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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Novelty Statement

- Sodium-glucose co-transporter 2 inhibitors (SGLT-2is) and glucagon-like peptide-1 receptor agonists (GLP-1RAs) are two classes of anti-hyperglycaemic drugs with additional benefits in reducing cardiovascular risks.
- Comparisons between SGLT-2is and GLP-1RAs in cardiovascular outcome trials have not yet been done.
- In this analysis, a reduction of cardiovascular risk was observed for SGLT-2is and GLP-1RAs compared to placebo in people with type 2 diabetes but little differences were observed between the two treatments.
- SGLT-2is reduced heart failure risk to a greater extent compared to 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 inhibitors (SGLT-2is) and glucagon-like peptide-1 receptor agonists (GLP-1RAs) in adults with type 2 diabetes.

Methods: Electronic databases were searched from inception to 22nd October 2018 for randomised controlled trials designed to assess cardiovascular efficacy of SGLT-2is or GLP-1RAs on 3-point major adverse cardiovascular events (MACE; a composite measure of non-fatal stroke, non-fatal myocardial infarction and cardiovascular mortality). Cardiovascular and safety data were synthesised using Bayesian network meta-analyses.

Results: Eight trials, including 60,082 participants, were deemed eligible for the network meta-analysis. SGLT-2is (hazard ratio [95% credible interval]: 0.86 [0.74, 1.01]) and GLP-1RAs (0.88 [0.78, 0.98]) reduced 3-point MACE compared to placebo, with no evidence of differences between them (GLP-1RAs vs SGLT-2is: 1.02 [0.83, 1.23]). SGLT-2is reduced risk of hospital admission for heart failure compared to placebo (0.67 [0.53, 0.85]) and GLP-1RAs (0.71 [0.53, 0.93]). No differences were found between SGLT-2is and GLP-1RAs in non-fatal stroke, non-fatal myocardial infarction, cardiovascular mortality, all-cause mortality and safety outcomes.

Conclusions: SGLT-2is and GLP-1RAs reduced 3-point MACE risk compared to placebo, with no differences between them. Compared to GLP-1RAs and placebo, SGLT-2is showed larger reduction in hospital admission for heart failure risk.

Keywords: Cardiovascular disease, GLP-1RA, network meta-analysis, SGLT-2i, type 2 diabetes.

Acknowledgments

Competing Interests

KK has acted as a consultant and speaker for Novartis, Novo Nordisk, Sanofi-Aventis, Lilly and Merck Sharp & Dohme. KK 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. MD 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. SS 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. SS has received research grants from Jansen.

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Contributing Statement

HH developed this systemic review and network meta-analysis with input from LG, KK, FZ, SS, and MD. HH and FZ independently inspected titles and abstracts for inclusion. HH and SS extract data from relevant articles identified, independently. HH wrote the first draft of this manuscript, which LG, FZ, KK, SS and MD reviewed and edited. Final manuscript was approved by all authors.

Introduction

Type 2 diabetes is a chronic cardiometabolic condition characterised 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-transport-2 inhibitors (SGLT-2is) and glucagon-like peptide-1 receptor agonists (GLP-1RAs) are two new classes of glucose-lowering drug which, in randomised controlled trials (RCTs) of 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. SGLT-2is reduce blood glucose levels by inhibiting the re-absorption of glucose in the kidneys through the SGLT-2 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 of the molecular backbone of the drug (exendin based, e.g. lixisenatide and exenatide or analogues of human GLP-1 (non-exendin based), e.g. liraglutide and semaglutide).

In most guidelines, SGLT-2is 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 SGLT-2is or GLP-1RAs suggest that both drug classes provide a reduction in the risk of cardiovascular outcomes compared to placebo/control (10-13). However, to date, there are no direct (head-to-head) trials specifically designed to compare SGLT-2is 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 SGLT-2is compared to GLP-1RAs in adults with type 2 diabetes.

Methods

This study followed a pre-specified protocol (*Appendix Table 1*) and was conducted 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 (*Appendix Table 2*) (16, 17).

Data Sources and Searches

PubMed, the Cochrane Register of Controlled Trials (CENTRAL) and all databases in 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 22nd October 2018 for RCTs published in any language. The search strategy included key search terms for SGLT-2i and GLP-1RA specific drug names, which was updated from previous systematic reviews (18-20); the full search strategy is reported in *Appendix File 1*. Reference list of included papers were scanned manually to search for further relevant studies.

