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Review Article

Cardiovascular efficacy and safety of sodium-glucose co-transporter-2 inhibitors and glucagon-like peptide-1 receptor agonists: a systematic review and network meta-analysis

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What's new?

- Sodium-glucose co-transporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1RAs) are two classes of anti-hyperglycaemic drugs with additional benefits of reducing cardiovascular risk.
- Comparisons between SGLT2 inhibitors and GLP-1RAs in cardiovascular outcome trials have not yet been carried out.
- In the present analysis, a reduction of cardiovascular risk was observed for SGLT2 inhibitors and GLP-1RAs compared to placebo in people with Type 2 diabetes, but few differences were observed between the two treatments.
- SGLT2 inhibitors reduced heart failure risk to a greater extent than GLP-1RAs and placebo.
- Results from this study can aid clinicians in selecting suitable anti-hyperglycaemic therapies for individuals with Type 2 diabetes.

Abstract

Aims To compare the cardiovascular efficacy and safety of sodium-glucose co-transporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1RAs) in adults with Type 2 diabetes.
Methods Electronic databases were searched from inception to 22 October 2018 for randomized controlled trials designed to assess the cardiovascular efficacy of SGLT2 inhibitors or GLP-1RAs with regard to a three-point composite measure of major adverse cardiovascular events (non-fatal stroke, non-fatal myocardial infarction and cardiovascular mortality). Cardiovascular and safety data were synthesized using Bayesian network meta-analyses.
Results Eight trials, including 60 082 participants, were deemed eligible for the network meta-analysis. Both SGLT2 inhibitors [hazard ratio 0.86 (95% credible interval 0.74, 1.01]) and GLP-

1RAs [hazard ratio 0.88 (95% credible interval 0.78, 0.98)] reduced the three-point composite measure compared to placebo, with no evidence of differences between them [GLP-1RAs vs SGLT2 inhibitors: hazard ratio 1.02 (95% credible interval 0.83, 1.23)]. SGLT2 inhibitors reduced risk of hospital admission for heart failure compared to placebo [hazard ratio 0.67 (95% credible interval 0.53, 0.85)] and GLP-1RAs [hazard ratio 0.71 (95% credible interval 0.53, 0.93)]. No differences were found between the two drug classes in non-fatal stroke, non-fatal myocardial infarction, cardiovascular mortality, all-cause mortality or safety outcomes.

Conclusions SGLT2 inhibitors and GLP-1RAs reduced the three-point major adverse cardiovascular event risk compared to placebo, with no differences between them. Compared with GLP-1RAs and placebo, SGLT2 inhibitors led to a larger reduction in hospital admission for heart failure risk.

Introduction

Type 2 diabetes is a chronic cardiometabolic condition characterized by high blood glucose levels and is associated with an increased risk of myocardial infarction, stroke, heart failure and cardiovascular death [1–3].

Sodium-glucose co-transporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1RAs) are two new classes of glucose-lowering drug which, in randomized controlled trials (RCTs) in people with Type 2 diabetes, have been shown to reduce the risk of cardiovascular complications [4]. The mechanisms of action of these two classes in reducing blood glucose levels differ, with further dissimilarities within the GLP-1RA class. SGLT2 inhibitors reduce blood glucose levels by inhibiting the re-absorption of glucose in the kidneys through the SGLT2 receptors [5], while GLP-1RAs mimic the action of the GLP-1 hormone by binding to and activating the GLP-1 receptors, which promote the release of insulin in response to high blood glucose levels [6]. GLP-1RAs differ within the class in terms of duration of action (long-acting, e.g. exenatide once weekly or short-acting, e.g. exenatide once daily) as well as the molecular backbone of the drug (exendin-based, e.g. lixisenatide and exenatide, or non-exendin based analogues of human GLP-1, e.g. liraglutide and semaglutide).

In most guidelines, SGLT2 inhibitors or GLP-1RAs are recommended for the treatment of hyperglycaemia in Type 2 diabetes in combination with other glucose-lowering drugs, after monotherapy and dual therapy failure [4,7–9]. Pairwise meta-analyses, conducted to assess the cardiovascular effects of SGLT2 inhibitors or GLP-1RAs, suggest that both drug classes provide a reduction in the risk of cardiovascular outcomes compared with placebo/control [10–13]; however, to date, there have been no direct (head-to-head) trials specifically designed to compare SGLT2 inhibitors and GLP-1RAs in terms of cardiovascular outcomes. When direct comparisons are unavailable, network meta-analysis allows the synthesis and comparison of treatments across available evidence to estimate direct and indirect comparisons of interest [14,15]. Using a network

meta-analysis, we aimed to investigate the cardiovascular efficacy and safety of SGLT2 inhibitors compared with GLP-1RAs in adults with Type 2 diabetes.

Methods

The present study was performed using a pre-specified protocol (Table S1) and according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Network Meta-Analyses (PRISMA-NMA) guidelines for conducting and reporting systematic reviews and network meta-analyses (Table S2) [16,17].

Data sources and searches

PubMed, the Cochrane Register of Controlled Trials (CENTRAL) and all databases in the ISI Web of Science (i.e. Web of Science Core Collection, MEDLINE, SciELO, Russian Science Citation Index and KCI-Korean Journal Database) were searched from inception to 22 October 2018 for RCTs published in any language. The search strategy included key search terms for SGLT2 inhibitor- and GLP-1RA-specific drug names, a strategy which was updated from previous systematic reviews [18–20]; the full search strategy is reported in File S1. The reference lists of included papers were scanned manually to search for further relevant studies.

