trial) examined heart failure with preserved ejection fraction; thus, our review results are mainly applicable to ppopulations with heart failure with reduced ejection fraction, when applicable.

Quality of the evidence

The overall certainty of the evidence ranged from low to high. Two major downgrading reasons were moderate to substantial heterogeneity in effect and that the 95% CI included no effect, with default values for appreciable harm (i.e. CI > 1.25), appreciable benefit (i.e. CI < 0.75), or both.

Potential biases in the review process

We conducted a comprehensive systematic search to obtain all eligible trials for this review. In order to minimise review bias, three review authors independently checked all results of the searches to identify relevant studies, and assessed risk of bias.

However, there were several methodological deviations between the review protocol and the review; namely, the lack of outcome data as measured within our pre-specified follow-up duration, and the absence of direct comparative studies (i.e. head-to-head trials). At the protocol stage, we planned to extract outcome data reported at 30 days, one year, and the longest follow-up duration. Despite these studies adopting variable treatment durations and follow-up periods, no included trials in this review reported 30-day or one-year outcomes. Thus, we undertook our analysis with only the longest follow-up outcomes, contrary to our original plan. We should take care of the duration of studies to interpret findings. For Bhatt 2021 and Margulies 2016, the longest follow-up was less than one year; thus; careful consideration is needed in outcome interpretation. Second, we defined worsening renal function as a safety outcome in the review, instead of the pre-defined outcomes of end-stage kidney disease, initiation of renal replacement therapy, and renal toxicity. It became apparent to us that many study investigators defined these renal outcomes as safety measures, and we were unable to clearly separate these outcomes. Thus, results of our review should be interpreted carefully, due to the differences in follow-up duration and the sub-optimal renal outcome definition.

With our network meta-analyses, which were designed to explore data from indirect comparisons, we identified only placebo-controlled trials; none of our included studies were head-to-head studies, comparing these drugs directly against each other. Therefore, none of the networks had any closed loops. We are aware of the limitations associated with our current network meta-analyses, without any mixed evidence.

Agreements and disagreements with other studies or reviews

We focussed on the effects of DPP4i, GLP-1RA and SGLT2i on secondary prevention of CVD, based on our review findings. Regarding DPP4i, our results showed almost the same results as previous reviews where a lack of significant difference was observed in the comparison with placebo in all-cause mortality, cardiovascular mortality, myocardial infarction, stroke, and HF hospitalisation (Savarese 2016; Zheng 2018). Although an existing meta-analysis reported a higher rate of HF hospitalisation in people with diabetes who were treated with DPP4i (Li 2016b), our review showed a slight increase in the odds ratio, with the result remaining statistically non-significant. When we discuss these outcomes, we should keep in mind that all referenced reviews did not focus on people with established CVD, but simply with diabetes.

Regarding GLP-1RA, our results for all-cause mortality, cardiovascular mortality, and HF hospitalisation were consistent with those reported in published reviews; treatment with GLP1-RA has been shown to reduce all-cause and cardiovascular mortality rates (Zheng 2018), but not HF hospitalisation (Li 2016a). Zheng 2018 suggested that GLP-1RA may lead to a reduced risk of stroke with no benefits on myocardial infarction, which was consistent with our results. In addition, in our review, network analysis revealed the same OR with a larger 95% CrI, which included no effects. Considering large sample sizes and the P value function theory, we could infer that GLP-1RA could reduce stroke. More relevant large-scale RCTs might be needed to determine the effectiveness of GLP-1RA on stroke outcomes.

For SGLT2i, our review showed nearly the same results as previous reviews, that SGLT2i significantly reduced all-cause mortality, cardiovascular mortality and hospitalisation for HF (McGuire 2021; Savarese 2016; Wu 2016; Zhang 2018; Zheng 2018). Although there are existing data indicating that SGLT2i could reduce the rate of myocardial infarction (Zheng 2018), no significant difference was found in our review. The main difference between our review and these others is the target population. Zhang 2018 included all diabetic people, especially the primary prevention group. The event rate of myocardial infarction was about 2.5% which was lower than we found in our review. In another study (McGuire 2021), investigators organised subgroup analysis according to the presence or absence of ASCVD and revealed that SGLT2i reduced MACE in the ASCVD subgroup (McGuire 2021). In our ASCVD-only subgroup (Cannon 2020; Zinman 2015), SGLT2i did not reduce cardiovascular mortality and all-cause mortality. First, in the previous study (McGuire 2021) MACE included evaluation of myocardial infarction and stroke. Second, the previous study included ASCVD subgroup analysis results in the main trial, which was mixed in regard to background cardiovascular disease (e.g. Wiviott 2019 included only 40% with established cardiovascular disease, in the main trial). Finally, Cannon 2020 used ertugliflozin, a relatively newer SGLT2i, and the study could not reveal its benefits on cardiovascular mortality and all-cause mortality. This largely explains why we could not identify benefits of SGLT2i in our review. More clinical trials examining ertugliflozin and people with ASCVD only (secondary prevention) could reveal whether SGLT2i can reduce mortality outcomes in people with ASCVD (not including heart failure). In HF subgroups, many articles are consistent with our review results (i.e. that SGLT2i could reduce cardiovascular mortality and all-cause mortality).

The use of SGLT2i could reduce the rate of myocardial infarction as a strategy for primary prevention; however, these drugs could not reduce the rate of myocardial infarction in people with existing CVDs. We are hopeful to synthesise additional research findings for future updates of this review involving a more diverse target population but currently, we do not have sufficient data to draw robust conclusions on the class effects of SGLT2i on cardiac outcomes in people with established CVD regardless of their diabetic status.

AUTHORS' CONCLUSIONS

Implications for practice

Our review findings suggest that among three classes of drugs, both glucagon-like peptide-1 receptor agonists (GLP-1RA) and sodium-glucose cotransporter 2 inhibitors (SGLT2i) may reduce cardiovascular and all-cause mortality, but dipeptidyl peptidase-4 inhibitors (DPP4i) may not. Additionally, SGLT2i may also reduce hospitalisation for heart failure (HF); treatment with GLP-1RA may exert beneficial effects on the rate of fatal or non-fatal stroke. As for safety outcomes, our review findings suggest that all three classes of drugs do not increase worsening of renal function, hypoglycaemia, and fractures; rather, GLP1-RA and SLGT2i may reduce worsening of renal function. DPP4i likely increased the risk of pancreatitis.

Our included studies mainly involved participants with diabetes, and these three classes of drugs were associated with better diabetic control. Thus, our results could just be a consequence of better diabetes control. Considering this possibility, we were unable to conclude that these new drugs could improve cardiovascular outcomes, regardless of diabetes. Further large-scale studies are thus warranted, with sufficient follow-up duration and involving participants without diabetes.

Implications for research

Current evidence suggests that GLP-1RA and SGLT2i may improve cardiovascular outcomes even for people with cardiovascular disease (CVD), but the underlying mechanisms are not entirely understood. A few studies in non-diabetic participants suggest that there could be positive effects of these drugs on cardiac outcomes in subpopulations without diabetes. Therefore, a larger body of evidence is warranted, investigating these seemingly promising treatment options for the non-diabetic population, to further explore their precise benefits and harms to the cardiovascular as well as other organ systems.

We are aware that the different treatment effects between subtypes of CVD as well as in people without CVD remain to be ascertained. Especially for the former, there is still a pressing need to establish whether these treatment options are useful for secondary prevention of CVD. It is worth highlighting that the follow-up periods and time points to evaluate clinical outcomes differed across studies. Future research exploring the comprehensive efficacy and safety profiles of DPP4i, GLP-1RA and SGLT2i should implement detailed evaluation of the onset of clinical events and unify outcome measurement time points to better understand the short- and long-term drug effectiveness, especially to learn when positive/negative effects start, and how long they continue. Future randomised studies should be designed with an overall objective to investigate the cardiovascular effects of these newer glucose-lowering agents, namely the effect on myocardial infarction and stroke, and other clinically relevant major cardiovascular events. At this stage, we were unable to retrieve sufficient data to explore direct comparative effects, and we eagerly await the release of head-to-head trials in this field.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Arturi 2017

Study characteristics	
Methods	**Title**: Liraglutide improves cardiac function in patients with type 2 diabetes and chronic heart failure **acronym of trial**: NA **study design**: a single-centre, open-label, randomised, 52-week active-comparator, parallel-group, pilot study **total duration of study**: 52 weeks **number of study centres and location:** single centre, Italy **date of study**: NA
Participants	**Intervention**: i) 1.8 mg liraglutide, ii) 100 mg sitagliptin, iii) glargine insulin **Cardiovascular disease categories:** history of previous acute myocardial infarction, and NYHA class II/ III and/or LVEF ≤ 45 %. All groups are ASCVD: (100%), HF: (100%) **N randomised**: i) 10, ii) 10, iii) 12 **N lost to follow-up/withdrawn:** 0 in all groups **N analysed:** i) 10, ii) 10, iii) 12 **mean age, age range**: i) 59.5 ± 9, ii) 60.5 ± 10, iii) 60 ± 8 **gender (female)**: i) 3 (30%), ii) 4 (40%), iii) 3 (25%)

Arturi 2017 *(Continued)*

	body mass index (BMI): i) 33.2 ± 2, ii) 30.9 ± 2.8, iii) 30.8 ± 6 **diabetes mellitus (DM)**: 100% in all groups **chronic kidney disease (CKD)**: 0% in all groups **severity of condition (such as the commonly-used classification system, NYHA classification or the ACC/AHA stages of heart failure)**: NYHA II - III **left ventricular ejection fraction**: i) 41.5 ± 2.2, ii) 41.8 ± 2.6, iii) 42 ± 1.5 **baseline diabetes condition including HbA1c**: i) 8.2 ± 1, ii) 8.3 ± 0.9, iii) 7.9 ± 0.8 **smoking history**: NA **type of active treatment for DM**: all in addition to metformin and/or sulphonylurea **concomitant medications**: NA
Interventions	i) group 1 received 1.8 mg liraglutide (Novo Nordisk); **GLP-1RA** ii) group 2 received 100 mg sitagliptin (Merck & Co); **DPP4i** iii) group 3 received glargine insulin (Sanofi Aventis) the starting dose of glargine insulin was 10 IU, and dosage was titrated weekly according to daily self-monitored capillary fasting blood glucose measurements using glucometres (AccuChek Advantage; Roche Diagnostics) according to treat to target protocol with a target fasting plasma glucose of ≤ 100 mg/dl (≤ 5.6 mmol/l).
Outcomes	**Primary outcomes:** glycaemic and cardiovascular parameters: fasting plasma glucose level, HbA1c, blood pressure, LVEF (%), stroke volume, cardiac output, cardiac index, IVS. PW thickness, 6 min walking test, proBNP.
Notes	**Funding for trial**: this research did not receive any specific grant from any funding agency in the public, commercial or not for profit sector This study was included in our narrative synthesis since it did not report our pre-defined outcome measures of interest.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Research randomiser tool (available online at www.randomizer.org)
Allocation concealment (selection bias)	Low risk	Research randomiser tool (available online at www.randomizer.org)
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label; apparent drug differences.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Echocardiographic readings were made in random order by the investigator, who had no knowledge of patients ' blood pressure and other clinical data."
Incomplete outcome data (attrition bias)	Low risk	No loss to follow-up

Arturi 2017 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Low risk	All reported.
Other bias	Low risk	No other bias.

Bhatt 2021

Study characteristics	
Methods	**Title**: Sotagliflozin in patients with diabetes and recent worsening heart failure **acronym of trial**: SOLOIST-WHF **study design**: a phase 3, double-blind, randomised, placebo-controlled trial **total duration of study:** the median duration of follow-up was 9.2 months, the median duration of treatment was 7.8 months details of any 'run-in' period: unknown **number of study centres and location**: 466 locations **study setting:** outpatients **date of study:** from 11 June 2018 to 5 June 2020
Participants	**Cardiovascular disease categories:** HF: 100%, HF: ischaemic 712 (58.6%), ASCVD: 712 (58.6%) **N randomised**: i) intervention: 608, ii) comparison:614 **N lost to follow-up/withdrawn:** i) intervention: 20 (3.3%), ii) comparison: 23 (3.7%) **N analysed:** i) intervention: 608, ii) comparison: 614 **mean age, age range**: i) intervention: 69 (63-76), ii) comparison: 70 (64-76) **gender (female)**: i) intervention: 198 (32.6%), ii) comparison: 214 (34.9%) **body mass index (BMI)**: BMI, kg/m^2; (< 30): 558, (≥ 30) 661 **diabetes mellitus (DM)**: (100%) **chronic kidney disease (CKD)**: eGFR < 60 ml/min/1.73 m^2 : 854 (69.9%) **severity of condition (such as the commonly-used classification system, NYHA classification or the ACC/AHA stages of heart failure):** NYHA Class; I: 31, II: 552, III: 560, IV: 54 **left ventricular ejection fraction:** i) intervention: 35 (28-47) %, ii) comparison: 35 (28-45) % **baseline diabetes condition including HbA1c**: i) intervention: 7.1 (6.4-8.3), ii) comparison: 7.2 (6.4-8.2)

Bhatt 2021 *(Continued)*

	smoking history: NA
Interventions	**Intervention:** 200 mg of sotagliflozin once daily (with a dose increase to 400 mg, depending on side effects); **SGLT2i** **Comparison:** placebo **Type of active treatment for DM:** i) intervention: Any glucose-lowering medication: 522 (85.9%), Metformin 320 (52.6%), SU 114 (18.8%), DPP4i 96 (15.8%), Insulin 217 (35.7%), GLP-1RA 17 (2.8%) ii) comparison: Any glucose-lowering medication: 522 (85.0%), Metformin 320 (52.1%), SU 114 (18.6%), DPP4i inhibitor 102(16.6%), Insulin 217 (35.3%), GLP-1RA 23 (3.7%) **concomitant medications:** i) intervention: ACEi 254, ARB 245, ARNI 93, MRA 403, BB 564, Loop 580, other diuretic 66 ii) comparison: ACEi 241, ARB 270, ARNI 112, MRA 385, BB 561, Loop 581, other diuretic 62
Outcomes	**Primary outcomes:** total number of deaths from cardiovascular causes and hospitalizations and urgent visits for heart failure (first and subsequent) **Secondary outcomes:** total number of hospitalisations and urgent visits for heart failure; the incidence of death from cardiovascular causes; the incidence of death from any cause; the total number of deaths from cardiovascular causes, hospitalizations for heart failure, nonfatal myocardial infarctions, and nonfatal strokes; the total number of deaths from cardiovascular causes, hospitalizations and urgent visits for heart failure, and events of heart failure during hospitalization; the change in score on the Kansas City Cardiomyopathy Questionnaire-12 item (KCCQ-12; scores range from 0 to 100, with higher scores indicating better quality of life) to month 4; and the change in the estimated GFR
Notes	**Funding for trial:** Sanofi and Lexicon Pharmaceuticals NCT03521934

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed centrally with the use of interactive-response technology and was stratified according to left ventricular ejection fraction (< 50% or ≥ 50%) and geographic region of enrolment (North America, Latin America, western Europe, eastern Europe, or rest of the world) at baseline.
Allocation concealment (selection bias)	Low risk	Randomisation was performed centrally, with the use of interactive-response technology.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind.

Bhatt 2021 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Method of blinding outcomes was not described clearly.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data were unlikely to have an impact on the results of the trial. Drop-out rate was not high (lower than 20%).
Selective reporting (reporting bias)	High risk	Several secondary and other endpoints were not presented in the report; Time to first occurrence of the composite of positively adjudicated sustained ≥ 50% decrease in eGFR from baseline (for ≥ 30 days), chronic dialysis, renal transplant, or positively adjudicated sustained eGFR < 15 mL/min/1.73 m^2 (for ≥ 30 days) in the total patient population Proportion of patients with HHF or urgent HF visit within 30 days of randomisation Time to ≥ 50% decrease in eGFR from baseline Proportion of patients with ≥ 1 new onset of atrial fibrillation, atrial flutter, or ventricular arrhythmia from randomisation Time to first MI (fatal) Time to first stroke (fatal) Changes from baseline to Month 1 and Month 4 for NT-proBNP Changes from baseline in loop diuretics Changes in haemoconcentration from baseline at Week 2, Month 1, Month 4, Month 12, and EOT Changes from baseline to Month 4, Month 12, and Month 24 in: - Haemoglobin A1c - Body weight
Other bias	Low risk	There were no other biases.

Cannon 2020

Study characteristics	
Methods	**Title**: Cardiovascular outcomes with ertugliflozin in type 2 diabetes **acronym of trial**: VERTIS CV **study design**: Interventional, randomised, parallel assignment, double masking **total duration of study**: 3.5 years **number of study centres and location:** 567 centres in 34 countries **date of study**: From December 2013 through 27 December 2019
Participants	**Cardiovascular disease categories:** Patients were eligible if they were at least 40 years of age and had type 2 diabetes and established atherosclerotic cardiovascular disease involving the coronary, cerebrovascular, or peripheral arterial systems. i) intervention: ASCVD: 5499 (100%), HF: 1286 (23.4%) ii) comparison: ASCVD: 2747 (100%), HF: 672 (24.5%) **N randomised:** 2752 (5 mg), 2747 (15 mg), 2747 (placebo) **N lost to follow-up/withdrawn**: 330 (5 mg), 346 (15 mg), 358 (placebo)

Cannon 2020 *(Continued)*

	N analysed: 2752 (5 mg), 2747 (15 mg), 2747 (placebo) **mean age, age range**: i) intervention: 64.4 ± 8.1, ii) comparison: 64.4 ± 8.0 **gender (female):** i) intervention: 1633 (29.7%), ii) comparison: 844 (30.7%) **body mass index (BMI):** i) intervention: 31.9 ± 5.4, ii) comparison: 32.0 ± 5.5 **diabetes mellitus (DM)**: (100%) **chronic kidney disease (CKD):** i) intervention: eGFR (<60 mL/min/1.73m^2) ： 1199 (21.8%), ii) comparison: eGFR (<60 mL/min/1.73m^2) ： 608 (22.1%) **baseline diabetes condition including HbA1c:** i) intervention: 8.2 ± 1.0 %, ii) comparison: 8.2 ± 0.9 %
Interventions	**Intervention**: 5 mg or 15 mg of ertugliflozin once daily; **SGLT2i** **Comparison**: placebo once daily (these were each given in addition to standard-of-care treatment) **Type of active treatment for DM:** i) intervention: Metformin 4168 (75.8%), Insulin 2556 (46.5%), SU 2268 (41.2%), DPP4i 619 (11.3%), GLP-1RA 192 (3.5%) ii) comparison: Metformin 2124 (77.3%), Insulin 1344 (48.9%), SU 1122 (40.8%), DPP4i 292 (10.6%), GLP-1RA 86 (3.1%) **concomitant medications:** i) intervention: ACEi/ARB 4447 (80.9%), BB 3789 (68.9%), CCB 1847 (33.6%), Diuretic (any) 2346 (42.7%), Diuretic (loop) 826 (15.0%) ii) comparison: ACEi/ARB 2239 (81.5%), BB 1903 (69.3%), CCB 950 (34.6%), Diuretic (any)1196 (43.5%), Diuretic (loop)426 (15.5%)
Outcomes	**Primary outcomes:** a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke (i.e., a major adverse cardiovascular event) **Secondary outcomes:** a composite of death from cardiovascular causes or hospitalisation for heart failure; death from cardiovascular causes; and a composite of death from renal causes, renal replacement therapy, or doubling of the serum creatinine level
Notes	**Funding for trial:** Merck Sharp & Dohme and Pfizer NCT01986881

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	”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.“

Cannon 2020 *(Continued)*

Allocation concealment (selection bias)	Low risk	"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."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Method of blinding outcomes was not described clearly.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data were unlikely to have an impact on the results of the trial. Dropped out rate was not high (lower than 20%).
Selective reporting (reporting bias)	High risk	Several secondary endpoints were not presented in the report; • Proportion of patients with HbA1c <7% (53 mmol/mol) and <6.5% (48 mmol/mol) at 12, 24 and 36 months and annually thereafter. • Time to the first occurrence of a subject receiving glycaemic rescue therapy during the first 18 weeks of the study. • Time to initiation of insulin for patients not on insulin at randomisation. • Change in insulin dose from baseline at Week 18, Week 52 and annually thereafter. • Change from baseline in systolic and diastolic blood pressure at Week 18, Week 52 and annually thereafter. • Change from baseline in eGFR and serum creatinine at Week 18, Week 52 and annually thereafter. • Change from baseline in albuminuria as measured by the urinary albumin to creatinine ratio at Week 18, Week 52 and annually thereafter stratified by albuminuria category at baseline (normoalbuminuria, microalbuminuria and macroalbuminuria). • Progression of nephropathy as measured by the progression of normoalbuminuria to microalbuminuria and/or macroalbuminuria as well as measurement of regression of albuminuria (e.g. macroalbuminuria → microalbuminuria).
Other bias	Low risk	There were no other biases.

Cefalu 2015

Study characteristics	
Methods	**Title**: Dapagliflozin's effects on glycemia and cardiovascular risk factors in high-risk patients with type 2 diabetes: a 24-week, multicenter, randomized, double-blind, placebo-controlled study with a 28-week extension **acronym of trial**: NA **study design**: a multicentre, randomised, double-blind, placebo-controlled, international, phase 3 study **total duration of study**: 24 weeks

Cefalu 2015 *(Continued)*

	number of study centres and location: 141 study locations in Europe, Asia, the U.S., Canada, and Argentina **date of study**: from February 2010 to December 2012
Participants	**Cardiovascular disease categories:** **i) intervention**: ASCVD: (100%), HF: NA Qualifying CVD event, n (%): Coronary heart disease; 338 (74.3%), Stroke or TIA; 100 (22.0%), Peripheral artery disease; 15 (3.3%), Not reported 2 (0.4%) **ii) comparison**: ASCVD: (100%), HF: NA Qualifying CVD event, n (%): Coronary heart disease; 349 (76.0%), Stroke or TIA; 89 (19.4%), Peripheral artery disease; 18 (3.9%), Not reported 3 (0.7%) **N randomised**: i) intervention: 462, ii) comparison: 460 **N lost to follow-up/withdrawn:** i) intervention: 40, ii) comparison: 30 **N analysed:** i) intervention: 459, ii) comparison: 455 **mean age, age range**: i) intervention: 62.8 ± 7.0, ii) comparison: 63 ± 7.7 **gender (female)**: i) intervention: 146 (32.1), ii) comparison: 144 (31.4) **body mass index (BMI)**: i) intervention: 32.6 ± 5.9, ii) comparison: 32.9 ± 6.1 **diabetes mellitus (DM):** (100%) **chronic kidney disease (CKD):** NA **severity of condition (such as the commonly-used classification system, NYHA classification or the ACC/AHA stages of heart failure)**: NYHAⅠ–Ⅲ **left ventricular ejection fraction**: NA **baseline diabetes condition including HbA1c**: i) intervention: 8.18 ± 0.84, ii) comparison: 8.08 ± 0.80 **smoking history**: NA
Interventions	**Intervention**: once-daily dapagliflozin 10 mg: **SGLT-2i** **Comparison**: placebo **type of active treatment for DM**: i) intervention: oral antidiabetic drugs (OAD) 221 (48.6%), OAD plus insulin 158 (34.7%), Insulin only 76 (16.7%) ii) comparison: oral antidiabetic drugs (OAD) 217 (47.3%), OAD plus insulin 165 (35.9%), Insulin only 77 (16.8) **concomitant medications**: i) intervention: Anti hypertensive 455 (98.9%), ACEi/ARB 408 (88.7%), Diuretics 212 (46.1%), Loop diuretics 81 (17.6%), Lipid-lowering medications 387 (84.1%), ASA 329 (71.5%) ii) comparison: Antihypertensive 454 (98.3%), ACEi/ARB 409 (88.5%), Diuretics 241 (52.24%), Loop diuretics 100 (21.6%), Lipid-lowering medications 409 (88.5%), ASA 341 (73.8%)
Outcomes	**Primary outcomes:** The primary end points evaluated in the overall population and in the predefined age strata included the mean change in HbA1c level from baseline to week 24 and the proportion of responders achieving a

Cefalu 2015 *(Continued)*

three-item end point of combined clinical benefit at week 24. The three-item composite end point consisted of an absolute drop from baseline in HbA1c of ≧0.5% (5.5 mmol/mol), a relative drop of ≧3% for total BW, and an absolute drop of ≧3 mmHg from baseline in seated SBP. These end points were also evaluated in a post hoc subgroup analysis of insulin use.

Secondary outcomes:

Key secondary variables included the mean change in seated SBP from baseline (at weeks 8 and 24), the mean percentage change in BW, and the proportion of patients with baseline BMI of ≧27 kg/m^2 with a ≧5% reduction in BW. Other secondary end points included the mean change in seated diastolic blood pressure (DBP), the proportion of patients with seated SBP of <130 mmHg in the group of patients with a baseline seated SBP of ≧130 mmHg, the mean change in BW from baseline, the mean change in HbA1c level in patients with a baseline HbA1c level of ≧8.0% (64 mmol/mol) and an HbA1c level of ≧9.0% (75 mmol/mol), the proportion of patients achieving an HbA1c level of <7.0% (53 mmol/mol), the mean change in FPG at weeks 1 and 24, the proportion of patients rescued for failing to maintain FPG/HbA1c levels below the prespecified rescue criteria at weeks 4, 8, 16, 24, and 52 (see Supplementary Data), the proportion of patients achieving a reduction in HbA1c of ≧0.5% (5.5 mmol/mol), the proportion of patients achieving a reduction in seated SBP from baseline of ≧3 or ≧5 mmHg, and the mean change in calculated average daily insulin dose in patients treated with insulin at baseline.

Notes	**Funding for trial**: "Acknowledgments. Initial medical writing assistance was provided by Alexandra Silveira, PhD, of PPSI (a PAREXEL company), and was funded by Bristol-Myers Squibb. Funding. W.T.C. was supported in part by a grant from the National Institute of General Medical Sciences of the National Institutes of Health (1-U54-GM-104940)." Primary endpoint is not feasible in this study: narrative synthesis. This could not be well differentiated from a similar study (Leiter 2014). NCT01031680

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were assigned a unique enrolment number using Interactive Web Response System (IWRS) or Interactive Voice Response System (IVRS) at visit 1 (Enrollment Visit)" in supplement file.
Allocation concealment (selection bias)	Low risk	"Patients were assigned a unique enrolment number using Interactive Web Response System (IWRS) or Interactive Voice Response System (IVRS) at visit 1 (Enrollment Visit)" in supplement file.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, placebo controlled.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not clearly declared
Incomplete outcome data (attrition bias) All outcomes	Low risk	807 of 922 patients (87.5%) completed 52 weeks of the study.
Selective reporting (reporting bias)	Low risk	Results reported for all measures.
Other bias	Low risk	No other bias.

Gantz 2017

Study characteristics	
Methods	**Title:** A randomised, placebo-controlled study of the cardiovascular safety of the once-weekly DPP-4 inhibitor omarigliptin in patients with type 2 diabetes mellitus **study design**: Interventional, randomised, parallel assignment, triple masking (participant, investigator, outcomes assessor) **total duration of study**: 96.1 weeks (range 1.1 – 178.6) in the omarigliptin group, 95.6 weeks (range 1.3 – 176.0) in the placebo group **number of study centres and location:** 559 centres in 40 countries **date of study**: from October 5, 2012 through March 22, 2017
Participants	**Cardiovascular disease categories:** Eligible patients were at least 40 years old with a history of T2DM and established CVD. Established CVD included the presence of one of the following: (1) coronary artery disease; (2) Ischaemic cerebrovascular disease; (3) carotid arterial disease; or (4) atherosclerotic peripheral arterial disease. i) intervention: ASCVD: 2100 (100%), HF: 341 (16.2%) ii) comparison: ASCVD: 2102 (100%), HF: 300 (14.3%) **N randomised:** i) intervention: 2100, ii) comparison: 2102 **N lost to follow-up/withdrawn:** i) intervention: 0, ii) comparison: 0 **N analysed**: i) intervention: 2100, ii) comparison: 2102 **mean age, age range**: i) intervention: 63.7 (8.5) , ii) comparison: 63.6 (8.5) **gender (female)**: i) intervention: 30.4%, ii) comparison: 29.3% **body mass index (BMI)**: i) intervention: 31.2 ± 5.5, ii) comparison: 31.4 ± 5.6 **diabetes mellitus (DM):** (100%) **chronic kidney** disease (CKD): eGFR < 60 mL/min/1.73 m^2: 11.7% **baseline diabetes condition including HbA1c:** i) intervention: 8.0 ± 0.9, ii) comparison: 8.0 ± 0.9
Interventions	**Intervention:** omarigliptin 25 mg q.w.;**DPP4i** **Comparison:** placebo (these were each given in addition to standard-of-care treatment) **Type of active treatment for DM:** i) Insulin 769 (36.6%), Metformin 1646 (78.4%), SU 817 (38.9%), SGLT2i 4 (0.2%), TZD 24 (1.1%), Other 55 (2.6%) ii) Insulin 699 (33.3%), Metformin 1606 (76.4%), SU 826 (39.3%), SGLT2i 4 (0.2%), TZD 21 (1.0%), Other 55 (2.6%) **Concomitant medications:** i) NA, ii) NA
Outcomes	**Primary outcomes:**

Gantz 2017 *(Continued)*

	CVD endpoints analysed included (1) time to first event of MACE (confirmed CV-related death, nonfatal MI, nonfatal stroke); (2) time to confirmed CV-related death; (3) time to first event of confirmed MI (fatal and nonfatal); (4) time to first event of stroke (fatal and nonfatal); (5) time to all-cause mortality; (6) time to first event of confirmed HF; and (7) time to the composite of first confirmed event HF or CVD death. Change from baseline over time in HbA1c and non-CVD safety, including hypoglycaemia, was analysed. **Secondary outcomes:** none
Notes	**Funding for trial:** Funding for this trial was provided by Merck & Co., Inc. Kenilworth, NJ, USA. NCT01703208

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were randomly assigned using an interactive voice-response system."
Allocation concealment (selection bias)	Low risk	"Patients were randomly assigned using an interactive voice-response system."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Method of blinding outcomes was not described clearly.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data were unlikely to have an impact on the results of the trial. Dropped out rate was not high (lower than 20%).
Selective reporting (reporting bias)	Low risk	The prespecified outcomes were available on a clinical trials database and all outcomes were reported.
Other bias	Low risk	There were no other biases.

Green 2015

Study characteristics

Methods	**Title:** Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes **acronym of trial:** TECOS **study design**: interventional, randomised, parallel assignment, double masking **total duration of study:** 3.0 years **number of study centres and location:** 673 sites in 38 countries **date of study**: from 10 December 2008 through 30 March 2015
Participants	**Cardiovascular disease categories:**

Green 2015 *(Continued)*

	Eligible patients had type 2 diabetes with established cardiovascular disease. i) intervention: ASCVD: Prior cardiovascular disease (MI, > 50% coronary stenosis, Prior PCI, and CABG): 5397 (73.6%), Prior cerebrovascular disease: 1806 (24.6%), Prior Peripheral arterial disease: 1217 (16.6%), HF: 1303 (17.8%) ii) comparison: ASCVD: Prior cardiovascular disease (MI, > 50% coronary stenosis, Prior PCI, CABG): 5466 (74.5%), Prior cerebrovascular disease: 1782 (24.3%), Prior Peripheral arterial disease: 1216 (16.6%), HF: 1340 (18.3%) **N randomised**: i) intervention: 7332, ii) comparison: 7339 **N lost to follow-up/withdrawn:** i) intervention: 360, ii) comparison: 434 **N analysed:** i) intervention: 7257, ii) comparison: 7266 **mean age, age range:** i) intervention: 65.4 ± 7.9, ii) comparison: 65.5 ± 8.0 **gender (female)**: i) intervention: 2134 (29.1%), ii) comparison: 2163 (29.5%) **body mass index (BMI)**: i) intervention: 30.2 ± 5.6, ii) comparison: 30.2 ± 5.7 **diabetes mellitus (DM):** (100%) **chronic kidney disease (CKD):** i) intervention: eGFR < 50 mL/min/1.73 m^2: 686 (9.5%), ii) comparison: eGFR < 50 mL/min/1.73 m^2: 683 (9.4%) severity of condition (such as the commonly-used classification system, NYHA classification or the ACC/AHA stages of heart failure): i) NYHA class III or higher 171 (2.3%), ii) NYHA class III or higher 202 (2.8%) **baseline diabetes condition including HbA1c**: i) 7.2 ± 0.5 %, ii) 7.2 ± 0.5 % smoking history: i) 3649 (51.1%), ii) 3773 (51.4%)
Interventions	**Intervention**: sitagliptin at a dose of 100 mg daily (or 50 mg daily if the baseline eGFR was ≥ 30 and <50 ml per minute per 1.73 m^2); **DPP4i** **Comparison**: placebo (these were each given in addition to standard-of-care treatment) **Type of active treatment for DM:** i) intervention: Metformin 5936 (81.0%), SU 3346 (45.6%), TZD 196 (2.7%), Insulin 1724 (23.5%) ii) comparison: Metformin 6030 (82.2%), SU 3299 (45.0%), TZD 200 (2.7%), Insulin 1684 (22.9%) **concomitant medications:** i) intervention: BB 4647 (63.4%), ACEi/ARB 5743 (78.3%), CCB 2444 (33.3%), Diuretic 2976 (40.6%), ASA 5764 (78.6%), Other antiplatelet 1593 (21.7%), Statin 5851 (79.8%), Ezetimibe 386 (5.3%) ii) comparison: BB 4675 (63.7%), ACEi/ARB 5812 (79.2%), CCB 2517 (34.3%), Diuretic 3044 (41.4%), ASA 5754 (78.4%), Other antiplatelet 1594 (21.7%), Statin 5868 (80.0%), Ezetimibe 375 (5.1%)
Outcomes	**Primary outcomes:** the first confirmed event of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalisation for unstable angina **Secondary outcomes:**

Green 2015 *(Continued)*

	the first confirmed event of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke the occurrence of the individual components of the primary composite cardiovascular outcome, fatal and nonfatal myocardial infarction, fatal and nonfatal stroke, death from any cause, and hospitalisation for heart failure
Notes	**Funding for trial:** Merck Sharp & Dohme NCT00790205

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	”An interactive voice-response system randomly assigned the study medication in a double-blind manner, blocked within each site.”
Allocation concealment (selection bias)	Low risk	”An interactive voice-response system randomly assigned the study medication in a double-blind manner, blocked within each site.”
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Method of blinding outcomes was not described clearly.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data were unlikely to have an impact on the results of the trial. Drop-out rate was not high (lower than 20%).
Selective reporting (reporting bias)	Low risk	Some secondary outcomes were not reported in the full trial report but we could find them in the trial register records (ClinicalTrials.gov: NCT00790205).
Other bias	Low risk	There were no other biases.