Study Selection

RCTs of any duration, with at least two arms consisting of intervention(s) or control, conducted in adults (≥18 years old) with type 2 diabetes and specifically designed to assess cardiovascular safety or efficacy of SGLT-2is or GLP-1RAs, were included. 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 (3-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 number of participants with a 3-point MACE event were extracted. Secondary outcomes included the number of participants with each component of 3-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 (UTI), pancreatitis or diabetic ketoacidosis (DKA). Data were extracted following the intention-to-treat principle by two independent reviewers using standardised pre-defined forms. This included: first author, clinicaltrials.gov trial number, year of publication, median follow-up length of the trial (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 number of participants randomised 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

Due to 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: SGLT-2is, GLP-1RAs and placebo. Studies with multiple arms of the same drug with different doses were combined in 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 comparisons in Stata-MP (version 15.1, StataCorp, College Station, Texas, USA). Heterogeneity was assessed using I^2 values. Larger values of I^2 ($\geq$75%) indicated higher levels of heterogeneity, which could possibly suggest these studies should not be combined in 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 generalised linear models were fitted using a Markov Chain Monte Carlo (MCMC) simulation method. Vague priors were used for all parameters. When analysing cardiovascular outcomes, to estimate hazard ratios 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 between treatments (22). In order to assess differences in the primary outcome within the GLP-1RA class, subgroup analysis included splitting this node in the network in terms GLP-1RAs duration of action (i.e. long- vs. short-acting) and molecular backbone of drug (exendin vs. non-exendin based). Placebo was used as treatment reference for all analyses. For each outcome, median effect estimates, along with 95% credible intervals (CrI), 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 auto-correlation plots suggested possible auto-correlation. 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 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

16,981 reports were identified by the search strategy; after removal of duplicates, 8,847 reports titles and abstracts were screened, of which 20 were selected for full text screening (PRISMA diagram - *Appendix Figure 1*). Of these, 13 were excluded (reasons are reported in *Appendix Figure 1*), 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*). 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 male participants in the EMPA-REG OUTCOME trial (77.4%) compared to other trials (range: 60.7-69.5%). The mean baseline HbA_{1c} measurements were broadly similar across all trials (range: 61-72mmol/mol, 7.7-8.7%). The number of participants randomised and reporting an event for each outcome in each trial is reported in *Appendix Table 3*.

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 low risk of bias for all trials included in the analyses (*Appendix Table 4*).

Primary Outcome: 3-point MACE

Pairwise meta-analysis showed reductions in 3-point MACE for SGLT-2is and GLP-1RAs when compared to placebo (*Appendix Figure 2*). There was little heterogeneity for SGLT-2is compared to placebo (I^2=0.0%), while it was higher for GLP-1RAs, with I^2 being 58.6%.

Figure 1 shows the network plot for 3-point MACE. When compared to placebo**,** network meta-analysis results indicated 3-point MACE reduction for both SGLT-2is (hazard ratio [95% CrI]: 0.86 [0.74, 1.01]) and GLP-1RAs (0.88 [0.78, 0.98]) (*Table 2*), with a slightly greater reductions for SGLT-2is (58.8% probability of being the most effective treatment (*Appendix Figure 3*)). However, there was no evidence of difference between GLP-1RAs and SGLT-2is (hazard ratio GLP-1RAs vs. SGLT-2is: 1.02 [0.83, 1.23]).

Secondary Outcomes

Pairwise meta-analysis results for secondary outcomes are displayed in *Appendix Figure* 2.

There was no evidence in network meta-analyses of differences when GLP-1RAs and SGLT-2is 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 SGLT-2is vs. placebo (0.77 [0.61, 0.99], 0.80 [0.68, 0.95] and 0.67 [0.53, 0.85], respectively) was observed; and a lower risk for SGLT-2is vs. GLP-1RAs in hospital admissions for heart failure (0.71 [0.53, 0.93]) (*Table 2*). SGLT-2is had the highest probability of being the most effective treatment in reducing hospital admission for heart failure (98.7%) (*Appendix Figure 3*).

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 displayed in *Appendix Figure 4*. In the network meta-analyses, no evidence for differences were found when GLP-1RAs and SGLT-2is were compared against placebo and against each other for, all safety outcomes investigated (*Appendix Table 5*). Treatment ranking are shown in *Appendix Figure 5*.

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 to placebo, estimates from the network meta-analysis indicated a hazard ratio of 0.85 [0.73, 0.95] for long-acting GLP-1RAs and 1.02 [0.80, 1.30] for short-acting GLP-1RAs (*Appendix table 6*). However, no differences were observed when long and short-acting GLP-1RAs were compared to SGLT-2is.

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, utilised in the LEADER, SUSTAIN-6 and HARMONY trials, respectively, are non-exendin based. When compared to placebo, network meta-analysis results indicated a hazard ratio of 0.96 [0.84, 1.12] for exendin based GLP-1RAs and 0.81 [0.71, 0.92] for non-exendin based GLP-1RAs (*Appendix Table 6*). There was no evidence of any differences when exendin and non-exendin based GLP-1RAs were compared to SGLT-2is.