Study selection

We included RCTs of any duration, with at least two arms consisting of intervention(s) or control, conducted in adults (age ≥18 years) with Type 2 diabetes and specifically designed to assess cardiovascular safety or efficacy of SGLT2 inhibitors or GLP-1RAs. Interventions in this analysis included all specific drug names defined in the search strategy, while the control was placebo. Trials were included regardless of background treatments given to participants. Studies were excluded if the primary outcome of this meta-analysis, three-point major adverse cardiovascular events (MACE; a composite measure of the number of participants to have a first MACE, including non-fatal stroke, non-fatal myocardial infarction or cardiovascular mortality) was not available. Relevant studies were identified by two independent reviewers, with discrepancy resolved by arbitration.

Data extraction and quality assessment

For each RCT, arm-specific data on the number of participants with an event included in the three-point MACE were extracted. Secondary outcomes included the number of participants who experienced each component of the three-point MACE (non-fatal stroke, non-fatal myocardial infarction and cardiovascular mortality), all-cause mortality and hospital admissions for heart failure. Safety outcomes included the number of participants reporting at least one hypoglycaemic event, bone fracture, amputation, urinary tract infection, pancreatitis or diabetic ketoacidosis. Data were extracted according to the intention-to-treat principle by two independent reviewers using standardized pre-defined forms. This included: first author; clinicaltrials.gov trial number; year of publication; median

length of trial follow-up (years); sample size; intervention(s); and baseline characteristics of participants [age (years), sex (%), duration of diabetes (years) and HbA_{1c} (mmol/mol, %)]. For cardiovascular and safety outcomes, the numbers of participants randomized and reporting an event in each arm of the trial were extracted. Risk of bias was assessed using the Cochrane risk of bias assessment tool [21].

Data synthesis and analysis

Because of the limited number of studies available, it was not possible to compare individual drugs; therefore, the network meta-analysis consisted of three nodes for each outcome analysed: SGLT2 inhibitors, GLP-1RAs and placebo. Studies with multiple arms of the same drug with different doses were combined into a single arm for each drug. A continuity correction factor of 0.5 was added to trials when one arm reported zero events. For each outcome, a random-effect pairwise meta-analysis was initially conducted within each direct treatment comparison in STATA-MP (version 15.1, StataCorp, College Station, TX, USA). Heterogeneity was assessed using I^2 values. Higher values of I^2 (≥75%) indicated higher levels of heterogeneity, which could suggest these studies should not be combined into a single node in the network meta-analysis.

A network plot for the primary outcome was produced in STATA to visually represent available comparisons of treatments. A Bayesian network meta-analysis was conducted in WINBUGS (version 1.4.3), where random-effects generalized linear models were fitted using a Markov Chain Monte Carlo simulation method. Vague priors were used for all parameters. When analysing cardiovascular outcomes, to estimate hazard ratios (HRs) between treatment arms and overall treatment effects, assuming constant hazard over the follow-up time in each arm of each trial, a binomial likelihood with a complementary log link function was used as it accounted for follow-up time [22]. For safety outcomes, a logistic regression model was used which consisted of a binomial likelihood with a logit link to estimate odds ratios for between-treatment comparisons [22]. To assess differences in the primary outcome within the GLP-1RA class, subgroup analysis included splitting this node in the network in terms of both the GLP-1RAs' duration of action (i.e. long- vs short-acting) and the molecular backbone of the drug (exendin vs non-exendin based). Placebo was used as the treatment reference for all analyses. For each outcome, median effect estimates, along with 95% credible intervals (CrIs), were reported. Publication bias was assessed using 'comparison-adjusted' funnel plots [23], which are scatter plots of an estimate for the difference between the observed treatment effect for each trial and a comparison-specific treatment effect. In these plots, symmetry suggests the absence of small-study effects and publication bias.

For each model fitted, the simulation ran for 50 000 samples with a burn-in length of 10 000 simulations that were discarded. Treatments were ranked according to greatest improvement in cardiovascular and safety outcomes; this is the probability (reported in percentage) of a particular treatment being the most effective. History plots and trace plots were assessed to check convergence

of models, and auto-correlation plots were assessed for correlations of parameters between simulations for each model. The chain was thinned if visual inspection of autocorrelation plots suggested possible autocorrelation. For each outcome analysed, the residual deviance was calculated and compared against the number of data-points in each study. Small differences between the residual deviance and number of data-points indicated a good fit of the model. Various sensitivity analyses were conducted to assess the robustness of results for all outcomes, which included varying choices of vague prior distributions, varying burn-in and simulation length and changing initial values for parameters.

Results

Study characteristics

A total of 16 981 reports were identified using the search strategy; after removal of duplicates, 8847 reports titles and abstracts were screened, of which 20 were selected for full-text screening (see Fig. S1 for PRISMA diagram). Of these, 13 were excluded (reasons are reported in Fig. S1), resulting in seven reports (eight RCTs) included in the quantitative analysis (Table 1): EMPA-REG OUTCOME study [24]; CANVAS [25]; CANVAS-R [25]; ELIXA [26]; LEADER [27]; SUSTAIN-6 [28]; EXSCEL [29]; and the HARMONY study [30]. Although the CANVAS and CANVAS-R trials were run separately, the results were published in a single report. Overall, 60 082 participants were included in the analysis with median follow-up for included RCTs ranging between 1.6 and 5.7 years (Table 1). The characteristics of participants in these trials were similar. The mean age of participants ranged between 60 and 65 years, with the mean duration of Type 2 diabetes ranging between 9 and 14 years. There was a higher percentage of men in the EMPA-REG OUTCOME trial (77.4%) compared with the other trials (range 60.7–69.5%). The mean baseline HbA_{1c} measurements were broadly similar across all trials [range 61–72 mmol/mol (7.7–8.7%)]. The numbers of participants randomized and reporting an event for each outcome in each trial are shown in Table S3.

