Efficacy and safety of sodium–glucose cotransporter 2 inhibitors in type 2 diabetes mellitus

Systematic review and network meta–analysis

Running title: SGLT2 inhibitors in type 2 diabetes

Francesco Zaccardi

David R Webb

Zin Z Htike

Dalia Youssef

Kamlesh Khunti

Melanie J Davies

Diabetes Research Centre, University of Leicester, Leicester, UK
Leicester Diabetes Centre, UHL NHS Trust, Gwendolen Road, Leicester LE5 4PW, UK

Corresponding Author
Dr Francesco Zaccardi
Diabetes Research Centre, Leicester General Hospital, Leicester, UK
Phone: +44 0116 258 4389 – Fax: +44 0116 258 4499
Email: frazac@fastwebnet.it

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Supplementary Appendix: Search strategy; 8 Tables; 8 Figures; PRISMA checklist

ABSTRACT

Aims

To assess the comparative efficacy and safety of SGLT2 inhibitors in adults with type 2 diabetes.

Materials and Methods

We electronically searched up to November 3, 2015, randomised controlled trials (e 24 weeks) including canagliflozin, dapagliflozin, or empagliflozin. Data were collected for cardiometabolic and safety outcomes and synthesized with network meta–analyses.

Results

38 trials (23997 participants) were included. Compared to placebo, all SGLT2 inhibitors reduced HbA1c, fasting plasma glucose (FPG), body weight (BW), and blood pressure (BP), and slightly increased HDL-cholesterol. Canagliflozin 300mg reduced HbA1c, FPG, and systolic BP and increased LDL-cholesterol to a greater extent compared to other inhibitors at any dose. At their highest doses, canagliflozin 300mg reduced HbA1c by 0.2% (95% CI: 0.1 to 0.3) compared to both dapagliflozin 10mg and empagliflozin 25mg; FPG by 0.6mmol/l (0.3 to 0.9) and 0.5mmol/l (0.1 to 0.8), vs dapagliflozin and empagliflozin, respectively; systolic BP by 2mmHg (1 to 3) vs dapagliflozin; and increased LDL-cholesterol of 0.13mmol/l (0.03 to 0.23) and 0.15mmol/l (0.06 to 0.23) vs dapagliflozin and empagliflozin, respectively; highest doses of inhibitors had similar effects on BW reduction. Canagliflozin 300mg and 100mg increased the risk of hypoglycaemia compared to placebo, dapagliflozin 10mg, and empagliflozin 10mg (odds ratios (ORs), 1.4 to 1.6). Dapagliflozin 10mg increased the risk of urinary tract infection compared to placebo and empagliflozin 25mg

(ORs, 1.4). All inhibitors similarly increased the risk of genital infection (ORs, 4 to 6 compared to placebo).

Conclusions

Although increasing the risk of genital infection, SGLT2 inhibitors are effective in improving cardiometabolic markers in type 2 diabetes, with canagliflozin 300mg performing better in this respect than other inhibitors. Further studies will clarify whether these differences are likely to translate in different long term outcomes.

INTRODUCTION

Type 2 diabetes mellitus is a complex disorder characterised by hyperglycaemia and progressive dysregulation of insulin–glucose feedback mechanisms [1]. Multiple intervention studies have demonstrated the importance of glucose control in the reduction of long-term microvascular and, to some extent, macrovascular complications of the disease [2].

A range of glucose–lowering treatments are currently available and they exert their main effects by modulating peripheral insulin resistance or ² –cell insulin secretion [3]. More recently, a new class of glucose–lowering agents, which act by the inhibition of renal glucose reabsorption in the kidney, has been introduced [4]. In physiological conditions, glycosuria arises when the tubular threshold for glucose reabsorption is exceeded. As sodium–glucose cotransporter 2 (SGLT2) is the major cotransporter involved in tubular glucose reuptake, inhibitors of its activity have been developed with the aim of enhancing glycosuria and reducing blood glucose levels [5].

The efficacy and safety of SGLT2 inhibitors have been investigated in several randomised controlled trials (RCTs), showing improved glucose control and a reduction of body weight and blood pressure with a low risk of hypoglycaemia [5]. These drugs are recommended by the American Diabetes Association and European Association for the Study of Diabetes as a treatment option in patients on metformin with or without another glucose–lowering treatment if the personalised glucose target is not achieved [3]. However, no direct comparisons between specific SGLT2 inhibitors are available to date, thus limiting the possibility of a comparative assessment of their efficacy and safety.

