Longer-term Benefits and Risks of Sodium-Glucose Cotransporter-2 Inhibitors in Type 2 Diabetes: a Systematic Review and Meta-analysis

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BACKGROUND: Sodium-glucose cotransporter-2 inhibitors (SGLT2Is) are a recent class of medication approved for the treatment of type 2 diabetes (T2D). Previous meta-analyses have quantified the benefits and harms of SGLT2Is; however, these analyses have been limited to specific outcomes and comparisons and included trials of short duration. We comprehensively reviewed the longer-term benefits and harms of SGLT2Is compared to placebo or other anti-hyperglycemic medications.

METHODS: We searched PubMed, Scopus, and clinicaltrials.gov from inception to July 2019 for randomized controlled trials of minimum 52 weeks' duration that enrolled adults with T2D, compared an SGLT2I to either placebo or other anti-hyperglycemic medications, and reported at least one outcome of interest including cardiovascular risk factors, microvascular and macrovascular complications, mortality, and adverse events. We conducted random effects meta-analyses to provide summary estimates using weighted mean differences (MD) and pooled relative risks (RR). The study was registered a priori with PROSPERO (CRD42018090506).

RESULTS: Fifty articles describing 39 trials (vs. placebo, $n=28$; vs. other anti-hyperglycemic medication, $n=12$; vs. both, $n=1$) and 112,128 patients were included in our analyses. Compared to placebo, SGLT2Is reduced cardiovascular risk factors (e.g., hemoglobin A1c, MD −0.55%, 95% CI −0.62, −0.49), macrovascular outcomes (e.g., hospitalization for heart failure, RR 0.70, 95% CI 0.62, 0.78), and mortality (RR 0.87, 95% CI 0.80, 0.94). Compared to other anti-hyperglycemic medications, SGLT2Is reduced cardiovascular risk factors, but insufficient data existed for other outcomes. About a fourfold increased risk of genital yeast infections for both genders was observed for comparisons vs. placebo and other anti-hyperglycemic medications.

DISCUSSION: We found that SGLT2Is led to durable reductions in cardiovascular risk factors compared to both placebo and other anti-hyperglycemic medications. Reductions in macrovascular complications and mortality were only observed in comparisons with placebo, although trials comparing SGLT2Is vs. other anti-hyperglycemic medications were not designed to assess longer-term outcomes.

KEY WORDS: sodium-glucose cotransporter-2 inhibitors; diabetes; systematic review; meta-analysis.

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INTRODUCTION

Type 2 diabetes (T2D) affects more than 450 million people worldwide and remains a major cause of myocardial infarction, stroke, and kidney failure.[1] Recently, sodium-glucose cotransporter-2 inhibitors (SGLT2Is) have taken an increasingly prominent role in the management of patients with T2D. After lifestyle modification and metformin, current diabetes guidelines recommend adding SGLT2Is in patients with T2D with coexistent, or at high risk for, atherosclerotic cardiovascular disease (ASCVD), heart failure, or chronic kidney disease.[2] These recommendations are based largely on the results of several large cardiovascular (CV) outcome trials[3–5] that compared SGLT2Is to placebo.

Systematic reviews of the CV outcome trials and the less well-known drug comparison trials have found that SGLT2Is may reduce mortality,[6–10] major adverse cardiovascular events (MACE),[11–13] stroke,[14] renal events,[13,15,16]

and hospitalizations for heart failure.[13,17,18] However, there are several important limitations to these previous reviews. First, previous reviews summarized the effects of SGLT2Is vs. placebo, even though in clinical practice, patients and clinicians choose between SGLT2Is and another anti-hyperglycemic medication.[6,12,17] Second, reviews selected very narrow inclusion criteria (e.g., only including trials that enrolled large numbers of patients), such that only the large CV outcome trials were included, even though there are many smaller SGLT2I trials.[6,11–13,19] Third, previous reviews permitted inclusion of trials with very short durations of follow-up ($\leq$6 months),[7,9,10,14,15,18] which can lead to both underestimation and overestimation of benefits and risks.[20,21] Fourth, few reviews have examined the adverse events associated with SGLT2Is.[22–24] Lastly, no previous systematic review has simultaneously reviewed the full range of durable benefits and risks due to SGLT2Is, even though these factors are important to clinical decision-making.