Sensitivity Analysis

Changes in the prior distributions of the standard deviations for the trial specific hazard ratios and pooled hazard ratios 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 little changes in overall treatment effects (data not shown).

Model Assessments

There were little 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 (*Appendix Table 7*). “Comparison adjusted” funnel plots showed no conclusive evidence of publication bias for all outcomes (*Appendix Figure 6, 7*).

Discussion

Although several RCTs assessed the risk of cardiovascular events for SGLT-2is or GLP-1RAs compared to placebo in individuals with type 2 diabetes, to date there are 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 SGLT-2is or GLP-1RAs to placebo in order to obtain an indirect estimate of the cardiovascular effects of GLP-1RAs compared to SGLT-2is.

Based on eight RCTs enrolling 60,082 participants with type 2 diabetes, our findings indicate that both SGLT-2is and GLP-1RA reduce 3-point MACE risk when compared to placebo, with no differences between the two classes. Similarly, no differences were found between SGLT-2is and GLP-1RAs when looking at each component of 3-point MACE separately (i.e. non-fatal stroke, non-fatal myocardial infarction and cardiovascular mortality) as well as all-cause mortality.

Of note, SGLT-2is performed better than GLP-1RAs in reducing the risk of hospitalisation for heart failure: the risk of hospital admission for heart failure was 33% lower in SGLT-2is compared to placebo and 29% lower compared to GLP-1RAs, with SGLT-2is having an overall probability of ≈99% of being the most effective treatment for this outcome. Hospital admissions due to heart failure is 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 hospitalisation as a pre-specified outcome of interest; therefore, results can be sparse (33, 34). In a meta-analysis of GLP-1RAs, evidence suggested no reductions in heart failure risk for GLP-1RAs vs. other anti-hyperglycaemic medications (34). Reductions in the hospital admission for heart failure have been observed in nonrandomised studies within SGLT-2is. In a retrospective analysis, treatment with SGLT-2is was associated with a lower risk of hospitalisation for heart failure compared to 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 SGLT-2is vs. other oral glucose-lowering drugs (36).

The beneficial effect of SGLT-2is on heart function are related to a number of biological mechanisms. A possible mechanism of action could be the natriuretic and hypovolaemic effect of SGLT-2is (37, 38). By excreting sodium in the urine, blood pressure decreases with subsequent reduced circulatory load and increased ventricular functions (37, 38). Additionally, SGLT-2is 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 the haematocrit 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 SGLT-2is for hypoglycaemic events, bone fractures, amputations, pancreatitis, UTI and DKA. However, very sparse data have been collected on some of these outcomes in the included RCTs, thus precluding a firm conclusion. Furthermore, although subgroup analysis was done and some differences were observed, due to 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 will be 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 this 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 SGLT-2i dapagliflozin on cardiovascular outcomes in people with type 2 diabetes (40). Although the primary outcome of this study was 3-point MACE, the definition differed from those available in the trials included in our analysis as the DECLARE study additionally including fatal stroke and myocardial infarction in 3-point MACE definition. The DECLARE study reported no differences between dapagliflozin and placebo in 3-point MACE reduction. However, this trial showed a reduction in the

risk of heart failure associated with SGLT-2i treatment, consistent with the effect estimates from this network meta-analysis.

A previous network meta-analysis has assessed cardiovascular outcomes' differences among dipeptidyl-peptidase-4 inhibitors, SGLT-2is and GLP-1RAs, evidencing that SGLT-2is and GLP-1RAs reduced cardiovascular risk; however, authors included all phase three trials as well as cardiovascular outcome trials together, potentially resulting in a higher heterogeneity (41). Moreover, most of the included RCTs have been 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 our study the similarity and transitivity assumption of network meta-analysis was strengthened. Despite the differences in the inclusion criteria, Zheng et al.'s results are generally in line with our findings, showing no differences between GLP-1RAs and SGLT-2is for cardiovascular mortality, all-cause mortality, stroke, myocardial infarction and hypoglycaemia.