Network meta–analysis is considered the methodology of choice to allow estimation of the comparative effectiveness of multiple treatments when direct 'head–to–head' data are unavailable [6]. Further to this, its value to inform health care decision making is increasingly recognised, given the possibility of ranking treatments according to efficacy and safety [7]. Within this context, we

conducted a systematic review and network meta–analysis to assess the comparative efficacy and safety of SGLT2 inhibitors canagliflozin, dapagliflozin, and empagliflozin.

MATERIALS AND METHODS

Data Sources and Searches

This study was conducted according to a pre–specified protocol and followed the standard guidelines for conducting and reporting systematic reviews and network meta–analysis (Supplementary Appendix) [8–10]. We searched PubMed, ISI Web of Science, and the Cochrane Library for RCTs published in any language from inception until November 3, 2015 and comparing licensed doses of canagliflozin (100mg or 300mg), dapagliflozin (5mg or 10mg), or empagliflozin (10mg or 25mg) with placebo or other glucose–lowering drugs in adults with type 2 diabetes.

Study Selection

RCTs lasting at least 24 weeks and reporting data on one or more cardiometabolic or safety outcomes were included. We excluded RCTs including only patients with chronic kidney disease at baseline. Cardiometabolic outcomes comprised HbA1c, fasting plasma glucose (FPG), body weight (primary outcomes); systolic and diastolic blood pressure, total cholesterol, low–density lipoprotein (LDL) and high–density lipoprotein (HDL) cholesterol, and triglycerides. Safety outcomes included all hypoglycaemic events, urinary tract infection, genital infection, diabetic ketoacidosis, and bone fractures. Reference lists of eligible studies, as well as systematic reviews and meta-analyses of SGLT2 inhibitors, were manually scanned for additional relevant studies.

Data Extraction and Quality Assessment

Three authors independently performed the literature search. After the identification of the eligible studies, the three authors independently extracted data, using standardised pre–defined forms, on: first author name, clinical trial registration number, year of journal article publication, background

glucose–lowering therapy, SGLT2 inhibitor(s) and comparator(s), duration of follow-up, sample size, gender distribution, age, diabetes duration, baseline HbA1c, and outcome measured. We extracted outcomes data as arm–specific counts (i.e., number of participants, mean difference and standard error (or standard deviation) for continuous outcomes in patients with baseline and at least one post-baseline measurement); total number of participants and participants with event for dichotomous outcomes in patients who were randomised and received treatment; or contrast–based estimations (i.e., pairwise comparisons). When studies reported outcomes data for different durations of follow-up, the longest was used. We retrieved data from ClinicalTrials.gov when it was not possible to extract relevant information from the published report. In cases where the independent reviewers disagreed on the eligibility of an article or data extraction, consensus was reached by arbitration. Study quality was assessed using the Cochrane risk of bias tool [11].

Data Synthesis and Analysis

We undertook a network meta–analysis within a frequentist model, an alternative to the Bayesian approach. Stata 14.1 (Stata Corp, College Station, TX, USA) was used for all analyses, Pairwise random–effects meta–analyses were performed using the DerSimonian and Laird method [12]. Network meta–analyses were based on the method of multivariate meta–analysis with the assumption that all treatment contrasts have the same heterogeneity variance [13–15]. Results were reported with 95% confidence intervals; we considered $p<0.05$ as statistically significant.

In three–arm trials reporting contrasted-based estimates for continuous outcomes, pairwise comparisons were available only for two out of the three possible contrasts (i.e., A *vs* B and B *vs* C, but not A *vs* C, where A, B, and C denote the three arms); in these cases, given the presence of correlations between the treatment differences, the standard error (Ã) of the missing contrast was

estimated using the formula: $\tilde{A}^2_{AC} = \tilde{A}^2_{AB} + \tilde{A}^2_{BC} - 2\acute{A}\tilde{A}_{AB}\tilde{A}_{BC}$ [16]. As Ávalues (correlations) were not reported, we used in the main analysis a value similar to those obtained from other comparable studies included in this systematic review (Á=0.5), as previously advocated [16]. We performed sensitivity analyses assuming different values of Á (0.2, 0.7, and 0.9). Comparable results were obtained and therefore we reported only the results of the main analysis.

We combined linagliptin and sitagliptin in a single group (dipeptidyl peptidase–4 inhibitors, DPP–4i) and glimepiride and gliclazide in another (sulphonylurea). For the primary outcomes, we reported random–effect pairwise meta–analyses with heterogeneity across studies estimated using the I^2 statistic. For dichotomous outcomes, we used odds ratio (OR) as effect measure and added 0.5 when studies reported zero events. For all outcomes, we summarised the evidence by using a network diagram [17]. We reported characteristics and summary data of included studies in tables. We presented results against a common comparator (placebo) in forest plots and showed comparisons across SGLT2 inhibitors in tables [18]; we also displayed graphically with radar plots the ranking probabilities (*network rank* command) for different cardiometabolic and safety outcomes and reported comparison-adjusted funnel plots (*netfunnel* command) to assess the association between study size and result. We assumed that participants of the included RCTs could be randomly allocated to any of the three treatments being compared (on average, the baseline characteristics of participants are similar as the treatments are tested for a wide range of patients). For each network, we assessed consistency between direct and indirect evidence by using the 'design by treatment' interaction model [19].