Risk-of-bias assessment included random sequence generation, allocation concealment, blinding of participants and personnel, blinding outcome assessment, incompleteness of data and reporting biases. All domains were judged as low risk of bias for all trials included in the analyses (Table S4).

Primary outcome: three-point MACE

Pairwise meta-analysis showed reductions in the three-point MACE for SGLT2 inhibitors and GLP-1RAs when compared with placebo (Fig. S2). There was little heterogeneity for SGLT2 inhibitors compared with placebo (I^2=0.0%), while heterogeneity was higher for GLP-1RAs, with I^2 being 58.6%.

Figure 1 shows the network plot for the three-point MACE. When compared with placebo**,** network meta-analysis results indicated three-point MACE reduction for both SGLT2 inhibitors [HR 0.86

(95% CrI 0.74, 1.01)] and GLP-1RAs [HR 0.88 (95% CrI 0.78, 0.98); Table 2], with slightly greater reductions for SGLT2 inhibitors (58.8% probability of being the most effective treatment; Fig. S3); however, there was no evidence of difference between GLP-1RAs and SGLT2 inhibitors [GLP-1RAs vs SGLT2 inhibitors: HR 1.02 (95% CrI 0.83, 1.23)].

Secondary outcomes

Pairwise meta-analysis results for secondary outcomes are shown in Fig. S2.

There was no evidence in network meta-analyses of differences when GLP-1RAs and SGLT2 inhibitors were compared against placebo and against each other, for most outcomes; however, a reduction in cardiovascular mortality, all-cause mortality and hospital admissions for heart failure comparing SGLT2 inhibitors vs placebo [HR 0.77 (95% CrI 0.61, 0.99), HR 0.80 (95% CrI 0.68, 0.95) and HR 0.67 (95% CrI 0.53, 0.85), respectively] was observed; and a lower risk for SGLT2 inhibitors vs GLP-1RAs in hospital admissions for heart failure [HR 0.71 (95% CrI 0.53, 0.93); Table 2]. SGLT2 inhibitors had the highest probability of being the most effective treatment in reducing hospital admission for heart failure (98.7%; Fig. S3).

Safety outcomes

The CANVAS programme only recorded adverse events for the CANVAS study rather than separately for the two studies included. The only safety outcomes analysed for the CANVAS-R included serious adverse events and adverse events leading to discontinuation of the trial, thus resulting in limited safety data availability for this particular trial.

Pairwise meta-analysis results for safety outcomes are shown in Fig. S4. In the network meta-analyses, no evidence for differences were found when GLP-1RAs and SGLT2 inhibitors were compared against placebo and against each other for all safety outcomes investigated (Table S5). Treatment ranking is shown in Fig. S5.

Subgroup analysis

The treatment analysed in the ELIXA trial was lixisenatide, which is a short-acting GLP-1RA given once daily, whereas the LEADER, SUSTAIN-6, EXSCEL and HARMONY trials analysed long-acting GLP-1RAs (liraglutide, semaglutide, exenatide once weekly and albiglutide, respectively). When compared with placebo, estimates from the network meta-analysis indicated an HR of 0.85 (95% CrI 0.73, 0.95) for long-acting GLP-1RAs and 1.02 (95% CrI 0.80, 1.30) for short-acting GLP-1RAs (Table S6); however, no differences were observed when long- and short-acting GLP-1RAs were compared with SGLT2 inhibitors.

The ELIXA and EXSCEL trials analysed the effect of lixisenatide and exenatide once weekly, respectively: these are exendin-based GLP-1RAs. Liraglutide, semaglutide and albiglutide, used in the LEADER, SUSTAIN-6 and HARMONY trials, respectively, are non-exendin-based. When compared

with placebo, network meta-analysis results indicated an HR of 0.96 (95% CrI 0.84, 1.12) for exendin-based GLP-1RAs and 0.81 (95% CrI 0.71, 0.92) for non-exendin-based GLP-1RAs (Table S6). There was no evidence of any differences when exendin- and non-exendin-based GLP-1RAs were compared with SGLT2 inhibitors.

Sensitivity analysis

Changes in the prior distributions of the standard deviations for the trial-specific HRs and pooled HRs between nodes showed little to no change in overall treatment effects for all outcomes (data not shown). Similarly, changes in burn-in and sample length of simulations and starting values showed few changes in overall treatment effects (data not shown).

Model assessments

There were few differences between the residual deviances calculated for each model and the number of unconstrained data-points (i.e. the sum of the total number of arms from all trials), suggesting all models provided an adequate fit (Table S7). 'Comparison-adjusted' funnel plots showed no conclusive evidence of publication bias for all outcomes (Figs S6 and S7).

Discussion

Although several RCTs assessed the risk of cardiovascular events for SGLT2 inhibitors or GLP-1RAs compared with placebo in individuals with Type 2 diabetes, to date there have been no direct head-to-head RCTs either completed or currently on-going [31,32]. Using a network meta-analysis approach, this study allowed us to combine evidence from multiple RCTs comparing SGLT2 inhibitors or GLP-1RAs with placebo in order to obtain an indirect estimate of the cardiovascular effects of GLP-1RAs compared with SGLT2 inhibitors.