Although to our knowledge this study is the first analysis comparing cardiovascular effects of SGLT-2is and GLP-1RAs collecting data from cardiovascular outcome trials, there are also some limitations that need to be recognised. Firstly, as there were no direct head-to-head comparisons of SGLT-2is 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 confidence intervals from the pairwise analyses conducted, suggesting little 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 DKA for SGLT-2is). For some outcomes, data were unavailable which could be due to data not being measured rather than events not occurring. Core outcome sets were defined in the

protocol of the RCTs, which aims 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 estimates from pairwise analyses and network meta-analyses in this study were similar to other meta-analyses conducted previously (10-13, 41). Further, it was not possible to assess individual treatments in the network but combined in treatment groups. However, by comparing the class effects of treatments, rather than individual treatment effects, statistical power has been increased. Thirdly, high heterogeneity was estimated within SGLT-2is for bone fractures and amputations. Although it was not possible to split this node due to the limited amount of studies, heterogeneity could possibly be introduced by the CANVAS study when analysing bone fracture events and the EMPA-REG OUTCOME study when analysing amputation events due to differences in estimates in comparison to 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 a 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 participants were randomised to, which could be potentially different between trials. Although there were differences in standard care, it is unlikely that they have affected estimates as these were established prior to baseline. There are cardiovascular outcome RCTs that are currently being conducted and have not yet been published, such as the REWIND (NCT01394952) and ITCA 650 (NCT01455896), which investigate 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 indicate that both SGLT-2is and GLP-1RAs lower the risk of 3-point MACE in comparison to placebo, with no differences between them. SGLT-2is reduced the risk of hospital admissions due to heart failure to a greater extent compared to 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 larger benefit to the individual patient.

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Tables

Table 1 Study characteristics of included trials.

First Author	Trial Name	Clinical Trial Number	Year	Median follow-up (Years)	Control	Intervention	Total participants randomised	Age (Years)	Male (%)	HbA_{1c} (mmol/mol, %)	Diabetes duration (Years)
Zinman	EMPA-REG OUTCOME (24)	NCT 01131676	2015	3.1	PLA	EMPA (10mg-25mg)	7,020	63.1	71.5	65, 8.1	Not reported
Neal	CANVAS (25)	NCT 01032629	2017	5.7	PLA	CANA (100mg-300mg)	4,330	62.4	66.1	66, 8.2	13.4
Neal	CANVAS-R (25)	NCT 01989754	2017	2.1	PLA	CANA (100mg-300mg)	5,812	64.0	62.8	67, 8.3	13.7
Pfeffer	ELIXA (26)	NCT 01147250	2015	2.1	PLA	LIX (10mcg-20mcg)	6,068	60.3	69.4	61, 7.7	9.3
Marso	LEADER (27)	NCT 01179048	2016	3.8	PLA	LIR (1.8mg)	9,340	64.3	64.3	72, 8.7	12.9
Marso	SUSTAIN-6 (28)	NCT 01720446	2016	2.1	PLA	SEM (0.5mg-1.0mg)	3,297	64.6	60.7	72, 8.7	13.9
Holman	EXSCEL (29)	NCT 01144338	2017	3.2	PLA	ExQW (2mg)	14,752	62.0	62.0	64, 8.0	12.0
Hernandez	HARMONY (30)	NCT 02465515	2018	1.6	PLA	ALB (30mg-50mg)	9,463	59.2	69.5	72, 8.7	14.2

Abbreviations: 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 (SGLT-2is), glucagon-like peptide-1 receptor analogues (GLP-1RAs) and placebo on cardiovascular outcomes.

A. 3-Point MACE		
		GLP-1RAs
	SGLT-2is	1.02 (0.83, 1.23)
Placebo	0.86 (0.74, 1.01)	0.88 (0.78, 0.98)
B. Non-fatal stroke		
		GLP-1RAs
	SGLT-2is	0.86 (0.55, 1.30)
Placebo	1.03 (0.74, 1.43)	0.89 (0.66, 1.15)
C. Non-fatal myocardial infarction		
		GLP-1RAs
	SGLT-2is	1.08 (0.82, 1.37)
Placebo	0.87 (0.72, 1.07)	0.94 (0.80, 1.08)
D. Cardiovascular mortality		
		GLP-1RAs
	SGLT-2is	1.18 (0.86, 1.59)
Placebo	0.77 (0.61, 0.99)	0.91 (0.76, 1.09)
E. All-cause mortality		
		GLP-1RAs
	SGLT-2is	1.13 (0.92, 1.39)
Placebo	0.80 (0.68, 0.95)	0.90 (0.80, 1.03)
F. Hospital admissions for heart failure		
		GLP-1RAs
	SGLT-2is	1.41 (1.07, 1.90)
Placebo	0.67 (0.53, 0.85)	0.94 (0.80, 1.13)

Comparisons are reported as hazard ratio (95% credible intervals) for column vs. row (i.e. for 3-point MACE: GLP-1RAs vs. placebo hazard ratio (95% credible interval): 0.88 (0.78, 0.98)).
Abbreviation: MACE, major adverse cardiovascular events.