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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 (Protocol)

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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 (Protocol).
Cochrane Database of Systematic Reviews 2020, Issue 6. Art. No.: CD013650.
DOI: 10.1002/14651858.CD013650.

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[Intervention Protocol]

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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Editorial group: Cochrane Heart Group, Cochrane Stroke Group.
Publication status and date: New, published in Issue 6, 2020.

Citation: Kanie T, Mizuno A, Yoneoka D, Tam WW, Morze J, Rynkiewicz A, Xin Y, Wu O, Kwong JSW. 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 (Protocol). *Cochrane Database of Systematic Reviews* 2020, Issue 6. Art. No.: CD013650. DOI: 10.1002/14651858.CD013650.

ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To systematically review the available evidence on the effects (benefits and harms) of DPP-4 inhibitors, GLP-1 receptor agonists, and SGLT-2 inhibitors in people with established CVD, using network meta-analysis.

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 (Maggioni 2015; Sato 2015; Conrad 2018).

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 incidence 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 micro-vascular 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 (DPP-4) inhibitors, glucagon-like peptide 1 (GLP-1) receptor agonists and sodium-glucose co-transporter-2 (SGLT-2) inhibitors, have been proposed as potential new pharmacological agents for modifying cardiovascular risks in people with or without diabetes mellitus (Zinman 2015; Marso 2016a; McMurray 2019).

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). The rationale behind the use of oral pharmacological agents is that while most people with type 1 diabetes mellitus could be treated with subcutaneous or bolus insulin infusion, for people with type 2 diabetes mellitus there could be additional treatment options available for oral administration (ADA 2018; ADA 2019). Metformin is 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 (UKPDS 1998; DPP Research Group 2012; Hong 2013; Tanabe 2015).

Recently, DPP-4 inhibitors, GLP-1 receptor agonists and SGLT-2 inhibitors were approved for treating people with type 2 diabetes mellitus (ADA 2018). Two large-scale randomised trials showed that adding a SGLT-2 inhibitor 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 SGLT-2 is currently unclear (Wiviott 2019), a recent systematic review reported that treatment with SGLT-2 inhibitors was effective in minimising the rates of HF-related hospitalisation, as well as renal disease progression, in people with type 2 diabetes mellitus (Zelniker 2019).

Several studies have also shown that add-on treatment of GLP-1 receptor agonists (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-1 receptor agonists (exenatide and lixisenatide) showed no effects against cardiovascular outcomes (Pfeffer 2015; Holman 2017); similarly, treatment with DPP-4 inhibitors did not lead to a reduction in cardiovascular risk (Scirica 2013; White 2013; Green 2015; Rosenstock 2019).

It is therefore clear that, despite increased global usage of DPP-4 inhibitors, GLP-1 receptor agonists, and SGLT-2 inhibitors (Kim 2019), their precise effects on reducing CV events in people with high cardiovascular risks with or without diabetes mellitus are yet to be fully evaluated.

How the intervention might work

Although metformin remains as the first-line pharmacotherapy to manage hyperglycaemia in people with type 2 diabetes mellitus with additional considerations of improved cardiac outcome (ADA 2019), evidence has recently emerged that DPP-4 inhibitors, GLP-1 receptor agonists and SGLT-2 inhibitors 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 (Zinman 2015; Marso 2016a; Marso 2016b; Neal 2017). 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 benefit in people with type 2 diabetes mellitus (ADA 2018). The guideline states that, for people with type 2 diabetes and atherosclerotic cardiovascular disease (ASCVD), therapy should start with lifestyle management with metformin. The above-mentioned three drugs (DPP-4 inhibitors, GLP-1 receptor agonists, and SGLT-2 inhibitors) will affect cardiovascular outcome as an *additional* agent.

Considering their biological mechanisms of action, both DPP-4 inhibitors and GLP-1 receptor agonists are classified as 'GLP-1-based therapies', referring to their actions on glycaemia 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. SGLT-2 inhibitors are expressed in the proximal tubule, and mediate reabsorption of approximately 90% of the filtered glucose load. The

effects of SGLT-2 inhibitors in people with diabetes are not only the reduction of blood glucose levels but also lowering blood pressure and body weight (Clar 2012).

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 heart failure (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).