RESULTS

Study characteristics

From 2174 identified records we excluded non-human and observational studies, leaving 79 reports for full-text assessment; after further selection (Figure S1 in the Supplementary Appendix), 38 unique RCTs fulfilled inclusion criteria (Table 1) [20–57]. RCTs were published between 2012 and 2015 included 23997 (range, 136–2072) participants with type 2 diabetes; 34 (89.5%) were multinational RCTs. Baseline HbA1c, age, and disease duration weighted means were 8.1%, 58 years old, and 8 years, respectively; 57% were males and follow up duration ranged from 24 to 208 weeks. Other characteristics of the RCTs, such as study-, drug-, and outcome-specific available data, are reported in Tables S1-S5.

Overall, the risk of bias for the domains included in the Cochrane tool of risk assessment were judged to be low, high, and unclear in 89.5%, 1.8%, and 8.7% of the cases, respectively; high or unclear domain-specific bias was lowest for blinding of outcome assessment (2.7%) and highest for random sequence generation (15.8%) (Table S5, Figure S2). The risk of bias was high or unclear in 1.8%, 10.8%, and 16.7% of canagliflozin, dapagliflozin, and empagliflozin RCTs, respectively. Networks of evidence for all outcomes are graphically displayed in Figure 1.

Meta-analyses

Primary outcomes: HbA1c, fasting plasma glucose, and body weight

Data on HbA1c were available from all RCTs. Direct pairwise random-effects meta-analyses showed significant reductions of HbA1c versus placebo, from -0.9% (95% confidence interval: -1.0 to -0.7) [-9.8mmol/mol; -10.9 to -7.6] for canagliflozin 300mg to -0.6% (-0.7 to -0.4) [-6.5mmol/mol; -7.6 to -4.4] for dapagliflozin 5mg (Figure S3). When compared to other glucose–lowering drugs (sulphonylurea, DPP–4i, or metformin), pairwise differences ranged from a significant reduction of -0.3% (-0.5 to -0.1) [-3.3mmol/mol; -5.4 to -1.1] comparing dapagliflozin 10mg with DPP–4i to a nonsignificant increase of 0.1% (-0.1 to 0.2) [1.1mmol/mol; -1.1 to 2.2] for empagliflozin 10mg versus metformin (Figure S3). The results of the network meta–analysis showed a mean HbA1c reduction, compared to placebo, of -0.9% (-1.0 to -0.8) for canagliflozin 300mg [-9.4mmol/mol; -10.5 to -8.3]; -0.8% (-0.9 to -0.7) for canagliflozin 100mg [-8.3mmol/mol; -9.4 to -7.2]; -0.7% (-0.8 to -0.6) for empagliflozin 25mg [-7.2mmol/mol; -8.3 to -6.1]; -0.7% for dapagliflozin 10mg (-0.7 to -0.6) [-7.2mmol/mol; -8.1 to -6.3]; -0.6% (-0.7 to 0.5) [-6.6mmol/mol; -7.7 to 5.5] for empagliflozin 10mg; and -0.6% (-0.7 to -0.4) [-6.1mmol/mol; -7.3 to 4.8] for dapagliflozin 5mg (Table 2; Figure 2). Comparisons across SGLT2 inhibitors showed greater HbA1c reductions with canagliflozin 300mg compared to all other SGLT2 drugs (from -0.3% [-3.3mmol/mol] versus dapagliflozin 5mg to -0.1% [-1.1mmol/mol] versus canagliflozin 100mg) and no significant differences between dapagliflozin and empagliflozin at different doses (Table 2). Figure S4 and Figure S5 show SGLT2 inhibitors according to the ranking probabilities and the mean rank, respectively.