Based on eight RCTs enrolling 60 082 participants with Type 2 diabetes, our findings indicate that both SGLT2 inhibitors and GLP-1RAs reduce three-point MACE risk when compared to placebo, with no differences between the two classes. Similarly, no differences were found between SGLT2 inhibitors and GLP-1RAs when looking both at each component of three-point MACE separately (i.e. non-fatal stroke, non-fatal myocardial infarction and cardiovascular mortality) and at all-cause mortality.

Notably, SGLT2 inhibitors performed better than GLP-1RAs in reducing the risk of hospitalization for heart failure: the risk of hospital admission for heart failure was 33% lower with SGLT2 inhibitors compared to placebo and 29% lower compared to GLP-1RAs, with SGLT2 inhibitors having an overall probability of ~99% of being the most effective treatment for this outcome. Hospital admissions for heart failure are rapidly becoming an important factor to consider in Type 2 diabetes [33]. Often, trials do not specify the number of participants with incident heart failure hospitalization

as a pre-specified outcome of interest, therefore, results are sparse [33,34]. A meta-analysis of GLP-1RAs suggested no evidence of reductions in heart failure risk for GLP-1RAs vs other anti-hyperglycaemic medications [34]. Reductions in hospital admissions for heart failure have been observed in non-randomized studies comparing SGLT2 inhibitors. In a retrospective analysis, treatment with SGLT2 inhibitors was associated with a lower risk of hospitalization for heart failure compared with other oral glucose-lowering drugs [35]. This effect remained even after excluding participants on GLP-1RAs at baseline [35]. This association was supported in the CVD-REAL 2 study, where a 50% reduction was observed for SGLT2 inhibitors vs other oral glucose-lowering drugs [36].

The beneficial effect of SGLT2 inhibitors on heart function is related to a number of biological mechanisms. A possible mechanism of action could be the natriuretic and hypovolaemic effect of SGLT2 inhibitors [37,38]. By excreting sodium in the urine, blood pressure decreases with subsequent reduced circulatory load and increased ventricular functions [37,38]. Additionally, SGLT2 inhibitor treatment is potentially associated with an increased production of ketones (increasing glucagon and reducing insulin synthesis), which could improve myocardial energy use, thus reducing the risk of heart failure [37]. Further, the decrease in plasma volume and its associated increase in haematocrit levels could improve oxygen delivery to the heart [37,39].

When looking at the safety outcomes, there was no evidence of differences in the effect of GLP-1RAs and SGLT2 inhibitors for hypoglycaemic events, bone fractures, amputations, pancreatitis, urinary tract infection and diabetic ketoacidosis; however, data collected on some of these outcomes in the included RCTs were very sparse, thus precluding a firm conclusion. Furthermore, although subgroup analysis was carried out and some differences were observed, because of the limited number of studies in each node of the network it was not possible to analyse whether duration of action or molecular formulation of GLP-1RAs influenced the results obtained from the network meta-analysis. When more data become available, it would be interesting to further test whether the molecular formulation and duration of action of GLP-1RAs may have an impact on cardiovascular outcomes in patients with Type 2 diabetes.

Since running the search for the present network meta-analysis, an additional paper has been published reporting the results of the DECLARE-TIMI study (NCT01730534), which looked at the effect of the SGLT2 inhibitor dapagliflozin on cardiovascular outcomes in people with Type 2 diabetes [40]. Although the primary outcome of that study was three-point MACE, the definition differed from those available in the trials included in the present analysis as the DECLARE study additionally included fatal stroke and myocardial infarction in its three-point MACE definition. The DECLARE study reported no differences between dapagliflozin and placebo in three-point MACE reduction; however, it showed a reduction in the risk of heart failure associated with SGLT2 inhibitor treatment, consistent with the effect estimates from the present network meta-analysis.

A previous network meta-analysis by Zheng *et al*. [41] assessed cardiovascular outcome differences among dipeptidyl-peptidase-4 inhibitors, SGLT2 inhibitors and GLP-1RAs, finding evidence that SGLT2 inhibitors and GLP-1RAs reduced cardiovascular risk; however, the authors included all phase III trials as well as cardiovascular outcome trials, potentially resulting in higher heterogeneity. Moreover, most of the included RCTs were specifically designed to assess the efficacy of these treatments in terms of intermediate biomarker (i.e. HbA_{1c}) instead of cardiovascular outcomes. By only including RCTs designed for cardiovascular outcomes in the present study, the similarity and transitivity assumption of network meta-analysis was strengthened. Despite the differences in the inclusion criteria, the results of the study by Zheng *et al.* [41] are generally in line with the present findings, showing no differences between GLP-1RAs and SGLT2 inhibitors for cardiovascular mortality, all-cause mortality, stroke, myocardial infarction or hypoglycaemia.

To our knowledge, the present study is the first analysis comparing the cardiovascular effects of SGLT2 inhibitors and GLP-1RAs by collecting data from cardiovascular outcome trials, however, it has some limitations that need to be recognized. Firstly, as there were no direct head-to-head comparisons of SGLT2 inhibitors vs GLP-1RAs for cardiovascular outcomes, it was not possible to assess inconsistency of the network. It is possible that estimates from indirect comparison may not reflect what would have been found if head-to-head trials were conducted; however, estimates from the network meta-analyses lay within the CIs from the pairwise analyses conducted, suggesting few inconsistencies.