Studies of SGLT-2 inhibitors have also demonstrated that blocking endothelial sodium-glucose cotransporter-2 led to improved endothelial function, which could be beneficial for non-diabetic populations (Bairey Merz 2019; Pulakazhi 2019). A recent study revealed that SLGT-2 inhibitors 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 SGLT-2 inhibitors 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 from glycaemic control (Heerspink 2017). The hypothesis that SGLT-2 inhibitors 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). Given that diabetes mellitus is a leading cause and an associated comorbidity of CVD, effective blood glycaemic control for people with or without CVD became a global management target for both prevention and treatment. Evidence for the beneficial effects of the new glucose-lowering agents (GLP-1 receptor agonists and SGLT-2 inhibitors) 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. We are aware of several published systematic reviews on this topic (Li 2016a; Li 2016b; Savarese 2016; Wu 2016; Mannucci 2017; Zheng 2018), but this is the first Cochrane Review to assess the cardiovascular effects of these novel agents in people with and without diabetes mellitus.

Among these three types of glucose-lowering interventions, SGLT-2 inhibitors has received considerable attention recently due to its class effect on CVD outcomes, even in non-diabetic populations. As highlighted in a previous meta-analysis (Zelniker 2019), the effectiveness of SGLT-2 inhibitors varies by baseline patient characteristics. SGLT-2 inhibitors reduced MACE (myocardial infarction, stroke, or cardiovascular death), with benefits only seen in people with ASCVD and not in the at-risk subgroup. In other studies of DPP-4 inhibitors, GLP-1 receptor agonists, and SGLT-2 inhibitors, people with CVD as well as people with cardiovascular risk factors were considered as one study population group and thus the true effects of these novel agents in the two separate subpopulations remain uncertain. A precise review of clinical characteristics and the relative treatment effects is therefore needed, since a better understanding of appropriate target populations for these new pharmacological agents is important for optimal treatment pathways.

It is worth noting that these novel glucose-lowering agents are provided either as an additional (add-on) treatment or as part of triple combination therapy. Although these combinations might be clinically valid and important, 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 or feasible. We therefore plan 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 DPP-4 inhibitors, GLP-1 receptor agonists, and SGLT-2 inhibitors in people with established CVD, using network meta-analysis.

METHODS

Criteria for considering studies for this review

Types of studies

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

Types of participants

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

- Atherosclerotic cardiovascular disease (ASCVD), i.e. people with a history of acute coronary syndrome or myocardial infarction, stable or unstable angina, coronary heart disease 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).

- Heart failure: heart failure with preserved ejection fraction (HFpEF) or heart failure 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 will extract only data from desired participant subgroups. If the subgroup data required are not provided, we will contact corresponding authors of the trial to request this information. If the subgroup data are still not available, we will exclude the whole trial if fewer than 80% of participants fit the inclusion criteria. If the transitivity assumption in the network meta-analysis is not plausible, we will implement the 're-analysis' approach on the subset of the participants who satisfy the above criteria.

Types of interventions

We will include RCTs comparing one or more of the following interventions:

- DPP-4 inhibitors (DPP-4i);
- GLP-1 receptor agonists (GLP-1 RA);
- SGLT-2 inhibitors (SGLT-2i).

We will include trials using any combination of the above drugs. We will not exclude trials on the basis of the route, dose, timing, or frequency of drug administration. The comparison groups will be as defined by the trial, which could be a placebo, a lifestyle/behavioural intervention (e.g. diet, exercise, diet + exercise), and another glucose-lowering pharmacological intervention. We will combine trials which use a placebo, a lifestyle/behavioural intervention, and another glucose-lowering pharmacological intervention as a single comparator for the direct comparison. Theoretically, the combination of DPP-4i and GLP-1 RA will not usually be recommended, but at this stage we do not exclude the possibility.

Our comparisons are based on the aforementioned three types of interventions, with each drug type corresponding to one node in our network meta-analysis. We assume the concept of 'jointly randomisable' could apply to all treatments included in the network comprising these interventions and comparators.

Types of outcome measures

We will include outcome data reported at 30 days, one year, and the longest follow-up duration.

Reporting one or more of the outcomes listed here is not a trial inclusion criterion for the review. Where a published trial does not report one of these outcomes, we will access the trial protocol and contact the trial authors to ascertain whether the outcomes were measured but not reported. Relevant trials which measured these outcomes but did not report the data at all, or not in a usable format, will be included in the review as part of the narrative synthesis.

Primary outcomes

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

Secondary outcomes

- All-cause mortality
- Hospitalisation for heart failure
- Development of end-stage kidney disease
- Initiation of renal replacement therapy
- Non-cardiac safety outcomes, including hypoglycaemia, renal toxicity, pancreatitis, fractures, and other adverse effects as reported by trial investigators

For the outcome of hospitalisation for heart failure, we will consider the initial hospitalisation as an outcome. We will analyse safety outcome data separately.

