Efficacy and tolerability 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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Abstract

Aim: To compare the efficacy and tolerability of sodium-glucose co-transporter 2 inhibitors (SGLT-2is) and glucagon-like peptide-1 receptor agonists (GLP-1RAs) in adults with type 2 diabetes.

Materials and methods: Electronic databases were searched from inception to 24th April 2019 for randomised controlled trials reporting change in glycated haemoglobin (HbA_{1c}) at approximately 24 and/or 52 weeks for SGLT-2is and/or GLP-1RAs (classified as short- and long-acting). Bayesian network meta-analyses were conducted to compare within and between SGLT-2i and GLP-1RA classes for cardiometabolic efficacy and adverse events (PROSPERO registration number: CRD42018091306).

Results: 64 trials (53 trials of 24 weeks; 7 trials of 52 weeks; 4 trials of both 24 and 52 weeks), comprising of 31,384 participants were identified. Compared to placebo, all treatments improved HbA_{1c}. Long-acting GLP-1RAs reduced HbA_{1c} compared to short-acting GLP-1RAs and SGLT-2is, with semaglutide showing greater reduction compared to placebo (24 weeks: -1.49% (95% credible interval [CrI]: -1.76, -1.22), 52 weeks: -1.38% (-2.05, -0.71)) and all other treatments. Long-acting GLP-1RAs showed benefits in body weight and waist circumference reduction, while SGLT-2is reduced blood pressure. SGLT-2is showed increased odds of genital infection in comparison to long-acting GLP-1RAs (odds ratio (95% CrI): 5.26 (1.45, 25.00)), while GLP-1RAs showed increased odds of diarrhoea in comparison to SGLT-2is (short-acting GLP-1RAs: 1.65 (1.09, 2.49), long-acting GLP-1RAs: 2.23 (1.51, 3.28)). No other differences were found between SGLT-2is and GLP-1RAs in adverse events.

Conclusion: Long-acting GLP-1RAs showed superiority in reducing HbA_{1c} levels, body weight and waist circumference. SGLT-2is showed reductions in blood pressure levels. This review provide essential evidence to guide treatment recommendations in the management of type 2 diabetes.

Introduction

Constant updates to guidelines and procedures to effectively manage hyperglycaemia in patients with type 2 diabetes are required as new medications are developed and made available. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium-glucose co-transporter 2 inhibitors (SGLT-2is) are among the newer classes of medications that are particularly gaining popularity due to the reduced risk of hypoglycaemia as well as reducing cardiovascular risks in high risk populations (1-5).

These two treatment classes differ in the mechanisms by which they reduce blood glucose levels. SGLT-2is increase glycosuria by inhibiting the reabsorption of glucose in the proximal tubule of the kidneys (6,7) whereas GLP-1RAs reduce glucose levels by mimicking the action of the gut hormone GLP-1 to bind to GLP-1 receptors, stimulating the release of insulin and inhibiting glucagon secretion (8). Although drugs within the class of SGLT-2is are fairly similar, GLP-1RAs are more heterogeneous. As the duration of action of GLP-1RAs differs, they are classified as short- or long-acting, depending on their therapeutic half-life (9). Other factors that further distinguish GLP-1RAs include the molecular formations (i.e. exendin and non-exendin based) as well as some differences on cardiovascular events reduction (1-3).

Consensus recommendations from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recommend a GLP-1RA or an SGLT-2i when metformin is not sufficient in meeting individual's glycaemic targets (1-3). Treatment selection algorithms recommend these medications in accordance to patients' established health profile. Current evidence suggests these interventions in patients with established cardiovascular disease (CVD) or chronic kidney disease (CKD); the evidence for treatment selection is less clear in those without CVD/CKD. In this context, guidelines recommend either a GLP-1RA or SGLT-2i, with no clear distinction made between these treatment classes.

While there are many randomised controlled trials (RCTs), pairwise and network meta-analysis (NMA) comparing a GLP-1RA or an SGLT-2i to placebo (10-13), to our knowledge, there has been only one trial to have reported a direct comparison between a GLP-1RA and an SGLT-2i (14, 15). However, there is no evidence available regarding differences among other GLP-1RAs and SGLT-2is. In the absence of evidence from direct comparisons, NMA has been suggested as the methodology

of choice to synthesise data and obtain an estimate between treatments of interest using indirect comparisons (16).

The aim of this study was to investigate with a systematic review and NMA the efficacy and tolerability profiles between and within GLP-1RAs and SGLT-2is in adults with type 2 diabetes.

Materials and methods

The protocol for this systematic review and network meta-analysis has been previously published and has been registered with the International Prospective Register of Systematic Reviews (PROSPERO registration number: CRD42018091306) (17). This study has been reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Network Meta-Analyses (PRISMA-NMA) (Appendix Table 1) (18, 19).

Data sources and searched

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 systematically searched for GLP-1RA and SGLT-2i specific drug names from inception to 24th April 2019 for RCTs published in any language; the full search strategy is reported in Appendix File 1. Reference lists of included papers were scanned manually to search for further relevant studies.

Study selection

RCTs were deemed eligible if they (1) recruited adults ($\geq$ 18 years) with type 2 diabetes; (2) reported follow-up data at 24 ($\pm$8) and/or 52 ($\pm$8) weeks; (3) reported change from baseline in HbA_{1c} (% or mmol/mol); (4) compared intervention(s) to each other at international guideline recommended doses or compared to placebo/standard care (SC) (20, 21). Interventions included in this review consisted of long-acting GLP-1RAs (albiglutide - withdrawn from market globally in July 2018, dulaglutide, exenatide once weekly (QW), liraglutide, semaglutide and taspoglutide - development program halted), short-acting GLP-1RAs (exenatide twice daily (BID) and lixisenatide) and SGLT-2is (canagliflozin, dapagliflozin, empagliflozin and ertugliflozin). All doses were extracted for treatments with no recommended dose (i.e taspoglutide). RCTs were excluded if they (1) recruited only certain populations (for example, entirely Asian populations) to minimise systematic biases introduced by regular use of lower doses in this population; (2) recruited patients based on additional chronic conditions (e.g. CKD); (3) randomised to ipragliflozin, luseogliflozin or tofogliflozin as they are licensed only in Japan.

Relevant studies were identified by two independent reviewers (HH and DK) with discrepancy resolved by arbitration (FZ).

Data extraction and quality assessment

Data were extracted using standardised pre-defined forms following the intention-to-treat principle, where possible. This included: first author, clinicaltrials.gov trial number, year of publication, median follow-up length of the trial, sample size, intervention(s) and baseline characteristics of participants. The primary outcome was the change in HbA_{1c} (%, mmol/mol) from baseline at approximately 24 and 52 weeks. Secondary outcomes included the change from baseline in: bodyweight (kg), systolic (SBP) and diastolic blood pressure (DBP) (mmHg), waist circumference (cm), total-, HDL- and LDL-cholesterol (mmol/L), triglycerides (mmol/L) and heart rate (bpm). Adverse event outcomes included: number of participants reporting at least one hypoglycaemic event, urinary tract infection (UTI), genital infection, diarrhoea, nausea, vomiting, injection site reactions, abdominal pain, bone fractures, pancreatitis, cancer or testing antidrug antibody positive.