Secondly, only eight trials were included. As data were sparse and there were not many studies, the credible intervals were in some cases wide, particularly for some safety outcomes which have not been systematically ascertained because they are drug-specific (for example, pancreatitis for GLP-1RAs and diabetic ketoacidosis for SGLT2 inhibitors). For some outcomes, data were unavailable which could be attributable to outcomes not being measured rather than events not occurring. Core outcome sets were defined in the protocol of the RCTs, which aimed to reduce selective reporting biases, but in many cases the unavailability of data was in safety (adverse events) outcomes. Despite sparse data for some outcomes, all models appeared to converge from visual analysis of history and trace plots, and the estimates from pairwise analyses and network meta-analyses in the present study were similar to those from meta-analyses conducted previously [10–13,41]. Furthermore, it was not possible to assess individual treatments in the network but only combined in treatment groups; however, by comparing the class effects of treatments, rather than individual treatment effects, statistical power was increased.

Thirdly, high heterogeneity was estimated within SGLT2 inhibitors for bone fractures and amputations. Although it was not possible to split this node because of the limited amount of studies, heterogeneity could possibly have been introduced by the CANVAS study when analysing bone

fracture events and by the EMPA-REG OUTCOME study when analysing amputation events owing to differences in estimates in comparison with other RCTs.

Fourthly, a composite measure of cardiovascular events was used as the primary outcome. The use of composite outcomes in cardiovascular clinical trials is usual and ensures sufficient statistical power [42]. However, as certain components in the outcome may account for a large number of events, this can lead to imbalances and make the interpretation difficult [42,43]; currently, there is limited available evidence on how to correct for these imbalances [43].

Lastly, background therapy and populations differed slightly among various trials. For example, the EMPA-REG OUTCOME study included participants with already established cardiovascular disease, while some of the other studies included participants with cardiovascular risk factors. Additionally, standard care was continued on top of interventions to which participants were randomized, which could potentially be different among trials. Although there were differences in standard care, it is unlikely that they have affected estimates as these were established prior to baseline. Cardiovascular outcome RCTs are currently being conducted and have not yet been published, such as the REWIND (NCT01394952) and ITCA 650 (NCT01455896), which are investigating the effect of dulaglutide and ITCA 650 (an implantable device with exenatide) [31]. Future work may include updating this network meta-analysis by including these trials.

In conclusion, available evidence indicates that both SGLT2 inhibitors and GLP-1RAs lower the risk of three-point MACE in comparison to placebo, with no differences between them. SGLT2 inhibitors reduced the risk of hospital admissions for heart failure to a greater extent than did GLP-1RAs, in line with their pharmacological properties. Although some benefits have been observed for these treatments, further risk factors, such as cardiometabolic and renal risk, would need to be considered in order to make an informed decision on which treatment would provide the greater benefit to the individual patient.

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Competing interests

K.K. has acted as a consultant and speaker for Novartis, Novo Nordisk, Sanofi-Aventis, Lilly and Merck Sharp & Dohme. K.K. has received grants in support of investigator and investigator-initiated trials from Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, Merck Sharp & Dohme, Pfizer and Boehringer Ingelheim, and has served on advisory boards for Novo Nordisk, Sanofi-Aventis, Lilly

and Merck Sharp & Dohme. M.D. has acted as consultant, speaker and advisory board member for Novo Nordisk, Sanofi-Aventis, Lilly, Merck Sharp & Dohme, Boehringer Ingelheim, AstraZeneca and Janssen. She has acted as a speaker for Mitsubishi Tanabe Pharma Corporation and has received grants in support of investigator and investigator initiated trials from Novo Nordisk, Sanofi-Aventis and Lilly. S.S. has acted as consultant, speaker and advisory board member for Novo Nordisk, Sanofi-Aventis, Lilly, Merck Sharp & Dohme, Boehringer Ingelheim, Amgen, AstraZeneca and Janssen, NAPP and Novartis. S.S. has received research grants from Jansen.

References

1. Ferrannini E, DeFronzo RA. Impact of glucose-lowering drugs on cardiovascular disease in type 2 diabetes. *Eur Heart J* 2015;**36**:2288–2296.
2. Gu K, Cowie CC, Harris MI. Diabetes and decline in heart disease mortality in US adults. *JAMA* 1999;**281**:1291–1297.
3. Shah AD, Langenberg C, Rapsomaniki E, Denaxas S, Pujades-Rodriguez M, Gale CP *et al.* Type 2 diabetes and incidence of cardiovascular diseases: a cohort study in 1· 9 million people. *Lancet Diabetes Endocrinol*. 2015;**3**:105–113.
4. Pharmacologic approaches to glycemic treatment: Standards of medical care in Diabetes - 2018. American Diabetes Association. *Diabetes Care* 2018;**41**(Suppl. 1):S73–S85.
5. Faillie JL. Pharmacological aspects of the safety of gliflozins. *Pharmacol Res* 2017;**118:**71–81.
6. Tran KL, Park YI, Pandya S, Muliyil NJ, Jensen BD, Huynh K *et al*. Overview of glucagon-like peptide-1 receptor agonists for the treatment of patients with type 2 diabetes. *Am Health Drug Benefits* 2017;**10**:178–188.
7. National Institute for Health and Care Excellence. Type 2 diabetes in adults: management (Last updated: May 2017): December 2015. Available at https://www.nice.org.uk/guidance/ng28. Last accessed 22 May 2018.
8. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M *et al.* Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2015;**38**:140–149.
9. Garber AJ, Abrahamson MJ, Barzilay JI, Blonde L, Bloomgarden ZT, Bush MA *et al.* Consensus statement by The American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm - 2018 Executive Summary. *Endocr Pract* 2018;**24**:91–120.
10. Bethel MA, Patel RA, Merrill P, Lokhnygina Y, Buse JB, Mentz RJ *et al.* Cardiovascular outcomes with glucagon-like peptide-1 receptor agonists in patients with type 2 diabetes: a meta-analysis. *Lancet Diabetes Endocrinol*. 2017;**6**:105–113.