Hernandez 2018

Study characteristics

Methods	**Title**: Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial **other name of trial:** "Harmony Outcomes" **study design**: Interventional, randomised, parallel assignment, quadruple masking (participant, care provider, investigator, outcomes assessor) **total duration of study**: The actual median duration of follow-up was 1.6 years (IQR 1.3 – 2.0; maximum 2.6) for the primary outcome. **number of study centres and location:** 610 sites across 28 countries **date of study**: from July 1, 2015 through March 14, 2018
Participants	**Cardiovascular disease categories:**

Hernandez 2018 *(Continued)*

	Men and women aged 40 years or older with a diagnosis of type 2 diabetes and established disease of the coronary, cerebrovascular, or peripheral arterial circulation who had a glycated haemoglobin concentration of more than 7.0% were eligible for participation in the trial. i) intervention: ASCVD: 4731 (100%), CAD: 3333 (70%), Stroke: 827 (17%), Peripheral artery disease 1195 (25%), HF: 954 (20%) ii) comparison: ASCVD: 4732 (100%), CAD: 3345 (71%), Stroke: 854 (18%), Peripheral artery disease 1159 (24%), HF: 968 (20%) **N randomised:** i) intervention: 4731, ii) comparison: 4732 **N lost to follow-up/withdrawn:** i) intervention: 111, ii) comparison: 154 **N analysed**: i) intervention: 4620, ii) comparison: 4578 **mean age, age range:** i) intervention: 64.1 (8.7), ii) comparison: 64.2 (8.7) **gender (female):** i) intervention: 1427 (30%), ii) comparison: 1467 (31%) **body mass index (BMI):** 32.3 **diabetes mellitus (DM):** (100%) **chronic kidney disease (CKD):** i) eGFR<60: 1098 (23.2%), ii) eGFR<60: 1124 (23.8%) **baseline diabetes condition including HbA1c**: i) 8.76% (1.5), ii) 8.72% (1.5)
Interventions	**Intervention**: subcutaneous injections of albiglutide once a week (Starting dose 30 mg may be increased to 50 mg if needed); **GLP-1RA** **Comparison:** subcutaneous injections of placebo once a week (these were each given in addition to standard-of-care treatment) **Type of active treatment for DM:** i) Biguanide 3463 (73%), SU 1346 (28%), Insulin 2860 (60%), DPP4i 698 (15%), SGLT2i 310 (7%), TZD 92 (2%), Glinide 66 (1%), AGI 34 (1%) , ii) Biguanide 3506 (74%), SU 1379 (29%), Insulin 2737 (58%), DPP4i 739 (16%), SGLT2i 265 (6%), TZD 102 (2%), Glinide 96 (2%), AGI 37 (1%) **concomitant medications:** i) BB 3128 (66%), CCB 1428 (30%), ACEi 2263 (48%), ARB 1599 (34%), Thiazide diuretic 1089 (23%), Loop diuretic 895 (19%), Statin 3967 (84%), ASA 3652 (77%), P2Y12 inhibitor 1224 (26%) ii) BB 3182 (67%), CCB 1431 (30%), ACEi 2353 (50%), ARB 1511 (32%), Thiazide diuretic 1037 (22%), Loop diuretic 899 (19%), Statin 3988 (84%), ASA 3639 (77%), P2Y12 inhibitor 1251 (26%)
Outcomes	**Primary outcomes:** first occurrence of any component of the composite outcome, which comprised death from cardiovascular causes, myocardial infarction, and stroke, in an intention-to-treat population. **Secondary outcomes:** the time to initiation of chronic insulin therapy, the time to the first occurrence of an important microvascular event, changes in glycated haemoglobin and body weight, and the proportion of partici-

Hernandez 2018 *(Continued)*

	pants who attained glycaemic control without severe hypoglycaemia and who gained less than 5% of their body weight by the end of the study.
Notes	**Funding for trial**: The trial protocol was developed by the members of the Executive Committee in conjunction with Duke Clinical Research Institute and the sponsor, GlaxoSmithKline Research and Development. These parties were also responsible for oversight of the trial. The funder of the study was involved in data collection, data analysis, and data interpretation. The funder of the study was not involved in the writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication. NCT02465515

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	”Patients were assigned according to a sequestered, fixed, computer-generated randomisation code that used balanced permuted blocks.”
Allocation concealment (selection bias)	Low risk	”Patients were assigned according to a sequestered, fixed, computer-generated randomisation code that used balanced permuted blocks.”
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Method of blinding outcomes was not described clearly.
Incomplete outcome data (attrition bias) All outcomes	High risk	Drop-out rate was more than 20%. 1161/4731 patients (24.5%) assigned to albiglutide and 1318/4732 patients (27.9%) assigned to placebo discontinued study drug.
Selective reporting (reporting bias)	Low risk	Some secondary outcomes were not reported in the full trial report but were available in ClinicalTrials.gov (NCT02465515).
Other bias	Low risk	There were no other biases.

Holman 2017

Study characteristics

Methods	**Title:** Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes **acronym of trial:** EXSCEL **study design**: Interventional, randomised, parallel assignment, triple masking (participant, investigator, outcomes assessor) **total duration of study**: The median duration of exposure to the trial regimen was 2.4 years (interquartile range, 1.4 to 3.8) in the exenatide group and 2.3 years (interquartile range, 1.2 to 3.6) in the placebo group. **number of study centres and location**: 687 sites in 35 countries

Holman 2017 *(Continued)*

	date of study: from 18 June 2010 through 24 April 2017
Participants	**Cardiovascular disease categories:** Prior CVD event data at randomisation, History of cardiovascular disease, and History of CHF were listed. i) intervention: ASCVD: 5394 (73.3%): Prior CVD event at randomisation, HF: 1161(15.8%): History of CHF ii) comparison: ASCVD: 5388 (72.9%): Prior CVD event at randomisation, HF: 1228 (16.6%): History of CHF **N randomised:** i) intervention: 7356, ii) comparison: 7396 **N lost to follow-up/withdrawn:** i) intervention: 262, ii) comparison: 303 **N analysed:** i) intervention: 7094, ii) comparison: 7093 **mean age, age range:** i) intervention: 62 (56.0, 68.0) , ii) comparison: 62 (56.0, 68.0) **gender (female):** i) intervention: 2794 (38.0%) , ii) comparison: 2809 (38.0%) **body mass index (BMI):** i) intervention: 31.8 (28.2, 36.2), ii) comparison: 31.7 (28.2, 36.1) **diabetes mellitus (DM):** (100%) **chronic kidney disease (CKD)**: i) eGFR<60: 1565 (21.3%), ii) eGFR<60: 1626 (22.0%) **baseline diabetes condition including HbA1c:** 8.0% (7.3, 8.9)
Interventions	**Intervention**: subcutaneous injections of extended-release exenatide at a dose of 2 mg once weekly; **GLP1RA** **Comparison**: subcutaneous injections of placebo once weekly (these were each given in addition to standard-of-care treatment) **Type of active treatment for DM:** i) Insulin 3397 (46.2%), Pramlintide 1 (<0.1%), Non-SU secretagogues 97 (1.3%), AGI 150 (2.0%), GLP-1RA (other than study drug)0 (0.0%), DPP-4i 1118 (15.2%), SGLT2i 49 (1.2%), ii) Insulin 3439 (46.5%), Pramlintide 2 (<0.1%), Non-SU secretagogues 105 (1.4%), AGI 150 (2.0%), GLP-1RA (other than study drug) 2 (<0.1%), DPP4i 1085 (14.7%), SGLT2i 28 (0.7%) **Concomitant medications:** i) ACEi 3535 (48.1%), ARB 2334 (31.7%), Diuretic 3216 (43.7%), BB 4082 (55.5%), MRA: 456 (6.2%) ii) ACEi 3647 (49.3%), ARB 2272 (30.7%), Diuretic 3227 (43.6%), BB 4129 (55.8%), MRA 456 (6.2%)
Outcomes	**Primary outcome:** The primary outcome was defined as the first occurrence of any component of the composite outcome of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke (three-component MACE outcome), in a time-to-event analysis. **Secondary outcome:**

Holman 2017 *(Continued)*

	Secondary outcomes included death from any cause, death from cardiovascular causes, and the first occurrence of nonfatal or fatal myocardial infarction, nonfatal or fatal stroke, hospitalisation for acute coronary syndrome, and hospitalisation for heart failure, in time-to-event analyses. 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.
Notes	**Funding for trial:** Funded by Amylin Pharmaceuticals NCT01144338

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	”An interactive voice-response system assigned patients on the basis of computer-generated block randomisation.”
Allocation concealment (selection bias)	Low risk	”An interactive voice-response system assigned patients on the basis of computer-generated block randomisation.”
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Method of blinding outcomes was not described clearly.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data were unlikely to have an impact on the results of the trial. Dropped out rate was not high (lower than 20%).
Selective reporting (reporting bias)	Low risk	The prespecified outcomes were available in a clinical trials database and all outcomes were reported.
Other bias	Low risk	There were no other biases.

Husain 2019

Study characteristics

Methods	**Title:** Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes **acronym of trial:** PIONEER 6 **study design**: Interventional, randomised, parallel assignment, double masking **total duration of study**: 15.9 months **number of study centres and location:** 214 sites in 21 countries **date of study**: from 17 January 2017 through 25 September 2018 (randomisation period)
Participants	**Cardiovascular disease categories:**

Husain 2019 *(Continued)*

	Patients were eligible to participate if they were 50 years of age or older and had established cardiovascular disease or chronic kidney disease, or if they were 60 years of age or older and had cardiovascular risk factors only. i) intervention: ASCVD: Age ≥ 50 years and presence of CV disease: 1350 (84.9%), prior MI: 561 (35.3%), prior stroke or TIA: 242 (15.2%), prior revascularisation: 733 (46.1%), symptomatic coronary heart disease: 356 (22.4%), asymptomatic cardiac ischaemia: 97 (6.1%), HF: CHF NYHA class II-III: 188 (11.8%) ii) comparison: ASCVD: Age ≥ 50 years and presence of CV disease: 1345 (84.5%), prior MI: 589 (37.0%), prior stroke or TIA: 263 (16.5%), prior revascularisation: 768 (48.2%), symptomatic coronary heart disease: 375 (23.6%), asymptomatic cardiac ischaemia: 92 (5.8%), HF: CHF NYHA class II-III: 200 (12.6%) **N randomised**: i) intervention: 1591, ii) comparison: 1592 **N lost to follow-up/withdrawn**: i) intervention: 5, ii) comparison: 6 **N analysed**: i) intervention: 1591, ii) comparison: 1592 **mean age, age range:** 66 ± 7 **gender (female):** i) intervention: 507 (31.9%), ii) comparison: 500 (31.4%) **body mass index (BMI):** i) intervention: 32.3 ± 6.6, ii) comparison: 32.3 ± 6.4 **diabetes mellitus (DM):** (100%) **chronic kidney disease (CKD):** i) intervention: 30 to <60 ml/min/1.73 m^2; 418 (26.3%) , <30 ml/min/1.73 m^2; 16 (1.0%), ii) comparison: 30 to <60 ml/min/1.73 m^2; 409 (25.7%) , <30 ml/min/1.73 m^2; 13 (0.8%) baseline diabetes condition including HbA1c: i) intervention: 8.2 ± 1.6, ii) comparison: 8.2 ± 1.6
Interventions	**Intervention:** once-daily oral semaglutide (target dose, 14 mg); **GLP-1RA** **Comparison:** placebo (these were each given in addition to standard-of-care treatment) **Type of active treatment for DM:** i) Biguanides 1221 (76.7%), Insulins 968 (60.8%), SU 517 (32.5%), SGLT2i 165 (10.4%), TZD 65 (4.1%), AGI 36 (2.3%), DPP4i 2 (0.1%), GLP-1RA 1 (0.1%), Other 26 (1.6%) ii) Biguanides 1242 (78.0%), Insulins 962 (60.4%), SU 510 (32.0%), SGLT2i 140 (8.8%), TZD 53 (3.3%), AGI 43 (2.7%), DPP4i 0, GLP-1RA 0, Other 26 (1.6%) **Concomitant medications:** i) Antihypertensives 1495 (94%), Lipid-lowering drugs 1336 (84.0%), Antithrombotic/antiplatelet medication 1248 (78.4%), Diuretics 621 (39.0%) ii) Antihypertensives 1493 (93.8%), Lipid-lowering drugs 1376 (86.4%), Antithrombotic/antiplatelet medication 1279 (80.3%), Diuretics 640 (40.2%)
Outcomes	**Primary outcomes:**

Husain 2019 *(Continued)*

	the time from randomisation to the first occurrence of a major adverse cardiovascular event, a composite of death from cardiovascular causes (including undetermined causes of death), nonfatal myocardial infarction, or nonfatal stroke **Secondary outcomes:** the time from randomisation to the first occurrence of the following: an expanded composite outcome consisting of the primary outcome plus unstable angina resulting in hospitalisation or heart failure resulting in hospitalisation; a composite of death from any cause, nonfatal myocardial infarction, or nonfatal stroke; and the individual components of these composite outcomes
Notes	**Funding for trial:** Novo Nordisk NCT02692716

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	”The randomisation session was performed in Interactive Voice Response System (IVRS) and the Web Response System (WRS) and included allocation of dispensing unit numbers to be dispensed to the subject.”
Allocation concealment (selection bias)	Low risk	”The randomisation session was performed in Interactive Voice Response System (IVRS) and the Web Response System (WRS) and included allocation of dispensing unit numbers to be dispensed to the subject.”
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"An independent data monitoring committee evaluated unblinded trial data." in the main trial supported low risk.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data were unlikely to have an impact on the results of the trial. Drop-out rate was not high (lower than 20%).
Selective reporting (reporting bias)	Low risk	The prespecified outcomes were available on a clinical trials database and all outcomes were reported.
Other bias	Low risk	There were no other biases.

Jorsal 2017

Study characteristics

Methods	**Title**: Effect of liraglutide, a glucagon-like peptide-1 analogue, on left ventricular function in stable chronic heart failure patients with and without diabetes (LIVE) - a multicentre, double-blind, randomised, placebo-controlled trial **acronym of trial**: LIVE **study design**: an investigator-initiated, randomised, double-blinded, placebo-controlled multi-centre trial

Jorsal 2017 *(Continued)*

	total duration of study: 24 weeks **number of study centres and location:** four Danish centres **date of study**: 1 February 2012 to 31 August 2015
Participants	**Cardiovascular disease categories:** Eligible patients had an acute coronary syndrome within 15 to 90 days before randomisation. **i) intervention**: ASCVD: Ischaemic heart disease 72 (59%), HF: (100%) **ii) comparison**: ASCVD: Ischaemic heart disease 73 (62%), HF: (100%) **N randomised**: i) intervention: 122, ii) comparison: 119 **N lost to follow-up/withdrawn:** 1 **N analysed:** i) intervention: 122, ii) comparison: 119 **mean age, age range**: i) intervention: 65 ± 9.2, ii) comparison: 65 ± 10.7 **gender (female):** i) intervention: 13/122, ii) comparison: 13/119 **body mass index (BMI)**: i) intervention: 28.0 (3.8), ii) comparison: 29.8 (4.6) **diabetes mellitus (DM):** i) intervention: 32%, ii) comparison: 29% **chronic kidney disease (CKD):** NA **severity of condition (such as the commonly-used classification system, NYHA classification or the ACC/AHA stages of heart failure)**: i) intervention: I 31%, II 55%, III 14%, ii) comparison: I 30%, II 56%, III 14% **left ventricular ejection fraction**: i) intervention: 33.7 (7.6%), ii) comparison: 35.4 (9.4%) **baseline diabetes condition including HbA1c**: i) intervention: 5.9 (0.7), ii) comparison: 6.0 (0.8) **smoking history**: i) intervention: 25 (21%), ii) comparison: 23 (19%)
Interventions	**Intervention**: liraglutide 1.8 mg once daily (subcutaneous); **GLP-1RA** **Comparison**: placebo **type of active treatment for DM**: i) intervention: metformin 77%, insulin 10%, SU 15% ii) comparison: metformin 63%, insulin 8%, SU 11% **concomitant medications**: i) intervention: ACEi/ARB 97%, Diuretic 74%, BB 93%, Statin 79%, MRA 48% ii) comparison: ACEi/ARB 97%, Diuretic 76%, BB 91%, Statin 77%, MRA 45%
Outcomes	**Primary outcomes:** The primary outcome measure was change in LVEF from randomisation to end of follow-up, as determined by three-dimensional contrast-enhanced echocardiography. **Secondary outcomes:** The secondary outcome measures included change in: peak systolic longitudinal tissue velocity (s 'max), global longitudinal strain, LVESV, LVEDV, diastolic function, functional capacity measured by the 6MWT, plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels, blood pressure, quality of

Jorsal 2017 *(Continued)*

	life, and adverse events. (In protocol paper, mortality was included. However, in clinicaltrial.gov., there were some missing descriptions about mortality as secondary outcome.)
Notes	**Funding for trial**: The study was investigator-initiated and investigator-designed. The investigators received an unrestricted grant from Novo Nordisk A/S, but the company was not involved in data collection, study management, analysis, or interpretation of data, or in preparation, in approval, or in the decision regarding to submit the manuscript. This study was included in our narrative synthesis since it did not report our pre-defined outcome measures of interest. NCT01472640

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation.
Allocation concealment (selection bias)	Low risk	Allocation carried out blinded.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind medication.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Echo technician blinded to treatment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Lost to follow-up: 16/122 (13.1%) in liraglutide group and 13/119 (10.9%) in placebo group
Selective reporting (reporting bias)	Low risk	Results reported for all measures.
Other bias	Low risk	No other bias.

Kato 2017

Study characteristics

Methods	**Title**: Effects of dipeptidyl peptidase-4 inhibitor sitagliptin on coronary atherosclerosis as assessed by intravascular ultrasound in type 2 diabetes mellitus with coronary artery disease **acronym of trial**: TOP-SCORE **study design**: a prospective, open, parallel, randomised, comparative, single-centre study **total duration of study**: 8–12 months **number of study centres and location:** Fukuoka University Hospital, Japan **date of study**: December 2011 to July 2015

Kato 2017 *(Continued)*

Participants	**Cardiovascular disease categories:** **i) intervention**: ASCVD: (100%), HF: NA Type of CAD; SCAD/NSTE-ACS/STEMI = 23/2/3 **ii) comparison**: ASCVD: (100%), HF: NA Type of CAD; SCAD/NSTE-ACS/STEMI = 22/0/2 **N randomised**: i) intervention: 38, ii) comparison: 34 **N lost to follow-up/withdrawn:** 0 **N analysed:** i) intervention: 38, ii) comparison: 34 **mean age, age range**: i) intervention: 70 ± 9, ii) comparison: 72 ± 10 **gender (female):** i) intervention: 21%, ii) comparison: 17% **body mass index (BMI)**: i) intervention: 24.8 ± 4.1, ii) comparison: 25.1 ± 4.1 **diabetes mellitus (DM):** (100%) **chronic kidney disease (CKD):** NA **severity of condition (such as the commonly-used classification system, NYHA classification or the ACC/AHA stages of heart failure)**: NA **left ventricular ejection fraction**: i) intervention: 65 (10) , ii) comparison: 66 (10) **baseline diabetes condition including HbA1c**: i) intervention: 7.2 (1.0), ii) comparison: 7.5 (1.5) **smoking history**: i) intervention: 14%, ii) comparison: 13%
Interventions	**Intervention**: receive sitagliptin at a standard dose of 50 mg/day; **DPP4i** **Comparison**: not to receive DPP4i (non-DPP4i group) as an add-on treatment to statins **type of active treatment for DM**: i) intervention: metformin 29%, insulin 11%, SU 11% ii) comparison: metformin 46%, insulin 46%, SU 13% **concomitant medications**: i) intervention: ACEi 11%, ARB 64%, Diuretic 18%, BB 14%, CCB 68%, Statin 93%, MRA 4% ii) comparison: ACEi 13%, ARB 67%, Diuretic 4%, BB 33%, CCB 71%, Statin 100%, MRA 4%
Outcomes	**Primary outcomes:** The primary endpoint was the nominal change in PAV (percent atheroma volume) at the selected segment from baseline to follow-up. **Secondary outcomes:** The secondary endpoint was the percent change in TAV (total atheroma volume) at the selected segment from baseline to follow-up, which was calculated as follows: Percent change in TAV = (TAV at follow-up - TAV at baseline)/ (TAV at baseline) x100 Other secondary endpoints included the nominal changes in the percent volumes of lipid, fibrosis, dense fibrosis, and calcification, and changes in clinical laboratory data during the study period.

Kato 2017 *(Continued)*

Notes	**Funding for trial**: This work was supported by grants-in-aid from the Ministry of Education, Culture, Sports, Science and Technology of Japan This study was included in our narrative synthesis since it did not report our pre-defined outcome measures of interest. UMIN000017861

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation process was unclear.
Allocation concealment (selection bias)	Unclear risk	Allocation process was unclear.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label, and blinding was not clearly reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	IVUS analysis was conducted by blinded physicians.
Incomplete outcome data (attrition bias) All outcomes	High risk	Loss to follow-up: 10/38 (26.3%) in sitagliptin group and 13/37 (35.1%) in non-DPP4i group.
Selective reporting (reporting bias)	High risk	Secondary outcomes such as association between lipid profile and the change in PAV were not fully reported.
Other bias	Low risk	No other bias.

Leiter 2014

Study characteristics

Methods	**Title**: Dapagliflozin added to usual care in individuals with type 2 diabetes mellitus with preexisting cardiovascular disease: a 24-week, multicentre, randomised, double-blind, placebo-controlled study with a 28-week extension **acronym of trial**: NA **study design**: multicentre, randomised, double-blind, age-stratified, placebo-controlled Phase III study **total duration of study**: 52 weeks **number of study centres and location:** 173 centres in the United States, Canada, Australia, Chile, Argentina, and five European countries **date of study**: March 2010 to December 2012
Participants	**Cardiovascular disease categories:**

Leiter 2014 *(Continued)*

	Cardiovascular disease was defined as (1) prior documented coronary heart disease, including history of MI or revascularization or coronary artery stenosis > 50%, confirmed with angiography or abnormal stress test imaging, compatible with ischaemia or prior MI; (2) prior documented stroke or transient Ischaemic attack; or (3) prior documented peripheral artery disease treated with revascularization (excluding amputation). **i) intervention**: ASCVD: (100%), HF: 86 (17.9%) **ii) comparison**: ASCVD: (100%), HF: 66 (13.7%) **N randomised**: i) intervention: 482, ii) comparison: 483 **N lost to follow-up/withdrawn:** i) intervention: 30, ii) comparison: 34 **N analysed:** i) intervention: 480, ii) comparison: 482 **mean age, age range**: i) intervention: 63.9 ± 7.6, ii) comparison: 63.6 ± 7.0 **gender (female)**: i) intervention: 159 (33.1%), ii) comparison: 159 (33%) **body mass index (BMI)**: i) intervention: 33 ± 5.3, ii) comparison: 32.7 ± 5.7 **diabetes mellitus (DM):** (100%) **chronic kidney disease (CKD):** NA **severity of condition (such as the commonly-used classification system, NYHA classification or the ACC/AHA stages of heart failure)**: NA **left ventricular ejection fraction**: NA **baseline diabetes condition including HbA1c**: i) intervention: 8.0 ± 0.8, ii) comparison: 8.1 ± 0.8 **smoking history**: NA
Interventions	**Intervention**: once-daily dapagliflozin 10 mg; **SGLT2i** **Comparison**: placebo **type of active treatment for DM** : i) intervention: Oral antihyperglycaemic agent 188 (39.2%), Oral antihyperglycaemic agent + insulin 203 (42.3%), Only insulin 89 (18.5%) ii) comparison: Oral antihyperglycaemic agent 192 (39.8%), Oral antihyperglycaemic agent+insulin 190 (39.4%), Only insulin 100 (20.7%) **concomitant medications** : i) intervention: ACEi/ARB 403 (83.6%), Loop diuretic 113 (23.4%), BB 359 (74.5%), ASA 350 (72.6%), Lipid-reducing agent 411 (85.3%) ii) comparison: ACEi/ARB 400 (82.8%), Loop diuretic 96 (19.9), BB 351 (72.7%), ASA 342 (70.8%), Lipid-reducing agent 400 (82.8%)
Outcomes	**Primary outcomes:** mean change in HbA1c from baseline and proportion of participants achieving a three- item outcome measure of combined clinical benefit: simultaneous HbA1c decrease of 0.5% or greater, total BW reduction of 3% or greater, and systolic BP (SBP) reduction of 3 mmHg or more from baseline **Secondary outcomes:** Key secondary endpoints included the mean percent change in total body weight (BW) from baseline to week 24, the proportion of patients with a baseline body mass index ≥ 27 kg/m^2 achieving a reduction

Leiter 2014 *(Continued)*

	in BW of ≥ 5% at week 24, seated systolic BP at weeks 8 and 24, and seated systolic BP in patients with a baseline seated systolic BP≥ 130 mmHg. Additional secondary endpoints included mean change from baseline in diastolic BP overall and in patients with seated baseline systolic BP ≥ 130 mmHg at weeks 8 and 24; mean change in seated systolic BP in patients who had baseline systolic BP ≥ 130 mmHg at week 24; mean change in BW from baseline to week 24; change in haemoglobin A1c (HbA1c) in patients with baseline HbA1c ≥ 8.0% and HbA1c ≥ 9.0% at week 24; change in FPG at week 1 and week 24; change in calculated average daily insulin dose in patients treated with insulin at baseline at week 24; and change in plasma uric acid levels at week 24.
Notes	**Funding for trial**: AstraZeneca and Bristol-Myers Squibb. This study was included in our narrative synthesis since it did not report our pre-defined outcome measures of interest. This study could not be well differentiated from a similar study (Cefalu 2015). NCT01042977

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Web Response System (IWRS) or Interactive Voice Response System (IVRS) at enrolment visit" (Supplement file)
Allocation concealment (selection bias)	Low risk	Allocation carried out blinded.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Body weight could be difficult to blind.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up: 423/483 (88.8%) in placebo group and 441/482 (91.5%).
Selective reporting (reporting bias)	Low risk	Results reported for all measures.
Other bias	Low risk	No other bias.

Margulies 2016

Study characteristics

Methods	**Title:** Effects of liraglutide on clinical stability among patients with advanced heart failure and reduced ejection fraction: a randomised clinical trial **acronym of trial:** FIGHT **study design:** Interventional, randomised, parallel assignment, double masking

Margulies 2016 *(Continued)*

	total duration of study: The median duration that participants received the study drug was 25.0 weeks (IQR, 8.6-25.9 weeks) in the liraglutide group and 25.0 weeks (IQR, 11.4-26.0 weeks) in the placebo group **number of study centres and location:** 24 sites in the United States **date of study:** from April 2013 through October 2015
Participants	**Cardiovascular disease categories:** Patients were required to have an established diagnosis of HF and LVEF of 40% or lower. i) intervention: ASCVD: 133 (86%), HF: 154 (100%) ii) comparison: ASCVD: 113 (77%), HF: 146 (100%) **N randomised:** i) intervention: 154, ii) comparison: 146 **N lost to follow-up/withdrawn:** i) intervention: NA, ii) comparison: NA **N analysed:** i) intervention: 154, ii) comparison: 146 **mean age, age range**: i) intervention: 62 (52-58), ii) comparison: 61 (51-67) **gender (female):** i) intervention: 31 (20%), ii) comparison: 33 (23%) **body mass index (BMI):** i) intervention: 31 (26-36), ii) comparison: 33 (25-38) **diabetes mellitus (DM):** i) intervention: 91 (59%), ii) comparison: 87 (60%) **chronic kidney disease (CKD):** NA **baseline diabetes condition including HbA1c:** i) intervention: 6.6% (6-7.6), ii) comparison: 6.7% (5.9-7.9)
Interventions	**Intervention:** liraglutide as a daily subcutaneous injection (the protocol involved uptitration of study drug dosage as tolerated every 14 days from 0.6 mg/d to 1.2 mg/d to 1.8 mg/d during the first 30 days of the trial); **GLP1RA** **Comparison:** placebo as a daily subcutaneous injection. There were no background treatment data for DM. **Type of active treatment for DM:** i) NA, ii) NA **concomitant medications:** i) BB: 143 (93%), ACEi/ARB: 112 (73%), MRA: 88 (57%), Loop diuretic: 151 (98%), Digoxin: 51 (33%), ii) BB: 139 (95%), ACEi/ARB: 104 (71%), MRA: 89 (61%), Loop diuretic: 146 (100%), Digoxin: 51 (35%),
Outcomes	**Primary outcomes:** The primary endpoint was a global rank score in which all participants, regardless of treatment assignment, were ranked across 3 hierarchical tiers: time to death, time to rehospitalization for heart failure, and time-averaged proportional change in N-terminal pro-B-type natriuretic peptide (NT-proBNP) level from baseline to 180 days. **Secondary outcomes:** The key exploratory secondary endpoints included (1) the individual components of the primary endpoint, (2) time to other prespecified cardiac events (including emergency department visits), (3) changes in cardiac structure and function (by echocardiographic measures) from baseline to 180 days,

Margulies 2016 *(Continued)*

	(4) functional status based on 6-minute walk distances at 30, 90, and 180 days, and (5) changes in the KCCQ clinical summary score.
Notes	**Funding for trial:** This research was supported by grants U10 HL084904 (awarded to the coordinating centre) and U01 HL084861, U10 HL110312, U10 HL110337, U10 HL110342, U10 HL110262, U10 HL110297, U10 HL110302, U10 HL110309, U10 HL110336, and U10 HL110338 (awarded to the regional clinical centres) from the National Heart, Lung, and Blood Institute (NHLBI) of the US National Institutes of Health (NIH). The study drug (liraglutide) and matching placebo injections were supplied by NovoNordisk Inc. NCT01800968

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	”A permuted block randomization scheme stratified by clinical site.”
Allocation concealment (selection bias)	Low risk	”Randomization was performed with an automated web-based system.”
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"End point assessments were blinded to treatment assignment"
Incomplete outcome data (attrition bias) All outcomes	High risk	Drop-out rate was more than 20%. 44/154 patients (28.6%) assigned to liraglutide and 42/146 patients (28.8%) assigned to placebo discontinued study drug.
Selective reporting (reporting bias)	Low risk	Some secondary outcome were not reported in the paper, but we could find them in ClinicalTrials.gov NCT01800968).
Other bias	Low risk	There were no other biases.

Marso 2016a

Study characteristics

Methods	**Title:** Liraglutide and cardiovascular outcomes in type 2 diabetes **acronym of trial:** LEADER **study design**: Interventional, randomised, parallel assignment, double masking **total duration of study:** 60 months **number of study centres and location:** 410 sites in 32 countries **date of study:** from August 31, 2010 through December 17, 2015
Participants	**Cardiovascular disease categories:**

Marso 2016a *(Continued)*

	More than 80% patients have Established CVD, and the others (less than 20%) are older than 60 years old and have at least one CVD risk factors. i) intervention: ASCVD: Established CVD: 3831 (82.1%), prior MI: 1464 (31.4%), prior stroke or TIA 730 (15.6%), prior revascularisation 1835 (39.3%), documented asymptomatic cardiac ischaemia 1241 (26.6%), HF: 835 (17.9%) ii) comparison: ASCVD: Established CVD: 3767 (80.6%), prior MI: 1400 (30.0%), prior stroke or TIA 777 (16.6%), prior revascularisation 1803 (38.6%), documented asymptomatic cardiac ischaemia 1231 (26.3%), HF: 832 (17.8%) **N randomised**: i) intervention: 4668, ii) comparison: 4672 **N lost to follow-up/withdrawn:** i) intervention: 139, ii) comparison: 159 **N analysed:** i) intervention: 4529, ii) comparison: 4513 **mean age, age range**: i) intervention: 64.2 ± 7.2, ii) comparison: 64.4 ± 7.2 **gender (female):** i) intervention: 1657 (35.5%), ii) comparison: 1680 (36%) **body mass index (BMI)**: i) intervention: 32.5 ± 6.3, ii) comparison: 32.5 ± 6.3 **diabetes mellitus (DM):** (100%) **chronic kidney disease (CKD):** i) intervention: eGFR <60 mL/min/1.73m^2: 1185 (25.4%), ii) comparison: eGFR <60 mL/min/1.73m^2: 1191 (25.5%) **baseline diabetes condition including HbA1c**: i) intervention: 8.7 ± 1.6, ii) comparison: 8.7 ± 1.5
Interventions	**Intervention:** 1.8 mg (or the maximum tolerated dose) of liraglutide once daily as a subcutaneous injection; **GLP1RA** **Comparison:** placebo once daily as a subcutaneous injection (these were each given in addition to standard-of-care treatment) **Type of active treatment for DM:** i) intervention: Metformin 3540 (75.8%), SU 2370 (50.8%), AGI 139 (3%), TZD 296 (6.3%), DPP4i 4 (<0.1%), GLP-1RA 0, SGLT2i N/A, Glinides 178 (3.8%), Insulin 2038 (43.7%), ii) comparison: Metformin 3604 (77.1%), SU 2363 (50.6%), AGI 123 (2.6%), TZD 279 (6.0%), DPP4i 2 (<0.1%), GLP-1RA 2 (<0.1%), SGLT2i N/A, Glinides 172 (3.7%), Insulin 2131 (45.6%) **Concomitant medications:** i) intervention: BB 2652 (56.8%), CCB 1538 (32.9%), ACEi 2417 (51.8%), ARB 1488 (31.9%), Renin inhibitors 42 (0.9%), Other antihypertensive drugs 468 (10%), Loop diuretics 824 (17.7%), Thiazides 829 (17.8%), MRA 254 (5.4%), Statins 3405 (72.9%), Ezetimibe 165 (3.5%), Fibrates 412 (8.8%), ASA 2977 (63.8%), Clopidogrel, Tichlopidine, Prasgurel, Ticagrelor 720 (15.4%) ii) comparison: BB 2529 (54.1%), CCB 1479 (31.7%), ACEi 2350 (50.3%), ARB 1486 (31.8%), Renin inhibitors 40 (0.9%), Other antihypertensive drugs 454(9.7%), Loop diuretics 837 (17.9%) Thiazides 788

Marso 2016a *(Continued)*

	(16.9%), MRA 251 (5.4%), Statins 3336 (71.4%), Ezetimibe 169 (3.6%), Fibrates 432 (9.2%), ASA 2899 (62.1%), Clopidogrel, Tichlopidine, Prasgurel, Ticagrelor 745 (15.9%)
Outcomes	**Primary outcomes:** the first occurrence of death from cardiovascular causes, non-fatal (including silent) MI, or non-fatal stroke **Secondary outcomes:** an expanded composite cardiovascular outcome (death from cardiovascular causes, non-fatal MI, non-fatal stroke, coronary revascularisation, or hospitalisation for unstable angina pectoris or HF), death from any cause, a composite renal and retinal microvascular outcome (nephropathy [defined as the new onset of macroalbuminuria or a doubling of the serum creatinine level and an eGFR of ≤ 45 ml per minute per 1.73 m^2, the need for continuous renal-replacement therapy, or death from renal disease] and retinopathy [defined as the need for retinal photocoagulation or treatment with intravitreal agents, vitreous haemorrhage, or the onset of diabetes-related blindness]), neoplasms, and pancreatitis - all of which were adjudicated in a blinded fashion by an external, independent event-adjudication committee
Notes	**Funding for trial:** Novo Nordisk and the National Institutes of Health NCT01179048

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A randomisation session was carried out for all subjects by using the Interactive Voice and Web Response System (IV/WRS)."
Allocation concealment (selection bias)	Low risk	"A randomisation session was carried out for all subjects by using the Interactive Voice and Web Response System (IV/WRS)."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Method of blinding outcomes was not described clearly.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data were unlikely to have an impact on the results of the trial. Dropped out rate was not high (lower than 20%).
Selective reporting (reporting bias)	High risk	Some secondary outcomes were not reported. • Change from baseline to the last assessment during the treatment period in: Laboratory parameters:− lipase− amylase− calcitonin− anti liraglutide antibodies− ALT− bilirubin (total)− calcium (total)− sodium− potassium− urinary albumin to creatinine ratio
Other bias	Low risk	There were no other biases.