Data were extracted by reviewers (HH and EP) and duplicated in 10% of randomly selected included trials by an independent reviewer (EI) to assess consistency. Risk of bias was assessed using the Cochrane risk of bias assessment tool (22).

Data synthesis and analysis

Network plots were drawn in order to present the network of direct evidence available (23). Outcomes with sparse networks (i.e. only one head-to-head comparison available between treatments) were not analysed due to insufficient data for analysis. Studies with multiple arms of the same drug with different doses within guideline recommendations were combined in a single arm for each drug (16). Due to the limited number of studies available, it was not possible to compare individual drugs for adverse events; therefore, treatment arms of trials were collapsed into the following groups: SGLT-2is, short-acting GLP-1RAs, long-acting GLP-1RAs and combination of GLP-1RAs and SGLT-2is. A continuity correction factor of 0.5 was added to trials when one arm reported zero events for adverse event outcomes.

For each outcome, a random effects pairwise meta-analysis was initially conducted within each direct treatment comparisons in Stata-MP (Version 15.1). Heterogeneity was assessed using I^2.

A Bayesian NMA 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. Placebo and SC treatment arms were combined and used as the treatment reference for all analyses.

For primary and secondary outcomes, to estimate the mean difference (MD) from baseline between treatment arms, a linear regression model was used (24). A logistic regression model was used for adverse events to estimate odds ratios (ORs) between treatments (24). Adjustments were made to models to account for multi-arm trials, where required (24). For each outcome analysed, the percentage ranking of each treatment was calculated, which is the probability of a particular treatment providing the greatest benefit in treatment efficacy or tolerability.

Bayesian hierarchical NMAs were performed in WinBUGs for primary and secondary outcomes to assess the efficacy of treatment classes (placebo, SGLT-2is, short-acting and long-acting GLP-1RAs) (25). In addition, NMA stratified by the maximum number of background treatments (i.e. no therapy, monotherapy, dual therapy and triple therapy or more) was performed for the primary outcome.

For each outcome, median effect estimates, along with 95% credible intervals (CrI), were reported. Models fitted were run for 50,000 simulations (with 10,000 simulations burn-in length). Sensitivity analyses conducted included varying choices of vague prior distributions, varying burn-in and simulation length and changing initial values for parameters. 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. Publication bias was assessed using “comparison-adjusted” funnel plots (23). Quality of evidence for the primary outcome was assessed using the GRADE working group approach for the primary outcome (26). Design-by-treatment models were fitted to assess inconsistency, where possible (27). Deviance information criterion (DIC) statistics calculated from the random effects model were compared to the design-by-treatment model, with smaller DIC values indicating better fit. If the design-by-treatment model could not be fitted, results from the NMA were compared to the pairwise meta-analysis; results were defined as consistent if NMA effect estimates fell within the 95% confidence intervals estimated from the pairwise meta-analysis.

Changes to study protocol have been reported in Appendix File 2. During peer-reviewing stages, two additional sensitivity analyses were performed: 1) for HbA1c, including only the highest dose of the investigated treatments; 2) for hypoglycaemia, excluding of trials where the background therapy was insulin or sulphonylurea.

Results

Study search and trial characteristics

Searches identified 19,484 potentially relevant records; after removal of duplicates, 13,409 records titles and abstracts were screened (Figure 1). 248 full texts were assessed for eligibility, resulting in 64 individual studies included in the analysis (Appendix Table 2). In total, 53 studies reported outcomes at 24 weeks only, 7 at 52 weeks only and 4 at 24 and 52 weeks. SGLT-2is (including canagliflozin, dapagliflozin, empagliflozin and ertugliflozin) were assessed in 28 studies, short-acting GLP-1RAs (including exenatide BID and lixisenatide) in 18 studies and long-acting GLP-1RAs (including albiglutide, dulaglutide, exenatide QW, liraglutide, semaglutide and taspoglutide) in 30 studies. Two studies assessed the effect of a combination of dapagliflozin, a SGLT-2i, with exenatide QW, a long-acting GLP-1RA.

Overall, 31,384 participants were included (Table 1); the mean number of participants recruited per trial was 490 (range: 50-2072 participants). Baseline characteristics of participants recruited to trials were similar in terms of age (mean: 55 years, range: 52-63 years), body weight (mean: 91kg, range: 77-115kg) and HbA_{1c} (%, mmol/mol) (mean: 8.2% [68.1 mmol/mol], range: 7.3-9.3% [58.3-80.1 mmol/mol]) across trials. The risk of bias assessments were deemed low for most domains across all trials (Appendix Table 3). The data extracted for each included study are given in Appendix File 3 for cardiometabolic outcomes and Appendix File 4 for adverse events.

Primary outcome: change in HbA_{1c}

For the primary outcomes, change in HbA_{1c}, a total of 57 trials, consisting of 26,324 participants, were analysed at 24 weeks and 11 trials, including 7,009 participants, were analysed at 52 weeks. Network plots showed there were 14 treatments analysed at 24 weeks and 9 at 52 weeks (Figure 2). Moderate to high levels of heterogeneity were observed for some comparisons ($I^2 \geq 75\%$). Full results from pairwise meta-analysis and NMA have been reported in Appendix Table 4a. Treatment rankings from the NMA have been reported in Appendix Table 5a.

Results from hierarchical models showed that long-acting GLP-1RAs had a greater benefits in reducing HbA1c compared to SGLT-2is (-0.28% (-0.47, -0.10), -3.06 mmol/mol (-5.14, -1.09)) and

short-acting GLP-1RAs (-0.46% (-0.67, -0.25), -5.03 mmol/mol (-7.32, 2.73)) at 24 weeks (Appendix Table 6a). Associations were attenuated at 52 weeks.

NMA results of treatments compared to placebo are shown in Figure 3. All treatments reduced HbA_{1c} levels from baseline in comparison to placebo across both time points analysed. The long-acting GLP-1RA semaglutide showed the greatest reduction in HbA_{1c} in comparison to placebo at both 24 weeks (-1.49% (-1.76, -1.22)) [-16.29mmol/mol (-19.24, -13.33)] and 52 weeks (-1.38% (-2.05, -0.71)) [-15.08mmol/mol (-22.41, -7.76)] and in comparison to other treatments in the network. Semaglutide also showed the greatest probability of being the most effective treatment (24 weeks: 89.2%, 52 weeks: 81.3%) (Appendix Table 5a). In comparison to placebo, the most effective SGLT-2i in reducing HbA_{1c} at 24 weeks was ertugliflozin, which showed a reduction of 0.84% (95% Credible Interval: -1.02, -0.66) [-9.18mmol/mol (-11.15, -7.21)]. This effect was similar at 52 weeks (-0.81% (-1.26, -0.35)) [-8.85mmol/mol (-13.77, -3.83)]. In comparison to placebo, lixisenatide (a short-acting GLP-1RA) reduced HbA_{1c} levels the least (-0.48% (-0.59, -0.37)) [-5.25mmol/mol (-6.45, 4.04)].

Sensitivity analysis including only the highest dose of the investigated treatments resulted in similar findings (Appendix Table 7).

Secondary outcomes

Change from baseline in body weight, SBP and DBP were analysed at both 24 and 52 weeks. Change in waist circumference, total, HDL and LDL cholesterol, triglyceride levels and heart rate were analysed at 24 weeks only. Network plots for secondary outcomes are presented in Appendix Figure 1. All pairwise and NMA results are reported in Appendix Table 4b. Treatment ranking have been reported in Appendix Table 5b.