11. Zhang XL, Zhu QQ, Chen YH, Li XL, Chen F, Huang JA *et al.* Cardiovascular safety, long-term noncardiovascular safety, and efficacy of sodium -glucose cotransporter 2 inhibitors in patients with type 2 diabetes mellitus: a systemic review and meta-analysis with trial sequential analysis. *J Am Heart Assoc* 2018;**7**(2):e007165.

12. Rådholm K, Wu JHY, Wong MG, Foote C, Fulcher G, Mahaffey KW *et al.* Effects of sodium-glucose cotransporter-2 inhibitors on cardiovascular disease, death and safety outcomes in type 2 diabetes - a systematic review. *Diabetes Res Clin Pract* 2018;**140**:118–128.

13. Wu JH, Foote C, Blomster J, Toyama T, Perkovic V, Sundström J *et al.* Effects of sodium-glucose cotransporter-2 inhibitors on cardiovascular events, death, and major safety outcomes in adults with type 2 diabetes: a systematic review and meta-analysis. *Lancet Diabetes Endocrinol*. 2016;**4**:411–419.

14. Higgins JP, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]: The Cochrane Collaboration; 2011. Available at http://handbook.cochrane.org. Last accessed XX Xxxx XXXX.

15. Tonin FS, Rotta I, Mendes AM, Pontarolo R. Network meta-analysis: a technique to gather evidence from direct and indirect comparisons. *Pharm Pract (Granada)* 2017;**15**:943.

16. Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C *et al.* The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med* 2015;**162**:777–784.

17. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M *et al.* Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015;349.

18. Htike ZZ, Zaccardi F, Papamargaritis D, Webb DR, Khunti K, Davies MJ. Efficacy and safety of glucagon-like peptide-1 receptor agonists in type 2 diabetes: a systematic review and mixed-treatment comparison analysis. *Diabetes Obes Metab* 2017;**19**:524–536.

19. Zaccardi F, Htike ZZ, Webb DR, Khunti K, Davies MJ. Benefits and harms of once-weekly glucagon-like peptide-1 receptor agonist treatments: a systematic review and network meta-analysis. *Ann Intern Med* 2016;**164**:102–113.

20. Zaccardi F, Webb DR, Htike ZZ, Youssef D, Khunti K, Davies MJ. Efficacy and safety of sodium-glucose co-transporter-2 inhibitors in type 2 diabetes mellitus: systematic review and network meta-analysis. *Diabetes Obes Metab* 2016;**18**:783–794.

21. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD *et al.* The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;**343**:d5928.

22. Dias S, Sutton AJ, Ades AE, Welton NJ. Evidence synthesis for decision making 2: a generalized linear modeling framework for pairwise and network meta- analysis of randomized controlled trials. *Med Decis Making* 2013;**33**:607–617.

23. Chaimani A, Higgins JPT, Mavridis D, Spyridonos P, Salanti G. Graphical tools for network meta-analysis in STATA. *PloS One* 2013;**8**(10):e76654.

24. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S *et al.* Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015;**373**:2117–2128.
25. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N *et al.* Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017;**377**:644–657.
26. Pfeffer MA, Claggett B, Diaz R, Dickstein K, Gerstein HC, Kober LV *et al.* Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. *N Engl J Med* 2015;**373**:2247–2257.
27. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA *et al.* Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2016;**375**:311–322.
28. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jodar E, Leiter LA *et al.* Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2016;**375**:1834–1844.
29. Holman RR, Bethel MA, Mentz RJ, Thompson VP, Lokhnygina Y, Buse JB *et al.* Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2017;**377**:1228–1239.
30. Hernandez AF, Green JB, Janmohamed S, D'Agostino RB, Sr, Granger CB, Jones NP *et al.* Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. *Lancet* 2018; **392**:1519–1529.
31. Schnell O, Rydén L, Standl E, Ceriello A. Updates on cardiovascular outcome trials in diabetes. *Cardiovasc Diabetol* 2017;**16**:128.
32. Anderson SL, Marrs JC. Antihyperglycemic medications and cardiovascular risk reduction. *Eur Endocrinol* 2017;**13**:86.
33. McMurray JJ, Gerstein HC, Holman RR, Pfeffer MA. Heart failure: a cardiovascular outcome in diabetes that can no longer be ignored. *Lancet Diabetes Endocrinol*. 2014;**2**:843–851.
34. Li L, Li S, Liu J, Deng K, Busse JW, Vandvik PO *et al.* Glucagon-like peptide-1 receptor agonists and heart failure in type 2 diabetes: systematic review and meta-analysis of randomized and observational studies. *BMC Cardiovasc Disord* 2016;**16**:91.
35. Kosiborod M, Cavender MA, Fu AZ, Wilding JP, Khunti K, Holl RW *et al.* Lower risk of heart failure and death in patients initiated on sodium-glucose cotransporter-2 inhibitors versus other glucose-lowering drugs clinical perspective: the CVD-REAL Study (Comparative Effectiveness of Cardiovascular Outcomes in New Users of Sodium-Glucose Cotransporter-2 Inhibitors). *Circulation* 2017;**136**:249–259.
36. Kosiborod M, Lam CS, Kohsaka S, Kim DJ, Karasik A, Shaw J *et al.* Cardiovascular events associated with SGLT-2 inhibitors versus other glucose-lowering drugs: the CVD-REAL 2 study. *J Am Coll Cardiol* 2018;**71**:2628–2639.
37. Lytvyn Y, Bjornstad P, Udell JA, Lovshin JA, Cherney DZI. Sodium glucose cotransporter-2 inhibition in heart failure: potential mechanisms, clinical applications, and summary of clinical trials. *Circulation* 2017;**136**:1643–1658.