Marso 2016b

Study characteristics	
Methods	**Title:** Semaglutide and cardiovascular outcomes in patients with type 2 diabetes **acronym of trial**: SUSTAIN 6 **study design:** Interventional, randomised, parallel assignment, double masking **total duration of study**: 109 weeks **number of study centres and location:** 230 sites in 20 countries **date of study**: from February 21, 2013 through March 15, 2016
Participants	**Cardiovascular disease categories:** total population: ischaemic heart disease: 1994 (60.5%), MI: 1072 (32.5%), ischaemic stroke: 383 (11.6%), and HF: 777 (23.6%). 4 groups: i)Semaglutide 0.5 mg, ii) Semaglutide 1.0 mg, iii) placebo 0.5 mg, iv) placebo 1.0 mg. intervention: ASCVD: Ischaemic heart disease: i) 493 (59.7%), ii) 495 (60.2%), MI: 266 (32.2%), ii) 264 (32.1%). Ischaemic stroke: i) 89 (10.8%), ii) 89 (10.8%), HF: i) 201 (24.3%), ii) 180 (21.9%) comparison: ASCVD: Ischaemic heart disease: iii) 510 (61.9%), iv) 496 (60.1%), MI: iii) 267 (32.4%), iv) 275 (33.3%). Ischaemic stroke: iii) 96 (11.7%), iv) 109 (13.2%), HF: iii) 190 (23.1%), iv) 206 (25.0%) **N randomised**: intervention (i and ii): 1648, comparison (iii and iv): 1649 **N lost to follow-up/withdrawn:** intervention (i and ii): 25, comparison (iii and iv): 40 **N analysed:** intervention (i and ii): 1648, comparison (iii and iv): 1649 **mean age, age range**: intervention: i) 64.6 ± 7.3 (0.5mg), ii) 64.7± 7.1 (1.0 mg), comparison: iii) 64.8 ± 7.6, iv) 64.4 ± 7.5 **gender (female):** intervention: i) 331 (40.1%), ii) 304 (37%), comparison: iii) 342 (41.5%), iv) 318 (38.5%) **body mass index (BMI)**: intervention: i) 32.7 ± 6.29, ii)32.9 ± 6.18, comparison: iii) 32.9 ± 6.35, iv) 32.7 ± 5.97 **diabetes mellitus (DM):** 100% in all groups. **chronic kidney disease (CKD):** i) intervention: eGFR 30-60: i) 229 (27.7%), ii) 194 (23.6%), eGFR 15-30: i) 20 (2.4%), ii) 21 (2.6%) , eGFR <15: i)1 (0.1%), ii) 4 (0.5%), ii) comparison: eGFR 30-60: iii) 215 (26.1%), iv) 194 (23.5%), eGFR 15-30: iii) 3 (0.4%), iv) 4 (0.5%) **baseline diabetes condition including HbA1c**: intervention: i) 8.7 ± 1.4 ii) 8.7 ± 1.5, comparison: iii) 8.7 ± 1.5, iv) 8.7 ± 1.5
Interventions	**Intervention**: 0.5 mg or 1.0 mg of once-weekly subcutaneous semaglutide ; **GLP-1RA** **Comparison**: volume-matched once-weekly subcutaneous placebo (these were each given in addition to standard-of-care treatment) **Type of active treatment for DM:**

Marso 2016b *(Continued)*

	Insulin i) 479 (58.0%) ii) 477 (58.0%), AGI i) 9 (1.1%), ii) 7 (0.9%), Biguanides i) 617 (74.7%), ii) 594 (72.3%), Glucose-lowering combination therapy i) 1 (0.1%), ii) 1 (0.1%), DPP4i i) 1 (0.1%), ii) 2 (0.2%), Meglitinides i) 25 (3.0%), ii) 23 (2.8%), SGLT2i i) 0 (0%), ii) 1 (0.1%), SU i) 349 (42.3%), ii) 349 (42.5%), TZD i) 14 (1.7%), ii) 21 (2.6%) Insulin iii) 478 (58.0%), iv) 479 (58.1%), AGI iii) 16 (1.9%), iv) 10 (1.2%), Biguanides iii) 586 (71.1%), iv) 617 (74.8%) , Glucose-lowering combination therapy, iii) 0 (0%), iv) 1 (0.1%), DPP4i iii) 2 (0.2%), iv) 0 (0%), Meglitinides iii) 24 (2.9%), iv) 15 (1.8), SGLT2i iii) 2 (0.2%), iv) 2 (0.2%), SU iii) 363 (44.1%), iv) 349 (42.3%), TZD iii) 18 (2.2%), iv) 23 (2.8%) **Concomitant medications:** BB i) 475 (57.5%), ii) 459 (55.8%), CCB i) 273 (33.1%), ii) 246 (29.9%), ACEi i) 420 (50.8%) , ii) 409 (49.8%), ARB i) 274 (33.2%), ii) 274 (33.3%), Other antihypertensives i) 63 (7.6%), ii) 60 (7.3%), Loop diuretics i) 146 (17.7%), ii) 134(16.3%), Thiazides i) 114 (13.8%), ii) 119 (14.5%), MRA i) 52 (6.3%), ii) 45 (5.5%), Statins i) 600 (72.6%), ii) 599 (72.9%), Ezetimibe i) 32 (3.9%), ii) 31 (3.8%), Vitamin K agonists i) 48 (5.8%) , ii) 40 (4.9%), Direct thrombin inhibitors i) 5 (0.6%) , ii) 4 (0.5%), Direct factor Xa inhibitors i) 2 (0.2%), ii) 1 (0.1%), ADP receptor inhibitors (excluding ASA i) 175 (21.2%) , ii) 164 (20.0%), ASA i) 509 (61.6%), ii) 542 (65.9%) BB iii) 475 (57.6%), iv) 485 (58.8%), CCB iii) 266 (32.3%), iv) 270 (32.7%), ACEi iii) 402(48.8%), iv) 411 (49.8%), ARB iii) 266 (32.3%) , iv) 297 (36.0%), Other antihypertensives iii) 67 (8.1%) , iv) 68 (8.2%), Loop diuretics iii) 133 (16.1%), iv) 143 (17.3%), Thiazides iii) 107 (13.0%), iv) 129 (15.6%), MRA iii) 55 (6.7%), iv) 42 (5.1%), Statins iii) 590 (71.6%), iv) 610 (73.9%), Ezetimibe iii) 34 (4.1%), iv) 32 (3.9%), Vitamin K agonists iii) 40 (4.9%), iv) 36 (4.4%), Direct thrombin inhibitors iii) 4 (0.5%), iv) 5 (0.6%), Direct factor Xa inhibitors iii) 9 (1.1%), iv) 1 (0.1%), ADP receptor inhibitors (excluding ASA) iii) 168 (20.4%) , iv) 189 (22.9%), ASA iii) 522 (63.3%), iv) 535 (64.8%)
Outcomes	**Primary outcomes:** the first occurrence of death from cardiovascular causes, non-fatal MI (including silent), or non-fatal stroke **Secondary outcomes:** the first occurrence of an expanded composite cardiovascular outcome (death from cardiovascular causes, non-fatal MI, non-fatal stroke, revascularisation [coronary or peripheral], and hospitalisation for unstable angina or HF), an additional composite outcome (death from all causes, non-fatal MI, or non-fatal stroke), the individual components of the composite outcomes, retinopathy complications, and new or worsening nephropathy
Notes	**Funding for trial:** Novo Nordisk NCT01720446

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	”The Interactive Voice and Web Response System (IV/WRS) allocated trial product to the subject at randomisation.”
Allocation concealment (selection bias)	Low risk	”The Interactive Voice and Web Response System (IV/WRS) allocated trial product to the subject at randomisation.”
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded.

Marso 2016b *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Method of blinding outcomes was not described clearly.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data were unlikely to have an impact on the results of the trial. Dropped out rate was not high (lower than 20%).
Selective reporting (reporting bias)	High risk	Some secondary outcomes were not reported. Beta-cell function (HOMA-B), urinary albumin to creatinine ratio (UACR). Changes from baseline in electrocardiogram (ECG). Change from baseline to last assessment during the treatment period in SF-36v2TM patient-reported outcome (PRO) scores.
Other bias	Low risk	There were no other biases.

McMurray 2018

Study characteristics	
Methods	**Title:** Effects of vildagliptin on ventricular function in patients with type 2 diabetes mellitus and heart failure: a randomized placebo-controlled trial **acronym of trial:** VIVIDD **study design**: Interventional, randomised, parallel assignment, double masking **total duration of study**: 52 weeks **number of study centres and location**: 67 sites in 15 countries **date of study**: from May 2009 through August 2012
Participants	**Cardiovascular disease categories:** HFrEF (LVEF < 40%), and in NYHA functional class I to III were eligible. i) intervention: ASCVD: MI: 82 (64.1%), Angina pectoris: 55 (43.0%), CABG: 30 (23.4%), PCI: 24 (18.8%), stroke: 12 (9.4%), HF: 128 (100%) ii) comparison: ASCVD: MI : 80 (63.5%), Angina pectoris: 548 (38.1%), CABG: 30 (23.8%), PCI: 22 (17.5%), stroke: 111 (8.7%), HF: 126 (100%) **N randomised:** i) intervention: 128, ii) comparison: 126 **N lost to follow-up/withdrawn:** i) intervention: 27, ii) comparison: 26 **N analysed:** i) intervention: analysed for safety 128 analysed for efficacy 115 per protocol analysis 89, ii) comparison: analysed for safety 125 analysed for efficacy 112 per protocol analysis 90 **mean age, age range:** i) intervention: 62.9 ± 8.5, ii) comparison: 63.4 ± 10.2 **gender (female):** i) intervention: 29 (22.7%), ii) comparison: 30 (23.8%) **body mass index (BMI):** i) intervention: 29.6 ± 4.6, ii) comparison: 29.3 ± 4.7

McMurray 2018 *(Continued)*

	diabetes mellitus (DM): (100%) **chronic kidney disease (CKD):** NA **baseline diabetes condition including HbA1c:** i) intervention: 7.8 ± 0.95, ii) comparison: 7.8 ± 1.07
Interventions	**Intervention**: vildagliptin, 50 mg twice daily (50 mg once daily if concomitant treatment with a SU) ; **DPP4i** **Comparison:** placebo (these were each given in addition to standard-of-care treatment) **Type of active treatment for DM:** i) Insulin Monotherapy 24.2%, Insulin Any 35.2%, SU 46.9%, Metformin 36.7%, AGI 0.8%, Glinide 1.6%, Any oral anti-diabetes therapy 63.3% ii) Insulin Monotherapy 24.6%, Insulin Any 33.3%, SU 53.2%, Metformin 32.5%, AGI 3.2%, Glinide 0%, Any oral anti-diabetes therapy 68.3% **concomitant medications:** i) ACEi 71.8%, ARB 23.4%, BB 79.7%, MRA 46.1%, Digitalis glycoside 28.9%, Diuretic (loop) 71.1% ii) ACEi 61.9%, ARB 28.6%, BB 76.2%, MRA 37.3%, Digitalis glycoside 23.0%, Diuretic (loop) 70.7%
Outcomes	**Primary outcomes:** between-treatment change from baseline in echocardiographic LVEF using a noninferiority margin of -3.5% **Secondary outcomes:** a change in HbA1c from baseline to 16 weeks (with censoring for use of rescue therapy before that time point)
Notes	**Funding for trial:** Novartis NCT00894868

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	”Patients were randomly assigned according to a central randomisation scheme.”
Allocation concealment (selection bias)	Low risk	”Randomization was conducted using an interactive voice response system.”
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Method of blinding outcomes was not described clearly.
Incomplete outcome data (attrition bias) All outcomes	High risk	Drop-out rate was more than 20%.

McMurray 2018 *(Continued)*

		27/128 patients (21.1%) assigned to vildagliptin and 26/126 patients (20.6%) assigned to placebo discontinued study drug. The rate of discontinuation was relatively high, and only 70% of patients who completed the study according to protocol without major protocol deviations had at least 1 follow-up echocardiogram 22 or more weeks after randomisation, although the number of patients with at least 2 analysable echocardiograms was more than needed according to their power calculations.
Selective reporting (reporting bias)	Low risk	All primary and secondary outcomes were described in the paper (protocol absent, and endpoints were shown in ClinicalTrial.gov: NCT00894868)).
Other bias	Low risk	There were no other biases.

McMurray 2019

Study characteristics	
Methods	**Title:** Dapagliflozin in patients with heart failure and reduced ejection fraction **acronym of trial:** DAPA-HF **study design**: Interventional, randomised, parallel assignment, quadruple masking (participant, care provider, investigator, outcomes assessor) **total duration of study**: The median duration of follow-up was 18.2 months (range, 0 to 27.8). **number of study centres and location**: 410 centres in 20 countries **date of study**: from February 8, 2017 through July 17, 2019
Participants	**Cardiovascular disease categories:** ASCVD: only found the number of patients with Ischaemic heart failure. i) intervention: ASCVD: 1316 (55.5%), HF: 2373 (100%) ii) comparison: ASCVD: 1358 (57.3%), HF: 2371 (100%) **N randomised**: i) intervention: 2373, ii) comparison: 2371 **N lost to follow-up/withdrawn:** i) intervention: 14, ii) comparison: 20 **N analysed:** i) intervention: 2373, ii) comparison: 2371 **mean age, age range**: i) intervention: 66.2 SD 11, ii) comparison: 66.5 SD 10.8 **gender (female):** i) intervention: 23.8%, ii) comparison: 23.0% **body mass index (BMI)**: i) intervention: 28.2 ± 6.0, ii) comparison: 28.1 ± 5.9 **diabetes mellitus (DM)**: i) intervention: 993 (41.8%), ii) comparison: 990 (41.8%) **chronic kidney disease (CKD)**: i) intervention: eGFR < 60: 962 (40.6%), ii) comparison: eGFR < 60: 964 (40.7%) **baseline diabetes condition including HbA1c**: NA
Interventions	**Intervention**: dapagliflozin (at a dose of 10 mg once daily); **SGLT2i** **Comparison**: placebo

McMurray 2019 *(Continued)*

	(these were each given in addition to standard-of-care treatment) **Type of active treatment for DM:** i) Biguanide 504 (50.8%), SU 228 (23.0%), DPP4i 161 (16.2%), GLP-1RA 11 (1.1%), insulin 274 (27.6%) ii) Biguanide 512 (51.7%), SU 210 (21.2%), DPP4i 149 (15.1%), GLP-1RA 10 (1.0%), insulin 266 (26.9%) **concomitant medications:** i) ACEi 1332, ARB 675, BB 2278, Diuretics 445, MRA 1696, ARNI 250, Digitalis 445 ii) ACEi 1329, ARB 632, BB 2280, Diuretics 442, MRA 1674, ARNI 258, Digitalis 442
Outcomes	**Primary outcomes:** a composite of worsening HF or death from cardiovascular causes. **Secondary outcomes:** a composite of hospitalisation for HF or cardiovascular death The additional secondary outcomes were the total number of hospitalisations for HF (including repeat admissions) and cardiovascular deaths; the change from baseline to 8 months in the total symptom score on the Kansas City Cardiomyopathy Questionnaire, which is scored on a scale from 0 to 100, with a higher score indicating fewer symptoms and a change of 5 or more points considered to be clinically meaningful14; a composite of worsening renal function, which was defined as a sustained decline in the eGFR of 50% or greater, end-stage renal disease (defined as a sustained [≥28 days] eGFR of <15 mL/m/1.73 m^2, sustained dialysis, or renal transplantation), or renal death; and death from any cause.
Notes	**Funding for trial:** Funded by AstraZeneca NCT03036124

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	”Patients were randomly assigned in accordance with the sequestered, fixed-randomisation schedule, with the use of balanced blocks.”
Allocation concealment (selection bias)	Low risk	”Investigators used an interactive voice- or Web- response system to determine treatment assignment. “
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Method of blinding outcomes was not described clearly.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data were unlikely to have an impact on the results of the trial. Dropped out rate was not high (lower than 20%).
Selective reporting (reporting bias)	Low risk	The prespecified outcomes were available on a clinical trials database and all outcomes were reported.
Other bias	Low risk	There were no other biases.

Neal 2017a

Study characteristics	
Methods	**Title:** Canagliflozin and cardiovascular and renal events in type 2 diabetes **acronym of trial:** CANVAS (part of CANVAS program) The CANVAS Program integrated data from two trials; CANVAS and CANVAS-R. **study design:** Interventional, randomised, parallel assignment, quadruple masking (participant, care provider, investigator, outcomes assessor) **total duration of study**: 78 weeks **number of study centres and location**: 667 centres in 30 countries **date of study**: CANVAS: from December 9, 2009 through February 22, 2017. CANVAS-R: from 16 January 2014 through 23 February 2017.
Participants	**Cardiovascular disease categories:** i) intervention: ASCVD: 4127 (71.2%), HF: 803 (13.9%) ii) comparison: ASCVD: 3197 (73.5%), HF: 658 (15.1%) **N randomised**: i) intervention: 5795, ii) comparison: 4347 **N lost to follow-up/withdrawn:** i) intervention: 224, ii) comparison: 184 **N analysed:** i) intervention: 5795, ii) comparison: 4347 **mean age, age range**: i) intervention: 63.2 ± 8.3, ii) comparison: 63.4 ± 8.2 **gender (female):** i) intervention: 2036 (35.1%), ii) comparison: 1597 (36.7%) **body mass index (BMI)**: i) intervention: 31.9 ± 5.9, ii) comparison: 32.0 ± 6.0 **diabetes mellitus (DM):** (100%) **chronic kidney disease (CKD):** no data **baseline diabetes condition including HbA1c**: i) intervention: 8.2 ± 0.9, ii) comparison: 8.2 ± 0.9
Interventions	**Intervention:** CANVAS; canagliflozin at a dose of 300 mg, or 100 mg. CANVAS-R; canagliflozin, administered at an initial dose of 100 mg daily with an optional increase to 300 mg starting from week 13. ; **SGLT2i** **Comparison**: placebo (these were each given in addition to standard-of-care treatment) **Type of active treatment for DM:** i) Insulin 2890 (49.9%), SU 2528 (43.6%), Metformin 4447 (76.7%), GLP-1RA 222 (3.8%), DPP4i 697 (12.0%) ii) Insulin 2205 (50.7%), SU 1833 (42.2%), Metformin 3378 (77.7%), GLP-1RA 185 (4.3%), DPP4i 564 (13.0%) **concomitant medications:**

Neal 2017a *(Continued)*

	i) Statin 4329 (74.7%), Antithrombotic 4233 (73.0%), RAAS inhibitor 4645 (80.2%), BB 3039 (52.4%), Diuretic 2536 (43.8%) ii) Statin 3270 (75.2%), Antithrombotic 3233 (74.4%), RAAS inhibitor 3471 (79.8%), BB 2382 (54.8%), Diuretic 1954 (45.0%)
Outcomes	**Primary outcomes:** a composite of death from cardiovascular causes, non-fatal MI, or non-fatal stroke **Secondary outcomes:** death from any cause, death from cardiovascular causes, progression of albuminuria, and the composite of death from cardiovascular causes and hospitalisation for HF
Notes	**Funding for trial:** Funded by AstraZeneca CANVAS and CANVAS-R ClinicalTrials.gov numbers: NCT01032629 and NCT01989754, respectively

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	”a computer-generated randomization”
Allocation concealment (selection bias)	Low risk	”Randomization was performed centrally through an interactive Web-based response system.”
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Method of blinding outcomes was not described clearly.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data were unlikely to have an impact on the results of the trial. Dropped out rate was not high (lower than 20%).
Selective reporting (reporting bias)	High risk	Some secondary outcomes were not reported. Change From baseline in Proinsulin/Insulin (PI/I) Ratio at the end of treatment . Change From baseline in Urinary Albumin/Creatinine Ratio at end of treatment .
Other bias	Low risk	There were no other biases.

Neal 2017b

Study characteristics

Methods	**Title:** Canagliflozin and cardiovascular and renal events in type 2 diabetes

Neal 2017b *(Continued)*

	acronym of trial: CANVAS-R (part of CANVAS program) The CANVAS Program integrated data from two trials; CANVAS and CANVAS-R **study design:** Interventional, randomised, parallel assignment, quadruple masking (participant, care provider, investigator, outcomes assessor) **total duration of study**: 78 weeks **number of study centres and location**: 667 centres in 30 countries **date of study**: CANVAS; from December 9, 2009 through February 22, 2017. CANVAS-R; from January 16, 2014 through February 23, 2017.
Participants	**Cardiovascular disease categories:** i) intervention: ASCVD: 4127 (71.2%), HF: 803 (13.9%) ii) comparison: ASCVD: 3197 (73.5%), HF: 658 (15.1%) **N randomised**: i) intervention: 5795, ii) comparison: 4347 **N lost to follow-up/withdrawn:** i) intervention: 224, ii) comparison: 184 **N analysed:** i) intervention: 5795, ii) comparison: 4347 **mean age, age range**: i) intervention: 63.2 ± 8.3, ii) comparison: 63.4 ± 8.2 **gender (female):** i) intervention: 2036 (35.1%), ii) comparison: 1597 (36.7%) **body mass index (BMI)**: i) intervention: 31.9 ± 5.9, ii) comparison: 32.0 ± 6.0 **diabetes mellitus (DM):** (100%) **chronic kidney disease (CKD):** no data **baseline diabetes condition including HbA1c**: i) intervention: 8.2 ± 0.9, ii) comparison: 8.2 ± 0.9
Interventions	**Intervention:** CANVAS; canagliflozin at a dose of 300 mg, or 100 mg. CANVAS-R; canagliflozin, administered at an initial dose of 100 mg daily with an optional increase to 300 mg starting from week 13; **SGLT2i** **Comparison**: placebo (these were each given in addition to standard-of-care treatment) **Type of active treatment for DM:** i) Insulin 2890 (49.9%), SU 2528 (43.6%), Metformin 4447 (76.7%), GLP-1RA 222 (3.8%), DPP4i 697 (12.0%) ii) Insulin 2205 (50.7%), SU 1833 (42.2%), Metformin 3378 (77.7%), GLP-1RA 185 (4.3%), DPP4i 564 (13.0%) **concomitant medications:** i) Statin 4329 (74.7%), Antithrombotic 4233 (73.0%), RAAS inhibitor 4645 (80.2%), BB 3039 (52.4%), Diuretic 2536 (43.8%) ii) Statin 3270 (75.2%), Antithrombotic 3233 (74.4%), RAAS inhibitor 3471 (79.8%), BB 2382 (54.8%), Diuretic 1954 (45.0%)
Outcomes	**Primary outcomes:**

Neal 2017b *(Continued)*

	a composite of death from cardiovascular causes, non-fatal MI, or non-fatal stroke **Secondary outcomes:** death from any cause, death from cardiovascular causes, progression of albuminuria, and the composite of death from cardiovascular causes and hospitalisation for HF
Notes	Funding for trial: Funded by AstraZeneca CANVAS and CANVAS-R ClinicalTrials.gov numbers: NCT01032629 and NCT01989754, respectively

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	”a computer-generated randomization”
Allocation concealment (selection bias)	Low risk	”Randomization was performed centrally through an interactive Web-based response system.”
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Method of blinding outcomes was not described clearly.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data were unlikely to have an impact on the results of the trial. Dropped out rate was not high (lower than 20%).
Selective reporting (reporting bias)	High risk	Some secondary outcomes were not reported. Change From baseline in Proinsulin/Insulin (PI/I) Ratio at the end of treatment . Change From baseline in Urinary Albumin/Creatinine Ratio at end of treatment .
Other bias	Low risk	There were no other biases.

Packer 2020

Study characteristics

Methods	**Title:** Cardiovascular and renal outcomes with empagliflozin in heart failure **acronym of trial:** EMPEROR-Reduced **study design:** Interventional, randomised, parallel assignment, double masking **total duration of study**: The median duration of follow-up was 16 months. **number of study centres and location:** 520 centres in 20 countries

Packer 2020 *(Continued)*

	date of study: from March 6, 2017 through May 28, 2020
Participants	**Cardiovascular disease categories:** i) intervention: ASCVD: 983 (52.8%), HF: 1863 (100%) ii) comparison: ASCVD: 946 (50.7%), HF: 1867 (100%) **N randomised**: i) intervention: 1863, ii) comparison: 1867 **N lost to follow-up/withdrawn:** i) intervention: 22, ii) comparison: 20 **N analysed:** i) intervention: 1863, ii) comparison: 1867 **mean age, age range**: i) intervention: 67.2 ± 10.8, ii) comparison: 66.5 ± 11.2 **gender (female):** i) intervention: 437 (23.5%) , ii) comparison: 456 (24.4%) **body mass index (BMI)**: i) intervention: 28.0 ± 5.5, ii) comparison: 27.8 ± 5.3 **diabetes mellitus (DM):** i) intervention: 927 (49.8%), ii) comparison: 929 (49.8%) **chronic kidney disease (CKD):** i) intervention: eGFR <60 ml/min/1.73 m^2 ：893 (48.0%), ii) comparison: eGFR <60 ml/min/1.73 m^2 ：906 (48.6%) **baseline diabetes condition including HbA1c**: no data
Interventions	**Intervention:** empagliflozin (at a dose of 10 mg daily); **SGLT2i** **Comparison:** placebo (there were no data for background treatment for DM) **Type of active treatment for DM**: NA **concomitant medications:** i) ACEi/ARB: 1314 (70.5%), ARNI: 340 (18.3%), MRA: 1306 (70.1%), BB 1765 (94.7%), Implantable cardioverter defibrillator: 578 (31.0%), cardiac resynchronisation therapy: 220 (11.8%) ii) ACEi/ARB: 1286 (68.9%), ARNI: 387 (20.7%), MRA: 1355 (72.6%), BB 1768 (94.7%), Implantable cardioverter defibrillator: 593 (31.8%), cardiac resynchronisation therapy: 222 (11.9%)
Outcomes	**Primary outcomes:** Primary composite outcome: no. (%) of Hospitalisation for HF or cardiovascular death **Secondary outcomes:** Secondary outcomes specified in hierarchical testing procedure Total no. of hospitalizations for HF, Mean slope of change in eGFR (mL/min/1.73 m^2 per year)
Notes	**Funding for trial:** Boehringer Ingelheim and Eli Lilly NCT03057977

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	”Randomization was performed with an interactive-response system that used a permuted-block design.”

Packer 2020 *(Continued)*

Allocation concealment (selection bias)	Low risk	”Randomization was performed with an interactive-response system that used a permuted-block design.”
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessment was also blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data were unlikely to have an impact on the results of the trial. Dropped out rate was not high (lower than 20%).
Selective reporting (reporting bias)	Low risk	Primary and secondary endpoints were all reported. "Further endpoints" were not fully reported. (e.g.. new onset of atrial fibrillation)
Other bias	Low risk	There were no other biases.

Pfeffer 2015

Study characteristics	
Methods	**Title:** Lixisenatide in patients with type 2 diabetes and acute coronary syndrome **acronym of trial**: ELIXA **study design:** Interventional, randomised, parallel assignment, triple masking (participant, investigator, outcomes assessor) **total duration of study:** The mean duration of exposure to study medication was 690 days in the lixisenatide group, The mean duration of exposure to study medication was 712 days in the placebo group **number of study centres and location**: from 49 countries **date of study**: from June 2010 through February 2015
Participants	**Cardiovascular disease categories:** Eligible patients had an acute coronary event within 180 days i) intervention: ASCVD: 3034 (100%), HF: 682 (22.5%) ii) comparison: ASCVD: 3034 (100%), HF: 676 (22.3%) **N randomised**: i) intervention: 3034, ii) comparison: 3034 **N lost to follow-up/withdrawn:** i) intervention: 0, ii) comparison: 0 **N analysed:** i) intervention: 3034, ii) comparison: 3034 **mean age, age range**: i) intervention: 59.9 SD 9.7, ii) comparison: 60.6 SD 9.6 **gender (female):** i) intervention: 30.4%, ii) comparison: 30.9%

Pfeffer 2015 *(Continued)*

	body mass index (BMI): i) intervention: 30.1 ± 5.6, ii) comparison: 30.2 ± 5.8 **diabetes mellitus (DM):** (100%) **chronic kidney disease (CKD):** i) intervention: eGFR (ml/min/1.73m^2)[15-30]: 4 (0.1%), [30-60]: 655 (21.6%) , ii) comparison: eGFR (ml/min/1.73m^2)[15-30]: 4 (0.1%), [30-60]: 744 (24.6%) **baseline diabetes condition including HbA1c**: i) intervention: 7.6±1.3 %, ii) comparison: 7.7±1.3 %
Interventions	**Intervention:** once-daily subcutaneous injections of lixisenatide. A starting dose of 10 µg of lixisenatide per day was administered during the first 2 weeks and then increased, at the investigator's discretion, to a maximum dose of 20 µg of lixisenatide per day; **GLP-1RA** **Comparison:** placebo (these were each given in addition to standard-of-care treatment) **Type of active treatment for DM:** i) Insulin 1190, Metformin 2038, SU 988, TZD 43 ii) Insulin 1184, Metformin 1983, SU 1016, TZD 52 **concomitant medications:** i) ACEi/ARB 2577, BB 2537, Antiplatelet 2962, Statin 2831 ii) ACEi/ARB 2579, BB 2587, Antiplatelet 2955, Statin 2796
Outcomes	**Primary outcomes:** The primary endpoint in the time-to-event analysis was a composite of the first occurrence of any of the following: death from cardiovascular causes, non-fatal MI, non-fatal stroke, or hospitalisation for unstable angina. **Secondary outcomes:** Secondary endpoints included a composite of the primary endpoint or hospitalisation for HF and a composite of the primary endpoint, hospitalisation for HF, or coronary revascularisation procedures.
Notes	**Funding for trial:** Funded by Sanofi NCT01147250

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Two types of centralized treatment allocation system were used, the Interactive Voice Response System (IVRS) and the Interactive Web Response System (IWRS) depending on the choice of the site."
Allocation concealment (selection bias)	Low risk	"Two types of centralized treatment allocation system were used, the Interactive Voice Response System (IVRS) and the Interactive Web Response System (IWRS) depending on the choice of the site."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded.

Pfeffer 2015 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Method of blinding outcome assessment was not described clearly.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data were unlikely to have an impact on the results of the trial. Dropped out rate was not high (lower than 20%).
Selective reporting (reporting bias)	High risk	Not reported Fasting plasma glucose Cardiovascular risk markers: hs-CRP, BNP, NT-proBNP.
Other bias	Low risk	There were no other biases.