When considering hierarchical models, SGLT-2is reduced SBP levels in comparison to short-acting GLP-1RAs (-1.62mmHg (-3.18, -0.05)) and DBP levels in comparison to long-acting GLP-1RAs (-1.32mmHg (-2.05, -0.65)) at 24 weeks (Appendix Table 6b). Long-acting GLP-1RAs reduced total (-0.24mmol/L (-0.39, -0.09)), HDL (-0.08mmol/L (-0.15, -0.01)) and LDL cholesterol levels (-0.19mmol/L (-0.31, -0.07)) in comparison to SGLT-2is, while they increased heart rate by 2 beats per minute (bmp) (0.75, 3.89) at 24 week.

NMA results of treatments compared to placebo are reported in Figure 3. Semaglutide (-3.40kg (-4.51, -2.33)) and exenatide QW and dapagliflozin given in combination (-3.43kg (-4.48, -2.40)) had similar reductions in body weight in comparison to placebo. The reduction in body weight between semaglutide vs placebo was maintained at 52 weeks (-5.00kg (-9.62, -0.41)). SGLT-2is reduced SBP and DBP levels in comparison to placebo at 24 weeks; the greatest reduction was observed in canagliflozin (SBP: -4.92mmHg (-6.17, -3.65), DBP: -2.01mmHg (-2.95, -1.12)).

Adverse events

Hypoglycaemic events, UTIs, genital infection and diarrhoea outcomes were analysed at 24 and 52 weeks, whereas nausea, vomiting, injection site reactions, abdominal pain, bone fractures pancreatitis and cancer events were analysed at 24 weeks only. Network plots of adverse event outcomes analysed are presented in Appendix Figure 2. All pairwise and NMA results are reported in Appendix Table 4c. Compared to placebo, all treatment classes had higher odds of hypoglycaemic events (Figure 4). No differences were found comparing treatment classes with each other. However, at 52 weeks, long-acting GLP-1RAs showed no difference in hypoglycaemic events in comparison to placebo (OR: 1.59 (0.86, 3.03)). Results were consistent in a sensitivity analysis after excluding trials with insulin or sulphonylurea as background therapy (Appendix Table 8).

In comparison to placebo, SGLT-2is had 4.46 higher odds (3.02, 7.03) of genital infection at 24 weeks and 6.06 higher odds (3.62, 11.11) at 52 weeks. Further, SGLT-2is had a higher odds of genital infection events in comparison to long-acting GLP-1RAs (5.26 (1.45, 25.00)) at 24 weeks; long-acting GLP-1RAs had the greatest probability of being the most effective treatment (58.2%) (Appendix Table 5b). Short-acting and long-acting GLP-1RAs had higher odds of diarrhoea in comparison to SGLT-2is (short-acting GLP-1RAs: 1.65 (1.09, 2.49), long-acting GLP-1RAs: 2.23 (1.51, 3.28)). No other differences were found between treatments for adverse events outcomes.

Subgroup analysis

Stratifying trials by the maximum number of background therapies given to patients for HbA_{1c} at 24 weeks, the results showed that in comparison to placebo treatment efficacy reduced with increasing number of background therapies (Appendix Table 9). Stratified model fitted for 52 weeks data did not converge.

Model and quality assessments

Sensitivity analysis conducted by changing prior distributions, varying burn-in, simulation length and changing initial values for parameters showed little to no changes in overall treatment effects (data not shown).

Model fit checks showed adequate fit of the random effects model and assessment of inconsistency suggested NMA effect estimates were mostly consistent (Appendix Table 10). "Comparison-adjusted" funnel plots fitted were mostly centred about the mean and fairly symmetrical, suggesting no conclusive evidence of publication biases (Appendix Figure 3). Following the GRADE approach, most treatment comparisons showed high to moderate quality of evidence for HbA_{1c} at 24 and 52 weeks (Appendix Table 11).

Discussion

In this systematic review and NMA of 64 trials enrolling a total 31,384 participants, long-acting GLP-1RAs showed greater reductions in HbA_{1c} in comparison to short-acting GLP-1RAs and SGLT-2is. In particular, semaglutide treatment reduced HbA_{1c} levels to a greater extent compared to other short- and long-acting GLP-1RAs as well as SGLT-2is and placebo, both at 24 and 52 weeks.

Semaglutide also showed a larger reduction in body weight in comparison to all GLP-1RAs, except liraglutide, and SGLT-2is at 24 weeks while small differences among treatments were observed at 52 weeks. Further, semaglutide alone showed a similar efficacy in HbA_{1c} reduction as compared to the combination of exenatide QW and dapagliflozin at both time points. Notably, the HbA1c reduction of GLP-1RAs and SGLT-2is compared to placebo was progressively smaller with an increase in the number of background therapies. Although semaglutide showed the greatest benefit in reducing waist circumference in comparison to placebo, no differences were found when compared to other treatments. SGLT-2is reduced SBP and DBP at 24 weeks in comparison to placebo, with the largest difference being between canagliflozin and placebo. Further, GLP-1RAs increased heart rate in comparison to placebo and few SGLT-2is.

While current evidence supports the use of GLP-1RAs and SGLT-2is in subjects with established CVD or CKD (1-3), data are more limited about which of these glucose-lowering medications should be preferred in subjects without established cardio-renal disease. Notably, there are very few direct comparisons between GLP-1RAs and SGLT-2is in subjects without established cardio-renal disease; by combining direct and indirect evidence, the results of this systematic review and network meta-analysis provides useful guidance by comparing the efficacy and tolerability of these two classes of medications.

Currently, the decision of use of GLP-1RAs and SGLT-2is is mainly founded on their ability to reduce cardiovascular risk; however, glycaemic efficacy and impact on weight reduction of these treatments remains an important factor, particularly in those with limited cardiovascular risk (1-3). Further, the cardiometabolic efficacy profile of GLP-1RAs and SGLT-2is needs to be considered alongside the tolerability of these treatments. These two treatment classes have been suggested to have lower risk of adverse events in comparison to other glucose-lowering medications (3, 28); little is known,

however, on the tolerability profiles of these classes compared to each other. In this review, SGLT-2is showed lower odds of gastrointestinal symptoms but an increased odds of genital infection in comparison to GLP-1RAs. The increased odds of genital infection with SGLT-2is is well recognised and is likely related to the increased glycosuria (10, 29). As regards hypoglycaemic events, there were no differences between the two classes of medication. Overall, these results would suggest that, while deciding the most appropriate individualised approach to glucose reduction, in terms of tolerability gastrointestinal and genitourinary side effects rather than hypoglycaemia should guide the decision among these two classes of medication. Most of the differences for the cardiometabolic risk factors were observed at 24 weeks, particularly for HbA_{1c} and body weight reduction; such differences were not only statistically significant but also clinically relevant. Indeed, compared to SGLT-2is, semaglutide reduced HbA_{1c} at least by 0.7% (vs ertugliflozin) and up to 0.9% (vs dapagliflozin). These improvements potentially result in long-term reduction of microvascular complications as each 1% HbA1c reduction has been associated with a 30% lower risk a microvascular events over a follow-up of 5 years (30). For body weight, differences were also mainly observed for semaglutide, and ranged from a 6-month reduction of 1.4 kg vs empagliflozin to 1.8 kg vs ertugliflozin. Therefore, the two parameters HbA_{1c} and body weight are important factors when deciding between these two classes. However, in contrast with some differences observed within GLP-1RAs for both HbA_{1c} and body weight, the clinical profile of SGLT-2is for the same outcomes was more similar (largest HbA_{1c} difference, 0.2%; no difference in body weight reduction).