Values of FPG were available from 37 RCTs. Pairwise random–effects meta-analyses evidenced significant reductions of FPG versus placebo for all SGLT2 inhibitors, from -2.0mmol/l (-2.4 to -1.6) for canagliflozin 300mg to -1.1mmol/l (-1.5 to -0.7) for dapagliflozin 5mg (Figure S3). Comparing

SGLT2 inhibitors to other glucose–lowering drugs, differences ranged from -1.2mmol/l (-1.6 to -0.8) for canagliflozin 300mg versus DPP–4i to -0.3mmol/l (-0.6 to -0.1) for empagliflozin 10mg versus metformin (Figure S3). Network meta–analysis results similarly showed a reduction of FPG for all SGLT2 inhibitors compared to placebo: -1.9mmol/l (-2.2 to -1.7) for canagliflozin 300mg; -1.6mmol/l (-1.9 to -1.4) for canagliflozin 100mg; -1.5mmol/l (-1.7 to -1.3) for empagliflozin 25mg; -1.4 mmol/l (-1.6 to -1.2) for dapagliflozin 10mg; -1.3mmol/l (-1.6 to -1.1) for empagliflozin 10mg; and -1.1mmol/l (-1.4 to -0.9) for dapagliflozin 5mg (Table 2; Figure 2). Among SGLT2 inhibitors, canagliflozin 300mg reduced FPG to a greater extent compared to all other inhibitors (from -0.8mmol/l versus dapagliflozin 5mg to -0.3mmol/l versus canagliflozin 100mg) (Table 2).

Data on body weight were available from 37 RCTs. Pairwise random–effects meta–analyses showed significant reductions of body weight versus placebo for all SGLT2 treatments, from -2.8kg (-3.2 to -2.4) for canagliflozin 300mg to -1.6kg (-2.1 to -1.0) for dapagliflozin 5mg (Figure S3). When compared to other glucose–lowering drugs, SGLT2 inhibition effects ranged from a -4.4kg (-4.8 to -4.1) reduction for empagliflozin 25mg versus sulphonylurea to -1.2 (-1.9 to -0.6) for dapagliflozin 5mg versus metformin (Figure S3). The results of the network analysis showed a reduction of body weight compared to placebo of -2.5kg (-2.8 to -2.1) for canagliflozin 300mg; -2.3kg (-2.6 to -1.9) for empagliflozin 25mg; -2.2kg (-2.5 to 1.9) for dapagliflozin 10mg; -2.1kg (-2.5 to -1.8) for empagliflozin 10mg; -1.9kg (-2.2 to -1.5) for canagliflozin 100mg; and -1.6kg (-2.0 to -1.2) for dapagliflozin 5mg (Table 2; Figure 2). There was a statistical inconsistency for the body weight network (Table S6); funnel plots for primary outcomes are shown in Figure S6.

Comparable results were found for HbA1c, FPG, and body weight in analyses restricted to studies with a similar duration of follow-up (Table S7).

Secondary cardiometabolic outcomes

Data for other cardiometabolic outcomes ranged from 7828 participants (18 RCTs) for total cholesterol to 17600 participants (33 RCTs) for systolic blood pressure. Compared to placebo, network meta–analysis results showed a reduction of systolic (from -4.9mmHg with canagliflozin 300mg to -2.8mmHg with dapagliflozin 5mg) and diastolic (from -2.0mmHg with canagliflozin 300mg to -1.5mmHg with dapagliflozin 5mg) blood pressure for all SGLT2 inhibitors (Table 2; Figure 2). Canagliflozin 300mg reduced systolic blood pressure to a greater extent compared to other SGLT2 inhibitors, while no differences were found among inhibitors for diastolic blood pressure. All SGLT2 inhibitors slightly increased HDL–cholesterol levels compared to placebo (highest increase, 0.07mmol/l for canagliflozin 300mg and dapagliflozin 10mg), and no differences were found among SGLT2 inhibitors. Canagliflozin at all doses reduced triglycerides levels compared to placebo and empagliflozin while canagliflozin 300mg increased LDL–cholesterol versus placebo and all other SGLT2 inhibitors. No differences were found among SGLT2 for total cholesterol, although data were not available for all treatments (Table 2). There was no statistical inconsistency for all outcomes, although p-values were "borderline" for triglycerides and systolic blood pressure (Table S6).

Safety outcomes

Data on hypoglycaemic events were available from 37 RCTs, reporting a total of 4347 participants with event. The results of the network meta–analysis showed an increased risk of hypoglycaemia compared to placebo for canagliflozin 300mg and 100mg, with respective ORs of 1.6 (1.3 to 1.9) and 1.5 (1.3 to 1.8) (Table 3; Figure S7). Among SGLT2 inhibitors, canagliflozin at both doses significantly increased the risk of hypoglycaemia compared to dapagliflozin 10mg (ORs 1.5) and

empagliflozin 10mg (ORs 1.4) (Table 3). In a sensitivity analysis excluding studies with insulin or sulfonylurea as background therapy, canagliflozin at both doses increased the risk of hypoglycaemia compared to dapagliflozin 10mg (ORs 1.7 to 1.9), although no significant differences were found versus placebo for all SGLT2 inhibitors (Table S8).