Phrommintikul 2019

Study characteristics	
Methods	**Title**: Effects of dapagliflozin vs vildagliptin on cardiometabolic parameters in diabetic patients with coronary artery disease: a randomised study **acronym of trial**: NA **study design**: prospective randomised double-blinded study **total duration of study**: 6 months **number of study centres and location:** single centre: Chiang Mai University, Chiang Mai, Thailand **date of study**: from October 2014 to July 2018
Participants	**Cardiovascular disease categories:** People with established CAD were eligible for the study. Established CAD was defined as stable angina with >70% stenosis of at least 1 major epicardial artery from coronary angiogram or coronary computed tomography angiography, or post MI (>30 days) with at least one non–infarct-related artery stenosis (>70% stenosis) from coronary angiogram. Prior MI (n, %): 15 (60%), Coronary revascularisation (n, %): 17(68%) i) intervention: ASCVD: 100%, HF: 5 (20%) ii) comparison: ASCVD: 100%, HF: 7 (29.2%) **N randomised**: i) intervention: 25, ii) comparison: 24 **N lost to follow-up/withdrawn:** i) intervention: 0, ii) comparison: 0 **N analysed:** i) intervention: 21, ii) comparison: 22 **mean age, age range**: i) intervention: 62.6 ± 8.3, ii) comparison: 63.9 ± 7.7 **gender (female)**: i) intervention: 11 (44%), ii) comparison: 12 (50%) **body mass index (BMI)**: i) intervention: 25.6 ± 3.0, ii) comparison: 24.9 ± 3.2 **diabetes mellitus (DM)**: (100%) **chronic kidney disease (CKD)**: i) intervention: 2 (8%), ii) comparison: 4 (16.7%)

Phrommintikul 2019 *(Continued)*

	severity of condition (such as the commonly-used classification system, NYHA classification or the ACC/AHA stages of heart failure): NYHA I - II **left ventricular ejection fraction**: i) intervention: 57.2 ± 16.3, ii) comparison: 57.0 ± 13.1 **baseline diabetes condition including HbA1c**: i) intervention: 8.2 ± 1.4, ii) comparison: 8.3 ± 1.1 **smoking history**: NA
Interventions	**Intervention**: 10 mg of dapagliflozin;**SGLT2i** **Comparison**: 50–100 mg of vildagliptin (according to glomerular filtration rate); **DPP4i** **type of active treatment for DM**: i) intervention: SU 20 (80.0%), Metformin 23 (92.0%), TZD 2 (8.0%) ii) comparison: SU 17 (70.8%), Metformin 21 (87.5%), TZD 3 (12.5%) **concomitant medications**: i) intervention: ASA 23 (92.0%), Clopidogrel 11 (44.0%), BB 23 (92.0%), ACEi 12 (48.0%), ARB 7 (28.0%), CCB 6 (24.0%), Nitrate 5 (20.0%), Diuretic 12 (48.0%), Statin 24 (96.0%) ii) comparison: ASA 23 (95.8%), Clopidogrel 11 (41.7%), BB 23 (91.7%), ACEi 14 (58.3%), ARB 7 (29.2%), CCB 5 (20.8%), Nitrate 6 (25.0%), Diuretic 12 (50.0%), Statin 24 (100.0%)
Outcomes	**Primary outcomes:** changes in the haemodynamic biomarkers, metabolic biomarkers and inflammatory biomarkers at 6 months **Secondary outcomes:** major adverse cardio-vascular events including all causes of death, non-fatal MI, non-fatal stroke or HF hospitalisation during the 6 months. These secondary endpoints were not declared in the trials registry (www.clinicaltrials.gov/ct2/show/NCT03178591).
Notes	**Funding for trial**: Thailand Research Fund This study was supported by the Thailand Research Fund grants RSA5780040 (A.P.), RSA5780039 (W.W.), RTA6080003 (S.C.C.), and MRG6180239 (S.K.), and the National Science and Technology Development Agency NSTDA Research Chair Grant (N.C.) This study was included in our narrative synthesis since it did not report our pre-defined outcome measures of interest. NCT03178591

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer - generated random - sequence number in block-of-4 randomisation manner."
Allocation concealment (selection bias)	Low risk	Allocation carried out blinded.
Blinding of participants and personnel (performance bias)	Unclear risk	Double-blinded, but not clearly declared.

Phrommintikul 2019 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blood pressure could not be blinded, we suspect.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up: 4/25 (16%) in Dapagliflozin group and 2/24 (8.3%) in vildagliptin group.
Selective reporting (reporting bias)	High risk	QT interval was not reported.
Other bias	Low risk	No other bias

Rosenstock 2019

Study characteristics	
Methods	**Title:** 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 **acronym of trial:** CARMELINA **study design**: Interventional, randomised, parallel assignment, double masking **total duration of study:** Median observation time was 1.9 (IQR, 1.2 - 2.6) yrs, Median observation time was 1.7 (IQR, 1.2 - 2.5) yrs **number of study centres and location:** 605 centres across 27 countries **date of study:** from 10 July 2013 through 18 January 2018
Participants	**Cardiovascular disease categories:** i) intervention: ASCVD: 2029 (58.1%), HF: 952 (27.2%) ii) comparison: ASCVD: 2052 (58.9%), HF: 921 (26.4%) **N randomised**: i) intervention: 3499, ii) comparison: 3492 **N lost to follow-up/withdrawn:** i) intervention: 36, ii) comparison: 55 **N analysed:** i) intervention: 3494, ii) comparison: 3485 **mean age, age range**: i) intervention: 66.1 SD 9.1, ii) comparison: 65.6 SD 9.1 **gender (female):** i) intervention: 38.5%, ii) comparison: 35.7% **body mass index (BMI)**: i) intervention: 31.4 (5.3) , ii) comparison: 31.3 (5.4) **diabetes mellitus (DM):** (100%) **chronic kidney disease (CKD):** i) intervention: eGFR [45-60] :690 (19.7%) , [30-45] : 994 (28.4%) , [<30]: 516 (14.8%), ii) comparison: eGFR [45-60] : 658 (18.9%) , [30-45]: 944 (27.1%) , [<30]: 546 (15.7%) **baseline diabetes condition including HbA1c**: i) intervention: HbA1c = 7.9 SD = 1.0, ii) comparison: HbA1c = 8.0 SD = 1.0
Interventions	**Intervention:** once-daily oral linagliptin 5 mg; **DPP4i**

Rosenstock 2019 *(Continued)*

	Comparison: placebo (these were each given in addition to standard-of-care treatment) **Type of active treatment for DM:** i) Metformin 1881 (53.8%), SU 1102 (31.5%), insulin 2056 (58.8%) ii) Metformin 1927 (55.3%), SU 1140 (32.7%), insulin 1995 (57.2%) **concomitant medications:** i) ACEi/ARB2860 (81.9%), BB2080 (59.5%), Diuretics 1892 (54.1%), CCB 1433 (41.0%) ii) ACEi/ARB 2798 (80.3%), BB 2073 (59.5%), Diuretics 1936 (55.6%), CCB 1446 (41.5%)
Outcomes	**Primary outcomes:** Primary outcome was time to first occurrence of the composite of CV death, non-fatal MI, or non-fatal stroke. **Secondary outcomes:** Secondary outcome was time to first occurrence of adjudicated death due to renal failure, ESRD, or sustained 40% or higher decrease in eGFR from baseline
Notes	**Funding for trial**: Obtained funding: Johansen, Woerle, George. NCT01897532

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	”Treatment assignment was determined by computer-generated random sequence with stratification by geographical region.”
Allocation concealment (selection bias)	Low risk	”An interactive telephone/web–based system in a block size of 8.”
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Method of blinding outcomes was not described clearly.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data were unlikely to have an impact on the results of the trial. Dropped out rate was not high (lower than 20%).
Selective reporting (reporting bias)	High risk	"Tertiary endpoints" and "Other endpoints" were not fully reported. e.g.. stent thrombosis, Transient Ischaemic Attack (TIA)
Other bias	Low risk	There were no other biases.

Scirica 2013

Study characteristics	
Methods	**Title:** Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus **acronym of trial:** SAVOR-TIMI 53 **study design:** interventional, randomised, parallel assignment, quadruple masking (participant, care provider, investigator, outcomes assessor) **total duration of study**: 2.1 years **number of study centres and location:** 788 sites in 26 countries **date of study**: from May 2010 through May 2013
Participants	**Cardiovascular disease categories:** i) intervention: ASCVD: 6494 (78.4%), HF: 1056 (12.8%) ii) comparison: ASCVD: 6465 (78.7%), HF: 1049 (12.8%) **N randomised**: i) intervention: 8280, ii) comparison: 8212 **N lost to follow-up/withdrawn:** i) intervention: 202, ii) comparison: 214 **N analysed:** i) intervention: 8280, ii) comparison: 8212 **mean age, age range**: i) intervention: 65.1 ± 8.5, ii) comparison: 65 ± 8.6 **gender (female):** i) intervention: 2768 (33.4%), ii) comparison: 2687 (32.7%) **body mass index (BMI)**: i) intervention: 31.1 ± 5.5, ii) comparison: 31.2 ± 5.7 **diabetes mellitus (DM):** (100%) **chronic kidney disease (CKD):** i) intervention: eGFR < 30 ml/min 172 (2.1%), 30 to ≦ 50 ml/min 1122 (13.6%), > 50 ml/min 6986 (84.4%), ii) comparison: eGFR < 30 ml/min 164 (2.0%), 30 to ≦ 50 ml/min 1118 (13.6%), > 50 ml/min 6930 (84.4%) **baseline diabetes condition including HbA1c**: i) intervention: 8.0 ± 1.4 %, ii) comparison: 8.0 ± 1.4 %
Interventions	**Intervention:** saxagliptin at a dose of 5 mg daily (or 2.5 mg daily in patients with an estimated glomerular filtration rate [GFR] of ≤ 50 ml per minute); **DPP4i** **Comparison**: placebo (these were each given in addition to standard-of-care treatment) **Type of active treatment for DM:** i) Metformin 5789 (69.9%), SU 3352 (40.5%), TZD 513 (6.2%), Insulin 3448 (41.6%), Other antihyperglycaemic medications 52 (0.6%) ii) Metformin 5684 (69.2%), SU 3281 (40.0%), TZD 465 (5.7%), Insulin 3384 (41.2%), Other antihyperglycaemic medications 50 (0.6%) **concomitant medications:** i) ASA 6249 (75.5%), Statin 6482 (78.3%), ACEi 4435 (53.6%), ARB 2332 (28.2%), BB 5101 (61.6%) ii) ASA 6155 (75.0%), Statin 6435 (78.4%), ACEi 4505 (54.9%), ARB 2263 (2762%), BB 5061 (61.6%)
Outcomes	**Primary outcomes:** A composite of cardiovascular death, non-fatal MI, or non-fatal ischaemic stroke

Scirica 2013 *(Continued)*

	Secondary outcomes: The primary composite endpoint plus hospitalisation for HF, coronary revascularization, or unstable angina
Notes	**Funding for trial**: AstraZeneca and Bristol-Myers Squibb NCT01107886

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	”Randomization was performed by means of a central computerized telephone or Web-based system in blocks of 4.”
Allocation concealment (selection bias)	Low risk	”Randomization was performed by means of a central computerized telephone or Web-based system in blocks of 4.”
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Method of blinding outcomes was not described clearly.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data were unlikely to have an impact on the results of the trial. Dropped out rate was not high (lower than 20%).
Selective reporting (reporting bias)	High risk	"Other efficacy endpoints" and "Exploratory endpoints" were not fully reported. e.g.. Documented laser treatment due to development of and/or deterioration in diabetic retinopathy, Change from baseline in FPG, HOMA-β.
Other bias	Low risk	There were no other biases.

Shimizu 2020

Study characteristics

Methods	**Title**: Effects of empagliflozin versus placebo on cardiac sympathetic activity in acute myocardial infarction patients with type 2 diabetes mellitus: the EMBODY trial. **acronym of trial**: EMBODY **study design**: prospective, multicentre, randomised, double-blind, placebo-controlled trial **total duration of study**: 24 weeks **number of study centres and location:** Japan **date of study**: in February 2018 and ended in March 2019
Participants	**Cardiovascular disease categories:**

Shimizu 2020 *(Continued)*

	all patient had acute MI. **i) intervention**: ASCVD: (100%), HF: NA **ii) comparison**: ASCVD: (100%), HF: NA **N randomised**: 105 **N lost to follow-up/withdrawn:** 9 **N analysed:** i) intervention: 46, ii) comparison: 50 **mean age, age range**: i) intervention: 63.9 ± 10.4, ii) comparison: 64.6 ± 11.6 **gender (female):** i) intervention: 17.4%, ii) comparison: 22.0% **body mass index (BMI)**: i) intervention: 25.2 (3.7), ii) comparison: 25.2 (4.1) **diabetes mellitus (DM)**: (100%) **chronic kidney disease (CKD)**: NA **severity of condition (such as the commonly-used classification system, NYHA classification or the ACC/AHA stages of heart failure)**: NA **left ventricular ejection fraction**: NA **baseline diabetes condition including HbA1c**: i) intervention: 6.8 (1.0), ii) comparison: 6.9 (0.9) **smoking history**: i) intervention: 24 (52.2%) current smoker, ii) comparison: 27 (54.0%) current smoker
Interventions	**Intervention**: empagliflozin (10 mg/day); **SGLT2i** **Comparison**: placebo **type of active treatment for DM** : i) intervention: metformin 7 (15.2%), DPP4i 20 (43.5%) ii) comparison: metformin 6 (12.0%), DPP4i 23 (46.0%) **concomitant medications** : i) intervention: ARB 22 (47.8%), ACEi 23 (50.0%), Statin 44 (95.7%), MRA 11 (23.9%), BB 41 (89.1%) ii) comparison: ARB 19 (38.0%), ACEi 28 (56.0%), Statin 48 (96.0%), MRA 12 (24.0%), BB 38 (76.0%)
Outcomes	**Primary outcomes:** The primary endpoint of this trial was the change in HRV (heart rate variability) from baseline to 24 weeks. **Secondary outcomes:** Secondary endpoints were the changes from baseline to 24 weeks in the following measurements in the empagliflozin group compared with those in the placebo group throughout the trial period.
Notes	**Funding for trial**: This trial is funded by Boehringer Ingelheim and Eli Lilly and Company. Grant number is 1245-0175. The funding agencies had no role in designing or conducting the trial. This study was included in our narrative synthesis since it did not report our pre-defined outcome measures of interest. UMIN000030158

Shimizu 2020 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated.
Allocation concealment (selection bias)	Low risk	Allocation carried out blinded.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Outcome analysis was not clearly blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up: 11.5 % in empagliflozin group and 9.5% in placebo group.
Selective reporting (reporting bias)	Low risk	Results reported for all measures.
Other bias	Low risk	No other bias.

Tanaka 2019

Study characteristics	
Methods	**Title**: Effect of empagliflozin on endothelial function in patients with type 2 diabetes and cardiovascular disease: results from the multicenter, randomized, placebo-controlled, double-blind EMBLEM trial **acronym of trial**: EMBLEM **study design**: prospective, multicentre, randomised, placebo-controlled, double-blind clinical trial **total duration of study**: 24 weeks **number of study centres and location:** undertaken in 16 centres in Japan **date of study**: 4 January 2016 to 29 March 2018
Participants	**Cardiovascular disease categories:** CVD (MI 24%, angina 31%, stroke 20%, and HF 40%), and 77% of patients had been receiving treatment for hypertension (66% on ACEi/ARB, 49% on CCB, and 36% on BB) or dyslipidaemia (75% on statins) - ASCVD: (100%), HF: (40%) **N randomised**: i) intervention: 58, ii) comparison: 59 **N lost to follow-up/withdrawn:** NA **N analysed:** i) intervention: 52, ii) comparison: 53 **mean age, age range**: i) intervention: 65 ± 11, ii) comparison: 64 ± 10

Tanaka 2019 *(Continued)*

	gender (female): i) intervention: 16%, ii) comparison: 17% **body mass index (BMI)**: i) intervention: 26 (5), ii) comparison: 27 (6) **diabetes mellitus (DM):** (100%) **chronic kidney disease (CKD):** NA **severity of condition (such as the commonly-used classification system, NYHA classification or the ACC/AHA stages of heart failure)**: NA **left ventricular ejection fraction**: NA **baseline diabetes condition including HbA1c**: i) intervention: 7.2% (0.8%), ii) comparison: 7.2% (0.8%) **smoking history**: NA
Interventions	**Intervention**: Empagliflozin 10 mg/day is administered orally before or after breakfast; **SGLT2i** **Comparison**: Placebo is administered orally before or after breakfast for 24 weeks **type of active treatment for DM** : i) intervention: metformin 25 (48%), insulin 5 (10%), DPP4i 37 (71%) ii) comparison: metformin 28 (53%), insulin 5 (9%), DPP4i 36 (68%) **concomitant medications** : 66% on ACEi/ARB, 49% on CCB, 36% on BB, and 75% on statins
Outcomes	**Primary outcomes:** Change in RHI (reactive hyperemia peripheral arterial tonometry index) from baseline to 24 weeks **Secondary outcomes:** Change and correlation with RHI change from baseline to 24 weeks in following items: 1) Double product (systolic blood pressure x heart rate) 2) baPWV (both sides) 3) Coefficient of variation of the R-R intervals in the ECG at rest and deep breathing (including the differences between the results at rest and deep breathing) and standard deviation of heartbeat intervals 4) LVEF, E/e' (echocardiogram) 5) Blood biomarkers NT-proBNP, interleukin-8, high-sensitivity troponin I, receptor for advanced glycation end products (RAGE), angiopoietin-like protein 2 (ANGPTL2) 6) Renal function Serum creatinine, eGFR, albumin excretion in urine corrected by creatinine, L-FABP in urine corrected by creatinine 7) Glycemic control HbA1c, fasting blood glucose, glycoalbumin 8) Other laboratory tests

Tanaka 2019 *(Continued)*

	Blood pressure, pulse pressure, heart rate, body weight, BMI, total cholesterol, HDL-C, LDL-C, triglyceride, non-HDL-C, AST, ALT, gamma-GTP, uric acid, RBC, haemoglobin, hematocrit 9) Parameters measured by RH-PAT test other than RHI (e.g.. AI, HRV)
Notes	**Funding for trial**: This study was funded by Boehringer Ingelheim and Eli Lilly and Company. A.T. received modest honoraria from Astellas, AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo, Kowa, Merck, Mitsubishi Tanabe, Novo Nordisk, Taisho Toyama, Takeda, and Teijin. M.S. received an honorarium and endowed chair from Boehringer Ingelheim. H.T. received lecture fees from Bayer, Boehringer Ingelheim, Daichi Sankyo, Kowa, Takeda, Mitsubishi Tanabe, and Sanwa Kagaku Kenkyusho. Y.O. received lecture fees from Astellas, AstraZeneca, Merck Sharp & Dohme (MSD), Ono, Mitsubishi Tanabe, Bayer, Novo Nordisk, Eli Lilly and Company, Boehringer Ingelheim, Daiichi Sankyo, Kissei, Novartis, Kowa, and Sanwa Kagaku Kenkyusho and research funds from Kowa and Mitsubishi Tanabe. T.T. received honoraria from MSD, Astellas, AstraZeneca, Mitsubishi Tanabe, Boehringer Ingelheim, Novo Nordisk, and Taisho Toyama; research funding from Kowa; and scholarships from Novartis, AstraZeneca, Astellas, and Novo Nordisk. M.Y-T. received honoraria from Bayer, Mitsubishi Tanabe, Itamar, MSD, Nippon Shinyaku, Boehringer Ingelheim, and Daiichi Sankyo. S.U. received research grants from Bristol-Myers Squibb and Kowa; nonpurpose research grants from Bristol-Myers Squibb, Chugai, MSD, Pfizer, and Takeda; and lecture fees from Boehringer Ingelheim and MSD. Y.H. received consulting fees from Mitsubishi Tanabe related to this study, as well as honoraria and grants from Teijin, Boehringer Ingelheim, MSD, Sanofi, AstraZeneca, Kyowa Hakko Kirin, Takeda, Astellas, Daiichi Sankyo, Mochida, Nihon Kohden, Shionogi, Nippon Sigmax, Sanwa Kagaku Kenkyusho, Unex, and Kao and honoraria from Radiometer, Omron, Sumitomo Dainippon, Otsuka, Torii, Kowa, Fujiyakuhin, Amgen, Nippon Shinyaku, Itamar, Bayer, Eli Lilly and Company, and Ono. K.N. received honoraria from Eli Lilly and Company, Astellas, Ono, Takeda, Daiichi Sankyo, Boehringer Ingelheim, MSD, Mitsubishi Tanabe, and AstraZeneca; research grants from Amgen, Teijin, Terumo, Mitsubishi Tanabe, Asahi Kasei, Astellas, Boehringer Ingelheim, and Bayer; and scholarships from Bayer, Daiichi Sankyo, Teijin, Astellas, Takeda, and Bristol-Myers Squibb. No other potential conflicts of interest relevant to this article were reported. This study was included in our narrative synthesis since it did not report our pre-defined outcome measures of interest. UMIN000024502

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated.
Allocation concealment (selection bias)	Low risk	Allocation carried out blinded.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The participants and investigators remained masked to group assignments until the database lock"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The blindedness of the reactive hyperaemia peripheral arterial tonometry index (RHI) was not clearly reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Of the 117 patients, 105 were included in the full analysis set. (89.7%)
Selective reporting (reporting bias)	Unclear risk	Outcomes other than RHI were not clearly reported.

Tanaka 2019 *(Continued)*

Other bias	Low risk	No other bias

Tanaka 2020

Study characteristics	
Methods	**Title**: Effects of canagliflozin in patients with type 2 diabetes and chronic heart failure: a randomised trial (CANDLE) **acronym of trial**: CANDLE **study design**: an investigator initiated, multicentre, prospective, randomised, open-label, blinded-endpoint trial **total duration of study**: 24 weeks **number of study centres and location:** 34 centres in Japan **date of study**: 25 May 2015 to 29 July 2020
Participants	**Cardiovascular disease categories:** NYHA class I– III CHF were eligible. **i) intervention**: ASCVD: MI 32 (28.3%), Angina pectoris 24 (21.2%), CABG 12 (10.6%), Stroke 11 (9.7%), HF (Ischaemia) 54 (47.8%), HF: (100%) **ii) comparison**: ASCVD: MI 24 (20.0%), Angina pectoris 27 (22.5%), CABG 10 (8.3%), Stroke 5 (4.2%), HF (Ischaemia) 46 (38.3%), HF: (100%) **N randomised**: i) intervention: 122, ii) comparison: 123 **N lost to follow-up/withdrawn:** i) intervention: 6, ii) comparison: 1 **N analysed:** i) intervention: 113, ii) comparison: 120 **mean age, age range**: i) intervention: 68.3 ± 9.8, ii) comparison: 68.9 ± 10.4 **gender (female):** i) intervention: 25 (22.1%), ii) comparison: 34 (28.3%) **body mass index (BMI)**: i) intervention: 24.1 ± 6.4, ii) comparison: 25.4 ± 4.8 **diabetes mellitus (DM):** (100%) **chronic kidney disease (CKD):** NA **severity of condition (such as the commonly-used classification system, NYHA classification or the ACC/AHA stages of heart failure)**: i) intervention: NYHA I 72 (63.7%), NYHA II 39 (34.5%), NYHA III 2 (1.8%), ii) comparison: NYHA I 76 (63.9%), NYHA II 40 (33.6%), NYHA III 3 (2.5%) **left ventricular ejection fraction**: i) intervention: 57.4 ± 15.0, ii) comparison: 57.7 ± 14.2 **baseline diabetes condition including HbA1c**: i) intervention: 6.9 ± 0.7, ii) comparison: 7.1 ± 0.9 **smoking history**: NA
Interventions	**Intervention**: canagliflozin 100 mg once daily; **SGLT2i**

Tanaka 2020 *(Continued)*

For patients who could not achieve their glycaemic goal, increasing the dose of background therapy or adding glucose-lowering agents other than SGLT2i and SU in both groups was allowed.

Comparison: glimepiride 0.5 mg once daily; **SU**

For patients who could not achieve their glycaemic goal, increasing the dose of background therapy or adding glucose-lowering agents other than SGLT2i and SU in both groups was allowed. In the glimepiride group, a dose increase of up to 6.0 mg daily was permitted.

type of active treatment for DM :

i) intervention: Insulin 4 (3.5%), Metformin18 (15.9%), AGI 16 (14.2%), DPP4i 64 (56.6%), GLP-1RA 1 (0.9%)

ii) comparison: Insulin 3 (2.5%), Metformin 26 (21.7%), AGI 24 (20.0%), DPP4i 63 (52.5%), GLP-1RA 1 (0.8%)

concomitant medications :

i) intervention: ACEi/ARB 89 (78.8%), BB 82 (72.6%), CCB 46 (40.7%), MRA 42 (37.2%), Diuretic 46 (40.7%), Digitalis 12 (10.6%), Statin 87 (77.0%), Anti-platelet or anti-coagulant 71 (62.8%)

ii) comparison: ACEi/ARB 88 (73.3%), BB 82 (68.3%), CCB 44 (36.7%), MRA 44 (36.7%), Diuretic 53 (44.2%), Digitalis 8 (6.7%), Statin 86 (71.7%), Anti-platelet or anti-coagulant 66 (55.0%)

Outcomes

Primary outcomes:

the percentage change (post/pre -1) from baseline in NT-proBNP at Week 24

Secondary outcomes:

In the secondary endpoints, we evaluated the changes in parameters after 24 weeks of treatment or at early termination visits, including (1) NT-proBNP level, (2) vital signs (body weight, blood pressure, and heart rate), (3) glycaemic control (HbA1c, fasting plasma glucose), (4) estimated plasma volume (ePV) calculated by the Strauss formula,10,11 (5) echocardiographic measures (LVEF and mitral inflow to mitral relaxation velocity ratio; E/e'), (6) NYHA functional classification, and (7) CHF-related quality of life evaluated by scaled responses to the Minnesota Living with Heart Failure (MLHF) questionnaire.

Notes

Funding for trial: Mitsubishi Tanabe Pharma Corporation

This study was included in our narrative synthesis since it did not report our pre-defined outcome measures of interest.

UMIN000017669

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Methods not clearly stated, but randomised.
Allocation concealment (selection bias)	Low risk	Allocation carried out blinded.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Open-label design. However, "the assessor(s) will be blinded to treatment randomisation. BNP will not be affected by this process."
Blinding of outcome assessment (detection bias)	Low risk	"The assessors will also be blinded to the primary end point, NT-proBNP level, by measurement at a central laboratory."

Tanaka 2020 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up: 8.0% in canagliflozin group and 2.4% in placebo group.
Selective reporting (reporting bias)	Low risk	Results reported for all measures.
Other bias	Low risk	No other bias.

Verma 2019

Study characteristics	
Methods	**Title**: 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 **acronym of trial**: EMPA-HEART CardioLink-6 **study design**: a double-blind, placebo-controlled, randomised investigator-initiated clinical trial **total duration of study**: 6 months **number of study centres and location:** Canada **date of study**: Between November 2016 and April 2018
Participants	**Cardiovascular disease categories:** Diabetes (HbA1c: 6.5-10.0%) with known coronary artery disease **i) intervention**: ASCVD: (100%), HF: (4%) Previous MI: 19 (39%), PCI >2 months before screening: 26 (53%), CABG surgery >2 months before screening: 28 (57%) **ii) comparison**: ASCVD: (100%), HF: (8%) Previous MI: 21 (44%), PCI >2 months before screening: 19 (40%), CABG surgery >2 months before screening: 27 (56%) **N randomised**: 152 **N lost to follow-up/withdrawn:** 55 **N analysed:** i) intervention: 49, ii) comparison: 48 **mean age, age range**: i) intervention: 64 (57-69), ii) comparison: 64 (56-72) **gender (female):** i) intervention: 10%, ii) comparison: 4% **body mass index (BMI)**: i) intervention: 26.7 (24.5-30.2), ii) comparison: 26.6 (24.4-29.3) **diabetes mellitus (DM):** (100%) **chronic kidney disease (CKD):** NA **severity of condition (such as the commonly-used classification system, NYHA classification or the ACC/AHA stages of heart failure)**: NA **left ventricular ejection fraction**: i) intervention: 58.0 (7.5), ii) comparison: 55.5 (8.7)

Verma 2019 *(Continued)*

	baseline diabetes condition including HbA1c: i) intervention: 7.9 (7.5-8.4), ii) comparison: 7.9 (7.3-8.7) **smoking history**: i) intervention: 41%, ii) comparison: 46%
Interventions	**Intervention**: empagliflozin 10 mg daily;**SGLT2i** **Comparison**: placebo **type of active treatment for DM** : i) intervention: metformin 96%, insulin 25% ii) comparison: metformin 92%, insulin 25% **concomitant medications** : i) intervention: ACEi/ARB 82%, Diuretic 4%, BB 78%, Statin 96%, CCB 12%, ASA/P2Y12 82% ii) comparison: ACEi/ARB 85%, Diuretic 13%, BB 81%, Statin 96%, CCB 31%, ASA/P2Y12 85%
Outcomes	**Primary outcomes:** The primary outcome was the 6-month change in LV mass indexed to body surface area from baseline as measured by cMRI. **Secondary outcomes:** Secondary outcomes included the between-groups (empagliflozin vs placebo) baseline to 6-month changes in LV end-diastolic and end-systolic volumes (non-indexed and indexed to baseline body surface area), LVEF, and NT-proBNP.
Notes	**Funding for trial**: This trial was supported by an unrestricted investigator-initiated study grant from Boehringer Ingelheim to Drs Verma and Zinman. The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation or decision to submit the manuscript for publication. The database for the study was located, and the data analyses were conducted, at the not-for-profit academic research organization Applied Health Research Centre (AHRC), which is integrated with the Li Ka Shing Knowledge Institute of St. Michael's Hospital, and not shared with the funder. The manuscript was modified after consultation with the co-authors. The authors had unrestricted rights to publish the results and the final decision on content was exclusively retained by the authors. This study was included in our narrative synthesis since it did not report our pre-defined outcome measures of interest. NCT02998970

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation via REDCAP.
Allocation concealment (selection bias)	Low risk	Allocation was blinded.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded.

Verma 2019 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	All assays and MRI endpoints were conducted, and data analysed by personnel blinded to treatment group and study visit.
Incomplete outcome data (attrition bias) All outcomes	Low risk	90/97 (92.7%) were followed up.
Selective reporting (reporting bias)	Low risk	Results reported for all measures.
Other bias	Low risk	No other bias.

Wang 2020

Study characteristics	
Methods	**Title**: Comparison between the effects of sitagliptin and liraglutide on blood glucose and cognitive function of patients with both type 2 diabetes mellitus and post-stroke mild cognitive impairment **acronym of trial**: NA **study design**: Single centre, non-blinded, randomised trial **total duration of study**: 6 months **number of study centres and location:** 1 hospital, Shandong Province, China. **date of study**: January 2017 to June 2018
Participants	**Cardiovascular disease categories:** all post-stroke patients **i) intervention**: ASCVD: (100%), HF: NA **ii) comparison**: ASCVD: (100%), HF: NA **N randomised**: i) intervention: 30, ii) comparison: 30 **N lost to follow-up/withdrawn:** i) intervention: 0, ii) comparison: 0 **N analysed:** i) intervention: 30, ii) comparison: 30 **mean age, age range**: i) intervention: 67.2 ± 7.1, ii) comparison: 67.2 ± 7.1 **gender (female):** i) intervention: 13 (43.3%), ii) comparison: 16 (53.3%) **body mass index (BMI)**: i) intervention: 25.8 ± 3.8, ii) comparison: 25.7 ± 4.3 **diabetes mellitus (DM):** (100%) **chronic kidney disease (CKD):** NA **severity of condition (such as the commonly-used classification system, NYHA classification or the ACC/AHA stages of heart failure)**: NA **left ventricular ejection fraction**: NA **baseline diabetes condition including HbA1c**: i) intervention: 8.6 ± 3.3, ii) comparison: 8.9 ± 3.2

Wang 2020 *(Continued)*

	smoking history: NA
Interventions	**Intervention**: 100 mg of sitagliptin orally once a day, one tablet each time; **DPP4i** **Comparison**: liraglutide through subcutaneous injection at an initial amount of 0.6 mg/d, and an amount of 1.2 mg/d after one week; **GLP-1RA** **type of active treatment for DM**: NA **concomitant medications**: NA
Outcomes	**Primary outcomes:** (1) The fasting blood glucose (FBG), 2-hour postprandial blood glucose (2hPG), and glycosylated haemoglobin (HbA1c) of the patients were determined before treatment and at 6 months after treatment. FBG and 2hPG were determined using the German Roche portable blood glucose meter, and HbA1c was determined using the German Bayer DCA 2000 detector. (2) The cognition of the patients was assessed using MMSE and MoCA before treatment and at 6 months after treatment. **Secondary outcomes:** Blood indexes (CRP, TNF-α, IL-6, Aβ1-40, and Aβ1-42) of the patients were determined as follows: two tubes of venous blood (5 mL for each tube) were sampled from each patient at 8 o'clock in the morning before treatment and at 6 months after treatment, respectively. The sampled blood was stored in ethylenediamine tetra acetic acid (EDTA) tubes in a refrigerator at 4°C for 15 min, and then the samples were separated by centrifugation at 3300 rpm to separate plasma and serum. The separated plasma was added with phosphate buffered solution (Guangzhou Dingguo Biotechnology Co., Ltd., China) containing 40 μL of protease inhibitor, and then stored in a refrigerator at -80°C. C-reactive protein (CRP), tumour necrosis factor-α (TNF-α), and interleukin-6 (IL-6) in the serum were determined using the immune turbidimetry, and Aβ1-40 and Aβ1-42 in the plasma were determined using the enzyme-linked immunosorbent assay.
Notes	**Funding for trial**: none This study was included in our narrative synthesis since it did not report our pre-defined outcome measures of interest. Unclear about study design.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table method.
Allocation concealment (selection bias)	Unclear risk	Not clear.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label and observation.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up.

Wang 2020 *(Continued)*

Selective reporting (reporting bias)	Low risk	Results reported for all measures.
Other bias	Low risk	No other bias.

White 2013

Study characteristics	
Methods	**Title:** Alogliptin after acute coronary syndrome in patients with type 2 diabetes **acronym of trial:** EXAMINE **study design:** Interventional, randomised, parallel assignment, quadruple masking (participant, care provider, investigator, outcomes assessor) **total duration of study**: intervention group: 533 (280-751) days, comparison group: 520 (273-744) days. **number of study centres and location:** 898 centres in 49 countries **date of study:** from September 2009 through June 2013
Participants	**Cardiovascular disease categories:** Eligible patients had an acute coronary syndrome within 15 to 90 days before randomisation. i) intervention: ASCVD: 2701 (100%), HF: 757 (28.0%) ii) comparison: ASCVD: 2679 (100%), HF: 744 (27.8%) **N randomised**: i) intervention: 2701, ii) comparison: 2679 **N lost to follow-up/withdrawn:** i) intervention: 9, ii) comparison: 16 **N analysed:** i) intervention: 2701, ii) comparison: 2679 **mean age, age range**: i) intervention: 61, ii) comparison: 61 **gender (female):** i) intervention: 873 (32.3%), ii) comparison: 856 (32.0%) **body mass index (BMI)**: i) intervention: 28.7 (15.7-55.9), ii) comparison: 28.7 (15.6-68.3) **diabetes mellitus (DM):** (100%) **chronic kidney disease (CKD):** i) intervention: eGFR < 60 ml/min/1.73 m^2 ：772 (28.6%), ii) comparison: eGFR < 60 ml/min/1.73 m^2 ：793 (29.6%) **baseline diabetes condition including HbA1c**: i) intervention: 8.0 ± 1.1 %, ii) comparison: 8.0 ± 1.1 %
Interventions	**Intervention:** alogliptin (25 mg in patients with an estimated glomerular filtration rate (GFR), calculated with the use of the Modification of Diet in Renal Disease formula, of at least 60 mL per minute per 1.73 m^2 of body-surface area; 12.5 mg in patients with an estimated GFR of 30 to less than 60 mL per minute per 1.73 m^2; and 6.25 mg in patients with an estimated GFR of less than 30 mL per minute per 1.73 m^2); **DPP4i** **Comparison:** placebo (these were each given in addition to standard-of-care treatment) **Type of active treatment for DM:**

White 2013 *(Continued)*

	i) Insulin 793 (29.4%), Metformin 1757 (65%), SU 1266 (46.9%), TZD 67 (2.5%) ii) Insulin 812 (30.3%), Metformin 1805 (67.4%), SU 1237 (46.2%), TZD 64 (2.4%) **concomitant medications:** i) Antiplatelet agents: 2630 (97.4%), BB: 2208 (81.7%), CCB; 586 (21.7%), Diuretics: 1005 (37.2%), ACEi/ARB: 2201 (81.5%) ii) Antiplatelet agents: 2602 (97.1%), BB: 2203 (82.2%), CCB; 611 (22.8%), Diuretics: 1009 (37.7%), ACEi/ARB: 2210 (82.5%)
Outcomes	**Primary outcomes:** The primary endpoint was a composite of death from cardiovascular causes, non-fatal MI, or non-fatal stroke. **Secondary outcomes:** The principal secondary safety endpoint was the primary composite endpoint with the addition of urgent revascularization due to unstable angina within 24 hours after hospital admission
Notes	**Funding for trial:** Funded by Takeda Development Center Americas NCT00968708

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	”Patients were randomised using an interactive voice response system (IVRS).”
Allocation concealment (selection bias)	Low risk	”Patients were randomised using an interactive voice response system (IVRS).”
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Method of blinding outcomes was not described clearly.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data were unlikely to have an impact on the results of the trial. Drop-out rate was not high (lower than 20%).
Selective reporting (reporting bias)	High risk	Exploratory endpoints o Stent thrombosis. o Hospitalisation for other CV causes. o Lower extremity amputation. Other safety endpoints # Electrocardiograms (ECGs). # Vital sign measurements (blood pressure and heart rate).