During manuscript preparation, results from the PIONEER-4 trial, assessing the effect of oral semaglutide (a long-acting GLP-1RA) has been published (31, 32). This trial recruited 711 participants randomly assigned to oral semaglutide (14mg), liraglutide and placebo, reporting results at 26 and 52 weeks. Additionally, results from the SUSTAIN-8 trial, recruiting and randomising 788 patients to subcutaneous semaglutide or canagliflozin has also been published (33). This direct comparison between a GLP-1RA and SGLT-2i showed a greater reduction of HbA1c at 52 weeks for semaglutide (-0.49 [-0.65, -0.33]. Of note, repeating the analysis for HbA_{1c} while including oral semaglutide as a separate node in the network resulted in little changes to estimates (Appendix Table 12). Moreover, although oral semaglutide showed a lower efficacy profile to subcutaneous semaglutide at FDA approved dosages, a phase 2 dose ranging trial has shown higher doses of oral semaglutide (20-40mg) had similar HbA_{1c} reductions as subcutaneous semaglutide (34).

Strengths and limitations

There are number of strengths of this review. Using NMA techniques, it was possible to combine evidence from a large number of RCTs to synthesise direct and indirect evidence to obtain comparisons between GLP-1RAs and SGLT-2is. To our knowledge, this study is the first NMA conducted comparing individual treatments with GLP-1RAs and SGLT-2is for several important cardiometabolic efficacy and tolerability factors. Further, distinctions have been made within the GLP-1RA class due to the differing duration of action of treatments. However, there are a number of limitations that need to be considered. Firstly, due to the sparsity of some networks, inconsistency could not be assessed using the design-by-treatment models for all outcomes. Inconsistency is one of the key assumptions that need to be considered when conducting a NMA (35). Although inconsistency could not be assessed in all outcomes, most effect estimates from the NMA were within the confidence intervals of pairwise meta-analysis, suggesting results were mostly consistent. Another important assumption to consider when conducting an NMA is transitivity. While a strict inclusion/exclusion criteria has been considered to maximise the homogeneity of trials included in the analyses, there is still a possibility that some heterogeneous characteristics (i.e., pre-randomisation body weight or HbA1c) may have impacted on the results. Secondly, although phase III trials of taspoglutide were suspended, this treatment was included in the NMAs to contribute to indirect effects estimated. Excluding taspoglutide arms in adverse event outcomes showed a decrease in odds of nausea, vomiting and injection site reactions in long-acting GLP-1RAs in comparison to adverse events analysis conducted including taspoglutide (Appendix Table 13). Although odds ratios estimated were slightly smaller when excluding taspoglutide, conclusions remained the same throughout. Third, in this review GLP-1RAs were considered by duration of action (i.e. short-acting vs long-acting). However, they can also differ by their molecular formulation; some are exendin based (i.e. exenatide BID, exenatide QW and lixisenatide) while others are not (i.e. albiglutide, dulaglutide, liraglutide, taspoglutide and semaglutide). These differences may also impact on the results, in particular injection site reactions, and may be related to the different pharmacological formulations; therefore, further analysis would be required to consider the impact of these differences on the risk of injection site reactions. Fourth, due to limited follow-up time, cardiovascular outcomes were not analysed in the original studies and have not been considered in this NMA. Fifth, in the network utilised in this study, studies comparing GLP-1RAs and SGLT-2is to

placebo or each other were included; however, to date there is no clear consensus or guidelines on the optimal strategy to identify relevant studies and interventions which should be included in a network of comparisons (36). Lastly, although the quality of evidence was assessed for the primary outcome using the GRADE approach, it was not possible to assess the quality for all outcomes. In the GRADE system of evaluation, several domains for direct and indirect effect estimates are assessed for high, moderate, low or very low quality. Although assessing quality of evidence using the GRADE approach could not be completed for all outcomes, risk of bias, publication bias and inconsistency showed that most comparisons provided high quality of evidence in this analysis.

In conclusion, this review highlighted the benefits and harms of various GLP-1RAs and SGLT-2is. Semaglutide showed greater reductions in HbA_{1c}, body weight and waist circumference. SGLT-2is reduced SBP and DBP levels in comparison to placebo. The tolerability profile between these two classes were different, with long-acting GLP-1RAs associated with a higher risk of gastrointestinal side effects and SGLT-2is with genital infection. Such evidence is important given the increase in treatment options with little head-to-head data available and could guide the decision in glucose-lowering treatment management.

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Conflict of interest

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.

FZ has acted as a speaker for NAPP.

Contributing statement

HH developed this systematic review and network meta-analysis with input from LG, KK, FZ, ND and MD. HH and DK independently inspected titles and abstracts for inclusion. HH and EP extracted data from relevant articles identified, while EI duplicated data extraction. HH wrote the first draft of this manuscript, which LG, FZ, KK, ND, EP, DK, EI and MD reviewed and edited. The final manuscript was approved by all authors.

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Legends to figures

Figure 1 Flow diagram of paper inclusion for systematic review and network meta-analysis

Figure 2 Network plot for HbA1c (%, mmol/mol) (A) Network plot at 24 weeks; (B) Network plot at 52 weeks

Abbreviations: PLA/SC, Placebo/Standard Care; CANA, Canagliflozin; DAPA, Dapagliflozin; EMPA, Empagliflozin; ERTU, Ertugliflozin; ExBID, Exenatide Twice Daily; LIX, Lixisenatide; ALB, Albiglutide; DUL, Dulaglutide; ExQW, Exenatide Once Weekly; LIR, Liraglutide; SEM, Semaglutide; TAS, Taspoglutide.

Figure 3 Network meta-analysis results for the mean difference in primary and secondary at 24 and 52 weeks in comparison to placebo/standard care

Note: to convert change in HbA1c measured in % to mmol/mol: change in HbA1c (mmol/mol) = 10.93×change in HbA1c (%)

Abbreviations: MD, mean difference; CrI, Credible Interval; PLA/SC, Placebo/Standard Care; CANA, Canagliflozin; DAPA, Dapagliflozin; EMPA, Empagliflozin; ERTU, Ertugliflozin; ExBID, Exenatide Twice Daily; LIX, Lixisenatide; ALB, Albiglutide; DUL, Dulaglutide; ExQW, Exenatide Once Weekly; LIR, Liraglutide; SEM, Semaglutide; TAS, Taspoglutide.

Figure 4 Network meta-analysis results reporting odds ratios for safety outcomes at 24 and 52 weeks in comparison to placebo/standard care

Note: Combination treatment arm is a long-acting GLP-1RA combined with an SGLT-2i (i.e. Exenatide QW with Dapagliflozin).