38. Inzucchi SE, Zinman B, Fitchett D, Wanner C, Ferrannini E, Schumacher M *et al.* How Does Empagliflozin Reduce Cardiovascular Mortality? Insights From a Mediation Analysis of the EMPA-REG OUTCOME Trial. *Diabetes Care* 2018;**41**:356–363.
39. Martens P, Mathieu C, Verbrugge FH. Promise of SGLT2 Inhibitors in Heart Failure: Diabetes and Beyond. *Curr Treat Options Cardiovasc Med* 2017;**19**:23.
40. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A *et al.* Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med* 2018; doi: 10.1056/NEJMoa1812389. [Epub ahead of print].
41. Zheng SL, Roddick AJ, Aghar-Jaffar R, Shun-Shin MJ, Francis D, Oliver N *et al.* Association between use of sodium-glucose cotransporter 2 inhibitors, glucagon-like peptide 1 agonists, and dipeptidyl peptidase 4 inhibitors with all-cause mortality in patients with type 2 diabetes: a systematic review and meta-analysis. *JAMA* 2018;**319**:1580–1591.
42. Marx N, McGuire DK, Perkovic V, Woerle HJ, Broedl UC, von Eynatten M *et al.* Composite Primary End Points in Cardiovascular Outcomes Trials Involving Type 2 Diabetes Patients: Should Unstable Angina Be Included in the Primary End Point? *Diabetes Care* 2017;**40**:1144–1151.
43. Armstrong PW, Westerhout CM. Composite end points in clinical research: a time for reappraisal. *Circulation* 2017;**135**:2299–2307.

Supporting information

Additional Supporting Information may be found in the online version of this article:

File S1 Search strategies used for each electronic database searched.

Table S1. Protocol for systematic review and network meta-analysis following the PRISMA-P guideline.
Table S2. PRISMA NMA checklist of items to include when reporting a systematic review involving a network meta-analysis.
Table S3. Number of participants randomised and to have an event in each trial for each outcome analysed.
Table S4. Risk of bias assessment table.
Table S5. Comparison of sodium-glucose co-transporter-2 inhibitors (SGLT-2is), glucagon-like peptide-1 receptor agonists (GLP-1RAs) and placebo concerning safety outcomes.
Table S6. Subgroup analysis comparing sodium glucose co-transporter 2 inhibitors (SGLT-2is) and glucagon-like peptide-1 receptor agonists (GLP-1RAs), split by duration of action and molecular formulation, for 3-point major adverse cardiovascular events.
Table S7. Residual deviance for each outcome analysed to assess model fit.
Figure S1. PRISMA flow diagram for study inclusion.

Figure S2. Pairwise forest plots for primary and secondary cardiovascular outcomes.

Figure S3. Bar charts of ranking of treatments (%) for primary and secondary cardiovascular outcomes.

Figure S4. Pairwise forest plots for safety outcomes.

Figure S5. Bar charts of ranking of treatments (%) for safety outcomes.

Figure S6. Comparison adjusted funnel plots for primary and secondary cardiovascular outcomes.

Figure S7. Comparison adjusted funnel plots for safety outcomes.

FIGURE 1 Network plots for three-point major adverse cardiovascular events (MACE). Circles (nodes) represent treatments. Solid lines between nodes (edges) represent direct treatment comparison available from trials and numbers on edges represent the number of trials that had these comparisons available. Dashed line represents indirect treatment comparison estimated by the network. GLP-1RA, glucagon-like peptide-1 receptor agonist; SGLT2, sodium-glucose co-transporter 2.

Table 1 Study characteristics of included trials

First author	Trial name	Clinical trial number	Year	Median follow-up, years	Control	Intervention	Total participants randomized	Ag (Y
Zinman	EMPA-REG OUTCOME [24]	NCT 01131676	2015	3.1	PLA	EMPA (10mg-25mg)	7020	63.
Neal	CANVAS [25]	NCT 01032629	2017	5.7	PLA	CANA (100mg-300mg)	4330	62.
Neal	CANVAS-R [25]	NCT 01989754	2017	2.1	PLA	CANA (100mg-300mg)	5812	64.
Pfeffer	ELIXA [26]	NCT 01147250	2015	2.1	PLA	LIX (10mcg-20mcg)	6068	60.
Marso	LEADER [27]	NCT 01179048	2016	3.8	PLA	LIR (1.8mg)	9340	64.
Marso	SUSTAIN-6 [28]	NCT 01720446	2016	2.1	PLA	SEM (0.5mg-1.0mg)	3297	64.
Holman	EXSCEL [29]	NCT 01144338	2017	3.2	PLA	ExQW (2mg)	14 752	62.
Hernandez	HARMONY [30]	NCT 02465515	2018	1.6	PLA	ALB (30mg-50mg)	9463	59.

ALB, albiglutide; CANA, canagliflozin; EMPA, empagliflozin; ExQW, exenatide once weekly; LIR, liraglutide; LIX, lixisenatide; mg, milligrams; mcg, micrograms; PLA, placebo; SEM, semaglutide.