White 2013 *(Continued)*

		were not reported in original article.
Other bias	Low risk	There were no other biases.

Zinman 2015

Study characteristics	
Methods	**Title**: Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes **acronym of trial:** EMPA-REG outcome **study design**: Interventional, randomised, parallel assignment, double masking **total duration of study:** intervention group: 3.2 (2.2 – 3.6) IQR, comparison group: 3.1 (2.2 – 3.5) IQR **number of study centres and location**: 590 sites in 42 countries **date of study**: from July 2010 through April 2015
Participants	**Cardiovascular disease categories:** All the patients had established cardiovascular disease; i) intervention: ASCVD: (100%), Coronary artery disease: 3545 (75.6%), History of stroke: 1084 (23.1%), and Peripheral artery disease: 982 (21.0%), HF: 462 (9.9%) ii) comparison: ASCVD: (100%), Coronary artery disease: 1763 (75.6%), History of stroke: 553 (23.7%), and Peripheral artery disease: 479 (20.5%), HF: 244 (10.5%) **N randomised**: i) intervention: 4687, ii) comparison: 2333 **N lost to follow-up/withdrawn:** i) intervention: 144, ii) comparison: 67 **N analysed:** i) intervention: 4687, ii) comparison: 2333 **mean age, age range**: i) intervention: 63.1 SD 8.6, ii) comparison: 63.2 SD 8.8 **gender (female):** i) intervention: 28.8%, ii) comparison: 28.0% **body mass index (BMI)**: i) intervention: 30.6 ± 5.3, ii) comparison: 30.7 ± 5.2 **diabetes mellitus (DM):** (100%) **chronic kidney disease (CKD):** i) intervention: eGFR < 60 ml/min/1.73 m^2: 1212 (25.9%), ii) comparison: eGFR < 60 ml/min/1.73 m^2: 607 (26.0%) **baseline diabetes condition including HbA1c**: i) intervention: Glycated hemoglobin 8.1 ± 0.9, ii) comparison: Glycated hemoglobin 8.1 ± 0.8
Interventions	**Intervention**: 10 mg or 25 mg of empagliflozin; **SGLT2i** **Comparison**: placebo

Zinman 2015 *(Continued)*

	(these were each given in addition to standard-of-care treatment) **Type of active treatment for DM:** i) Insulin 2252, Metformin 3459, SU 2014, TZD 198, GLP-1RA 126, DPP4i 529 ii) Insulin 1135, Metformin 1734, SU 992, TZD 101, GLP-1RA 70, DPP4i 267 **concomitant medications:** i) ACEi/ARB 3798, BB 3056, Diuretics 2047, CCB 1529, MRA 305, Anticoagulant 4162, Statin 3630 ii) ACEi/ARB 1868, BB 1498, Diuretics 988, CCB 788, MRA 136, Anticoagulant 2090, Statin 1773
Outcomes	**Primary outcomes:** The primary outcome was a composite of death from cardiovascular causes, non-fatal MI (excluding silent MI), or non-fatal stroke. **Secondary outcomes:** The key secondary outcome was a composite of the primary outcome plus hospitalisation for unstable angina.
Notes	**Funding for trial:** Funded by Boehringer Ingelheim and Eli Lilly NCT01131676

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	”Randomization was performed with the use of a computer-generated random-sequence and interactive voice- and Web-response system. “
Allocation concealment (selection bias)	Low risk	”Randomization was performed with the use of a computer-generated random-sequence and interactive voice- and Web-response system. “
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Method of blinding outcomes was not described clearly.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data were unlikely to have an impact on the results of the trial. Dropped out rate was not high (lower than 20%).
Selective reporting (reporting bias)	High risk	Some "secondary endpoints" were not reported in original article. • Vitreous haemorrhage • Diabetes-related blindness
Other bias	Low risk	There were no other biases.

ACC: American College of Cardiology; ACEi: angiotensin-converting enzyme inhibitor; AGI: alpha-glucosidase inhibitors; AHA: American Heart Association; AHA: anti-hyperglycaemic agent; ARB: angiotensin receptor blocker; ARNI: angiotensin receptor-neprilysin inhibitor; ASA: acetylsalicylic acid; ASCVD: atherosclerotic cardiovascular disease; BB: beta-blocker; CABG: coronary artery bypass grafting; CAD:

coronary artery disease; CCB: calcium channel blockers; CHF: congestive heart failure; cMRI: cardiac magnetic resonance imaging; DPP4i: dipeptidyl peptidase 4 inhibitor; E/A: the ratio of peak velocity of the E wave to the A wave; ESRD: end-stage renal disease; GLP-1RA: glucagon-like peptide-1 receptor agonist; HF: heart failure; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; HVD: heart valve disease; IVC: inferior vena cava; IVS: interventricular septum; LVMI: left ventricular mass index; LAD: left atrial dimension; LAV: left atrial volume; LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume; LVEF: left ventricular ejection fraction; MRA: mineralocorticoid receptor antagonists; MI: myocardial infarction; NA: not available; NSTE-ACS: non-ST elevation acute coronary syndrome; NYHA: New York Heart Association; PAD: peripheral arterial disease; PCI: percutaneous coronary intervention; PW: posterior wall; SCAD: spontaneous coronary artery dissection; SGLT2i: sodium-glucose co-transporter-2 inhibitor; STEMI: ST elevation myocardial infarction; SU: sulfonylurea; TIA: transit ischemic attack; TZD: thiazolidinedione.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Anholm 2014	Wrong duration (intervention period < 24 weeks)
Arjona 2013	Participants with cardiovascular disease < 80%
Arnott 2020	Participants with cardiovascular disease < 80%
Bajaj 2020	Participants with cardiovascular disease < 80%
Bays 2017	Participants with cardiovascular disease < 80%
Besch 2017	Wrong duration (intervention period < 24 weeks)
Bremholm 2017	Participants with cardiovascular disease < 80%
Brenner 2016	Wrong duration (intervention period < 24 weeks)
Brown 2017	Participants with cardiovascular disease < 80%
Brown 2020	Participants with cardiovascular disease < 80%
Brown-Frandsen 2019	Participants with cardiovascular disease < 80%
Cahn 2020a	Participants with cardiovascular disease < 80%
Cahn 2020b	Participants with cardiovascular disease < 80%
Cannon 2020b	Participants with cardiovascular disease < 80%
Chacra 2017	Participants with cardiovascular disease < 80%
Damman 2020	Wrong duration (intervention period < 24 weeks)
Davies 2016	Participants with cardiovascular disease < 80%
Dejgaard 2016	Participants with cardiovascular disease < 80%
Doupis 2019	Participants with cardiovascular disease < 80%
Ejiri 2019	Wrong duration (intervention period < 24 weeks)
Ferdinand 2019	Participants with cardiovascular disease < 80%
Furtado 2019a	Participants with cardiovascular disease < 80%

Study	Reason for exclusion
Furtado 2019b	Participants with cardiovascular disease < 80%
Furuhashi 2020	Participants with cardiovascular disease < 80%
Gallwitz 2012	Participants with cardiovascular disease < 80%
Gause-Nilsson 2014	Participants with cardiovascular disease < 80%
Gerstein 2018	Participants with cardiovascular disease < 80%
Gerstein 2019a	Participants with cardiovascular disease < 80%
Gerstein 2019b	Participants with cardiovascular disease < 80%
Gerstein 2020	Participants with cardiovascular disease < 80%
Gross 2016	Wrong duration (intervention period < 24 weeks)
Haering 2015	Participants with cardiovascular disease < 80%
Hamal 2020	Participants with cardiovascular disease < 80%
Haneda 2016	Participants with cardiovascular disease < 80%
Heerspink 2020	Participants with cardiovascular disease < 80%
Hulst 2020	Wrong duration (intervention period < 24 weeks)
Imazu 2019	Participants with cardiovascular disease < 80%
Irie 2018	Participants with cardiovascular disease < 80%
Jaiswal 2015	Participants with cardiovascular disease < 80%
Januzzi 2017	Participants with cardiovascular disease < 80%
Jardine 2017	Participants with cardiovascular disease < 80%
Jardine 2020	Participants with cardiovascular disease < 80%
Kadowaki 2020	Participants with cardiovascular disease < 80%
Kato 2019	Participants with cardiovascular disease < 80%
Koyama 2018	Wrong duration (intervention period < 24 weeks)
Li 2020	Participants with cardiovascular disease < 80%
Marx 2015	Participants with cardiovascular disease < 80%
Matsubara 2013	Not a randomised controlled trial
McGill 2015	Participants with cardiovascular disease < 80%
Mosenzon 2019	Participants with cardiovascular disease < 80%

Study	Reason for exclusion
Natali 2017	Participants with cardiovascular disease < 80%
Nauck 2016	Participants with cardiovascular disease < 80%
Oe 2015	Participants with cardiovascular disease < 80%
Otterbeck 2011	Participants with cardiovascular disease < 80%
Paiman 2020	Participants with cardiovascular disease < 80%
Perkovic 2019	Participants with cardiovascular disease < 80%
Pi-Sunyer 2015	Participants with cardiovascular disease < 80%
Pratley 2019	Participants with cardiovascular disease < 80%
Rodbard 2017	Participants with cardiovascular disease < 80%
Roos 2016	Wrong duration (intervention period < 24 weeks)
Rosenstock 2019a	Participants with cardiovascular disease < 80%
Tolba 2017	Not a randomised controlled trial
Tripolt 2018	Wrong duration (intervention period < 24 weeks)
Wiviott 2018	Participants with cardiovascular disease < 80%
Wiviott 2019	Participants with cardiovascular disease < 80%
Yamada 2017	Not a randomised controlled trial
Zinman 2019	Participants with cardiovascular disease < 80%

Characteristics of studies awaiting classification *[ordered by study ID]*

EMPA-HEART2

Methods	Double-blind, randomised, placebo-controlled, parallel-group study
Participants	patients with cardiovascular risk factors, but without diabetes ≥ 1 of the major criteria or ≥ 2 of the minor criteria below: Major criteria: • Increased LVMi of ≥ 96 g/m^2 for women and ≥ 116 g/m^2 for men (as calculated by echocardiogram); or LVMi ≥ 81 g/m^2 for women and ≥ 85 g/m^2 for men (as calculated by cMRI) • ECG evidence of LV hypertrophy (as per the Sokolow-Lyon criteria) • Structural heart disease defined as interventricular septal thickness or posterior wall thickness at end- diastole of ≥ 11 mm (as measured by 2D echocardiography or cMRI) • Persistent hypertension (defined as office blood pressure ≥ 140/90 mmHg) despite being on ≥ 3 antihypertensive medications Minor criteria:

EMPA-HEART2 *(Continued)*

	• Prior history of a MI (≥ 3 months ago)- eGFR ≥ 30 and ≤ 60 mL/min/1.73 m^2 (as measured by the CKD-EPI formula) Body mass index (BMI) ≥ 27 and ≤ 40 kg/m^2 • Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other trial procedures
Interventions	**Intervention**: Empagliflozin. Single 10 mg tablet, administered orally once daily for 6 months; **SGLT2i** **comparison**: placebo
Outcomes	**Primary Outcome Measures :** Change in Left Ventricular (LV) mass (time frame: 6 months) This will be measured using CMRI. **Secondary Outcome Measures :** Change in LV end-diastolic volume, LV end-systolic volume, Left Ventricular Ejection Fraction (LVEF), LV wall stress, LV systolic function, and LV diastolic function. (time frame: 6 months). These will be measured using cMRI. Change in NT-proBNP (time frame: 6 months), change in Systolic and diastolic blood pressure (time frame: 6 months), change in Hematocrit (time frame: 6 months)
Notes	

EXCEED

Methods	Randomised two-arm comparison design
Participants	Diabetes mellitus and chronic HF
Interventions	**Intervention**: A arm to which an additional dose of Ipragliflozin L-Proline was administered.; **SGLT2i** **Comparison**: Regular anti-diabetic drugs other than SGLT2i arm.
Outcomes	**Primary outcomes** Change in echocardiography-based cardiac function test parameters(E/e', e') **Key secondary outcomes** Change in echocardiography-based cardiac function test parameters (LVMI, LAD, LAV, LVEF, LVEDV, LVESV, E/A, IVC), Change in NT-proBNP, Change in NYHA Functional Classification, and other assessments
Notes	UMIN000027095

SUPERIOR

Methods	Parallel, randomised
Participants	Coronary artery disease, Type 2 diabetes mellitus
Interventions	**Interventions:** sitagliptin treatment group; **DPP4i** **Control:** Intensification of conventional treatment group

SUPERIOR *(Continued)*

Outcomes	**Primary outcomes** Cardiovascular events (composite of cardiovascular death, non-fatal MI, unstable angina pectoris, non-fatal ischaemic stroke, hospitalization fordecompensated HF, coronary revascularization, deep vein thrombosis, pulmonary embolism, or hospitalization for peripheral artery disease) **Key secondary outcomes** All cause death Hypoglycemic and hyperglycemic coma Event The change of parameters (GLP-1, BNP, high sensitivity CRP, IL-6 and other biochemical markers, blood pressure, body weight, heart rate, and waist circumference) Coronary angiography finding (Percent atheroma volume, the change of percent atheroma volume) The change of parameters in echocardiography Endothelial function assessed by reactive hyperemia peripheral arterial tonometry
Notes	UMIN000011894

cMRI: cardiac magnetic resonance imaging, DPP4i: dipeptidyl peptidase 4 inhibitor, E/A: the ratio of peak velocity of the E wave to the A wave, HF: heart failure, IVC: inferior vena cava, LVMI: left ventricular mass index, LAD: left atrial dimension, LAV: left atrial volume, LVEDV: left ventricular end-diastolic volume, LVESV: left ventricular end-systolic volume, LVEF: left ventricular ejection fraction, LVMi: left ventricular mass index, MI: myocardial infarction, NYHA: New York Heart Association, SGLT2i: sodium-glucose co-transporter-2 inhibitor

Characteristics of ongoing studies *[ordered by study ID]*

CANONICAL

Study name	Canagliflozin heart failure with preserved ejection fraction study in type 2 diabetes mellitus (CANONICAL Study)
Methods	Parallel, randomised
Participants	HFpEF in type 2 diabetes mellitus
Interventions	**Interventions:** Canagliflozin 100 mg/day; **SGLT2i** The period of intervention: 0-24 weeks **Comparison:** Control (The group without Canagliflozin)
Outcomes	**Primary outcomes** 1) The change in BNP at week 24 from the baseline. 2) The change in body weight at week 24 from the baseline. **Key secondary outcomes** 1) Hospitalization for HF 2) Cardiovascular death / total death 3) The change of body weight at each measurement point from the baseline. 4) The change of dose under loop diuretics. 5) The change in HbA1c from the baseline. 6) The change in BNP and NT-proBNP at each measurement point from the baseline. 7) Echocardiography 8) CONUT score and GNRI 9) FT3, FT4, TSH
Starting date	1 Oct 2017

CANONICAL *(Continued)*

Contact information	Yoshihiko Saito, yssaito@naramed-u.ac.jp, Nara Medical University Department of cardiovascular Medicine
Notes	

DAPPER

Study name	An Exploratory Study of Dapagliflozin for the Attenuation of Albuminuria in Patients with Heart Failure and Type 2 Diabetes Mellitus (DAPPER)
Methods	Multicentre, randomised, open-labelled, parallel-group, standard treatment-controlled study
Participants	Type 2 Diabetes Mellitus patients with Chronic HF
Interventions	**Interventions:** Dapagliflozin 5-10 mg/day; **SGLT2i** **control:** administration of anti-diabetic drugs administered other than SGLT2i
Outcomes	**Primary objective:** Changes in the urinary albumin-to-creatinine ratio from the baseline after 2-year treatment. **Secondary objectives:** (1) the safety of dapagliflozin and (2) the cardiovascular and renal efficacies of dapagliflozin.
Starting date	1 March 2017
Contact information	Fumiki Yoshihara, dapper-study@ml.ncvc.go.jp, Hyogo College Of Medicine
Notes	UMIN000025102

DELIVER

Study name	Dapagliflozin evaluation to improve the lives of patients with preserved ejection fraction heart failure (DELIVER)
Methods	An international, multicentre, parallel-group, event-driven, randomised, double-blind study
Participants	Adult patients aged ≥40 years with HFpEF (LVEF >40% and evidence of structural heart disease) and New York Heart Association (NYHA) class II-IV
Interventions	**Intervention:** Dapagliflozin10 mg tablets given once daily, per oral use. **Comparison:** placebo
Outcomes	**Primary Outcome Measures:** 1. Time to the first occurrence of any of the components of this composite: 1) CV death; 2) Hospitalisation for HF; 3) Urgent HF visit (e.g. emergency department or outpatient visit) within approximately 39 months To determine whether dapagliflozin is superior to placebo, when added to standard of care, in reducing the composite of CV death and HF events (hospitalisation for HF or urgent HF visit) in patients with HF and preserved systolic function in

DELIVER *(Continued)*

	• full study population • subpopulation with LVEF <60% **Secondary Outcome Measures:** 1. Total number of HF events (first and recurrent) and CV death within approximately 39 months 2. Change from baseline in the total symptom score (TSS) of the KCCQ at 8 months after randomization To determine whether dapagliflozin is superior to placebo in improving patient-reported outcomes measured by KCCQ 3. Time to the occurrence of CV death within approximately 39 months. To determine whether dapagliflozin is superior to placebo in reducing CV death 4. Time to the occurrence of death from any cause within approximately 39 months. To determine whether dapagliflozin is superior to placebo in reducing all-cause mortality To determine whether dapagliflozin is superior to placebo in reducing the total number of HF events (hospitalisation for HF or urgent HF visit) and CV death in • full study population • subpopulation with LVEF <60%
Starting date	15 Oct ober2018
Contact information	AstraZeneca
Notes	

EMMY

Study name	Impact of EMpagliflozin on cardiac function and biomarkers of heart failure in patients with acute MYocardial infarction-The EMMY trial
Methods	A multicentre, randomised, double-blind, placebo-controlled, phase 3b trial
Participants	Patients with AMI and characteristics suggestive of severe myocardial necrosis
Interventions	empagliflozin (10mg once daily)
Outcomes	The primary endpoint is the impact of empagliflozin on changes in NT-proBNP within 6 months after AMI. Secondary endpoints include changes in echocardiographic parameters, levels of ketone body concentrations, HbA1c levels and body weight, respectively. Hospitalization rate due to heart failure or other causes, the duration of hospital stay and all-cause mortality will be assessed as exploratory secondary endpoints.
Starting date	14 March 2017
Contact information	Harald Sourij, ha.sourij@medunigraz.at, Medical University of Graz
Notes	

EMPA-TROPISM

Study name	Are the "Cardiac Benefits" of Empagliflozin Independent of Its Hypoglycemic Activity? (ATRU-4). (EMPA-TROPISM)

EMPA-TROPISM *(Continued)*

Methods	Single-site, double-blind, randomised placebo-controlled trial
Participants	Non-diabetic HFrEF patients
Interventions	Empagliflozin 10 mg/day
Outcomes	**Primary endpoint:** Change in left ventricle end-diastolic volume (LVEDV) and left ventricle end-systolic volume (LVESV) assessed by cardiac magnetic resonance. **Secondary endpoint:** Changes in LV mass, LVEF, peak oxygen consumption in the cardiopulmonary exercise test, 6-minute walk test, and quality of life
Starting date	21 May 2018
Contact information	Juan Badimon, Icahn School of Medicine at Mount Sinai
Notes	

EMPEROR-Preserved

Study name	Evaluation of the effects of sodium-glucose co-transporter 2 inhibition with empagliflozin on morbidity and mortality in patients with chronic heart failure and a preserved ejection fraction
Methods	Phase III international, multicentre, randomised, double-blind, parallel-group, placebo-controlled trial
Participants	Patients with HFpEF (ejection fraction > 40%), with and without type 2 diabetes
Interventions	Empagliflozin 10 mg daily
Outcomes	**Primary endpoint:** the time-to-first-event analysis of the combined risk for cardiovascular death or hospitalisation for HF The trial will also evaluate the effects of empagliflozin on renal function, cardiovascular death, all-cause mortality and recurrent hospitalisation events, and will assess a wide range of biomarkers that reflect important pathophysiological mechanisms that may drive the evolution of HFpEF.
Starting date	18 September 2018
Contact information	CT Disclosure & Data Transparency, clintriage.rdg@boehringer-ingelheim.com, Boehringer Ingelheim Pharma GmbH & Co. KG
Notes	

LEADPACE

Study name	Efficacy and safety of liraglutide in type 2 diabetes with lower extremity arterial disease
Methods	A prospective, 24-week, multicentre, randomised, controlled clinical study

LEADPACE *(Continued)*

Participants	diabetes patients with peripheral arterial disease (PAD)
Interventions	**Intervention:** Liraglutide + standard-of-care treatment Liraglutide is available if pre-filled pens (6 mg/ml) as a solution for injection (Victoza). One ml of solution contains 6 mg of Liraglutide (human glucagon-like peptide-1 analogue produced by recombinant DNA technology in Saccharomyces cerevisiae). One pre-filled pen contains 18 mg Liraglutide in 3 ml. Liraglutide is added to existing standard-of-care treatment containing one or more oral anti-hyperglycemic agents or insulin or a combination of these agents with the exception of other incretin and SGLT2i therapies in accordance with local clinical practice guidelines. **Control:** Standard-of-care treatment including: metformin should be given as the first line therapy as long as it is tolerated and not contraindicated; other agents, including sulphonylureas or glucosidase inhibitor or insulin, should be added to metformin.Glycemic control will be managed by the investigators in accordance with local clinical practice guidelines by the adjustment of concomitant glucose-lowering agents or the addition of new antidiabetic medications with the exception of incretin and SGLT2i therapies. This approach expect to yield similar glycemic control in the two study groups.
Outcomes	**Primary Outcome Measures:** 1. Initial and absolute claudication distance **Secondary Outcome Measures:** 1. Assess the effects on ABI of a six-month treatment with Liraglutide compared to control group (standard-of-care treatment). 2. Assess the effects on endothelial function of a six-month treatment with Liraglutide compared to control group (standard-of-care treatment). 3. Muscle microvascular perfusion by CEU 4. Assess the effects on the endothelial circulating progenitor cells concentration of a six-month treatment with Liraglutide compared to control group (standard-of-care treatment). 5. Changes from baseline in HbA1c
Starting date	1 May 2020
Contact information	Chao Zheng, wallbb_1022@163.com, The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University
Notes	

Li 2018

Study name	Effects of a dipeptidyl peptidase-4 Inhibitor sitagliptininsulin on the progression of coronary atherosclerosis in patients with type 2 diabetes
Methods	Randomised, parallel assignment Total duration of study: 18 months
Participants	type 2 diabetes mellitus and coronary heart disease

Li 2018 *(Continued)*

Interventions	**Intervention:** Sitagliptin 100mg once a day **Comparison:** Acarbose
Outcomes	**Primary Outcome Measure:** Coronary calcification score (Changes from baseline in coronary calcification score at 18 months). Changes in coronary calcification score in patients with coronary heart disease complicated with type 2 diabetes were measured with computed tomography angiography.
Starting date	1 October 2018
Contact information	Li Bo, Chinese PLA General Hospital
Notes	

MEASURE-HF

Study name	Mechanistic evaluation of glucose-lowering strategies in patients with heart failure (MEASURE-HF)
Methods	Multicentre, randomised, double-blind, parallel-group, placebo-controlled study Total duration of study: 24 weeks
Participants	patients with type 2 diabetes (T2DM) mellitus and heart failure (HF)
Interventions	**Intervention 1:** Saxagliptinone; tablet of saxagliptin 5 mg or 2.5 mg + one placebo capsule matching sitagliptin **Intervention 2:** Sitagliptinone; capsule of sitagliptin 100 mg or 50 mg + one placebo tablet matching saxagliptin **Comparison:** Placebo; one placebo tablet matching saxagliptin + one placebo capsule matching sitagliptin
Outcomes	**Primary Outcome Measure:** 1. Change from baseline in Left Ventricular End Diastolic Volume (LVEDV) Index measured by magnetic resonance imaging (MRI) at 24 Weeks. **Secondary Outcome Measures:** 1. Change from baseline in Left Ventricular End Systolic Volume (LVESV) Index, measured by MRI at 24 weeks. 2. Change from baseline in Left Ventricular Ejection Fraction (LVEF) measured by MRI at 24 weeks. 3. Change from baseline in Left Ventricular Mass (LVM) measured by MRI at 24 weeks. 4. Change from baseline in NT-proBNP after 24 weeks of treatment. 5. Number of participants with adverse events from screening (Days -28 to -1) until Week 28 (follow-up visit).
Starting date	10 January 2017
Contact information	AstraZeneca
Notes	

REFORM

Study name	Safety and effectiveness of SGLT-2 inhibitors in patients with heart failure and diabetes (REFORM)
Methods	Randomised, parallel assignment, quadruple-masking (participant, care provider, investigator, outcomes assessor) Total duration of study: 1 year
Participants	Patients with diabetes and heart failure
Interventions	**Intervention:** Dapagliflozin 10mg once daily **Control:** Capsules containing microcrystalline cellulose Ph Eur overencapsulated in a hard gelatine capsule shell to match the active comparator
Outcomes	**Primary Outcome Measures:** 1. Change in LV end systolic volume (absolute value and indexed for BSA) or LV end diastolic volume (absolute value and indexed for BSA) **Secondary Outcome Measures:** 1. Change in LV mass, LV ejection fraction, RV end diastolic volume, RV end systolic volume, RV ejection fraction, atrial dimensions and volumes, and LV remodelling index (LV mass / LVEDV) 2. Fluid status (Bioelectrical Impedence Analysis (BIA) 3. Objective functional capacity (6 Minute Walk Test (6MWT) 4. Exercise capacity (Cardio-pulmonary Exercise Testing (CPET) 5. Quality of life (Minnesota Living with Heart Failure and SF-36 questionnaire) 6. Cardiac and inflammatory biomarkers 7. Diuretic requirement (total diuretic requirement to maintain euvolemia) 8. Change in degree of microalbuminuria 9. Quantify amount of natriuresis 10. The safety of dapagliflozin use in diabetic, heart failure patients with regard to worsening HF, hospitalization and death will be evaluated
Starting date	March 2015
Contact information	Jagdeep Singh Surmukh Singh, University of Dundee
Notes	

SELECT

Study name	Semaglutide effects on heart disease and stroke in patients with overweight or obesity (SELECT)
Methods	Randomised, parallel assignment, quadruple-masking (participant, care provider, investigator, outcomes assessor)
Participants	Patients with overweight or obesity and with prior cardiovascular disease
Interventions	**Intervention:** Semaglutide Semaglutide will be injected into a skin fold, in the stomach, thigh or upper arm once a week at the same day of the week (to the extent possible) throughout the trial. Subjects will start semaglutide treatment at 0.24 mg; dose will gradually be increased every 4 weeks up to 2.4 mg.

SELECT *(Continued)*

	Control: Placebo (semaglutide) Placebo will be injected into a skin fold, in the stomach, thigh or upper arm once a week at the same day of the week (to the extent possible) throughout the trial. Participants will receive placebo at an equivalent dose to semaglutide.
Outcomes	**Primary Outcome Measures :** 1. Time to first occurrence of a composite endpoint consisting of: cardiovascular (CV) death, non-fatal MI, or non-fatal stroke within 59 months. **Secondary Outcome Measures :** 1. Time to CV death within59 months. 2. Time to all-cause death within59 months. 3. Time to first occurrence of an expanded composite CV endpoint consisting of: CV death, non-fatal myocardial infarction, non-fatal stroke, coronary revascularisation or unstable angina requiring hospitalisation within59 months. 4. Time to first occurrence of a composite heart failure endpoint consisting of: heart failure hospitalisation, urgent heart failure visit or CV death within59 months. 5. Time to first occurrence of a composite endpoint consisting of: all-cause death, non-fatal myocardial infarction, or non-fatal stroke within59 months. 6. Time to first occurrence of non-fatal myocardial infarction within59 months. 7. Time to first occurrence of non-fatal stroke within59 months. 8. Time to first occurrence of coronary revascularisation within59 months. 9. Time to first occurrence of unstable angina requiring hospitalisation within59 months. 10. Time to first occurrence of heart failure hospitalisation or urgent heart failure visit within59 months. 11. Time to first occurrence of HbA1c greater than or equal to 48 mmol/mol (6.5%) within59 months. 12. Time to first occurrence of a 5-component composite nephropathy endpoint within59 months. 13. Time to HbA1c greater than or equal to 39 mmol/mol (5.7%) for subjects with a screening HbA1c less than 39 mmol/mol (5.7%) within59 months. 14. Subjects with HbA1c less than 39 mmol/mol (5.7%) at each visit where HbA1c is assessed for subjects with a screening HbA1c greater than or equal to 39 mmol/mol (5.7%) within 59 months. 15. Change in systolic blood pressure between Week 0 and year 2. 16. Change in diastolic blood pressure between Week 0 and year 2. 17. Change in pulse between Week 0 and year 2. 18. Change in High sensitivity C-Reactive Protein (hsCRP) between Week 0 and year 2. 19. Change in total cholesterol between Week 0 and year 2. 20. Change in high-density lipoprotein (HDL) cholesterol between Week 0 and year 2. 21. Change in low-density lipoprotein (LDL) cholesterol between Week 0 and year 2. 22. Change in triglycerides between Week 0 and year 2. 23. Change in body weight between Week 0 and year 2. 24. Change in waist circumference between Week 0 and, year 2. 25. Change in EuroQol five dimensions five level (EQ-5D-5L) questionnaire between Week 0 and year 2. 26. Change in total score weight-related sign and symptom measure within Week 0 and year 2. 27. Change in haemoglobin A1c (HbA1c) between Screening (up to 3 weeks before randomisation at week 0) and week 104.
Starting date	24 October 2018
Contact information	Novo Nordisk
Notes	

STEXAS

Study name	Short-Term Exenatide Therapy in Hyperglycaemia and Acute Ischaemic Stroke
Methods	Randomised, open-label, parallel-group pilot study
Participants	Clinically defined acute ischaemic stroke with consistent neuroimaging (e.g. CT brain, CT perfusion or MRI brain) Blood glucose levels >10 mmol/L on blood glucose testing during the first 72 h after admission to the acute stroke ward
Interventions	**Intervention:** continuous intravenous administration of 20 µg/24 h of exenatide; **GLP-1RA** **Control:** Continuous intravenous administarion of insulin for up to 72 hours. The dose of insulin will be titration to maintain blood glucose level within the target range of 5 - 10mmol/L.
Outcomes	**Primary end point:** the percentage of time that the participant's blood glucose levels remain within a target glucose range of 5–10 mmol/L, as determined by continuous glucose monitoring (CGM) **secondary end point:** the frequency and duration of hypoglycaemia in participants receiving exenatide versus insulin therapy
Starting date	20 March 2015
Contact information	Prof Greg Fulcher, Department of Diabetes, Endocrinology & Metabolism, Level 3, Acute Services Building, Royal North Shore Hospital,
Notes	

SUGAR-DM-HF

Study name	Studies of empagliflozin and its cardiovascular, renal and metabolic effects (SUGAR-DM-HF)
Methods	Randomised, placebo-controlled trial Total duration of study: 36 weeks
Participants	Heart failure patients with type 2 diabetes (or pre-diabetes)
Interventions	**Intervention:** Empagliflozin 10mg tablets for oral self administration once a day; **SGLT2i** **Control:** placebo tablets for oral self administration once a day
Outcomes	**Primary Outcome Measures :** 1. Left Ventricular End Systolic Volume Index (LVESVI) 2. left ventricular global longitudinal strain (GLS) **Secondary Outcome Measures :** 1. Left ventricular end diastolic volume index (LVEDVI) 2. Left ventricular ejection fraction (LVEF) 3. Left ventricular mass index (LVMI)

SUGAR-DM-HF *(Continued)*	4. Left ventricular global function index (LVGFI) 5. Left atrial volume index (LAVI) 6. Microvascular perfusion 7. Extracellular volume fraction 8. Kansas City Cardiomyopathy Questionnaire (KCCQ) Total Symptom Score (TSS) 9. Six-minute walk distance (Exercise Capacity) 10.Pulmonary congestion 11.Biomarker profile -glycated haemoglobin (HbA1c) 12.Biomarker profile - creatine 13.Biomarker profile - estimated glomerular filtration rate (eGFR) 14.Biomarker profile - liver function tests (LFTs) 15.Biomarker profile - uric acid 16.Intensification of diuretic therapy
Starting date	16 March 2018
Contact information	Queen Elizabeth University Hospital
Notes	