Abbreviations: PLA/SC, Placebo/Standard Care; CANA, Canagliflozin; DAPA, Dapagliflozin; EMPA, Empagliflozin; ERTU, Ertugliflozin; ExBID, Exenatide Twice Daily; LIX, Lixisenatide; ALB, Albiglutide; DUL, Dulaglutide; ExQW, Exenatide Once Weekly; LIR, Liraglutide; SEM, Semaglutide; TAS, Taspoglutide.

Tables

Table 1 Study participant characteristics of included trials

PubMed ID[§]	First Author	Trial Name	Clinical Trial No	Trial Length (w)	Year	Background Therapy	Arm 1	Arm 2	Arm 3	N	Age (y)	BMI[¶]	Weight (kg)	Male (%)	HbA_{1c} (%)[§]	T2D duration (y)
24 weeks ± 8 weeks only																
26179619	Ahmann	-	NCT 01617434	26	2015	BI +/- Met	PLA/SC	LIR	-	450	58	32.25	91.04	56.85	8.25	-
23536584	Ahren	GetGoal-M	NCT 00712673	24	2013	Met	PLA/SC	LIX	-	680	54	32.91	89.76	43.06	8.06	6
20609968	Bailey	-	NCT 00528879	24	2010	Met	PLA/SC	DAPA	-	409	53	31.47	-	53.99	8.07	6
22776824	Bailey	-	-	24	2012	Diet + PA	PLA/SC	DAPA	-	136	52	31.72	87.70	50.75	7.85	1
21307137	Blevins	DURATION-5	NCT 00877890	24	2011	Diet+PA or Met +/- SU +/- TZD	ExBID	ExQW	-	252	55	33.31	95.68	57.56	8.45	7
23680739	Bode	-	NCT 01106651	26	2013	SC	PLA/SC	CANA	-	714	63	31.57	89.43	55.48	7.77	11
24117597	Bolli	GetGoal-F1	NCT 00763451	24	2014	Met	PLA/SC	LIX	-	482	56	32.50	88.74	44.67	8.03	5
15504997	Buse	-	-	30	2004	SU	PLA/SC	ExBID	-	377	55	33.33	96.31	59.70	8.60	6
21138825	Buse	-	NCT 00765817	30	2011	IN +/- Met +/- PIO	PLA/SC	ExBID	-	259	59	33.47	94.46	57.12	8.40	12
23141817	Buse	DURATION-6	NCT 01029886	26	2013	Diet+PA +/- Met +/- SU +/- PIO	ExQW	LIR	-	911	56	32.30	91.00	54.77	8.45	8
19515413	Buse	LEAD-6	NCT 00518882	26	2009	Met +/- SU	LIR	ExBID	-	464	56	32.90	93.05	51.99	8.15	8
15855572	DeFronzo	-	-	30	2005	Met	PLA/SC	ExBID	-	336	53	34.00	100.33	57.18	8.23	5
18782641	Drucker	DURATION-1	NCT 00308139	30	2008	Diet + PA +/- Met +/- SU +/- TZD	ExQW	ExBID	-	295	55	35.00	102.00	53.01	8.30	6
25018121	Dungan	AWARD-6	NCT 01624259	26	2014	Met	DUL	LIR	-	599	56	33.55	94.10	48.00	8.10	7
26799540	Dungan	AWARD-8	NCT 01769378	24	2016	Diet+PA + SU	PLA/SC	DUL	-	299	57	31.20	85.50	44.14	8.40	7
20566676	Ferrannini	-	NCT 00528372	24	2010	Diet + PA	PLA/SC	DAPA	-	353	52	32.79	90.43	46.43	7.88	0
24528605	Forst	CANTATA-MP	NCT 01106690	26	2014	Met + PIO	PLA/SC	CANA	-	342	57	32.53	94.13	63.16	7.97	10
27651331	Frias	DURATION-8	NCT 02229396	28	2016	Diet+PA + Met	ExQW+ DAPA	ExQW	DAPA	685	54	32.74	90.90	47.86	9.30	7
28205322	Gadde	DURATION-NEO-2	NCT 01652729	28	2017	Met	PLA/SC	ExQW	-	242	53	31.95	89.15	52.10	8.43	8
29473704	Guja	DURATION-7	NCT 02229383	28	2018	BI +/- Met +/- SU	PLA/SC	ExQW	-	461	57	33.70	94.00	47.95	8.53	11

22539590	Henry	T-Emerge 3	NCT 00744367	24	2012	Met + PIO	PLA/SC	TAS	-	313	54	32.63	92.17	54.13	8.13	7
23404788	Hollander	T-Emerge 7	NCT 00823992	24	2013	Met	PLA/SC	TAS	-	292	53	36.70	102.52	40.53	7.54	5
23963895	Häring	EMPA-REG METSU	NCT 01159600	24	2013	Met + SU	PLA/SC	EMPA	-	666	57	28.16	76.93	50.99	8.10	-
23906415	Kovacs	EMPA-REG PIO	NCT 01210001	24	2014	PIO +/- Met	PLA/SC	EMPA	-	498	54	29.20	78.33	48.38	8.13	-
24026211	Lavalle-González	CANTATA-D	NCT 01106677	26	2013	Met	PLA/SC	CANA	-	918	55	31.74	87.00	47.20	7.92	6
26512041	Lind	MDI Liraglutide	NCT 02113332	24	2015	BI	PLA/SC	LIR	-	122	63	33.60	99.28	64.76	9.00	17
30026333	Lingvay	-	NCT 02461589	26	2018	Diet + PA +/- Met	PLA/SC	LIR	-	258	55	32.75	94.52	53.87	8.10	6
20977576	Liutkus	-	-	26	2010	TZD +/- Met	PLA/SC	ExBID	-	165	54	33.67	93.88	59.02	8.23	6
29483060	Ludvik	AWARD-10	NCT 02597049	24	2018	SGLT-2i +/- Met	PLA/SC	DUL	-	423	57	32.66	91.48	50.01	8.04	9
25592197	Matthaei	-	NCT 01392677	24	2015	Met + SU	PLA/SC	DAPA	-	216	61	31.95	89.35	49.10	8.16	9
18803987	Moretto	-	NCT 00381342	24	2008	Diet+PA	PLA/SC	ExBID	-	232	54	31.67	85.67	56.36	7.83	1
24742660	Nauck	AWARD-5	NCT 00734474	26	2014	Met	PLA/SC	DUL	-	783	54	31.00	86.61	47.13	8.14	7
27311491	Nauck	LIRA-LIXA	NCT 01973231	26	2016	Met	LIR	LIX	-	404	56	34.70	101.25	60.00	8.40	6
23627775	Pinget	GetGoal-P	NCT 00763815	24	2013	TZD +/- Met	PLA/SC	LIX	-	484	55	33.93	94.16	52.33	8.10	8
24703047	Pratley	HARMONY 7	NCT 01128894	32	2014	Met +/- SU +/- TZD	ALB	LIR	-	812	55	32.80	92.25	50.01	8.16	8
22301126	Raz	T-emerge 1	NCT 00744926	24	2012	-	PLA/SC	TAS	-	354	54	32.30	86.86	36.66	7.61	2
23564915	Riddle	GetGoal-Duo 1	NCT 00975286	24	2013	BI + Met +/- TZD	PLA/SC	LIX	-	446	56	31.85	87.05	50.00	7.60	9
23628617	Riddle	GetGoal-L	NCT 00715624	24	2013	BI +/- Met	PLA/SC	LIX	-	495	57	32.14	87.71	46.35	8.40	12
29688502	Rodbard	SUSTAIN 5	NCT 02305381	30	2018	BI +/- Met	PLA/SC	SEM	-	396	58	32.20	91.69	56.06	8.37	13
27160639	Rodbard	-	-	26	2016	Met + DPP4i	PLA/SC	CANA	-	213	57	32.00	92.06	56.82	8.45	9
24622369	Roden	EMPA-REG MONO	NCT 01177813	24	2013	Diet + PA	PLA/SC	EMPA	-	676	54	28.40	78.13	60.63	7.88	-
28857451	Rosenstock	VERTIS MET	NCT 02033889	26	2018	Met	PLA/SC	ERTU	-	621	56	30.87	84.86	46.40	8.13	8
24650952	Rosenstock	GetGoal-S	NCT 00713830	24	2014	SU +/- Met	PLA/SC	LIX	-	859	57	30.20	83.23	50.53	8.27	9
23139373	Rosenstock	T-emerge 2	NCT 00717457	24	2013	Metformin and/or TZD	TAS	ExBID	-	1149	55	33.46	94.39	53.03	8.10	6
23698396	Rosenstock	GetGoal-X	NCT 00707031	24	2013	Met	LIX	ExBID	-	634	57	33.60	95.05	53.33	8.03	6