Search methods for identification of studies

Electronic searches

We will identify trials through systematic searches of the following bibliographic databases:

- Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library;
- MEDLINE (Ovid, from 1946 onwards);
- Embase (Ovid, from 1980 onwards);
- Conference Proceedings Citation Index-Science (CPCI-S) (Web of Science).

We will adapt the preliminary search strategy for MEDLINE (Ovid) (Appendix 1) for use in the other databases. We will apply the Cochrane sensitivity and precision-maximising RCT filter (Lefebvre 2019) to MEDLINE (Ovid) and adaptations of it to the other databases, except for CENTRAL.

We will also conduct a search of ClinicalTrials.gov/ and the WHO International Clinical Trials Registry Platform (ICTRP) Search Portal (apps.who.int/trialsearch/) for ongoing or unpublished trials.

We will search all databases from their inception to the present, and will impose no restriction by language of publication or publication status.

We will not perform a separate search for adverse effects, but will consider any adverse effects described in the included studies.

Searching other resources

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

Data collection and analysis

Selection of studies

Two review authors (TK, AM) will independently screen titles and abstracts for inclusion of all the potential studies we identify as a result of the search, and will code them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve' (clearly irrelevant). If there are any disagreements, we will ask a third review author (JSWK) to arbitrate. We will retrieve the full-text study reports/publication, and the two review authors (TK, AM) will independently screen the full text and identify trials for inclusion, recording reasons for exclusion of the ineligible studies. We will

resolve any disagreement through discussion or, if required, we will consult a third person (DY, JSWK). We will identify and exclude duplicates and collate multiple reports of the same study, so that each study rather than each report is the unit of interest in the review. We will record 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 will use a data collection form for study characteristics and outcome data which has been piloted on at least one study in the review. One review author (TK) will extract study characteristics from included studies. We will extract 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 will use very similar inclusion criteria and find comparable baseline characteristics. From each study, we will extract the following characteristics that may have acted as effect modifiers: age, gender, BMI, and comorbidities.

Two review authors (TK, AM) will independently extract outcome data from included studies. We will resolve disagreements by consensus or by involving a third person (JSWK). One review author (TK) will transfer data into the Review Manager 5 software file (Review Manager 2014). We will double-check that data are entered correctly by comparing the data presented in the review with the data extraction form. A second review author (AM) will spot-check study characteristics for accuracy against the trial report.

Assessment of risk of bias in included studies

Two review authors (TK, AM) will independently assess risks of bias for each study, using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019a). We will resolve any disagreements by discussion or by involving another review author (JSWK). We will assess 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 will grade each potential source of bias as high, low or unclear, and will provide a quote from the trial report together with a justification for our judgement in the 'Risk of bias' table. We will summarise 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 will note this in the 'Risk of bias' table.

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

Assessment of bias in conducting the systematic review

We will conduct the review according to this published protocol, and will report any deviations from it in the 'Differences between protocol and review' section of the full review.

Measures of treatment effect

We will analyse all our outcome measures, which are all dichotomous outcomes, using risk ratios (RRs) with 95% confidence intervals (CIs). For efficacy, an RR greater than 1.0 favours the intervention (as opposed to the comparator); when we address safety outcomes, an RR greater than 1.0 favours the comparator.

Unit of analysis issues

All of our included trials will be RCTs at the individual participant or at the cluster level. Our types of interventions of interest are less likely to be evaluated in a cluster-randomisation setting; however, if there is more than one eligible cluster-randomised trial, we will reduce participant numbers in cluster-randomised trials to an effective sample size by a sample size reduction calculation (Hauck 1991). We will analyse data from cluster-randomised trials with those from individually-randomised trials. If adjustment for the cluster design effect is missing from the trial reports, we will adjust the relevant summary statistics (such as sample sizes and standard deviations) according to the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019b), using an estimate of the intraclass correlation coefficient (ICC) derived from the trial where possible, or from a similar trial, or from a study of a similar population. If we use ICCs from other sources in updates, we will perform sensitivity analyses to test the effects of variation in the ICC.