AMI: acute myocardial infarction, CONUT score: controlling nutritional status score, GLP-1RA: glucagon-like peptide-1 receptor agonist, GNRI: geriatric nutritional risk index, HF: heart failure, HFpEF: heart failure with preserved ejection fraction, HFrEF: heart failure with reduced ejection fraction, LVEF: left ventricular ejection fraction, MI: myocardial infarction, SGLT2i: sodium-glucose co-transporter-2 inhibitor

DATA AND ANALYSES

Comparison 1. DPP4i

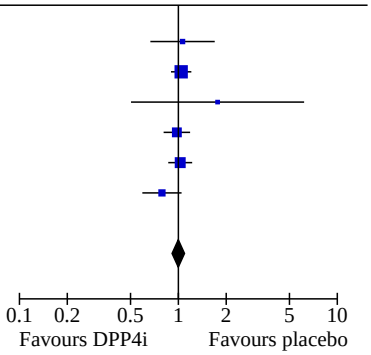
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Cardiovascular mortality	6	47968	Odds Ratio (M-H, Fixed, 95% CI)	1.00 [0.91, 1.09]
1.2 Fatal and non-fatal myocardial infarction	4	42334	Odds Ratio (M-H, Fixed, 95% CI)	0.97 [0.88, 1.08]
1.3 Fatal and non-fatal stroke	5	42588	Odds Ratio (M-H, Fixed, 95% CI)	1.00 [0.87, 1.14]
1.4 All-cause mortality	6	47968	Odds Ratio (M-H, Fixed, 95% CI)	1.03 [0.96, 1.11]
1.5 HF hospitalisation	4	42334	Odds Ratio (M-H, Random, 95% CI)	0.99 [0.80, 1.23]
1.6 Safety outcome (worsening renal function)	1	16492	Odds Ratio (M-H, Fixed, 95% CI)	1.08 [0.88, 1.33]
1.7 Safety outcome (hypoglycaemia)	3	25842	Odds Ratio (M-H, Fixed, 95% CI)	1.11 [0.95, 1.29]
1.8 Safety outcome (pancreatitis)	5	47684	Odds Ratio (M-H, Fixed, 95% CI)	1.63 [1.12, 2.37]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.9 Safety outcome (fracture)	1	16492	Odds Ratio (M-H, Fixed, 95% CI)	1.00 [0.83, 1.19]

Analysis 1.1. Comparison 1: DPP4i, Outcome 1: Cardiovascular mortality

	DPP4i		placebo			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Gantz 2017	37	2092	35	2100	3.6%	1.06 [0.67 , 1.69]	
Green 2015	380	7332	366	7339	36.3%	1.04 [0.90 , 1.21]	
McMurray 2018	7	128	4	126	0.4%	1.76 [0.50 , 6.18]	
Rosenstock 2019	221	3494	225	3485	22.1%	0.98 [0.81 , 1.19]	
Scirica 2013	269	8280	260	8212	26.4%	1.03 [0.86 , 1.22]	
White 2013	89	2701	111	2679	11.3%	0.79 [0.59 , 1.05]	
Total (95% CI)		**24027**		**23941**	**100.0%**	**1.00 [0.91 , 1.09]**	
Total events:	1003		1001				

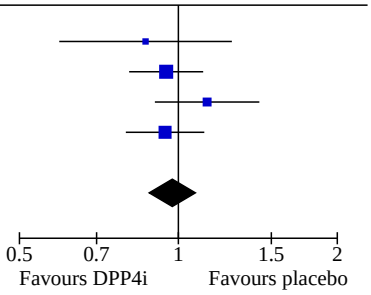
Heterogeneity: Chi² = 3.98, df = 5 (P = 0.55); I² = 0%
Test for overall effect: Z = 0.03 (P = 0.98)
Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1: DPP4i, Outcome 2: Fatal and non-fatal myocardial infarction

	DPP4i		placebo			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Gantz 2017	52	2092	60	2100	7.6%	0.87 [0.59 , 1.26]	
Green 2015	300	7332	316	7339	39.3%	0.95 [0.81 , 1.11]	
Rosenstock 2019	165	3494	146	3485	18.1%	1.13 [0.90 , 1.42]	
Scirica 2013	265	8280	278	8212	35.1%	0.94 [0.80 , 1.12]	
Total (95% CI)		**21198**		**21136**	**100.0%**	**0.97 [0.88 , 1.08]**	
Total events:	782		800				

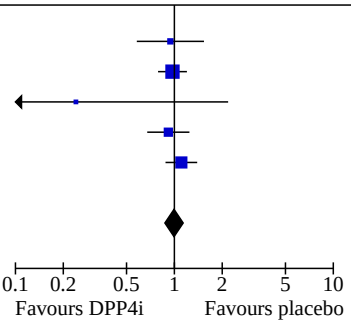
Heterogeneity: Chi² = 2.31, df = 3 (P = 0.51); I² = 0%
Test for overall effect: Z = 0.52 (P = 0.61)
Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1: DPP4i, Outcome 3: Fatal and non-fatal stroke

Study or Subgroup	DPP4i Events	DPP4i Total	placebo Events	placebo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Gantz 2017	32	2092	34	2100	7.6%	0.94 [0.58 , 1.54]
Green 2015	178	7332	183	7339	40.5%	0.97 [0.79 , 1.20]
McMurray 2018	1	128	4	126	0.9%	0.24 [0.03 , 2.18]
Rosenstock 2019	81	3494	88	3485	19.5%	0.92 [0.67 , 1.24]
Scirica 2013	157	8280	141	8212	31.5%	1.11 [0.88 , 1.39]
Total (95% CI)		**21326**		**21262**	**100.0%**	**1.00 [0.87 , 1.14]**
Total events:	449		450			

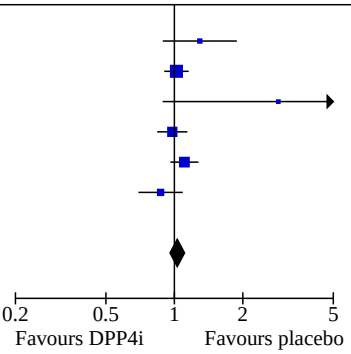
Heterogeneity: Chi² = 2.79, df = 4 (P = 0.59); I² = 0%
Test for overall effect: Z = 0.07 (P = 0.94)
Test for subgroup differences: Not applicable



Analysis 1.4. Comparison 1: DPP4i, Outcome 4: All-cause mortality

Study or Subgroup	DPP4i Events	DPP4i Total	placebo Events	placebo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Gantz 2017	64	2092	50	2100	3.4%	1.29 [0.89 , 1.88]
Green 2015	547	7332	537	7339	35.3%	1.02 [0.90 , 1.16]
McMurray 2018	11	128	4	126	0.3%	2.87 [0.89 , 9.26]
Rosenstock 2019	367	3494	373	3485	23.8%	0.98 [0.84 , 1.14]
Scirica 2013	420	8280	378	8212	25.6%	1.11 [0.96 , 1.28]
White 2013	153	2701	173	2679	11.6%	0.87 [0.69 , 1.09]
Total (95% CI)		**24027**		**23941**	**100.0%**	**1.03 [0.96 , 1.11]**
Total events:	1562		1515			

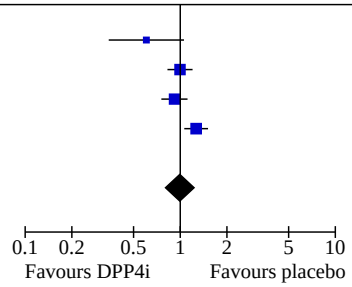
Heterogeneity: Chi² = 7.97, df = 5 (P = 0.16); I² = 37%
Test for overall effect: Z = 0.79 (P = 0.43)
Test for subgroup differences: Not applicable



Analysis 1.5. Comparison 1: DPP4i, Outcome 5: HF hospitalisation

Study or Subgroup	DPP4i Events	DPP4i Total	placebo Events	placebo Total	Weight	Odds Ratio M-H, Random, 95% CI
Gantz 2017	20	2092	33	2100	10.5%	0.60 [0.35 , 1.06]
Green 2015	228	7332	229	7339	29.8%	1.00 [0.83 , 1.20]
Rosenstock 2019	209	3494	226	3485	29.2%	0.92 [0.76 , 1.11]
Scirica 2013	289	8280	228	8212	30.5%	1.27 [1.06 , 1.51]
Total (95% CI)		**21198**		**21136**	**100.0%**	**0.99 [0.80 , 1.23]**
Total events:	746		716			

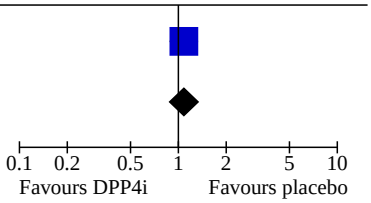
Heterogeneity: Tau² = 0.03; Chi² = 10.22, df = 3 (P = 0.02); I² = 71%
Test for overall effect: Z = 0.06 (P = 0.95)
Test for subgroup differences: Not applicable



Analysis 1.6. Comparison 1: DPP4i, Outcome 6: Safety outcome (worsening renal function)

Study or Subgroup	DPP4i Events	DPP4i Total	placebo Events	placebo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Scirica 2013	194	8280	178	8212	100.0%	1.08 [0.88 , 1.33]
Total (95% CI)		**8280**		**8212**	**100.0%**	**1.08 [0.88 , 1.33]**
Total events:	194		178			

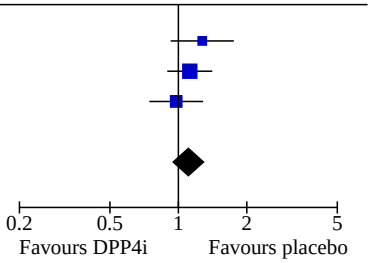
Heterogeneity: Not applicable
Test for overall effect: Z = 0.76 (P = 0.45)
Test for subgroup differences: Not applicable



Analysis 1.7. Comparison 1: DPP4i, Outcome 7: Safety outcome (hypoglycaemia)

Study or Subgroup	DPP4i Events	DPP4i Total	placebo Events	placebo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Gantz 2017	88	2092	70	2100	21.5%	1.27 [0.92 , 1.75]
Green 2015	160	7332	143	7339	44.9%	1.12 [0.89 , 1.41]
Rosenstock 2019	106	3494	108	3485	33.7%	0.98 [0.75 , 1.28]
Total (95% CI)		**12918**		**12924**	**100.0%**	**1.11 [0.95 , 1.29]**
Total events:	354		321			

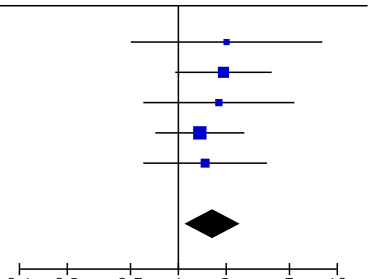
Heterogeneity: Chi² = 1.54, df = 2 (P = 0.46); I² = 0%
Test for overall effect: Z = 1.29 (P = 0.20)
Test for subgroup differences: Not applicable



Analysis 1.8. Comparison 1: DPP4i, Outcome 8: Safety outcome (pancreatitis)

Study or Subgroup	DPP4i Events	DPP4i Total	placebo Events	placebo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Gantz 2017	6	2092	3	2100	6.8%	2.01 [0.50 , 8.05]
Green 2015	23	7332	12	7339	27.2%	1.92 [0.96 , 3.86]
Rosenstock 2019	9	3494	5	3485	11.3%	1.80 [0.60 , 5.37]
Scirica 2013	22	8280	16	8212	36.4%	1.36 [0.72 , 2.60]
White 2013	12	2701	8	2649	18.3%	1.47 [0.60 , 3.61]
Total (95% CI)		**23899**		**23785**	**100.0%**	**1.63 [1.12 , 2.37]**
Total events:	72		44			

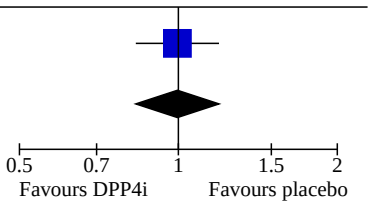
Heterogeneity: Chi² = 0.67, df = 4 (P = 0.95); I² = 0%
Test for overall effect: Z = 2.55 (P = 0.01)
Test for subgroup differences: Not applicable



Analysis 1.9. Comparison 1: DPP4i, Outcome 9: Safety outcome (fracture)

Study or Subgroup	DPP4i Events	DPP4i Total	placebo Events	placebo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Scirica 2013	241	8280	240	8212	100.0%	1.00 [0.83 , 1.19]
Total (95% CI)		**8280**		**8212**	**100.0%**	**1.00 [0.83 , 1.19]**
Total events:	241		240			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.05 (P = 0.96)
Test for subgroup differences: Not applicable



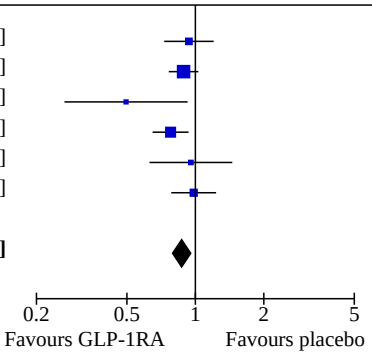
Comparison 2. GLP-1RA

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Cardiovascular mortality	6	46093	Odds Ratio (M-H, Fixed, 95% CI)	0.87 [0.79, 0.95]
2.2 Fatal and non-fatal myocardial infarction	5	42910	Odds Ratio (M-H, Random, 95% CI)	0.89 [0.78, 1.01]
2.3 Fatal and non-fatal stroke	5	42910	Odds Ratio (M-H, Fixed, 95% CI)	0.87 [0.77, 0.98]
2.4 All-cause mortality	7	46393	Odds Ratio (M-H, Fixed, 95% CI)	0.88 [0.82, 0.95]
2.5 HF hospitalisation	6	36930	Odds Ratio (M-H, Fixed, 95% CI)	0.95 [0.85, 1.06]
2.6 Safety outcome (worsening renal function)	1	3297	Odds Ratio (M-H, Fixed, 95% CI)	0.61 [0.44, 0.84]
2.7 Safety outcome (pancreatitis)	5	40035	Odds Ratio (M-H, Fixed, 95% CI)	0.96 [0.68, 1.35]

Analysis 2.1. Comparison 2: GLP-1RA, Outcome 1: Cardiovascular mortality

Study or Subgroup	GLP-1RA Events	GLP-1RA Total	placebo Events	placebo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Hernandez 2018	122	4731	130	4732	12.9%	0.94 [0.73 , 1.20]
Holman 2017	340	7356	383	7396	37.2%	0.89 [0.76 , 1.03]
Husain 2019	15	1591	30	1592	3.0%	0.50 [0.27 , 0.92]
Marso 2016a	219	4668	278	4672	27.0%	0.78 [0.65 , 0.93]
Marso 2016b	44	1648	46	1649	4.6%	0.96 [0.63 , 1.45]
Pfeffer 2015	156	3034	158	3024	15.3%	0.98 [0.78 , 1.23]
Total (95% CI)		**23028**		**23065**	**100.0%**	**0.87 [0.79 , 0.95]**
Total events:	896		1025			

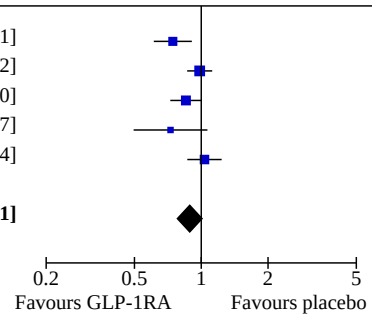
Heterogeneity: Chi² = 6.29, df = 5 (P = 0.28); I² = 20%
Test for overall effect: Z = 2.97 (P = 0.003)
Test for subgroup differences: Not applicable



Analysis 2.2. Comparison 2: GLP-1RA, Outcome 2: Fatal and non-fatal myocardial infarction

Study or Subgroup	GLP-1RA Events	GLP-1RA Total	placebo Events	placebo Total	Weight	Odds Ratio M-H, Random, 95% CI
Hernandez 2018	181	4731	240	4732	19.7%	0.74 [0.61 , 0.91]
Holman 2017	483	7356	493	7396	26.9%	0.98 [0.86 , 1.12]
Marso 2016a	292	4668	339	4672	23.3%	0.85 [0.73 , 1.00]
Marso 2016b	47	1648	64	1649	8.6%	0.73 [0.50 , 1.07]
Pfeffer 2015	270	3034	261	3024	21.6%	1.03 [0.87 , 1.24]
Total (95% CI)		**21437**		**21473**	**100.0%**	**0.89 [0.78 , 1.01]**
Total events:	1273		1397			

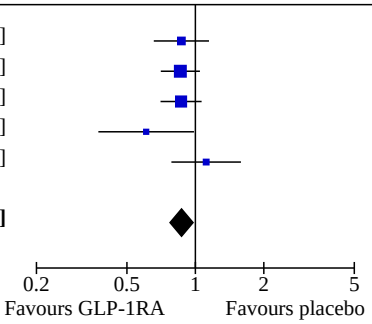
Heterogeneity: Tau² = 0.01; Chi² = 9.27, df = 4 (P = 0.05); I² = 57%
Test for overall effect: Z = 1.83 (P = 0.07)
Test for subgroup differences: Not applicable



Analysis 2.3. Comparison 2: GLP-1RA, Outcome 3: Fatal and non-fatal stroke

Study or Subgroup	GLP-1RA Events	GLP-1RA Total	placebo Events	placebo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Hernandez 2018	94	4731	108	4732	17.3%	0.87 [0.66 , 1.15]
Holman 2017	187	7356	218	7396	34.7%	0.86 [0.70 , 1.05]
Marso 2016a	173	4668	199	4672	31.3%	0.87 [0.70 , 1.07]
Marso 2016b	27	1648	44	1649	7.1%	0.61 [0.37 , 0.99]
Pfeffer 2015	67	3034	60	3024	9.6%	1.12 [0.78 , 1.59]
Total (95% CI)		**21437**		**21473**	**100.0%**	**0.87 [0.77 , 0.98]**
Total events:	548		629			

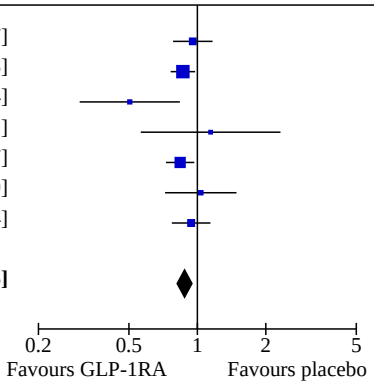
Heterogeneity: Chi² = 4.05, df = 4 (P = 0.40); I² = 1%
Test for overall effect: Z = 2.36 (P = 0.02)
Test for subgroup differences: Not applicable



Analysis 2.4. Comparison 2: GLP-1RA, Outcome 4: All-cause mortality

Study or Subgroup	GLP-1RA Events	GLP-1RA Total	placebo Events	placebo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Hernandez 2018	196	4731	205	4732	13.3%	0.95 [0.78 , 1.17]
Holman 2017	507	7356	584	7396	36.8%	0.86 [0.76 , 0.98]
Husain 2019	23	1591	45	1592	3.0%	0.50 [0.30 , 0.84]
Margulies 2016	19	154	16	146	1.0%	1.14 [0.56 , 2.32]
Marso 2016a	381	4668	447	4672	27.8%	0.84 [0.73 , 0.97]
Marso 2016b	62	1648	60	1649	3.9%	1.04 [0.72 , 1.49]
Pfeffer 2015	211	3034	223	3024	14.1%	0.94 [0.77 , 1.14]
Total (95% CI)		**23182**		**23211**	**100.0%**	**0.88 [0.82 , 0.95]**
Total events:	1399		1580			

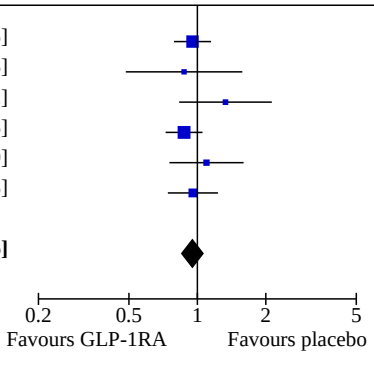
Heterogeneity: Chi² = 7.48, df = 6 (P = 0.28); I² = 20%
Test for overall effect: Z = 3.41 (P = 0.0007)
Test for subgroup differences: Not applicable



Analysis 2.5. Comparison 2: GLP-1RA, Outcome 5: HF hospitalisation

Study or Subgroup	GLP-1RA Events	GLP-1RA Total	placebo Events	placebo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Holman 2017	219	7356	231	7396	32.5%	0.95 [0.79 , 1.15]
Husain 2019	21	1591	24	1592	3.4%	0.87 [0.48 , 1.58]
Margulies 2016	63	154	50	146	4.4%	1.33 [0.83 , 2.12]
Marso 2016a	218	4668	248	4672	34.3%	0.87 [0.73 , 1.05]
Marso 2016b	59	1648	54	1649	7.6%	1.10 [0.75 , 1.60]
Pfeffer 2015	122	3034	127	3024	17.7%	0.96 [0.74 , 1.23]
Total (95% CI)		**18451**		**18479**	**100.0%**	**0.95 [0.85 , 1.06]**
Total events:	702		734			

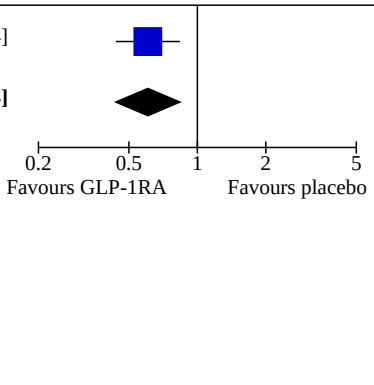
Heterogeneity: Chi² = 3.38, df = 5 (P = 0.64); I² = 0%
Test for overall effect: Z = 0.93 (P = 0.35)
Test for subgroup differences: Not applicable



Analysis 2.6. Comparison 2: GLP-1RA, Outcome 6: Safety outcome (worsening renal function)

Study or Subgroup	GLP-1RA Events	GLP-1RA Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Marso 2016b	62	1648	100	1649	100.0%	0.61 [0.44 , 0.84]
Total (95% CI)		**1648**		**1649**	**100.0%**	**0.61 [0.44 , 0.84]**
Total events:	62		100			

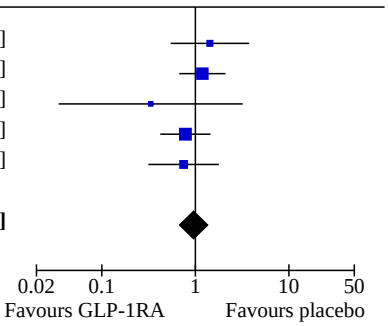
Heterogeneity: Not applicable
Test for overall effect: Z = 3.03 (P = 0.002)
Test for subgroup differences: Not applicable



Analysis 2.7. Comparison 2: GLP-1RA, Outcome 7: Safety outcome (pancreatitis)

Study or Subgroup	GLP1-RA Events	GLP1-RA Total	placebo Events	placebo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Hernandez 2018	10	4731	7	4732	10.5%	1.43 [0.54 , 3.76]
Holman 2017	26	7356	22	7396	32.8%	1.19 [0.67 , 2.10]
Husain 2019	1	1591	3	1592	4.5%	0.33 [0.03 , 3.21]
Marso 2016a	18	4668	23	4672	34.3%	0.78 [0.42 , 1.45]
Marso 2016b	9	1648	12	1649	17.9%	0.75 [0.31 , 1.78]
Total (95% CI)		**19994**		**20041**	**100.0%**	**0.96 [0.68 , 1.35]**
Total events:	64		67			

Heterogeneity: Chi² = 2.77, df = 4 (P = 0.60); I² = 0%
Test for overall effect: Z = 0.25 (P = 0.80)
Test for subgroup differences: Not applicable



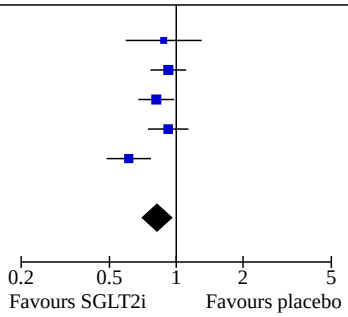
Comparison 3. SGLT2i

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Cardiovascular mortality	5	24962	Odds Ratio (M-H, Random, 95% CI)	0.82 [0.70, 0.95]
3.2 Fatal and non-fatal myocardial infarction	2	15266	Odds Ratio (M-H, Fixed, 95% CI)	0.97 [0.84, 1.12]
3.3 Fatal and non-fatal stroke	2	15266	Odds Ratio (M-H, Fixed, 95% CI)	1.12 [0.92, 1.36]
3.4 All-cause mortality	5	24962	Odds Ratio (M-H, Random, 95% CI)	0.84 [0.74, 0.96]
3.5 HF hospitalisation	5	24962	Odds Ratio (M-H, Fixed, 95% CI)	0.65 [0.59, 0.71]
3.6 Safety outcome (worsening renal function)	2	8474	Odds Ratio (M-H, Fixed, 95% CI)	0.59 [0.43, 0.82]
3.7 Safety outcome (hypoglycaemia)	4	21232	Odds Ratio (M-H, Fixed, 95% CI)	0.90 [0.75, 1.07]
3.8 Safety outcome (pancreatitis)	1	8246	Odds Ratio (M-H, Fixed, 95% CI)	0.85 [0.39, 1.86]
3.9 Safety outcome (fracture)	5	24962	Odds Ratio (M-H, Fixed, 95% CI)	1.02 [0.88, 1.18]

Analysis 3.1. Comparison 3: SGLT2i, Outcome 1: Cardiovascular mortality

Study or Subgroup	SGLT2i Events	SGLT2i Total	placebo Events	placebo Total	Weight	Odds Ratio M-H, Random, 95% CI
Bhatt 2021	51	608	58	614	10.6%	0.88 [0.59 , 1.30]
Cannon 2020	341	5499	184	2747	23.9%	0.92 [0.77 , 1.11]
McMurray 2019	227	2373	273	2371	23.8%	0.81 [0.67 , 0.98]
Packer 2020	187	1863	202	1867	21.7%	0.92 [0.75 , 1.13]
Zinman 2015	172	4687	137	2333	20.0%	0.61 [0.49 , 0.77]
Total (95% CI)		**15030**		**9932**	**100.0%**	**0.82 [0.70 , 0.95]**
Total events:	978		854			

Odds Ratio M-H, Random, 95% CI

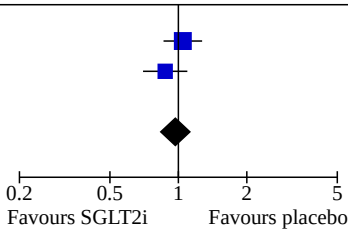


Heterogeneity: Tau² = 0.02; Chi² = 9.06, df = 4 (P = 0.06); I² = 56%
Test for overall effect: Z = 2.58 (P = 0.010)
Test for subgroup differences: Not applicable

Analysis 3.2. Comparison 3: SGLT2i, Outcome 2: Fatal and non-fatal myocardial infarction

Study or Subgroup	SGLT2i Events	SGLT2i Total	placebo Events	placebo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Cannon 2020	330	5499	158	2747	55.3%	1.05 [0.86 , 1.27]
Zinman 2015	223	4687	126	2333	44.7%	0.88 [0.70 , 1.10]
Total (95% CI)		**10186**		**5080**	**100.0%**	**0.97 [0.84 , 1.12]**
Total events:	553		284			

Odds Ratio M-H, Fixed, 95% CI

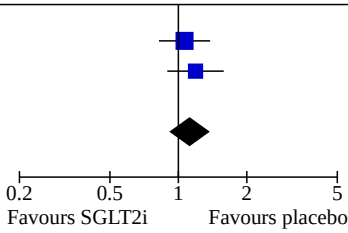


Heterogeneity: Chi² = 1.39, df = 1 (P = 0.24); I² = 28%
Test for overall effect: Z = 0.41 (P = 0.68)
Test for subgroup differences: Not applicable

Analysis 3.3. Comparison 3: SGLT2i, Outcome 3: Fatal and non-fatal stroke

Study or Subgroup	SGLT2i Events	SGLT2i Total	placebo Events	placebo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Cannon 2020	185	5499	87	2747	55.8%	1.06 [0.82 , 1.38]
Zinman 2015	164	4687	69	2333	44.2%	1.19 [0.89 , 1.58]
Total (95% CI)		**10186**		**5080**	**100.0%**	**1.12 [0.92 , 1.36]**
Total events:	349		156			

Odds Ratio M-H, Fixed, 95% CI

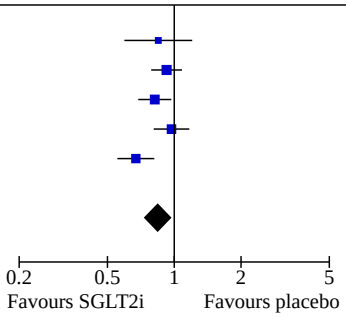


Heterogeneity: Chi² = 0.32, df = 1 (P = 0.57); I² = 0%
Test for overall effect: Z = 1.16 (P = 0.25)
Test for subgroup differences: Not applicable

Analysis 3.4. Comparison 3: SGLT2i, Outcome 4: All-cause mortality

Study or Subgroup	SGLT2i Events	SGLT2i Total	placebo Events	placebo Total	Weight	Odds Ratio M-H, Random, 95% CI
Bhatt 2021	65	608	76	614	10.3%	0.85 [0.60 , 1.20]
Cannon 2020	473	5499	254	2747	24.1%	0.92 [0.79 , 1.08]
McMurray 2019	276	2373	329	2371	23.0%	0.82 [0.69 , 0.97]
Packer 2020	259	1863	266	1867	21.6%	0.97 [0.81 , 1.17]
Zinman 2015	269	4687	194	2333	20.9%	0.67 [0.55 , 0.81]
Total (95% CI)		**15030**		**9932**	**100.0%**	**0.84 [0.74 , 0.96]**
Total events:	1342		1119			

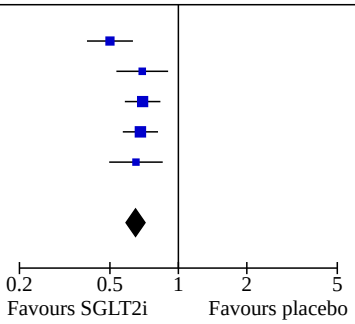
Heterogeneity: Tau² = 0.01; Chi² = 9.08, df = 4 (P = 0.06); I² = 56%
Test for overall effect: Z = 2.54 (P = 0.01)
Test for subgroup differences: Not applicable



Analysis 3.5. Comparison 3: SGLT2i, Outcome 5: HF hospitalisation

Study or Subgroup	SGLT2i Events	SGLT2i Total	placebo Events	placebo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Bhatt 2021	194	608	297	614	19.4%	0.50 [0.40 , 0.63]
Cannon 2020	139	5499	99	2747	12.4%	0.69 [0.53 , 0.90]
McMurray 2019	231	2373	318	2371	27.7%	0.70 [0.58 , 0.83]
Packer 2020	246	1863	341	1867	28.5%	0.68 [0.57 , 0.81]
Zinman 2015	126	4687	95	2333	11.9%	0.65 [0.50 , 0.85]
Total (95% CI)		**15030**		**9932**	**100.0%**	**0.65 [0.59 , 0.71]**
Total events:	936		1150			

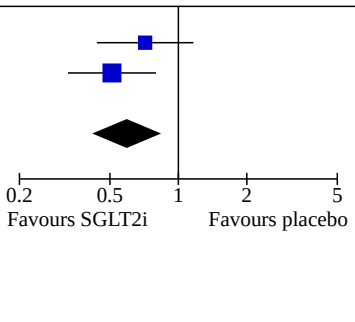
Heterogeneity: Chi² = 5.93, df = 4 (P = 0.20); I² = 33%
Test for overall effect: Z = 8.89 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 3.6. Comparison 3: SGLT2i, Outcome 6: Safety outcome (worsening renal function)

Study or Subgroup	SGLT2i Events	SGLT2i Total	placebo Events	placebo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
McMurray 2019	28	2373	39	2371	40.3%	0.71 [0.44 , 1.16]
Packer 2020	30	1863	58	1867	59.7%	0.51 [0.33 , 0.80]
Total (95% CI)		**4236**		**4238**	**100.0%**	**0.59 [0.43 , 0.82]**
Total events:	58		97			

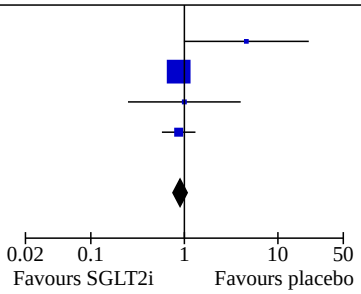
Heterogeneity: Chi² = 0.99, df = 1 (P = 0.32); I² = 0%
Test for overall effect: Z = 3.12 (P = 0.002)
Test for subgroup differences: Not applicable



Analysis 3.7. Comparison 3: SGLT2i, Outcome 7: Safety outcome (hypoglycaemia)

Study or Subgroup	SGLT2i Events	SGLT2i Total	placebo Events	placebo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Bhatt 2021	9	608	2	614	0.8%	4.60 [0.99 , 21.37]
Cannon 2020	284	5499	162	2747	79.3%	0.87 [0.71 , 1.06]
McMurray 2019	4	2373	4	2371	1.5%	1.00 [0.25 , 4.00]
Zinman 2015	63	4687	36	2333	18.4%	0.87 [0.58 , 1.31]
Total (95% CI)		**13167**		**8065**	**100.0%**	**0.90 [0.75 , 1.07]**
Total events:	360		204			

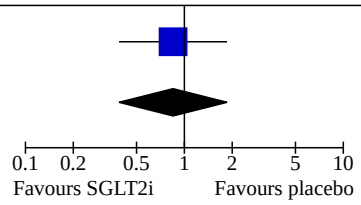
Heterogeneity: Chi² = 4.50, df = 3 (P = 0.21); I² = 33%
Test for overall effect: Z = 1.18 (P = 0.24)
Test for subgroup differences: Not applicable



Analysis 3.8. Comparison 3: SGLT2i, Outcome 8: Safety outcome (pancreatitis)

Study or Subgroup	SGLT2i Events	SGLT2i Total	placebo Events	placebo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Cannon 2020	17	5499	10	2747	100.0%	0.85 [0.39 , 1.86]
Total (95% CI)		**5499**		**2747**	**100.0%**	**0.85 [0.39 , 1.86]**
Total events:	17		10			