Based on 1959 participants with event from all RCTs, network meta–analysis showed an increased risk of urinary tract infection for dapagliflozin 10mg versus placebo and empagliflozin 25mg (ORs 1.4) (Table 3).

Data on genital infection were available from 37 RCTs (1285 participants reporting event). Compared to placebo, there was an increased risk of infection for all SGLT2 inhibitors, with ORs ranging from 4.2 (2.7 to 6.3) for empagliflozin 10mg to 5.9 (4.0 to 8.3) for canagliflozin 300mg. No differences were found among SGLT2 inhibitors (Table 3).

Mean ranks and ranking probabilities are graphically displayed in the Figure S5 and Figure S8, respectively. No inconsistency was found for all three safety outcome networks (Table S6).

Data on diabetic ketoacidosis and bone fractures were reported only in three and nine studies, respectively, limiting the possibility to perform a formal analysis.

DISCUSSION

Several randomised clinical trials have investigated the efficacy and safety of SGLT2 inhibitors compared to placebo or other glucose-lowering drugs (sulphonylurea, DPP–4i, or metformin); however, to date, no direct 'head-to-head' trials comparing SGLT2 inhibitors have been reported or are ongoing, thus limiting the possibility of a direct evaluation of their comparative clinical profiles. As network meta–analysis allows indirect assessment between treatments when direct evidence is unavailable, we used this approach to compare SGLT2 inhibitors for multiple outcomes.

While previous network meta-analysis assessed the efficacy and safety of a single SGLT2 inhibitor [58-61] or restricted the analyses only to efficacy outcomes and in patients with type 2 diabetes inadequately controlled with diet and exercise alone or metformin monotherapy [62], we collected data for inhibitors clinically available in most countries and for indicators usually considered when choosing glucose–lowering drugs as well as for other cardiometabolic and safety outcomes to provide a comprehensive picture of these inhibitors.

When compared to placebo, all SGLT2 inhibitors improved glucose control (0.6% to 0.9% decrease in HbA1c and 1.1mmol/l to 1.9mmol/l decrease in FPG) and reduced body weight (1.6kg to 2.5kg), systolic (2.8mmHg to 4.9mmHg), and diastolic (1.5mmHg to 2.0mmHg) blood pressure. Further to this, all SGLT2 inhibitors modestly increased HDL-cholesterol levels compared to placebo (greatest increase, 0.07mmol/l). Available evidence also suggested a small increase in LDL–cholesterol and a reduction of triglycerides with both doses of canagliflozin when compared to placebo. Given the limited data available for total cholesterol, however, the effects of SGLT2 inhibitors on the overall lipid profile should be further investigated. Overall change in these cardiometabolic biomarkers would suggest, at least theoretically, a potential microvascular and cardiovascular benefit. The recent EMPA-REG OUTCOME trial has indeed demonstrated a reduction of cardiovascular events in

patients with type 2 diabetes treated with empagliflozin [63]. On-going RCTs [64, 65] will confirm whether similar benefits could be extended to other drugs of the same class. Conversely, although SGLT2 inhibitors should not increase the risk of hypoglycaemia as they do not stimulate insulin secretion [5], the risk was ~50% greater for both canagliflozin doses but not different for empagliflozin and dapagliflozin when compared to placebo. Of note, the increased canagliflozin risk was nominally lower than metformin and significantly lower than sulphonylurea (~9–fold). Moreover, when the analysis was restricted to studies without background sulphonylureas or insulin, the risk of hypoglycaemia for all SGLT2 inhibitors was similar to placebo. This would suggest an imbalance of insulin or sulfonylurea use across studies where SGLT2 inhibitors were compared to placebo or some heterogeneity possibly due to study design (insulin studies are more likely to be open label and treat-to-target with no stable doses during trial). As expected, the most relevant undesirable effect of SGLT2 inhibition is an increased risk of genitourinary infection as a direct effect of glycosuria. Infections of the upper urinary tract, interestingly, were not consistently increased by SGLT2 inhibitors versus placebo (the risk was increased only by dapagliflozin 10mg), whereas all inhibitors significantly increased the risk of genital infection (balanitis, prosthetitis, vulvovaginitis; 4 to 6–fold versus placebo), with no difference across inhibitors.