For trials that measured outcomes at different time points, we are interested only in effects of the interventions from the longest follow-up duration. Network meta-analysis is particularly helpful in taking account of the comparison of multiple interventions. If we identify multi-arm trials, to perform direct pairwise comparisons we will treat these multiple treatment comparisons as individual, independent two-arm trials. Network meta-analysis gives consideration to a correlation between effect sizes from trials with more than two arms, and we will take into account the respective treatment effects from the same studies.

Dealing with missing data

We will contact the investigators/authors of the included trials to request any missing data. Our default approach will be to analyse data by following intention-to-treat principles. To explore the impact of missing data, we will conduct 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 will inspect forest plots to identify signs of heterogeneity for each direct comparison. We will assess 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 will follow the recommendations for thresholds in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2019):

- 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.

If we identify important heterogeneity we will report it and explore possible causes by prespecified subgroup analysis and meta-regression (Subgroup analysis and investigation of heterogeneity). If we find considerable heterogeneity, we will not pool the results but will describe them narratively.

Assessment of reporting biases

If we are able to pool more than 10 trials, we will create and examine a funnel plot to visually explore possible small-study biases for the primary outcomes, and will use Egger's test to examine the bias statistically (Egger 1997).

Data synthesis

Direct comparison

We will conduct direct pairwise meta-analysis using Review Manager 2014. If there are two or more included studies for an outcome measure, we will consider pooling the results depending on the level of statistical heterogeneity among the trials (Assessment of heterogeneity). We will use both fixed-effect and random-effects analytical models for direct comparison meta-analysis if we classify the heterogeneity as moderate. If the heterogeneity is considerable, we will not pool the results but instead will perform a narrative synthesis. We will also perform subgroup analyses if we detect any source of important heterogeneity between studies as assessed and quantified by the Chi^2 test and the I^2 statistics (Subgroup analysis and investigation of heterogeneity).

Network meta-analysis

For indirect and mixed comparisons, we will use network meta-analysis to obtain estimates for the outcomes, and present these estimates as risk ratios (RRs) with 95% confidence intervals (CIs). We will conduct our network meta-analysis for all outcome data measured at the following time points: 30 days, one year, and longest follow-up visit. We will perform network meta-analyses within a frequentist framework, assuming an equal heterogeneity parameter across all comparisons, and will then create network diagrams to visually check the direct or indirect comparisons. To estimate the relative ranking probability of an intervention being among the best options, we will calculate for all outcomes the surface under the cumulative ranking (SUCRA) curve, and mean ranks (Salanti 2011). Larger SUCRA scores mean a more effective or safer intervention. To check for the presence of inconsistency in the estimated diagram, we will use the loop-specific approach to analyse the statistical difference between direct and indirect estimates for a certain comparison in a loop. The measure of inconsistency will be based on the Bucher method, as described in Dias 2013 and Schwarzer 2015, who recommend the use of generalised Cochrane's Q and I^2 test statistics. We will also use a net-heat plot to highlight inconsistency in the network. The net-heat plot is a matrix imaging that emphasises hotspots of inconsistency in the network and renders possible drivers. If quantitative synthesis is not possible, we will give a narrative review of the findings.

We will perform the analysis using R, version 3.4.2 (R 2017), netmeta package (netmeta); the codes and description of the methodology can be found in netmeta itself.

Subgroup analysis and investigation of heterogeneity

We will investigate possible heterogeneity through subgroup analyses in both the direct and the network meta-analyses. This will be based on the presence of statistical heterogeneity considered to be important ($I^2 > 40\%$, as calculated by Review Manager 2014) in the standard direct-comparison meta-analysis, together with underlying clinical heterogeneity in baseline participant characteristics.

We will consider 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 heart failure (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 DPP-4 inhibitors/GLP-1 receptor agonists/SGLT-2 inhibitors).
- Type of control (placebo, lifestyle intervention, another glucose-lowering pharmacological intervention).
- Duration of study (≤ 52 weeks vs. > 52 weeks).
- Mode of therapy (monotherapy or combination therapy).

Our outcome measures for the above subgroup analyses are:

- cardiovascular mortality;

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

We will use the formal test for subgroup differences in Review Manager 2014, and base our interpretation on this.

Sensitivity analysis

We plan 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 will perform 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 are:

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

Reaching conclusions

We will base our conclusions only on findings from the quantitative or narrative synthesis of included studies for this review. We will avoid making recommendations for practice, and our implications for research will suggest priorities for future research, and will outline what the remaining uncertainties are in the area.