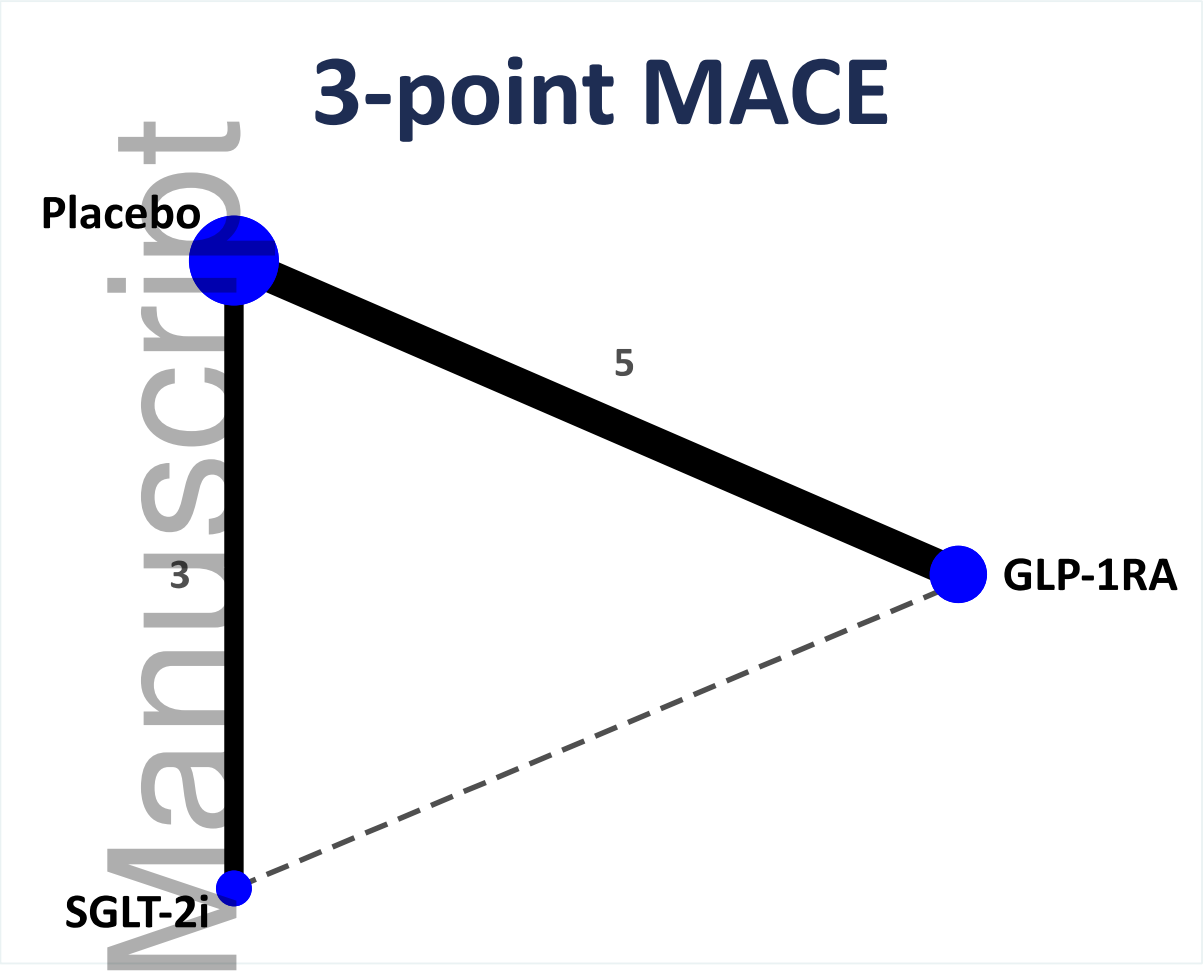
Table 2 Comparison of sodium-glucose co-transporter-2 inhibitors, glucagon-like peptide-1 receptor analogues and placebo on cardiovascular outcomes

Three-point MACE		
		GLP-1RAs
	SGLT2 inhibitors	1.02 (0.83, 1.23)
Placebo	0.86 (0.74, 1.01)	0.88 (0.78, 0.98)
Non-fatal stroke		
		GLP-1RAs
	SGLT2 inhibitors	0.86 (0.55, 1.30)
Placebo	1.03 (0.74, 1.43)	0.89 (0.66, 1.15)
Non-fatal myocardial infarction		
		GLP-1RAs
	SGLT2 inhibitors	1.08 (0.82, 1.37)
Placebo	0.87 (0.72, 1.07)	0.94 (0.80, 1.08)
Cardiovascular mortality		
		GLP-1RAs
	SGLT2 inhibitors	1.18 (0.86, 1.59)
Placebo	0.77 (0.61, 0.99)	0.91 (0.76, 1.09)
All-cause mortality		
		GLP-1RAs
	SGLT2 inhibitors	1.13 (0.92, 1.39)
Placebo	0.80 (0.68, 0.95)	0.90 (0.80, 1.03)

Hospital admissions for heart failure		
		GLP-1RAs
	SGLT2 inhibitors	1.41 (1.07, 1.90)
Placebo	0.67 (0.53, 0.85)	0.94 (0.80, 1.13)

CrI, credible interval; GLP-1RA, glucagon-like peptide-1 receptor agonist; HR, hazard ratio; MACE, major adverse cardiovascular events; SGLT2, sodium-glucose co-transporter-2.

Comparisons are reported as HR (95% CrI) for column vs row (i.e. for three-point MACE: GLP-1RAs vs placebo HR 0.88 (95% CrI 0.78, 0.98).



Circles (nodes) represent treatments. Solid lines between nodes (edges) represent direct treatment comparison available from trials and numbers on edges represent the number of trials that had these comparisons available. Dashed line represents indirect treatment comparison estimated by the network.

Abbreviations: GLP-1RA, glucagon-like peptide-1 receptor agonist; MACE, major cardiovascular adverse events; SGLT-2i, sodium-glucose co-transporter 2 inhibitor.

Figure 1 Network plots for 3-point MACE

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