Along with changes versus placebo, we also found some differences between SGLT2 inhibitors. The highest dose of canagliflozin reduced HbA1c, FPG, and systolic blood pressure to a greater extent compared to dapagliflozin and empagliflozin at any dose. Conversely, highest doses of SGLT2 inhibitors did not differ in the extent of body weight and diastolic blood pressure reduction or HDL-cholesterol increase. Whilst incomplete data on total cholesterol limited a comparative and overall assessment, differences among inhibitors were found for LDL–cholesterol and triglycerides (with the highest dose of canagliflozin decreasing triglycerides versus empagliflozin at any dose and

increasing LDL-cholesterol versus all other SGLT2 inhibitors). Among SGLT2 inhibitors, the risk of urinary tract and genital infection was similar, while at their highest doses canagliflozin increased the risk of hypoglycaemia compared to dapagliflozin also accounting for different background therapies. The differences observed for some clinical outcomes could in part be attributed to outcome definition, study design and/or analysis, or intrinsic pharmacological properties of individual drugs. Indeed, in addition to SGLT2, the SGLT1 receptor has also been implicated in glucose regulation [66], and each inhibitor is known to have a different receptor selectivity profile (for SGLT2 over SGLT1, >2500-fold with empagliflozin; >1200-fold with dapagliflozin; and >250-fold with canagliflozin) [67]. Our findings of a better glucose control and of an increase in LDL-cholesterol by canagliflozin would therefore underline the glicometabolic relevance of SGLT1 inhibition and support recent results on dual SGLT1/SGLT2 blockade [68, 69].

We should acknowledge some limitations of this study. First, we performed a study-level meta–analysis based only on data published in journal articles or available on ClinicalTrials.gov. This could introduce a bias as they are more likely to report 'positive' findings compared to unpublished reports. However, such risk of bias should be low for RCTs. Second, in some studies, outcomes were not reported or it was not possible to extract them in a suitable way. Information was retrieved from all 38 RCTs for HbA1c and urinary tract infection and from 37 RCTs for FPG, body weight, hypoglycaemia, and genital infection. Recently, several cases of diabetic ketoacidosis without frank hyperglycaemia ("euglycaemic diabetic ketoacidosis") have been reported in association with SGLT2 inhibitors [70, 71], along with an increased risk of bone fractures with canagliflozin [72, 73]. Given the limited availability of data on these outcomes, we could not perform formal assessments; future ad-hoc analyses and studies will clarify how such complications are drug- or class-specific. Third, across RCTs, ethnicities of participants included, follow-up durations, or outcomes selection,

definition, and ascertainment could to some extent differ. Yet, the majority of trials used the same classification system for urinary and genital tract infection (system organ class and preferred term, MedDRA). Further to this, analyses for the primary outcomes including studies with similar duration evidenced consistent results. Finally, we found a significant inconsistency for the body weight network (although not present for studies with similar follow-up) and caution is needed in interpreting these results. To our knowledge, this is the first attempt to summarise available data on SGLT2 inhibitors and to assess them comparatively for a wide range of outcomes.

In conclusion, SGLT2 inhibitors improved cardiometabolic markers in patients with type 2 diabetes, with canagliflozin 300mg generally performing better than other inhibitors. However, they increased the risk of genital infection. RCTs with direct SGLT2 comparisons would further delineate their comparative efficacy and tolerability. Moreover, given their effects on blood pressure and lipoproteins, ongoing RCTs with cardiovascular outcomes will clarify whether changes in intermediate biomarkers would also translate into a reduction in relevant vascular complications confirming early positive results of this class of glucose-lowering agents [63, 74].

AUTHOR CONTRIBUTION

FZ, MJD study idea and design

FZ, ZZH, DY literature search and data extraction

FZ data analysis

FZ, DRW, ZZH, DY, KK, MJD study critical revision and manuscript draft

All authors provided final approval of the version to publish. Statistical codes and datasets are available from the corresponding author. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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DECLARATION OF INTERESTS

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

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

DRW has received grant in support of investigator initiated studies and honoraria from Sanofi-Aventis and Novo Nordisk.

All other Authors have no conflict of interests to disclose.

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TABLES AND FIGURES LEGEND

Table 1: Baseline characteristics of the included studies
Table 2: Comparisons of SGLT2 inhibitors for cardiometabolic outcomes
Table 3: Comparisons of SGLT2 inhibitors for safety outcomes

Figure 1: Network maps for cardiometabolic and safety outcomes

Legend: Nodes represent the competing treatments and their size is proportional to the number of participants; edges represent the available direct comparisons between pairs of treatments and their width is proportional to the number of trials comparing every pair.