19688338	Russell-Jones	LEAD-5 met+SU	NCT 00331851	26	2009	Met + SU	PLA/SC	LIR	-	344	57	30.70	85.57	54.35	8.30	9
27913576	Softeland	-	NCT 01734785	24	2017	Met + DPP4i	PLA/SC	EMPA	-	327	55	30.24	85.04	60.26	7.97	-
28110911	Sorli	SUSTAIN 1	NCT 02054897	30	2017	Diet + PA	PLA/SC	SEM	-	387	53	32.93	91.97	54.40	8.06	4
23279307	Stenlöf	CANTATA-M	NCT 01081834	26	2013	Diet + PA	PLA/SC	CANA	-	584	55	31.60	86.76	44.16	8.03	4
28116776	Terra	VERTIS MONO	NCT 01958671	26	2017	-	PLA/SC	ERTU	-	461	56	33.00	92.93	56.63	8.20	4
27273731	Vanderheiden	-	NCT 01505673	26	2016	-	PLA/SC	LIR	-	71	54	41.16	115.36	36.54	8.95	-
24947583	Wit	ELEGANT	NCT 01392898	26	2014	IN +/- Met +/- SU	PLA/SC	LIR	-	50	57	33.04	100.09	61.98	7.34	7
24879836	Wysham	AWARD-1	NCT 01064687	26	2014	Met + TZD	PLA/SC	ExBID	DUL	976	55	33.28	95.99	58.43	8.10	9
52 weeks ± 8 weeks only																
29246950	Ahmann	SUSTAIN-3	NCT 01885208	56	2018	Met +/- TZD +/- SU	SEM	ExQW	-	809	56	33.80	95.80	55.25	8.35	9
30082326	Jabbour	DURATION-8	NCT 02229396	52	2018	Diet+PA + Met	ExQW+ DAPA	ExQW	DAPA	685	54	32.74	90.90	47.86	9.30	7
26212528	Matthaei	-	NCT 01392677	52	2015	Met + SU	PLA/SC	DAPA	-	216	61	31.95	89.35	49.10	8.16	9
26577795	Nauck	HARMONY 2	NCT 00849017	52	2016	Diet + PA	PLA/SC	ALB	-	301	52	33.53	96.06	55.13	8.07	3
25468945	Neal	CANVAS Insulin Substudy	NCT 01032629	52	2015	IN	PLA/SC	CANA	-	2072	62	32.03	94.67	66.00	8.30	16
25155146	Reusch	HARMONY 1	NCT 00849056	52	2014	TZD +/- Met	PLA/SC	ALB	-	301	55	34.15	98.90	59.80	8.10	7
26701110	Roden	EMPA-REG EXTEND MONO	NCT 01289990	52	2015	Diet + PA	PLA/SC	EMPA	-	676	54	28.40	78.13	60.63	7.88	-
24 weeks and 52 weeks ± 8 weeks																
28921862	Dagogo	VERTIS SITA2	NCT 02036515	26/52	2017	Met + Sit	PLA/SC	ERTU	-	462	59	30.80	86.87	56.93	8.03	9
22446170	Rosenstock	-	NCT 00683878	24/52	2012	TZD	PLA/SC	DAPA	-	420	53	-	86.34	49.51	8.37	5
24118688	Wilding	CANTATA-MSU	NCT 01106625	26/52	2013	Met + SU	PLA/SC	CANA	-	469	56	33.07	92.84	50.96	8.10	9
22431673	Wilding	Dapagliflozin 006	NCT 00673231	24/52	2012	IN	PLA/SC	DAPA	-	598	59	33.16	94.07	47.14	8.56	13

Baseline characteristics of trials are reported as mean.

§ *Full reference available in Appendix Table 2,* **§** *to convert to mmol/mol: HbA_{1c} (mmol/mol) = (10.93×HbA_{1c} (%))-21.5*

¶ *BMI=(weight (kg)/height (m)^2)*

Abbreviations: SU, Sulfonylurea; TZD, Thiazolidinediones; BI, Basal Insulin; Met, Metformin; PA, Physical Activity; PIO, Pioglitazones; Sit, Sitagliptin; DPP4i, DPP 4 inhibitors; IN, insulin; PLA/SC, Placebo/Standard Care; CANA, Canagliflozin; DAPA, Dapagliflozin; EMPA, Empagliflozin; ERTU, Ertugliflozin; ExBID, Exenatide Twice Daily; LIX, Lixisenatide; ALB, Albiglutide; DUL, Dulaglutide; ExQW, Exenatide Once Weekly; LIR, Liraglutide; SEM, Semaglutide; TAS, Taspoglutide.