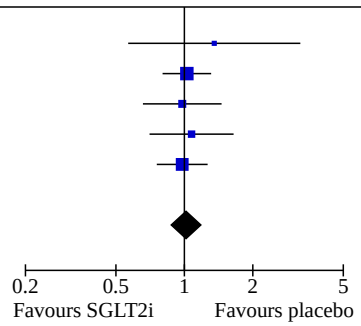
Heterogeneity: Not applicable
Test for overall effect: Z = 0.41 (P = 0.68)
Test for subgroup differences: Not applicable



Analysis 3.9. Comparison 3: SGLT2i, Outcome 9: Safety outcome (fracture)

Study or Subgroup	SGLT2i Events	SGLT2i Total	placebo Events	placebo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Bhatt 2021	12	608	9	614	2.6%	1.35 [0.57 , 3.24]
Cannon 2020	201	5499	98	2747	36.9%	1.03 [0.80 , 1.31]
McMurray 2019	49	2373	50	2371	14.3%	0.98 [0.66 , 1.46]
Packer 2020	45	1863	42	1867	12.0%	1.08 [0.70 , 1.65]
Zinman 2015	179	4687	91	2333	34.2%	0.98 [0.76 , 1.27]
Total (95% CI)		**15030**		**9932**	**100.0%**	**1.02 [0.88 , 1.18]**
Total events:	486		290			

Heterogeneity: Chi² = 0.61, df = 4 (P = 0.96); I² = 0%
Test for overall effect: Z = 0.22 (P = 0.82)
Test for subgroup differences: Not applicable



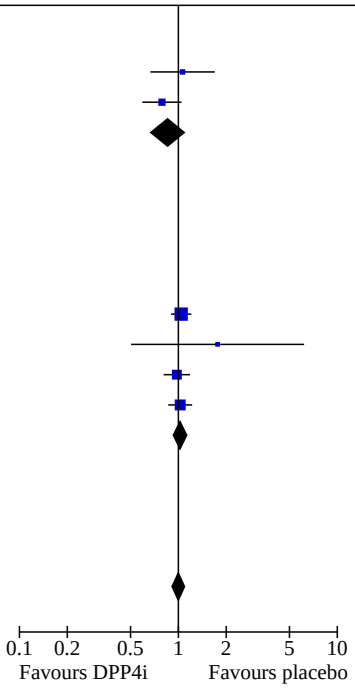
Comparison 4. Subgroup analysis: DPP4i

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Cardiovascular mortality: type of baseline CVD	6	47968	Odds Ratio (M-H, Fixed, 95% CI)	1.00 [0.91, 1.09]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1.1 All ASCVD	2	9572	Odds Ratio (M-H, Fixed, 95% CI)	0.85 [0.67, 1.09]
4.1.2 non-all ASCVD	4	38396	Odds Ratio (M-H, Fixed, 95% CI)	1.02 [0.93, 1.13]
4.2 All-cause mortality: type of baseline CVD	6	47968	Odds Ratio (M-H, Fixed, 95% CI)	1.03 [0.96, 1.11]
4.2.1 All ASCVD	2	9572	Odds Ratio (M-H, Fixed, 95% CI)	0.97 [0.80, 1.17]
4.2.2 non-all ASCVD	4	38396	Odds Ratio (M-H, Fixed, 95% CI)	1.04 [0.96, 1.13]

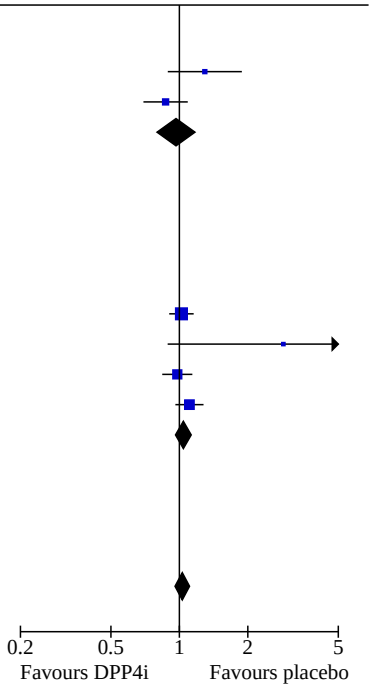
Analysis 4.1. Comparison 4: Subgroup analysis: DPP4i, Outcome 1: Cardiovascular mortality: type of baseline CVD

	DPP4i		placebo			Odds Ratio	Odds Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**	**M-H, Fixed, 95% CI**
4.1.1 All ASCVD							
Gantz 2017	37	2092	35	2100	3.6%	1.06 [0.67 , 1.69]	
White 2013	89	2701	111	2679	11.3%	0.79 [0.59 , 1.05]	
Subtotal (95% CI)		**4793**		**4779**	**14.9%**	**0.85 [0.67 , 1.09]**	
Total events:	126		146				
Heterogeneity: Chi² = 1.15, df = 1 (P = 0.28); I² = 13%							
Test for overall effect: Z = 1.27 (P = 0.20)							
4.1.2 non-all ASCVD							
Green 2015	380	7332	366	7339	36.3%	1.04 [0.90 , 1.21]	
McMurray 2018	7	128	4	126	0.4%	1.76 [0.50 , 6.18]	
Rosenstock 2019	221	3494	225	3485	22.1%	0.98 [0.81 , 1.19]	
Scirica 2013	269	8280	260	8212	26.4%	1.03 [0.86 , 1.22]	
Subtotal (95% CI)		**19234**		**19162**	**85.1%**	**1.02 [0.93 , 1.13]**	
Total events:	877		855				
Heterogeneity: Chi² = 0.99, df = 3 (P = 0.80); I² = 0%							
Test for overall effect: Z = 0.48 (P = 0.63)							
Total (95% CI)		**24027**		**23941**	**100.0%**	**1.00 [0.91 , 1.09]**	
Total events:	1003		1001				
Heterogeneity: Chi² = 3.98, df = 5 (P = 0.55); I² = 0%							
Test for overall effect: Z = 0.03 (P = 0.98)							
Test for subgroup differences: Chi² = 1.85, df = 1 (P = 0.17), I² = 46.0%							



Analysis 4.2. Comparison 4: Subgroup analysis: DPP4i, Outcome 2: All-cause mortality: type of baseline CVD

Study or Subgroup	DPP4i Events	DPP4i Total	placebo Events	placebo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
4.2.1 All ASCVD						
Gantz 2017	64	2092	50	2100	3.4%	1.29 [0.89 , 1.88]
White 2013	153	2701	173	2679	11.6%	0.87 [0.69 , 1.09]
Subtotal (95% CI)		**4793**		**4779**	**15.1%**	**0.97 [0.80 , 1.17]**
Total events:	217		223			
Heterogeneity: Chi² = 3.17, df = 1 (P = 0.07); I² = 68%						
Test for overall effect: Z = 0.35 (P = 0.73)						
4.2.2 non-all ASCVD						
Green 2015	547	7332	537	7339	35.3%	1.02 [0.90 , 1.16]
McMurray 2018	11	128	4	126	0.3%	2.87 [0.89 , 9.26]
Rosenstock 2019	367	3494	373	3485	23.8%	0.98 [0.84 , 1.14]
Scirica 2013	420	8280	378	8212	25.6%	1.11 [0.96 , 1.28]
Subtotal (95% CI)		**19234**		**19162**	**84.9%**	**1.04 [0.96 , 1.13]**
Total events:	1345		1292			
Heterogeneity: Chi² = 4.31, df = 3 (P = 0.23); I² = 30%						
Test for overall effect: Z = 1.00 (P = 0.32)						
Total (95% CI)		**24027**		**23941**	**100.0%**	**1.03 [0.96 , 1.11]**
Total events:	1562		1515			
Heterogeneity: Chi² = 7.97, df = 5 (P = 0.16); I² = 37%						
Test for overall effect: Z = 0.79 (P = 0.43)						
Test for subgroup differences: Chi² = 0.49, df = 1 (P = 0.48), I² = 0%						



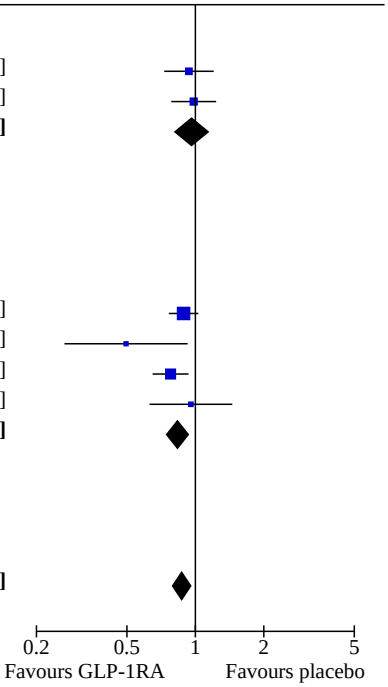
Comparison 5. Subgroup analysis: GLP-1RA

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Cardiovascular mortality: type of baseline CVD	6	46093	Odds Ratio (M-H, Fixed, 95% CI)	0.87 [0.79, 0.95]
5.1.1 all ASCVD	2	15521	Odds Ratio (M-H, Fixed, 95% CI)	0.96 [0.81, 1.14]
5.1.2 non-all ASCVD	4	30572	Odds Ratio (M-H, Fixed, 95% CI)	0.83 [0.75, 0.93]
5.2 Fatal and non-fatal myocardial infarction: type of baseline CVD	5	42910	Odds Ratio (M-H, Random, 95% CI)	0.89 [0.78, 1.01]
5.2.1 All ASCVD	2	15521	Odds Ratio (M-H, Random, 95% CI)	0.88 [0.64, 1.21]
5.2.2 non-all ASCVD	3	27389	Odds Ratio (M-H, Random, 95% CI)	0.90 [0.78, 1.03]
5.3 Fatal and non-fatal stroke: type of baseline CVD	5	42910	Odds Ratio (M-H, Fixed, 95% CI)	0.87 [0.77, 0.98]
5.3.1 all ASCVD	2	15521	Odds Ratio (M-H, Fixed, 95% CI)	0.96 [0.77, 1.19]
5.3.2 non-all ASCVD	3	27389	Odds Ratio (M-H, Fixed, 95% CI)	0.84 [0.73, 0.96]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.4 All-cause mortality: type of baseline CVD	7	46393	Odds Ratio (M-H, Fixed, 95% CI)	0.88 [0.82, 0.95]
5.4.1 all ASCVD	2	15521	Odds Ratio (M-H, Fixed, 95% CI)	0.95 [0.82, 1.09]
5.4.2 non-all ASCVD	5	30872	Odds Ratio (M-H, Fixed, 95% CI)	0.85 [0.78, 0.93]

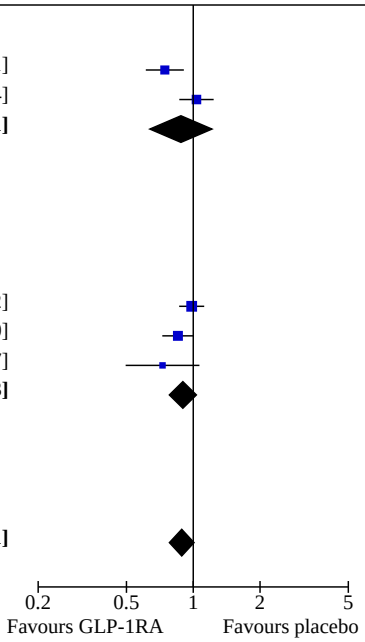
Analysis 5.1. Comparison 5: Subgroup analysis: GLP-1RA, Outcome 1: Cardiovascular mortality: type of baseline CVD

Study or Subgroup	GLP-1RA Events	GLP-1RA Total	placebo Events	placebo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
5.1.1 all ASCVD						
Hernandez 2018	122	4731	130	4732	12.9%	0.94 [0.73 , 1.20]
Pfeffer 2015	156	3034	158	3024	15.3%	0.98 [0.78 , 1.23]
Subtotal (95% CI)		**7765**		**7756**	**28.2%**	**0.96 [0.81 , 1.14]**
Total events:	278		288			
Heterogeneity: Chi² = 0.08, df = 1 (P = 0.78); I² = 0%						
Test for overall effect: Z = 0.45 (P = 0.65)						
5.1.2 non-all ASCVD						
Holman 2017	340	7356	383	7396	37.2%	0.89 [0.76 , 1.03]
Husain 2019	15	1591	30	1592	3.0%	0.50 [0.27 , 0.92]
Marso 2016a	219	4668	278	4672	27.0%	0.78 [0.65 , 0.93]
Marso 2016b	44	1648	46	1649	4.6%	0.96 [0.63 , 1.45]
Subtotal (95% CI)		**15263**		**15309**	**71.8%**	**0.83 [0.75 , 0.93]**
Total events:	618		737			
Heterogeneity: Chi² = 4.30, df = 3 (P = 0.23); I² = 30%						
Test for overall effect: Z = 3.25 (P = 0.001)						
Total (95% CI)		**23028**		**23065**	**100.0%**	**0.87 [0.79 , 0.95]**
Total events:	896		1025			
Heterogeneity: Chi² = 6.29, df = 5 (P = 0.28); I² = 20%						
Test for overall effect: Z = 2.97 (P = 0.003)						
Test for subgroup differences: Chi² = 1.94, df = 1 (P = 0.16), I² = 48.6%						



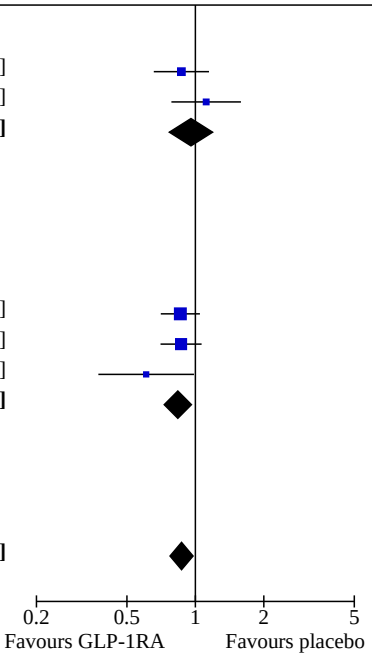
Analysis 5.2. Comparison 5: Subgroup analysis: GLP-1RA, Outcome 2: Fatal and non-fatal myocardial infarction: type of baseline CVD

Study or Subgroup	GLP-1RA Events	GLP-1RA Total	placebo Events	placebo Total	Weight	Odds Ratio M-H, Random, 95% CI
5.2.1 All ASCVD						
Hernandez 2018	181	4731	240	4732	19.7%	0.74 [0.61 , 0.91]
Pfeffer 2015	270	3034	261	3024	21.6%	1.03 [0.87 , 1.24]
Subtotal (95% CI)		**7765**		**7756**	**41.3%**	**0.88 [0.64 , 1.21]**
Total events:	451		501			
Heterogeneity: Tau² = 0.04; Chi² = 5.87, df = 1 (P = 0.02); I² = 83%						
Test for overall effect: Z = 0.78 (P = 0.44)						
5.2.2 non-all ASCVD						
Holman 2017	483	7356	493	7396	26.9%	0.98 [0.86 , 1.12]
Marso 2016a	292	4668	339	4672	23.3%	0.85 [0.73 , 1.00]
Marso 2016b	47	1648	64	1649	8.6%	0.73 [0.50 , 1.07]
Subtotal (95% CI)		**13672**		**13717**	**58.7%**	**0.90 [0.78 , 1.03]**
Total events:	822		896			
Heterogeneity: Tau² = 0.01; Chi² = 3.31, df = 2 (P = 0.19); I² = 40%						
Test for overall effect: Z = 1.51 (P = 0.13)						
Total (95% CI)		**21437**		**21473**	**100.0%**	**0.89 [0.78 , 1.01]**
Total events:	1273		1397			
Heterogeneity: Tau² = 0.01; Chi² = 9.27, df = 4 (P = 0.05); I² = 57%						
Test for overall effect: Z = 1.83 (P = 0.07)						
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.91), I² = 0%						

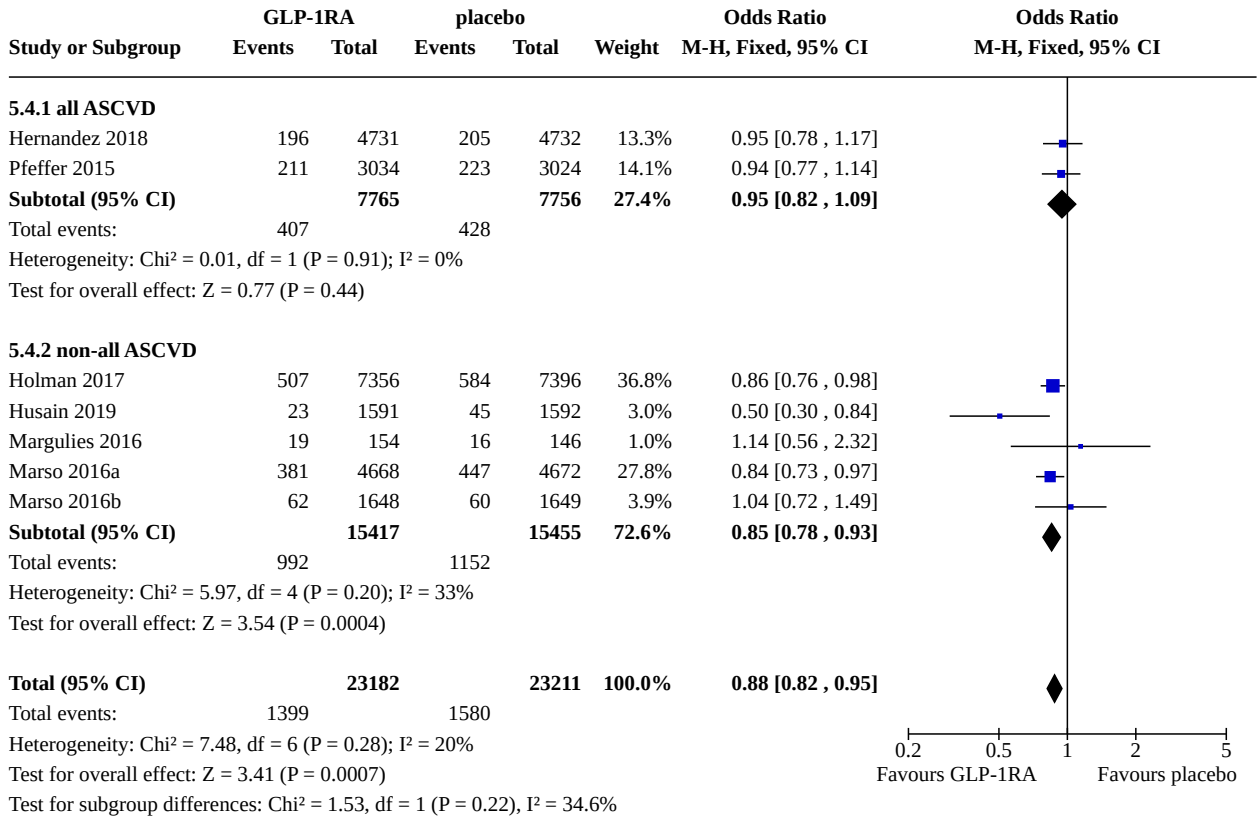


Analysis 5.3. Comparison 5: Subgroup analysis: GLP-1RA, Outcome 3: Fatal and non-fatal stroke: type of baseline CVD

Study or Subgroup	GLP-1RA Events	GLP-1RA Total	placebo Events	placebo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
5.3.1 all ASCVD						
Hernandez 2018	94	4731	108	4732	17.3%	0.87 [0.66 , 1.15]
Pfeffer 2015	67	3034	60	3024	9.6%	1.12 [0.78 , 1.59]
Subtotal (95% CI)		**7765**		**7756**	**26.9%**	**0.96 [0.77 , 1.19]**
Total events:	161		168			
Heterogeneity: Chi² = 1.20, df = 1 (P = 0.27); I² = 17%						
Test for overall effect: Z = 0.40 (P = 0.69)						
5.3.2 non-all ASCVD						
Holman 2017	187	7356	218	7396	34.7%	0.86 [0.70 , 1.05]
Marso 2016a	173	4668	199	4672	31.3%	0.87 [0.70 , 1.07]
Marso 2016b	27	1648	44	1649	7.1%	0.61 [0.37 , 0.99]
Subtotal (95% CI)		**13672**		**13717**	**73.1%**	**0.84 [0.73 , 0.96]**
Total events:	387		461			
Heterogeneity: Chi² = 1.84, df = 2 (P = 0.40); I² = 0%						
Test for overall effect: Z = 2.54 (P = 0.01)						
Total (95% CI)		**21437**		**21473**	**100.0%**	**0.87 [0.77 , 0.98]**
Total events:	548		629			
Heterogeneity: Chi² = 4.05, df = 4 (P = 0.40); I² = 1%						
Test for overall effect: Z = 2.36 (P = 0.02)						
Test for subgroup differences: Chi² = 1.02, df = 1 (P = 0.31), I² = 2.0%						



Analysis 5.4. Comparison 5: Subgroup analysis: GLP-1RA, Outcome 4: All-cause mortality: type of baseline CVD



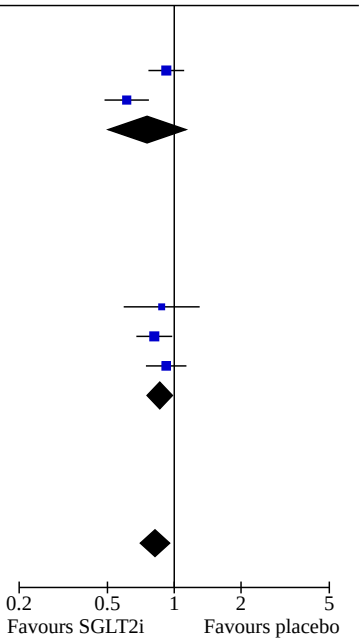
Comparison 6. Subgroup analysis: SGLT2i

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Cardiovascular mortality: type of baseline CVD	5	24962	Odds Ratio (M-H, Random, 95% CI)	0.82 [0.70, 0.95]
6.1.1 all ASCVD	2	15266	Odds Ratio (M-H, Random, 95% CI)	0.75 [0.50, 1.13]
6.1.2 all HF	3	9696	Odds Ratio (M-H, Random, 95% CI)	0.86 [0.75, 0.98]
6.2 Cardiovascular mortality: background comorbidities	5	24962	Odds Ratio (M-H, Random, 95% CI)	0.82 [0.70, 0.95]
6.2.1 all DM	3	16488	Odds Ratio (M-H, Random, 95% CI)	0.78 [0.59, 1.05]
6.2.2 non-all DM	2	8474	Odds Ratio (M-H, Random, 95% CI)	0.86 [0.75, 0.99]
6.3 All-cause mortality: type of baseline CVD	5	24962	Odds Ratio (M-H, Random, 95% CI)	0.84 [0.74, 0.96]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.3.1 all ASCVD	2	15266	Odds Ratio (M-H, Random, 95% CI)	0.79 [0.58, 1.08]
6.3.2 all HF	3	9696	Odds Ratio (M-H, Random, 95% CI)	0.88 [0.78, 0.99]
6.4 All-cause mortality: background comorbidities	5	24962	Odds Ratio (M-H, Random, 95% CI)	0.84 [0.74, 0.96]
6.4.1 All had diabetes at baseline	3	16488	Odds Ratio (M-H, Random, 95% CI)	0.80 [0.64, 1.01]
6.4.2 Not all participants had diabetes	2	8474	Odds Ratio (M-H, Random, 95% CI)	0.89 [0.75, 1.05]

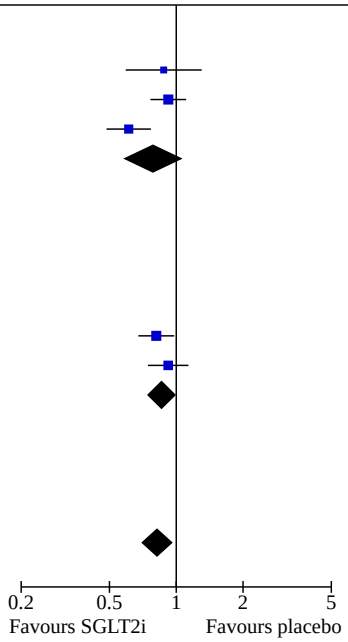
Analysis 6.1. Comparison 6: Subgroup analysis: SGLT2i, Outcome 1: Cardiovascular mortality: type of baseline CVD

Study or Subgroup	SGLT2i Events	SGLT2i Total	placebo Events	placebo Total	Weight	Odds Ratio M-H, Random, 95% CI
6.1.1 all ASCVD						
Cannon 2020	341	5499	184	2747	23.9%	0.92 [0.77 , 1.11]
Zinman 2015	172	4687	137	2333	20.0%	0.61 [0.49 , 0.77]
Subtotal (95% CI)		**10186**		**5080**	**43.9%**	**0.75 [0.50 , 1.13]**
Total events:	513		321			
Heterogeneity: Tau² = 0.07; Chi² = 7.42, df = 1 (P = 0.006); I² = 87%						
Test for overall effect: Z = 1.37 (P = 0.17)						
6.1.2 all HF						
Bhatt 2021	51	608	58	614	10.6%	0.88 [0.59 , 1.30]
McMurray 2019	227	2373	273	2371	23.8%	0.81 [0.67 , 0.98]
Packer 2020	187	1863	202	1867	21.7%	0.92 [0.75 , 1.13]
Subtotal (95% CI)		**4844**		**4852**	**56.1%**	**0.86 [0.75 , 0.98]**
Total events:	465		533			
Heterogeneity: Tau² = 0.00; Chi² = 0.75, df = 2 (P = 0.69); I² = 0%						
Test for overall effect: Z = 2.24 (P = 0.02)						
Total (95% CI)		**15030**		**9932**	**100.0%**	**0.82 [0.70 , 0.95]**
Total events:	978		854			
Heterogeneity: Tau² = 0.02; Chi² = 9.06, df = 4 (P = 0.06); I² = 56%						
Test for overall effect: Z = 2.58 (P = 0.010)						
Test for subgroup differences: Chi² = 0.37, df = 1 (P = 0.54), I² = 0%						



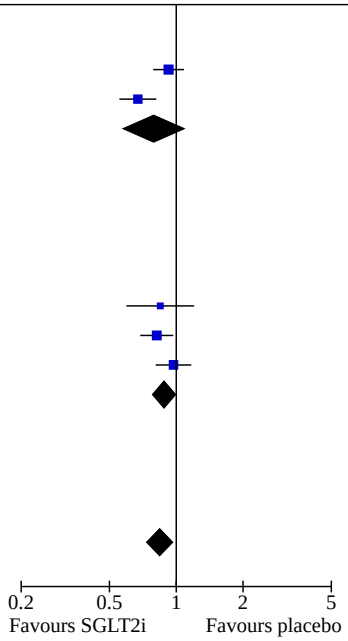
Analysis 6.2. Comparison 6: Subgroup analysis: SGLT2i, Outcome 2: Cardiovascular mortality: background comorbidities

Study or Subgroup	SGLT2i Events	SGLT2i Total	placebo Events	placebo Total	Weight	Odds Ratio M-H, Random, 95% CI
6.2.1 all DM						
Bhatt 2021	51	608	58	614	10.6%	0.88 [0.59 , 1.30]
Cannon 2020	341	5499	184	2747	23.9%	0.92 [0.77 , 1.11]
Zinman 2015	172	4687	137	2333	20.0%	0.61 [0.49 , 0.77]
Subtotal (95% CI)		**10794**		**5694**	**54.5%**	**0.78 [0.59 , 1.05]**
Total events:	564		379			
Heterogeneity: Tau² = 0.05; Chi² = 7.71, df = 2 (P = 0.02); I² = 74%						
Test for overall effect: Z = 1.64 (P = 0.10)						
6.2.2 non-all DM						
McMurray 2019	227	2373	273	2371	23.8%	0.81 [0.67 , 0.98]
Packer 2020	187	1863	202	1867	21.7%	0.92 [0.75 , 1.13]
Subtotal (95% CI)		**4236**		**4238**	**45.5%**	**0.86 [0.75 , 0.99]**
Total events:	414		475			
Heterogeneity: Tau² = 0.00; Chi² = 0.74, df = 1 (P = 0.39); I² = 0%						
Test for overall effect: Z = 2.15 (P = 0.03)						
Total (95% CI)		**15030**		**9932**	**100.0%**	**0.82 [0.70 , 0.95]**
Total events:	978		854			
Heterogeneity: Tau² = 0.02; Chi² = 9.06, df = 4 (P = 0.06); I² = 56%						
Test for overall effect: Z = 2.58 (P = 0.010)						
Test for subgroup differences: Chi² = 0.30, df = 1 (P = 0.59), I² = 0%						

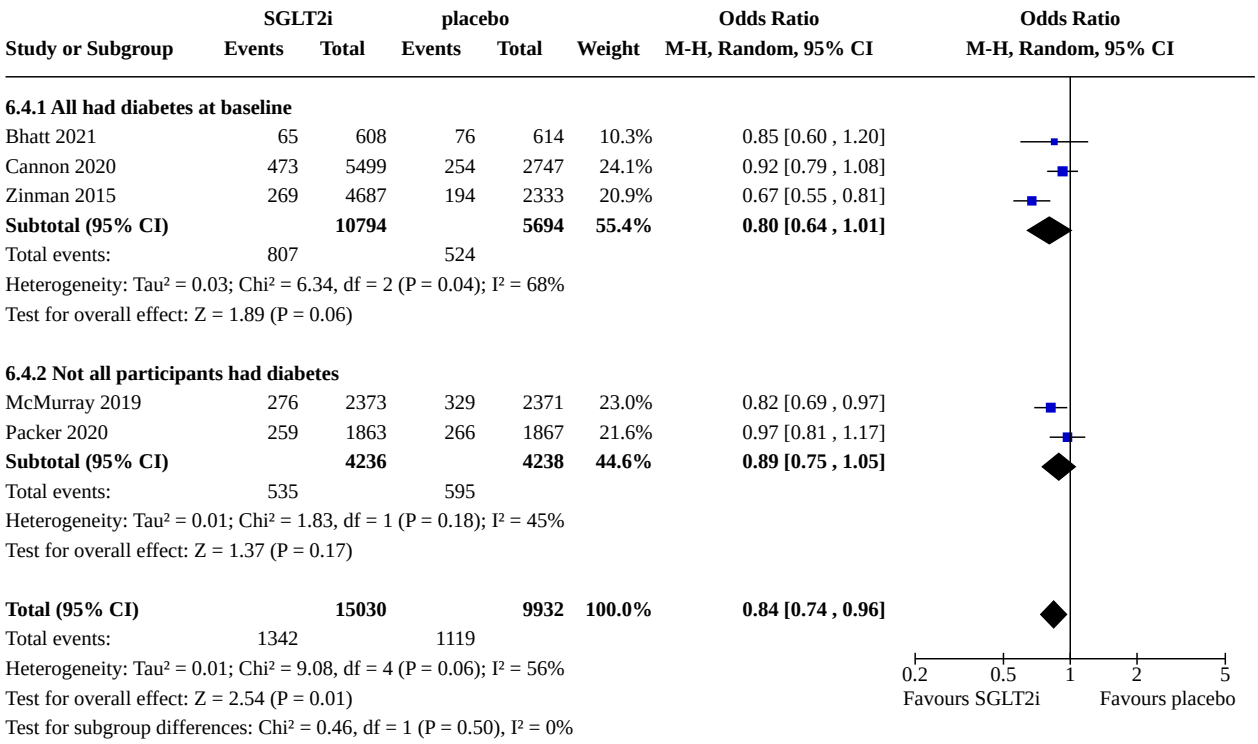


Analysis 6.3. Comparison 6: Subgroup analysis: SGLT2i, Outcome 3: All-cause mortality: type of baseline CVD

Study or Subgroup	SGLT2i Events	SGLT2i Total	placebo Events	placebo Total	Weight	Odds Ratio M-H, Random, 95% CI
6.3.1 all ASCVD						
Cannon 2020	473	5499	254	2747	24.1%	0.92 [0.79 , 1.08]
Zinman 2015	269	4687	194	2333	20.9%	0.67 [0.55 , 0.81]
Subtotal (95% CI)		**10186**		**5080**	**45.1%**	**0.79 [0.58 , 1.08]**
Total events:	742		448			
Heterogeneity: Tau² = 0.04; Chi² = 6.28, df = 1 (P = 0.01); I² = 84%						
Test for overall effect: Z = 1.47 (P = 0.14)						
6.3.2 all HF						
Bhatt 2021	65	608	76	614	10.3%	0.85 [0.60 , 1.20]
McMurray 2019	276	2373	329	2371	23.0%	0.82 [0.69 , 0.97]
Packer 2020	259	1863	266	1867	21.6%	0.97 [0.81 , 1.17]
Subtotal (95% CI)		**4844**		**4852**	**54.9%**	**0.88 [0.78 , 0.99]**
Total events:	600		671			
Heterogeneity: Tau² = 0.00; Chi² = 1.88, df = 2 (P = 0.39); I² = 0%						
Test for overall effect: Z = 2.10 (P = 0.04)						
Total (95% CI)		**15030**		**9932**	**100.0%**	**0.84 [0.74 , 0.96]**
Total events:	1342		1119			
Heterogeneity: Tau² = 0.01; Chi² = 9.08, df = 4 (P = 0.06); I² = 56%						
Test for overall effect: Z = 2.54 (P = 0.01)						
Test for subgroup differences: Chi² = 0.40, df = 1 (P = 0.53), I² = 0%						



Analysis 6.4. Comparison 6: Subgroup analysis: SGLT2i, Outcome 4: All-cause mortality: background comorbidities



ADDITIONAL TABLES

Table 1. Summary of findings table for NMA

Bayesian NMA-SoF table

Patient or population: participants with CVD

Interventions: dipeptidyl peptidase-4 inhibitors, glucagon-like peptide 1 receptor agonists and sodium-glucose co-transporter-2 inhibitors

Comparator (reference): placebo

Outcome: cardiovascular mortality, fatal or non-fatal myocardial infarction,fatal or non-fatal stroke, all-cause mortality, hospitalisation for heart failure, development of end-stage kidney disease, non-cardiac safety outcomes (hypoglycaemia), non-cardiac safety outcomes (pancreatitis), non-cardiac safety outcomes (fractures).