Abbreviations
Cana100=Canagliflozin 100mg; Cana300=Canagliflozin 300mg; Dapa5=Dapagliflozin 5mg; Dapa10=Dapagliflozin 10mg; Empa10=Empagliflozin 10mg; Empa25=Empagliflozin 25mg; DPP-4i= Dipeptidyl peptidase-4 inhibitor; Met=Metformin; SU=Sulphonylurea

Figure 2: Differences vs Placebo (dotted lines) in cardiometabolic outcomes for the drugs included in the network meta-analysis

Abbreviations
Cana100=Canagliflozin 100mg; Cana300=Canagliflozin 300mg; Dapa5=Dapagliflozin 5mg; Dapa10=Dapagliflozin 10mg; Empa10=Empagliflozin 10mg; Empa25=Empagliflozin 25mg; DPP-4i= Dipeptidyl peptidase-4 inhibitor; Met=Metformin; SU=Sulphonylurea

Figure 1

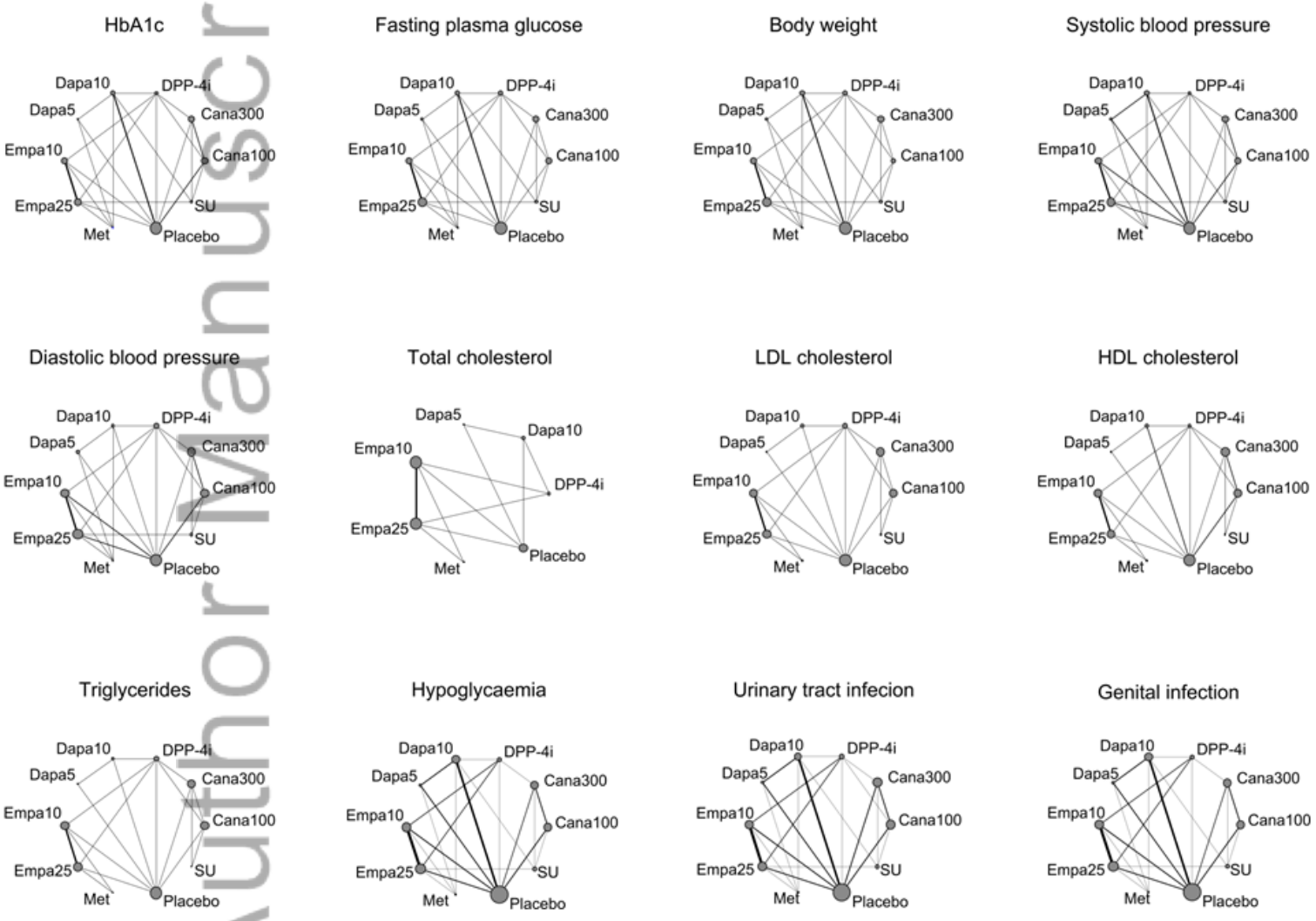