Figures

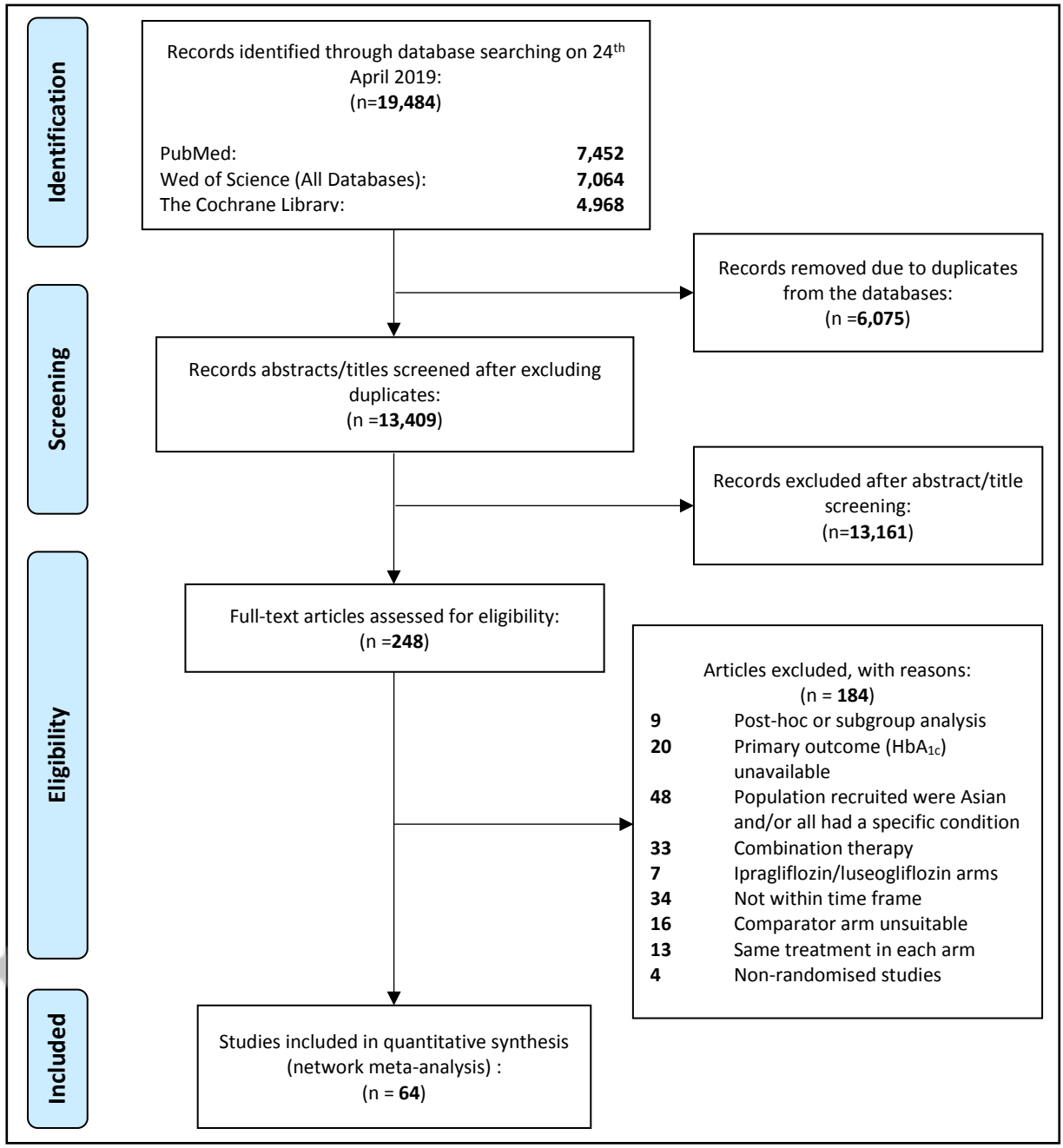

Figure 1 Flow diagram of paper inclusion for systematic review and network meta-analysis

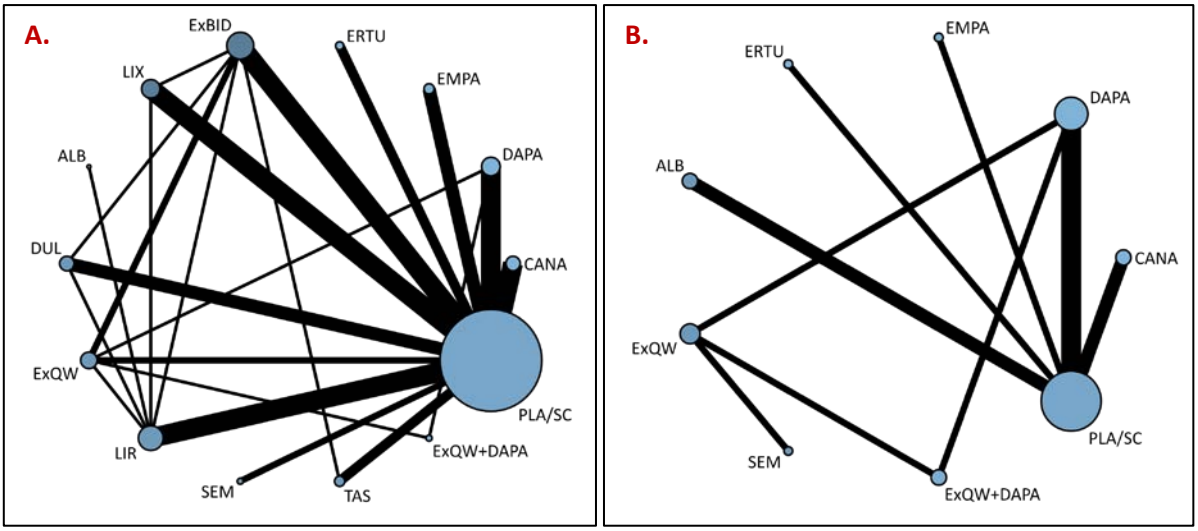

Figure 2 Network plot for HbA_{1c} (%, mmol/mol)

(A) Network plot at 24 weeks; (B) Network plot at 52 weeks.

Lines represent direct comparisons between treatments; line thickness is weighted so that a thicker line represents a higher number of direct comparisons.

Abbreviations: PLA/SC, Placebo/Standard Care; CANA, Canagliflozin; DAPA, Dapagliflozin; EMPA, Empagliflozin; ERTU, Ertugliflozin; ExBID, Exenatide Twice Daily; LIX, Lixisenatide; ALB, Albiglutide; DUL, Dulaglutide; ExQW, Exenatide Once Weekly; LIR, Liraglutide; SEM, Semaglutide; TAS, Taspoglutide.