Setting(s): outpatient

Geometry of the Network: separately attached (Figure 4)

Cardiovascular mortality	**Relative effect (network estimate)*** **OR (95% CrI)**	**Certainty of the evidence**	**Ranking****
Placebo	Reference comparator	Reference comparator	**1 (Worst)**
DPP4i	**0.99** (0.87 to 1.1)	⊕⊕⊕⊕	**2**

Table 1. Summary of findings table for NMA *(Continued)*

(Direct evidence; 47,968 participants, 6 RCTs)		**HIGH**	
GLP1-RA	**0.87** (0.76 to 0.98)	⊕⊕⊕⊕	**3**
(Direct evidence; 46,093 participants, 6 RCTs)		**HIGH**	
SGLT2i	**0.82** (0.72 to 0.94)	⊕⊕⊕⊖	**4 (Best)**
(Direct evidence; 24,962 participants, 5 RCTs)		**MODERATE** [1]	
Fatal or non-fatal myocardial infarction	**Relative effect (network estimate)** **OR (95% CrI)**	**Certainty of the evidence**	**Ranking****
Placebo	Reference comparator	Reference comparator	**1 (Worst)**
DPP4i	**0.98** (0.84 to 1.1)	⊕⊕⊕⊕	**2**
(Direct evidence; 42,334 participants, 4 RCTs)		**HIGH**	
GLP1-RA	**0.89** (0.77 to 1.0)	⊕⊕⊕⊖	**4 (Best)**
(Direct evidence; 42,910 participants, 5 RCTs)		**MODERATE** [1]	
SGLT2i	**0.97** (0.77 to 1.2)	⊕⊕⊕⊕	**3**
(Direct evidence; 15,266 participants, 2 RCTs)		**HIGH**	
Fatal or non-fatal stroke	**Relative effect (network estimate)** **OR (95% CrI)**	**Certainty of the evidence**	**Ranking****
Placebo	Reference comparator	Reference comparator	**2**
DPP4i	**0.99** (0.84 to 1.2)	⊕⊕⊕⊕	**3**
(Direct evidence; 42,588 participants, 5 RCTs)		**HIGH**	
GLP1-RA	**0.87** (0.75 to 1.0)	⊕⊕⊕⊕	**4 (Best)**
(Direct evidence; 42,910 participants, 5 RCTs)		**HIGH**	
SGLT2i	**1.1** (0.89 to 1.4)	⊕⊕⊕⊖	**1 (Worst)**
(Direct evidence; 15,266 participants, 2 RCTs)		**MODERATE** [2]	
All-cause mortality	**Relative effect (network estimate)**	**Certainty of the evidence**	**Ranking****

Table 1. Summary of findings table for NMA *(Continued)*

	OR (95% CrI)		
Placebo	Reference Comparator	Reference Comparator	**2**
DPP4i (Direct evidence; 47968 participants, 6 RCTs)	**1.0** (0.93 to 1.2)	⊕⊕⊕⊕ **HIGH**	**1 (Worst)**
GLP1-RA (Direct evidence; 46,393 participants, 7 RCTs)	**0.88** (0.79 to 0.98)	⊕⊕⊕⊕ **HIGH**	**3**
SGLT2i (Direct evidence; 24962 participants, 5 RCTs)	**0.84** (0.75 to 0.93)	⊕⊕⊕⊖ **Moderate** [1]	**4 (Best)**
Hospitalisation for heart failure	**Relative effect (network estimate)** **OR (95% CrI)**	**Certainty of the evidence**	**Ranking*****
Placebo	Reference comparator	Reference comparator	**2**
DPP4i (Direct evidence; 42,334 participants, 4 RCTs)	**1.0** (0.84 to 1.2)	⊕⊕⊕◯ **MODERATE** [1]	**1 (Worst)**
GLP1-RA (Direct evidence; 36,930 participants, 6 RCTs)	**0.97** (0.83 to 1.1)	⊕⊕⊕⊕ **HIGH**	**3**
SGLT2i (Direct evidence; 24962 participants, 5 RCTs)	**0.64** (0.55 to 0.74)	⊕⊕⊕⊕ **High**	**4 (Best)**
Safety outcome (worsening renal function)	**Relative effect (network estimate)** **OR (95% CrI)**	**Certainty of the evidence**	**Ranking****
Placebo	Reference Comparator	Reference Comparator	**2**
DPP4i (Direct evidence; 16,492 participants, 1 RCT)	**1.1** (0.50 to 2.4)	⊕⊕⊖⊖ **LOW** [2, 3]	**1 (Worst)**
GLP1-RA (Direct evidence; 3297 participants, 1 RCT)	**0.61** (0.27 to 1.4)	⊕⊕⊖⊖ **LOW** [5]	**3**

Table 1. Summary of findings table for NMA *(Continued)*

SGLT2i (Direct evidence; 8474 participants, 2 RCTs)	**0.60** (0.32 to 1.1)	⊕⊕⊖⊖ **LOW** [2, 4]	**4 (Best)**
Safety outcome (pancreatitis)	**Relative effect (network estimate)** **OR (95% CrI)**	**Certainty of the evidence**	**Ranking****
Placebo	Reference comparator	Reference comparator	**2**
DPP4i (Direct evidence; 47684 participants, 5 RCTs)	**1.6** (1.1 to 2.6)	⊕⊕⊕⊖ **MODERATE** [4]	**1 (Worst)**
GLP1-RA (Direct evidence; 40,035 participants, 5 RCTs)	**0.95** (0.62 to 1.4)	⊕⊕⊖⊖ **LOW** [2, 3]	**3**
SGLT2i (Direct evidence; 8,246 participants, 1 RCT)	**0.86** (0.35 to 2.2)	⊕⊕⊖⊖ **LOW** [5]	**4 (Best)**
Safety outcome (fracture)	**Relative effect (network estimate)** **OR (95% CrI)**	**Certainty of the evidence**	**Ranking****
Placebo	Reference comparator	Reference comparator	**2**
DPP4i (Direct evidence; 16,492 participants, 1 RCT)	**1.0** (0.73 to 1.4)	⊕⊕⊖⊖ **LOW** [2,3]	**3 (Best)**
GLP1-RA (No direct evidence; 0participants, 0 RCTs)	**-**	-	**-**
SGLT2i (Direct evidence; 24,962 participants, 5 RCTs)	**1.0** (0.84 to 1.2)	⊕⊕⊕⊕ **HIGH**	**1 (Worst)**

NMA-SoF table definitions

* Network meta-analysis estimates are reported as odds ratio. CrI: credible interval. Results are expressed in credible intervals as opposed to the confidence intervals since a Bayesian analysis has been conducted.

** Rank statistics is defined as the ranking order such that a treatment out of *n* treatments in a network meta-analysis is***the worst,*** the second, the third and so on until the***best*** effective treatment.

GRADE Working Group grades of evidence

Table 1. Summary of findings table for NMA *(Continued)*

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanatory Footnotes

[1]Moderate to substantial heterogeneity in effect (-1): Inconsistency

[2]The 95% CrI includes no effect and includes default values for appreciable harm (i.e. CI > 1.25), appreciable benefit (i.e. CI < 0.75), or both. (-1): Imprecision

[3]Only 1 RCT was included for this outcome. (-1): Imprecision

[4]The number of outcome events was small. (-1): Imprecision

[5]Downgrade with 2, 3, and 4. (-2): Imprecision

CI: confidence interval, CrI: credible interval, CVD: cardiovascular disease, DPP4i: dipeptidyl peptidase 4 inhibitor, GLP-1RA: glucagon-like peptide-1 receptor agonist, NMA: network meta-analysis, OR: odds ratio, RCT: randomized controlled trial, SGLT2i: sodium-glucose co-transporter-2 inhibitor

Table 2. Effect estimates (direct comparisons with placebo and indirect comparisons between each class of drug: upper triangle, OR (95% CrI); lower triangle, LOR (95% CrI))

Cardiovascular mortality	**DPP4i**	**GLP-1RA**	**SGLT2i**
Placebo	0.99 (0.87 to 1.1)	0.87 (0.76 to 0.98)	0.82 (0.72 to 0.94)
DPP4i	-	-	-
GLP_1RA	-0.134 (-0.315, 0.048)	-	-
SGLT2i	-0.189 (-0.374, -0.005)	-0.055 (-0.238, 0.129)	-
Fatal or non-fatal myocardial infarction	**DPP4i**	**GLP-1RA**	**SGLT2i**
Placebo	0.98 (0.84 to 1.1)	0.89 (0.77 to 1.0)	0.97 (0.77 to 1.2)
DPP4i	-	-	-
GLP_1RA	-0.089 (-0.308, 0.109)	-	-
SGLT2i	-0.011 (-0.285, 0.256)	0.078 (-0.177, 0.344)	-
Fatal or non-fatal stroke	**DPP4i**	**GLP-1RA**	**SGLT2i**
Placebo	0.99 (0.84 to 1.2)	0.87 (0.75 to 1.0)	1.1 (0.89 to 1.4)
DPP4i	-	-	-
GLP_1RA	-0.129 (-0.349, 0.092)	-	-

Table 2. Effect estimates (direct comparisons with placebo and indirect comparisons between each class of drug: upper triangle, OR (95% CrI); lower triangle, LOR (95% CrI)) *(Continued)*

SGLT2i	0.124 (-0.153, 0.412)	0.254 (-0.011, 0.524)	-
All-cause mortality	**DPP4i**	**GLP-1RA**	**SGLT2i**
Placebo	1.0 (0.93 to 1.2)	0.88 (0.79 to 0.98)	0.84 (0.75 to 0.93)
DPP4i	-	-	-
GLP_1RA	-0.16 (-0.311, -0.014)	-	-
SGLT2i	-0.211 (-0.372, -0.061)	-0.051 (-0.207, 0.1)	-
Hospitalisation for heart failure	**DPP4i**	**GLP-1RA**	**SGLT2i**
Placebo	1.0 (0.84 to 1.2)	0.97 (0.83 to 1.1)	0.64 (0.55 to 0.74)
DPP4i	-	-	-
GLP_1RA	-0.055 (-0.269, 0.206)	-	-
SGLT2i	-0.461 (-0.674, -0.218)	-0.405 (-0.637, -0.199)	-
Safety outcome (worsening renal function)	**DPP4i**	**GLP-1RA**	**SGLT2i**
Placebo	1.1 (0.50 to 2.4)	0.61 (0.27 to 1.4)	0.60 (0.32 to 1.1)
DPP4i	-	-	-
GLP_1RA	-0.583 (-1.697, 0.547)	-	-
SGLT2i	-0.601 (-1.594, 0.405)	-0.019 (-1.04, 1.009)	-
Safety outcome (hypoglycaemia)	**DPP4i**	**GLP-1RA**	**SGLT2i**
Placebo	1.1 (0.71 to 1.8)	0.94 (0.65 to 1.4)	1.0 (0.66 to 1.8)
DPP4i	-	-	-
GLP_1RA	-0.167 (-0.739, 0.459)	-	-
SGLT2i	-0.114 (-0.698, 0.661)	0.058 (-0.513, 0.757)	-
Safety outcome (pancreatitis)	**DPP4i**	**GLP-1RA**	**SGLT2i**
Placebo	1.6 (1.1 to 2.6)	0.95 (0.62 to 1.4)	0.86 (0.35 to 2.2)
DPP4i	-	-	-
GLP_1RA	-0.549 (-1.189, 0.049)	-	-
SGLT2i	-0.65 (-1.678, 0.4)	-0.097 (-1.095, 0.949)	-
Safety outcome (fracture)	**DPP4i**	**SGLT2i**	

Table 2. Effect estimates (direct comparisons with placebo and indirect comparisons between each class of drug: upper triangle, OR (95% CrI); lower triangle, LOR (95% CrI)) *(Continued)*

Placebo	1.0 (0.73 to 1.4)	1.0 (0.84 to 1.2)
DPP4i	-	-
SGLT2i	0.02 (-0.333, 0.385)	-

Upper triangle showed direct network estimate, OR (95% CrI); lower triangle showed indirect network estimate, LOR (95% CrI)
CrI: credible interval, DPP4i: dipeptidyl peptidase 4 inhibitor, GLP-1RA: glucagon-like peptide-1 receptor agonist, LOR: log odds ratio, OR: odds ratio, SGLT2i: sodium-glucose co-transporter-2 inhibitor

Table 3. Further characteristics of included studies: types of CVD and status of diabetes mellitus amongst participants

Included studies	Acronyms of trial	ASCVD	HF	DM
Arturi 2017	-	1	1	1
Bhatt 2021	SOLOIST-WHF	0	1	1
Cannon 2020	VERTIS CV	1	0	1
Cefalu 2015	-	1	-	1
Gants 2017	-	1	0	1
Green 2015	TECOS	0	0	1
Hernandez 2018	Harmony Outcomes	1	0	1
Holman 2017	EXSCEL	0	0	1
Husain 2019	PIONEER 6	0	0	1
Jorsal 2017	LIVE	0	1	0
Kato 2017	TOP-SCORE	1	-	1
Leiter 2014	-	1	0	1
Margulies 2016	FIGHT	0	1	0
Marso 2016a	LEADER	0	0	1
Marso 2016b	SUSTAIN 6	0	0	1
McMurray 2018	VIVIDD	0	1	1
McMurray 2019	DAPA-HF	0	1	0
Neal 2017a	CANVAS (CANVAS program)	0	0	1
Neal 2017b	CANVAS-R (CANVAS program)	0	0	1
Packer 2020	EMPEROR-Reduced	0	1	0

Table 3. Further characteristics of included studies: types of CVD and status of diabetes mellitus amongst participants *(Continued)*

Pfeffer 2015	ELIXA	1	0	1
Phrommintikul 2019	-	1	0	1
Rosenstock 2019	CARMELINA	0	0	1
Scirica 2013	SAVOR-TIMI 53	0	0	1
Shimizu 2020	EMBODY	1	-	1
Tanaka 2019	EMBLEM	1	0	1
Tanaka 2020	CANDLE	0	1	1
Verma 2019	EMPA-HEART CardioLink-6	1	0	1
Wang 2020	-	1	-	1
White 2013	EXAMINE	1	0	1
Zinman 2015	EMPA-REG outcome	1	0	1

[1]: All the study participants had comorbidities at baseline.
[0]: Some of the study participants had comorbidities at baseline.
[-]: data not available.
ASCVD: atherosclerotic cardiovascular disease, CVD: cardiovascular disease, DM: diabetes mellitus, HF: heart failure

Table 4. Overall interpretation of review findings

	Cardiovascular mortality	Myocardial infarction	Stroke	All-cause mortality	Hospitalisation for heart failure	Worsening renal function	Hypoglycaemia	Pancreatitis	Fracture
DPP4i	Do not reduce risk	Do not reduce risk	Do not reduce risk	Do not reduce risk	Probably do not reduce risk	May not increase risk	Probably do not increase risk	Likely to increase risk	May not increase risk
GLP-1RA	Reduce risk	Probably do not reduce risk	Reduce risk	Reduce risk	Do not reduce risk	May reduce risk	*See below* [1]	May have no impact	*See below* [2]
SGLT2i	Probably reduce	Do not reduce risk	Probably do not reduce risk	Probably reduce risk	Reduce risk	Probably reduce risk	Probably no effect	May have no impact	No effect

1. Data on hypoglycaemia across the GLP-1RA studies showed significant heterogeneity (I^2 = 76%, P = 0.002). Pooling of study findings was thus not performed (Effects of interventions).
2. No study reported data on the effects of GLP-1RA on (Effects of interventions).
DPP4i: dipeptidyl peptidase 4 inhibitor, GLP-1RA: glucagon-like peptide-1 receptor agonist, SGLT2i: sodium-glucose co-transporter-2 inhibitor

APPENDICES

Appendix 1. Search strategies

CENTRAL (Cochrane Library)

#1 MeSH descriptor: [Dipeptidyl-Peptidase IV Inhibitors] explode all trees

#2 ("Dipeptidyl peptidase 4" NEAR/2 inhibitor*):ti,ab,kw

#3 ("Dipeptidyl peptidase IV" NEAR/2 inhibitor*):ti,ab,kw

#4 DPP-4 inhibitor*:ti,ab,kw

#5 Gliptin*:ti,ab,kw

#6 Alogliptin:ti,ab,kw

#7 Anagliptin:ti,ab,kw

#8 Dutogliptin:ti,ab,kw

#9 Evogliptin:ti,ab,kw

#10 Gemigliptin:ti,ab,kw

#11 Gosogliptin:ti,ab,kw

#12 MeSH descriptor: [Linagliptin] this term only

#13 Linagliptin:ti,ab,kw

#14 Omarigliptin:ti,ab,kw

#15 Saxagliptin:ti,ab,kw

#16 Sitagliptin:ti,ab,kw

#17 Teneligliptin:ti,ab,kw

#18 Trelagliptin:ti,ab,kw

#19 MeSH descriptor: [Vildagliptin] this term only

#20 Vildagliptin:ti,ab,kw

#21 {OR #1-#20}

#22 Glucagon-like peptide-1 receptor agonist*:ti,ab,kw

#23 GLP-1 receptor agonist*:ti,ab,kw

#24 incretin mimetic*:ti,ab,kw

#25 albiglutide:ti,ab,kw

#26 dulaglutide:ti,ab,kw

#27 MeSH descriptor: [Exenatide] this term only

#28 exenatide:ti,ab,kw

#29 MeSH descriptor: [Liraglutide] this term only

#30 liraglutide:ti,ab,kw

#31 lixisenatide:ti,ab,kw

#32 semaglutide:ti,ab,kw

#33 taspoglutide:ti,ab,kw

#34 {OR #22-#33}

#35 MeSH descriptor: [Sodium-Glucose Transporter 2 Inhibitors] explode all trees

#36 sodium-glucose cotransporter-2 inhibitor*:ti,ab,kw

#37 SGLT-2 inhibitor*:ti,ab,kw

#38 gliflozin*:ti,ab,kw

#39 MeSH descriptor: [Canagliflozin] this term only

#40 canagliflozin:ti,ab,kw

#41 dapagliflozin:ti,ab,kw

#42 empagliflozin:ti,ab,kw

#43 ertugliflozin:ti,ab,kw

#44 {OR #35-#43}

#45 #21 OR #34 OR #44

#46 MeSH descriptor: [Cardiovascular Diseases] this term only

#47 Cardiovascular disease*:ti,ab,kw

#48 (CVD or ASCVD):ti,ab,kw

#49 MeSH descriptor: [Coronary Disease] this term only

#50 MeSH descriptor: [Coronary Artery Disease] this term only

#51 (Coronary NEAR/2 disease*):ti,ab,kw

#52 CAD:ti,ab,kw

#53 MeSH descriptor: [Acute Coronary Syndrome] this term only

#54 acute coronary syndrome:ti,ab,kw

#55 ACS:ti,ab,kw

#56 MeSH descriptor: [Myocardial Infarction] explode all trees

#57 myocardial infarction*:ti,ab,kw

#58 heart attack*:ti,ab,kw

#59 MeSH descriptor: [Angina Pectoris] explode all trees

#60 angina:ti,ab,kw

#61 MeSH descriptor: [Heart Diseases] explode all trees

#62 heart disease*:ti,ab,kw

#63 (CHD or IHD):ti,ab,kw

#64 revasculari?ation:ti,ab,kw

#65 MeSH descriptor: [Coronary Artery Bypass] explode all trees

#66 coronary artery bypass:ti,ab,kw

#67 CABG:ti,ab,kw

#68 MeSH descriptor: [Percutaneous Coronary Intervention] explode all trees

#69 (Percutaneous NEAR/2 coronary):ti,ab,kw

#70 PCI:ti,ab,kw

#71 MeSH descriptor: [Angioplasty] explode all trees

#72 Angioplast*:ti,ab,kw

#73 MeSH descriptor: [Stroke] this term only

#74 stroke*:ti,ab,kw

#75 MeSH descriptor: [Peripheral Arterial Disease] this term only

#76 peripheral arter* disease*:ti,ab,kw

#77 MeSH descriptor: [Heart Failure] this term only

#78 ((heart or cardiac) NEAR/2 failure):ti,ab,kw

#79 (HF or CHF or CCF):ti,ab,kw

#80 HFpEF:ti,ab,kw

#81 HFrEF:ti,ab,kw

#82 {OR #46-#81}

#83 #45 AND #82

MEDLINE (Ovid)

1 exp Dipeptidyl-Peptidase IV Inhibitors/ (4818)

2 (Dipeptidyl peptidase 4 adj2 inhibitor*).tw. (2338)

3 (Dipeptidyl peptidase IV adj2 inhibitor*).tw. (662)

4 DPP-4 inhibitor*.tw. (2390)

5 Gliptin*.tw. (256)

6 Alogliptin.tw. (462)

7 Anagliptin.tw. (77)

8 Dutogliptin.tw. (15)

9 Evogliptin.tw. (28)

10 Gemigliptin.tw. (61)

11 Gosogliptin.tw. (2)

12 Linagliptin/ (410)

13 Linagliptin.tw. (728)

14 Omarigliptin.tw. (44)

15 Saxagliptin.tw. (670)

16 Sitagliptin.tw. (2272)

17 Teneligliptin.tw. (150)

18 Trelagliptin.tw. (40)

19 Vildagliptin/ (636)

20 Vildagliptin.tw. (1003)

21 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 (7813)

22 Glucagon-like peptide-1 receptor agonist*.tw. (1657)

23 GLP-1 receptor agonist*.tw. (1760)

24 incretin mimetic*.tw. (342)

25 albiglutide.tw. (190)

26 dulaglutide.tw. (355)

27 Exenatide/ (2417)

28 exenatide.tw. (1901)

29 Liraglutide/ (1686)

30 liraglutide.tw. (2627)

31 lixisenatide.tw. (401)

32 semaglutide.tw. (349)

33 taspoglutide.tw. (58)

34 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 (7435)

35 exp Sodium-Glucose Transporter 2 Inhibitors/ (2377)

36 sodium-glucose cotransporter-2 inhibitor*.tw. (1037)

37 SGLT-2 inhibitor*.tw. (558)

38 gliflozin*.tw. (93)

39 Canagliflozin/ (620)

40 canagliflozin.tw. (968)

41 dapagliflozin.tw. (1109)

42 empagliflozin.tw. (1151)

43 ertugliflozin.tw. (93)

44 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 (4477)

45 21 or 34 or 44 (17324)

46 Cardiovascular Diseases/ (148021)

47 Cardiovascular disease*.tw. (168786)

48 (CVD or ASCVD).tw. (36732)

49 coronary disease/ or coronary artery disease/ (189577)

50 (Coronary adj2 disease*).tw. (144387)

51 CAD.tw. (38808)

52 Acute Coronary Syndrome/ (15577)

53 acute coronary syndrome.tw. (21483)

54 ACS.tw. (21827)

55 exp Myocardial Infarction/ (174953)

56 myocardial infarction*.tw. (181371)

57 heart attack*.tw. (5504)

58 exp Angina Pectoris/ (43354)

59 angina.tw. (52469)

60 exp Heart Diseases/ (1124840)

61 heart disease*.tw. (164662)

62 (CHD or IHD).tw. (30369)

63 revasculari?ation.tw. (56726)

64 exp Coronary Artery Bypass/ (52713)

65 coronary artery bypass.tw. (40393)

66 CABG.tw. (17851)

67 exp Percutaneous Coronary Intervention/ (53589)

68 (Percutaneous adj2 coronary).tw. (41423)

69 PCI.tw. (25554)

70 exp Angioplasty/ (61405)

71 Angioplast*.tw. (43312)

72 Stroke/ (101338)

73 stroke*.tw. (246690)

74 Peripheral Arterial Disease/ (7676)

75 peripheral arter* disease*.tw. (13670)

76 Heart Failure/ (118221)

77 ((heart or cardiac) adj2 failure).tw. (176819)

78 (HF or CHF or CCF).tw. (60061)

79 HFpEF.tw. (2403)

80 HFrEF.tw. (1826)

81 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 (1788488)

82 45 and 81 (3008)

83 randomized controlled trial.pt. (509536)

84 controlled clinical trial.pt. (93752)

85 randomized.ab. (486009)

86 placebo.ab. (209400)

87 clinical trials as topic.sh. (192068)

88 randomly.ab. (337008)

89 trial.ti. (221684)

90 83 or 84 or 85 or 86 or 87 or 88 or 89 (1300722)

91 exp animals/ not humans.sh. (4717597)

92 90 not 91 (1197185)

93 82 and 92 (1079)

Embase (Ovid)

1 exp dipeptidyl peptidase IV inhibitor/ (19292)

2 (Dipeptidyl peptidase 4 adj2 inhibitor*).tw. (3275)

3 (Dipeptidyl peptidase IV adj2 inhibitor*).tw. (832)

4 DPP-4 inhibitor*.tw. (4349)

5 Gliptin*.tw. (450)

6 Alogliptin.tw. (748)

7 Anagliptin.tw. (138)

8 Dutogliptin.tw. (28)

9 Evogliptin.tw. (41)

10 Gemigliptin.tw. (112)

11 Gosogliptin.tw. (6)

12 linagliptin/ (2516)

13 Linagliptin.tw. (1396)

14 Omarigliptin.tw. (63)

15 Saxagliptin.tw. (1251)

16 Sitagliptin.tw. (4265)

17 Teneligliptin.tw. (265)

18 Trelagliptin.tw. (52)

19 vildagliptin/ (3809)

20 Vildagliptin.tw. (1785)

21 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 (20068)

22 Glucagon-like peptide-1 receptor agonist*.tw. (2241)

23 GLP-1 receptor agonist*.tw. (3155)

24 incretin mimetic*.tw. (525)

25 albiglutide.tw. (338)

26 dulaglutide.tw. (761)

27 exendin 4/ (10139)

28 exenatide.tw. (3786)

29 liraglutide/ (8424)

30 liraglutide.tw. (5137)

31 lixisenatide.tw. (708)

32 semaglutide.tw. (615)

33 taspoglutide.tw. (100)

34 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 (18203)

35 exp sodium glucose cotransporter 2 inhibitor/ (10654)

36 sodium-glucose cotransporter-2 inhibitor*.tw. (1357)

37 SGLT-2 inhibitor*.tw. (1049)

38 gliflozin*.tw. (178)

39 canagliflozin/ (2983)

40 canagliflozin.tw. (1746)

41 dapagliflozin.tw. (2235)

42 empagliflozin.tw. (2130)

43 ertugliflozin.tw. (172)

44 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 (11033)

45 21 or 34 or 44 (40388)

46 cardiovascular disease/ (265906)

47 Cardiovascular disease*.tw. (241850)

48 (CVD or ASCVD).tw. (58024)

49 coronary artery disease/ (186936)

50 (Coronary adj2 disease*).tw. (207313)

51 CAD.tw. (66866)

52 acute coronary syndrome/ (57059)

53 acute coronary syndrome.tw. (40381)

54 ACS.tw. (40924)

55 exp heart infarction/ (360843)

56 myocardial infarction*.tw. (256569)

57 heart attack*.tw. (7716)

58 exp angina pectoris/ (92075)

59 angina.tw. (68665)

60 exp heart disease/ (1749916)

61 heart disease*.tw. (217863)

62 (CHD or IHD).tw. (47087)

63 revasculari?ation.tw. (86462)

64 exp coronary artery bypass graft/ (71213)

65 coronary artery bypass.tw. (53301)

66 CABG.tw. (32303)

67 exp percutaneous coronary intervention/ (101651)

68 (Percutaneous adj2 coronary).tw. (67478)

69 PCI.tw. (57875)

70 exp angioplasty/ (90328)

71 Angioplast*.tw. (60568)

72 cerebrovascular accident/ (203380)

73 stroke*.tw. (387690)

74 peripheral occlusive artery disease/ (34051)

75 peripheral arter* disease*.tw. (21497)

76 heart failure/ (232143)

77 ((heart or cardiac) adj2 failure).tw. (286660)

78 (HF or CHF or CCF).tw. (105521)

79 HFpEF.tw. (6161)

80 HFrEF.tw. (5041)

81 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 (2618395)

82 45 and 81 (10082)

83 random$.tw. (1533554)

84 factorial$.tw. (37636)

85 crossover$.tw. (74476)

86 cross over$.tw. (31451)

87 cross-over$.tw. (31451)

88 placebo$.tw. (303445)

89 (doubl$ adj blind$).tw. (203145)

90 (singl$ adj blind$).tw. (24789)

91 assign$.tw. (391068)

92 allocat$.tw. (152083)

93 volunteer$.tw. (250549)

94 crossover procedure/ (63463)

95 double blind procedure/ (170682)

96 randomized controlled trial/ (605488)

97 single blind procedure/ (39339)

98 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 (2304426)

99 (animal/ or nonhuman/) not human/ (5591375)

100 98 not 99 (2040074)

101 82 and 100 (2590)

102 limit 101 to embase (1625)

CPCI-S

39 #38 AND #37

38 TS=(random* or blind* or allocat* or assign* or trial* or placebo* or crossover* or cross-over*)

37 #36 AND #15

36 #35 OR #34 OR #33 OR #32 OR #31 OR #30 OR #29 OR #28 OR #27 OR #26 OR #25 OR #24 OR #23 OR #22 OR #21 OR #20 OR #19 OR #18 OR #17 OR #16

35 TS=(HFpEF or HFrEF)

34 TS=(HF or CHF or CCF)

33 TS=((heart or cardiac) NEAR/2 failure)

32 TS=peripheral arter* disease*

31 TS=(PCI or Angioplast* or stroke*)

30 TS=(Percutaneous NEAR/2 coronary)

29 TS=CABG

28 TS=coronary artery bypass

27 TS=revasculari?ation

26 TS=(CHD or IHD)

25 TS=heart disease*

24 TS=angina

23 TS=heart attack*

22 TS=myocardial infarction*

21 TS=ACS

20 TS=acute coronary syndrome

19 TS=CAD

18 TS=(Coronary NEAR/2 disease*)

17 TS=(CVD or ASCVD)

16 TS=Cardiovascular disease*

15 #14 OR #10 OR #5

14 #13 OR #12 OR #11

13 TS=(gliflozin* or canagliflozin or dapagliflozin or empagliflozin or ertugliflozin)

12 TS=SGLT-2 inhibitor*

11 TS=sodium-glucose cotransporter-2 inhibitor*

10 #9 OR #8 OR #7 OR #6

9 TS=(albiglutide or dulaglutide or exenatide or liraglutide or lixisenatide or semaglutide or taspoglutide)

8 TS=incretin mimetic*

7 TS=GLP-1 receptor agonist*

6 TS=Glucagon-like peptide-1 receptor agonist*

5 #4 OR #3 OR #2 OR #1

4 TS=(Gliptin* or Alogliptin or Anagliptin or Dutogliptin or Evogliptin or Gemigliptin or Gosogliptin or Linagliptin or Omarigliptin or Saxagliptin or Sitagliptin or Teneligliptin or Trelagliptin or Vildagliptin)

3 TS=DPP-4 inhibitor*

2 TS=(Dipeptidyl peptidase IV NEAR/2 inhibitor*)

1 TS=(Dipeptidyl peptidase 4 NEAR/2 inhibitor*)

ClinicalTrials.gov

Advanced search:

("DPP-4 inhibitor" OR "Dipeptidyl peptidase 4 inhibitor" OR "GLP-1 receptor agonist" OR "Glucagon-like peptide-1 receptor agonist" OR "SGLT-2 inhibitor" OR "sodium-glucose cotransporter-2 inhibitor") AND ("Cardiovascular disease" OR "heart failure")

WHO ICTRP Search Portal

Advanced search:

Intervention:

"DPP-4 inhibitor" OR "Dipeptidyl peptidase 4 inhibitor" OR "GLP-1 receptor agonist" OR "Glucagon-like peptide-1 receptor agonist" OR "SGLT-2 inhibitor" OR "sodium-glucose cotransporter-2 inhibitor"

Recruitment status: ALL

Phases: Phase 2, 3, 4

HISTORY

Protocol first published: Issue 6, 2020

CONTRIBUTIONS OF AUTHORS

TK: review development and revisions against feedback from all co-authors.

AM: review development and revisions against feedback from all co-authors.

YT: review development and revisions against feedback from all co-authors.

TS: review development and revisions against feedback from all co-authors.

DY: review development, statistical analysis, and revisions against feedback from all co-authors.

YN: review development and revisions against feedback from all co-authors.

WWST: review development and revisions against feedback from all co-authors.

JM: clinical and overall methodological expert advice.

AR: clinical and overall methodological expert advice.

YX: methodological and statistical expert advice.

OW: methodological and statistical expert advice.

RP: clinical and overall methodological expert advice.

JSWK: initial proposal and scope refinement; review development and revisions against feedback from all co-authors.

DECLARATIONS OF INTEREST

TK declares having no conflicts of interest.

AM declares having no conflicts of interest.

YT declares having no conflicts of interest.

TS declares having no conflicts of interest.

DY declares having no conflicts of interest.

YN declares having no conflicts of interest.

WWST declares having no conflicts of interest.

JM declares having no conflicts of interest.

AR has previously received honoraria for speaking and consultancy from Boehringer Ingelheim in Poland.

YX declares having no conflicts of interest.

OW: The CRSU is a support unit funded by NIHR to provide methodological advice to NIHR-funded evidence synthesis research. It is within the CRSU's remit to support Cochrane Reviews with research questions that are relevant to UK NHS patients. OW is the Director of the CRSU. OW also declares a research grant from Novo Nordisk (2017-2018), received via their institution, for a study to estimate the incidence and the economic burden of cardiovascular events in type 2 diabetes mellitus in Scotland, using routine linked health data.

RP declares having no conflicts of interest.

JSWK declares having no conflicts of interest.

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Internal sources

- None, Other

  No sources of internal support supplied

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

At the protocol stage, we planned to extract outcome data reported at 30 days, one year, and the longest follow-up duration; however, we noted that among the included studies none of the outcome data were reported at 30 days or one year. Thus we decided to include data measured at the longest follow-up period as defined by the individual study.

For renal outcomes, we originally considered 'development of end-stage kidney disease' and 'initiation of renal replacement therapy' as efficacy outcomes. However, as many studies reported these renal events as safety outcomes, for the full review finally decided to report them as one of the safety outcomes and we needed to put them in the summary of findings table.

In the review process, we became aware that the OR is a relatively more popular effect measure in this field to estimate the effectiveness of pharmacological interventions and thus we decided to use the OR with 95% credible interval (CrIs) instead of the RR to assure comparability of the pooled results with other published systematic reviews.

We did not identify any eligible studies that directly compared the effectiveness of our pre-specified types of interventions. Thus, our network meta-analysis did not combine direct and indirect effect estimates.

For subgroup analysis, the types of control intervention or types of combination therapy were not clearly reported by our included studies and thus these *a priori* subgroups were not investigated further.

Safety outcome data were analysed separately due to the inconsistent reporting across included studies. They were listed separately from efficacy outcome in our 'Summary of findings' tables.