Summary of findings and assessment of the certainty of the evidence

We will create a 'Summary of findings' table using the following primary and secondary outcomes (Types of outcome measures):

1. cardiovascular mortality;
2. fatal or non-fatal myocardial infarction;
3. fatal or non-fatal stroke;
4. all-cause mortality;
5. hospitalisation for heart failure;
6. non-cardiac safety outcomes including hypoglycaemia, renal toxicity, pancreatitis, fractures, and other adverse effects as reported by study investigators.

We will use the five Grading of Recommendations Assessment, Development and Evaluation (GRADE) considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of a body of evidence as it relates to the studies which contribute data to the meta-analyses for the prespecified outcomes. We will use methods and recommendations described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2019), using the GRADEpro software (GRADEpro GDT 2015).

We will 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;

We will justify all decisions to downgrade the quality of studies using footnotes and we will make comments to aid reader's understanding of the review where necessary.

Judgements about evidence quality will be made by two review authors (TK and AM*)* working independently, with disagreements resolved by discussion or involving a third author (JSWK). Judgements will be justified, documented and incorporated into reporting of results for each outcome. For rating of evidence across studies in a network meta-analysis, we will follow the approach recently released by the GRADE Working Group (Puhan 2014).

We plan to extract study data, format our comparisons in data tables and prepare a 'Summary of findings' table before writing the results and conclusions of our review. A template is included as Table 1, which refers to a 'Summary of findings' table for direct comparison. We will also include a separate table to illustrate results from our network meta-analysis as per the recent guidance from Yepes-Nuñez 2019.

ACKNOWLEDGEMENTS

We would like to thank the Cochrane Heart Group editorial team for their assistance and support throughout this process. We acknowledge the constructive comments from Prof. Peter Langhorne, Academic Section of Geriatric Medicine, Institute of Cardiovascular & Medical Sciences, University of Glasgow, Glasgow, UK, as peer reviewer of this protocol.

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ADDITIONAL TABLES

Table 1. Template of 'Summary of findings' table (direct comparison)

DPP4i, GLP-1RA, and SGLT2i for CVD

Patient or population: Adults with clinically diagnosed CVD
Setting: Hospital
Intervention: DPP4-inhibitors or GLP-1 receptor agonists or SGLT-2 inhibitors (monotherapy or combination therapy)
Comparison: A combined comparison group of controls such as placebo, lifestyle/behavioural intervention, and another glucose-lowering pharmacological intervention

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with *control*	Risk with *treatment*				

Table 1. Template of 'Summary of findings' table (direct comparison) *(Continued)*

Cardiovascular mortality	[value] percent	[value] percent	RR [value] ([value] to [value])	[value]	⊕○○○ very low ⊕⊕○○ low ⊕⊕⊕○ moderate ⊕⊕⊕⊕ high
Myocardial infarctions (fatal or non-fatal)	[value] percent	[value] percent	RR [value] ([value] to [value])	[value]	⊕○○○ very low ⊕⊕○○ low ⊕⊕⊕○ moderate ⊕⊕⊕⊕ high
Stroke (fatal or non-fatal)	[value] percent	[value] percent	RR [value] ([value] to [value])	[value]	⊕○○○ very low ⊕⊕○○ low ⊕⊕⊕○ moderate ⊕⊕⊕⊕ high
				[]	
All-cause mortality	[value] percent	[value] percent	RR [value] ([value] to [value])	[value]	⊕○○○ very low ⊕⊕○○ low ⊕⊕⊕○ moderate ⊕⊕⊕⊕ high
Hospitalisation for heart failure	[value] percent	[value] percent	RR [value] ([value] to [value])	[value]	⊕○○○ very low ⊕⊕○○ low ⊕⊕⊕○ moderate ⊕⊕⊕⊕ high
Non-cardiac safety outcomes	[value] percent	[value] percent	RR [value] ([value] to [value])	[value]	⊕○○○ very low ⊕⊕○○ low ⊕⊕⊕○ moderate ⊕⊕⊕⊕ 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).

Table 1. Template of 'Summary of findings' table (direct comparison) *(Continued)*

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio.