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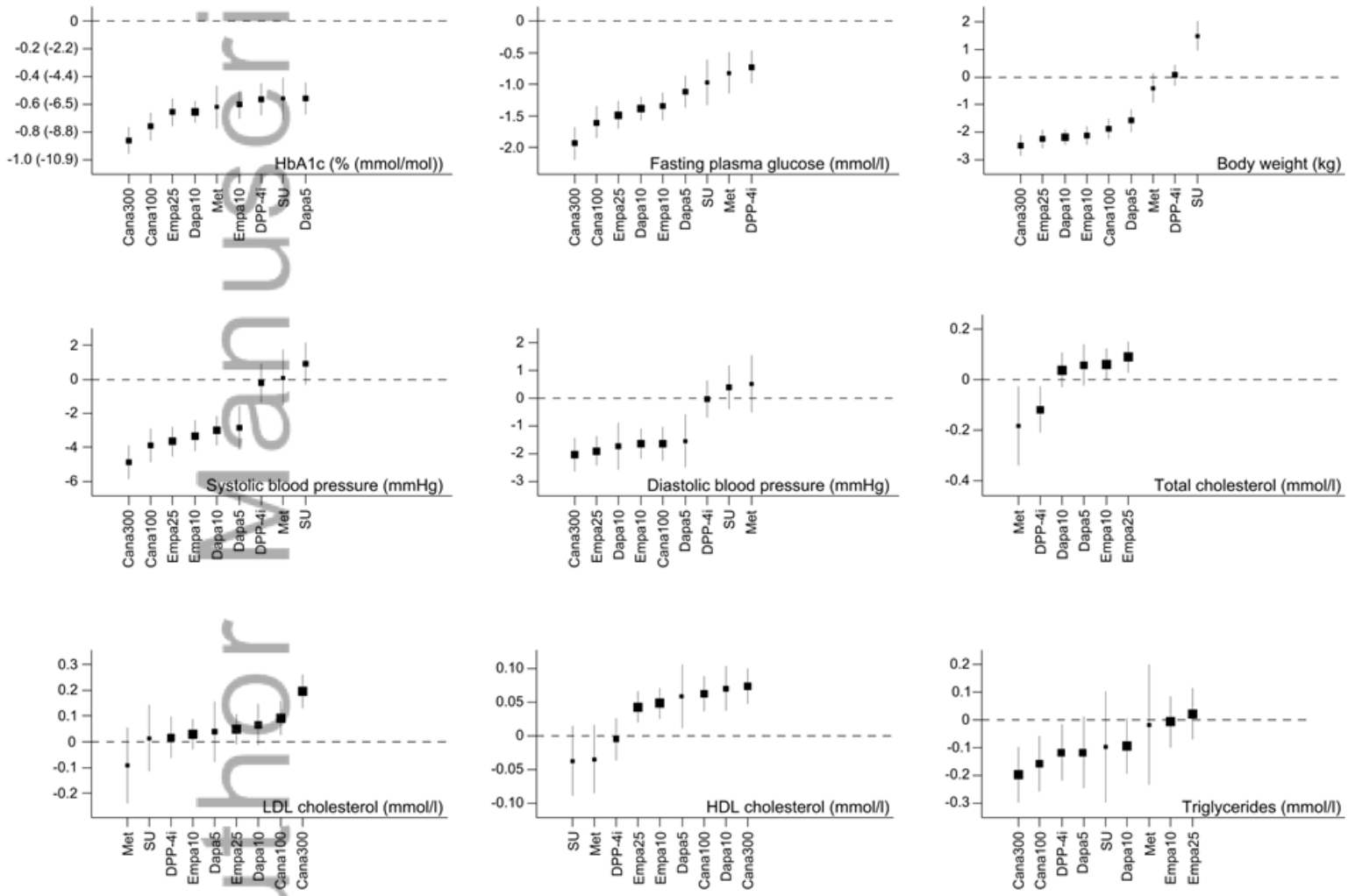
Figure 2: Differences vs Placebo (dotted lines) in cardiometabolic outcomes for the drugs included in the network meta-analysis



Abbreviations: Cana300=Canagliflozin 300mg; Cana100=Canagliflozin 100mg; Dapa10=Dapagliflozin 10mg; Dapa5=Dapagliflozin 5mg; Empa25=Empagliflozin 25mg; Empa10=Empagliflozin 10mg; DPP-4i=Dipeptidyl peptidase-4 inhibitor; Met=Metformin; SU=Sulphonylurea

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Author/s:
Zaccardi, F; Webb, DR; Htike, ZZ; Youssef, D; Khunti, K; Davies, MJ

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