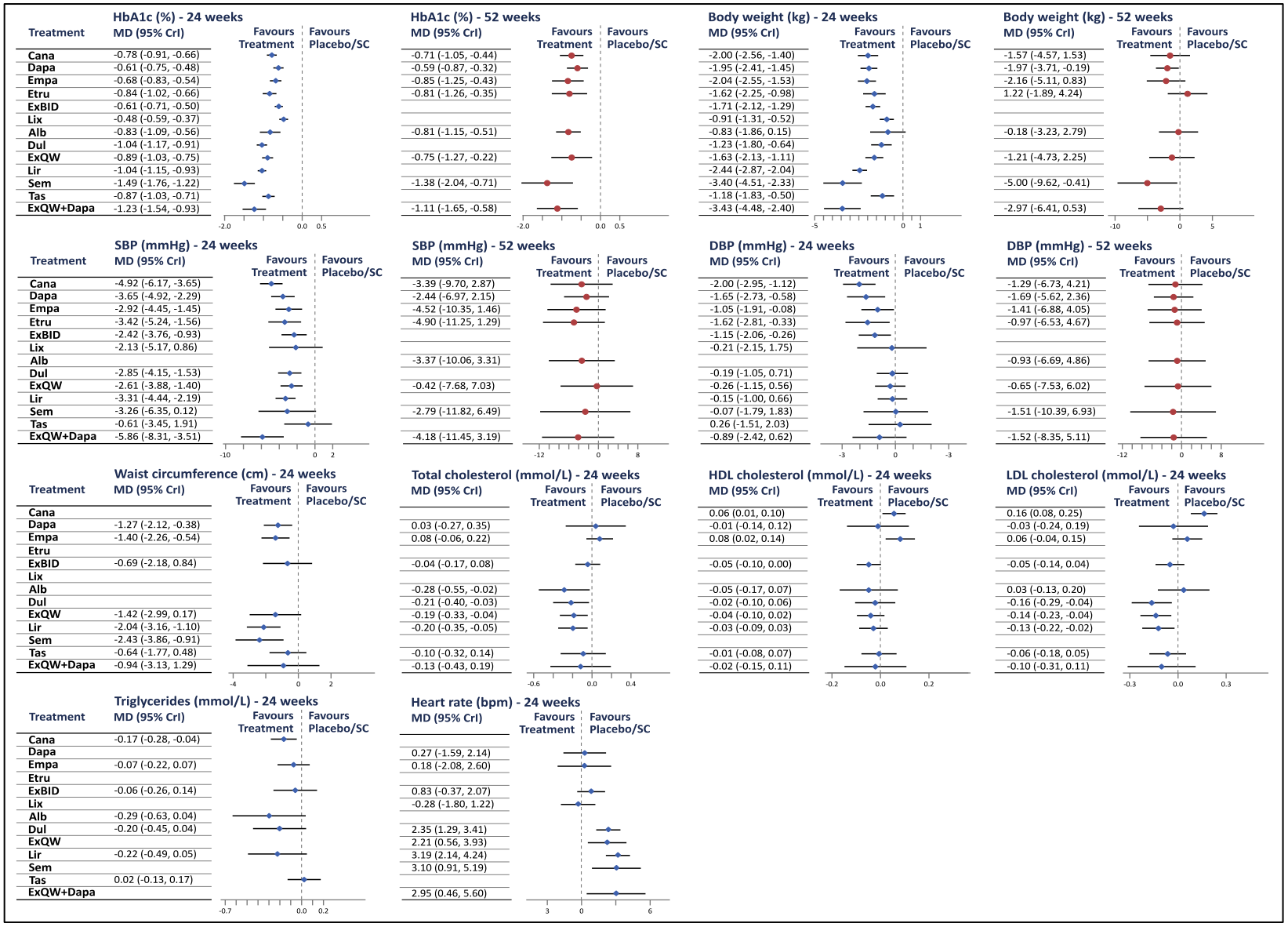

Figure 3 Network meta-analysis results for the mean difference in primary and secondary outcomes at 24 and 52 weeks in comparison to placebo/standard care

To convert change in HbA_{1c} measured in % to mmol/mol: change in HbA_{1c} (mmol/mol) = 10.93×change in HbA_{1c} (%)

Abbreviations: MD, mean difference; CrI, Credible Interval; PLA/SC, Placebo/Standard Care; CANA, Canagliflozin; DAPA, Dapagliflozin; EMPA, Empagliflozin; ERTU, Ertugliflozin; ExBID, Exenatide Twice Daily; LIX, Lixisenatide; ALB, Albiglutide; DUL, Dulaglutide; ExQW, Exenatide Once Weekly; LIR, Liraglutide; SEM, Semaglutide; TAS, Taspoglutide.

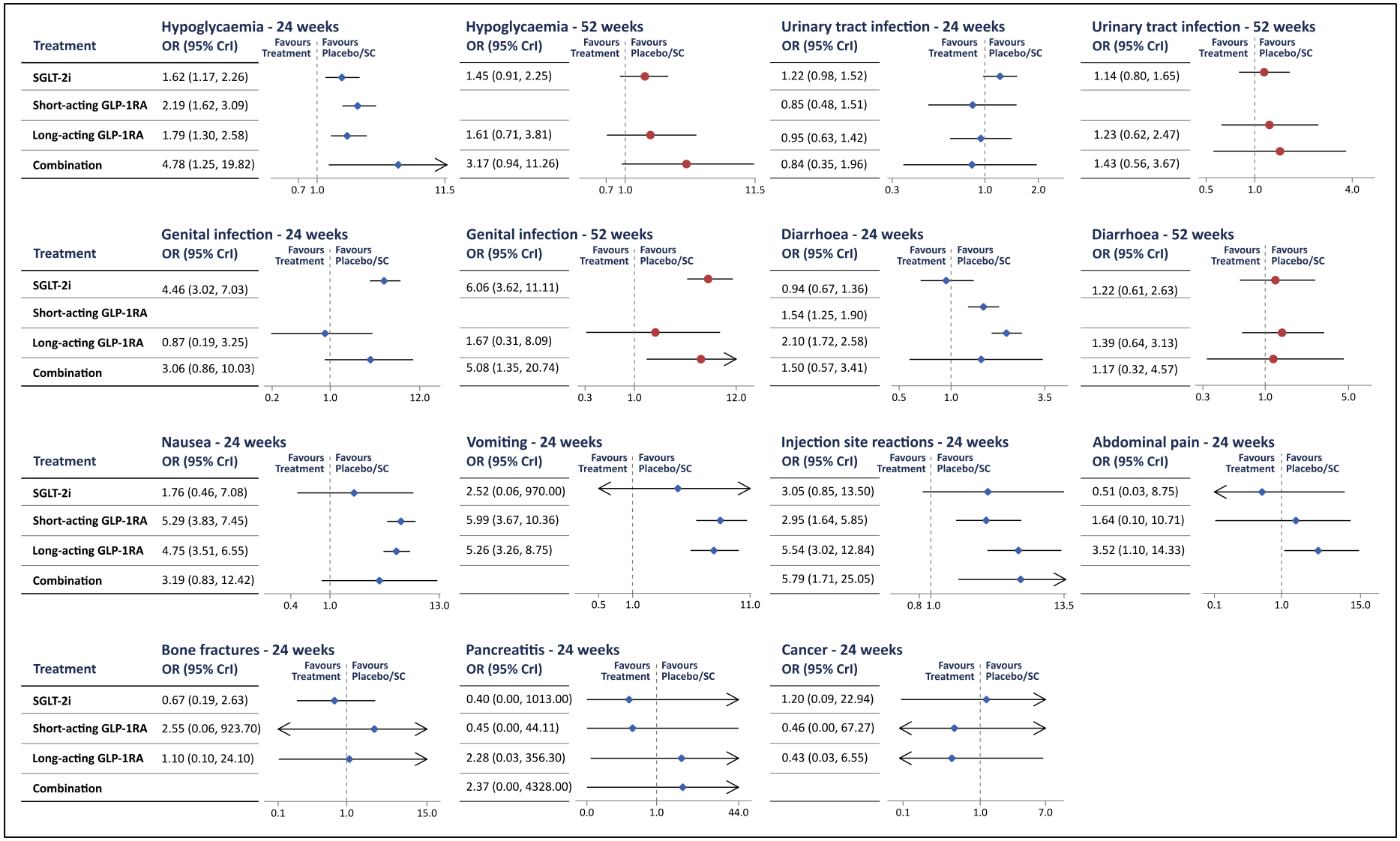

Figure 4 Network meta-analysis results reporting odds ratios for safety outcomes at 24 and 52 weeks in comparison to placebo/standard care

Combination treatment arm is a long-acting GLP-1RA combined with an SGLT-2i (i.e. Exenatide QW with Dapagliflozin).

Abbreviations: PLA/SC, Placebo/Standard Care; CANA, Canagliflozin; DAPA, Dapagliflozin; EMPA, Empagliflozin; ERTU, Ertugliflozin; ExBID, Exenatide Twice Daily; LIX, Lixisenatide; ALB, Albiglutide; DUL, Dulaglutide; ExQW, Exenatide Once Weekly; LIR, Liraglutide; SEM, Semaglutide; TAS, Taspoglutide.