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

APPENDICES

Appendix 1. Preliminary MEDLINE (Ovid) search strategy

1 exp Dipeptidyl-Peptidase IV Inhibitors/ (4613)

2 (Dipeptidyl peptidase 4 adj2 inhibitor*).tw. (2193)

3 (Dipeptidyl peptidase IV adj2 inhibitor*).tw. (642)

4 DPP-4 inhibitor*.tw. (2285)

5 Gliptin*.tw. (245)

6 Alogliptin.tw. (448)

7 Anagliptin.tw. (70)

8 Dutogliptin.tw. (15)

9 Evogliptin.tw. (26)

10 Gemigliptin.tw. (57)

11 Gosogliptin.tw. (2)

12 Linagliptin/ (392)

13 Linagliptin.tw. (679)

14 Omarigliptin.tw. (42)

15 Saxagliptin.tw. (645)

16 Sitagliptin.tw. (2161)

17 Teneligliptin.tw. (134)

18 Trelagliptin.tw. (39)

19 Vildagliptin/ (616)

20 Vildagliptin.tw. (968)

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 (7420)

22 Glucagon-like peptide-1 receptor agonist*.tw. (1480)

23 GLP-1 receptor agonist*.tw. (1663)

24 incretin mimetic*.tw. (335)

25 albiglutide.tw. (183)

26 dulaglutide.tw. (315)

27 Exenatide/ (2353)

28 exenatide.tw. (1843)

29 Liraglutide/ (1566)

30 liraglutide.tw. (2453)

31 lixisenatide.tw. (379)

32 semaglutide.tw. (310)

33 taspoglutide.tw. (56)

34 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 (6987)

35 exp Sodium-Glucose Transporter 2 Inhibitors/ (2077)

36 sodium-glucose cotransporter-2 inhibitor*.tw. (891)

37 SGLT-2 inhibitor*.tw. (500)

38 gliflozin*.tw. (85)

39 Canagliflozin/ (571)

40 canagliflozin.tw. (892)

41 dapagliflozin.tw. (974)

42 empagliflozin.tw. (1029)

43 ertugliflozin.tw. (80)

44 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 (3960)

45 21 or 34 or 44 (16166)

46 Cardiovascular Diseases/ (144221)

47 Cardiovascular disease*.tw. (162179)

48 (CVD or ASCVD).tw. (34799)

49 coronary disease/ or coronary artery disease/ (187621)

50 (Coronary adj2 disease*).tw. (141468)

51 CAD.tw. (37441)

52 Acute Coronary Syndrome/ (14963)

53 acute coronary syndrome.tw. (20545)

54 ACS.tw. (20938)

55 exp Myocardial Infarction/ (172644)

56 myocardial infarction*.tw. (177201)

57 heart attack*.tw. (5381)

58 exp Angina Pectoris/ (43141)

59 angina.tw. (51817)

60 exp Heart Diseases/ (1108135)

61 heart disease*.tw. (161229)

62 (CHD or IHD).tw. (29532)

63 revasculari?ation.tw. (55225)

64 exp Coronary Artery Bypass/ (52210)

65 coronary artery bypass.tw. (39637)

66 CABG.tw. (17425)

67 exp Percutaneous Coronary Intervention/ (52160)

68 (Percutaneous adj2 coronary).tw. (40001)

69 PCI.tw. (24438)

70 exp Angioplasty/ (60904)

71 Angioplast*.tw. (42817)

72 Stroke/ (97832)

73 stroke*.tw. (238460)

74 Peripheral Arterial Disease/ (7200)

75 peripheral arter* disease*.tw. (13152)

76 Heart Failure/ (115420)

77 ((heart or cardiac) adj2 failure).tw. (171042)

78 (HF or CHF or CCF).tw. (57803)

79 HFpEF.tw. (2129)

80 HFrEF.tw. (1591)

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 (1749014)

82 45 and 81 (2681)

83 randomized controlled trial.pt. (500168)

84 controlled clinical trial.pt. (93531)

85 randomized.ab. (469108)

86 placebo.ab. (204791)

87 clinical trials as topic.sh. (190121)

88 randomly.ab. (326911)

89 trial.ti. (212770)

90 83 or 84 or 85 or 86 or 87 or 88 or 89 (1267648)

91 exp animals/ not humans.sh. (4670680)

92 90 not 91 (1165893)

93 82 and 92 (939)

HISTORY

Protocol first published: Issue 6, 2020

CONTRIBUTIONS OF AUTHORS

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

AM; protocol development and revisions against feedback from all co-authors.

DY: protocol development and revisions against feedback from all co-authors.

WWST: protocol 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.

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

DECLARATIONS OF INTEREST

TK: none known.

AM: none known.

DY: none known.

WWST: none known.

JM: none known,

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

YX: none known.

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.

JSWK: none known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- NIHR Cochrane Incentive Funding, UK

  This project was supported by the National Institute for Health Research, via Cochrane Incentive funding to the Heart Group. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health and Social Care