Therefore, to comprehensively examine the long-term effectiveness and safety of SGLT2Is, we conducted a systematic review and meta-analysis of all randomized trials of SGLT2Is for patients with T2D, with study duration of at least 52 weeks, that reported cardiovascular risk factor changes, microvascular or macrovascular outcomes, all-cause mortality, or treatment-related adverse events.

METHODS

The study protocol was registered a priori with the International Prospective Register of Systematic Reviews (PROSPERO, CRD42018090506)[25] database in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (eTable 1).[26]

We systematically searched PubMed, Scopus, and clinicaltrials.gov from inception to July 2019. No language restrictions were used. We included terms reflecting the words "diabetes" and either "sodium-glucose cotransporter-2 inhibitors" or individual SGLT2I drug names; the full list of search terms is available in eTable 2. After removal of duplicates, we excluded articles sequentially by title, abstract, and full-text review. Additionally, a hand search was carried out of published systematic reviews (JTA) to verify all relevant articles were included. Two reviewers examined all articles at each stage of the exclusion process, and articles with disagreements were moved to the next stage of review. We resolved disagreements at the full-text review stage through discussion among five reviewers (JTA, EMS, MF, AK, and NL).

Studies were included if they were randomized controlled trials that (1) included adults of at least 18 years of age with T2D, (2) had a trial duration of at least 52 weeks, (3) compared treatment with an SGLT2I vs. either placebo and/or another anti-hyperglycemic medication, and (4) included at least one outcome of interest.

Outcomes of interest included cardiovascular risk factors, microvascular complications, macrovascular complications, all-cause mortality, and treatment-related adverse events. Cardiovascular risk factors included glycated hemoglobin (HbA_{1c}), systolic blood pressure (SBP), heart rate, body mass index (BMI), weight, low density lipoprotein (LDL), high density lipoprotein (HDL), and estimated glomerular filtration rate (eGFR). Microvascular complications included end-stage renal disease (ESRD), any renal event, and amputation. Macrovascular complications included myocardial infarction (MI), heart failure, stroke, and a three-component MACE composite outcome of CV death, MI, or stroke. Adverse events included any hypoglycemia, severe hypoglycemia, diabetic ketoacidosis (DKA), genital yeast infections (total, female, and male), urinary tract infections (UTIs) (total, female, and male), and bone fracture. Due to the variability in the definition of cardiovascular death across trials, we did not report this outcome. Further details about outcomes and adverse events are available in eTable 3.

Data were extracted and quality of evidence was judged independently by two of five reviewers (JTA, EMS, MF, AK, and NL) for each study using a standardized review form. We extracted all available outcomes at all study follow-up time periods. Risk of bias of individual studies was assessed for seven prioritized outcomes (HbA_{1c}, mortality, 3-component MACE, any MI, stroke, any renal event, and genital yeast infections) using the Cochrane Collaboration risk of bias for randomized trials tool that assesses five domains of bias including sequence generation, blinding, attrition, detection, and reporting biases.[27] When evaluating attrition bias, we assigned less than 10% loss to follow-up as low risk of bias; higher rates were judged as either moderate or high based on their risk of jeopardizing the internal validity of the results.[21]

Quality of evidence across trials was synthesized using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach. Overall quality of evidence assessments reflects our degree of confidence that the estimated effect approximates the true effect and is ranked high, moderate, low, and very low. Since only randomized trials were included in our literature search, we began with a high degree of confidence for each outcome and iteratively downgraded if there was substantial risk of bias, inconsistency, imprecision, indirectness, or publication bias present. Quality of evidence was downgraded on the basis of attrition bias only if there was substantial difference in lost to follow-up between treatment and control groups.

We employed several rules when synthesizing data. First, for studies that reported more than one time period, we included results for the time period with the lowest risk of bias for HbA_{1c}; if the risk of bias was the same, we included results from the longest follow-up period. Second, if a study had multiple treatment arms with different drug dosages, we included the treatment arm that most closely matched the

comparison group by utilizing a standardized dosing table to categorize potency and that most closely matched other included studies (eTable 4). Third, if the comparison group was placebo or had an unspecified dosage, we included the higher dose treatment arm. Finally, if drugs were titrated per protocol, we used the maximum allowable dose to categorize the dosage level.

Statistical Analysis

We conducted meta-analyses utilizing random effects. We calculated weighted mean differences (MDs) for continuous outcomes and pooled relative risks (RRs) for dichotomous outcomes. For RR calculations with no reported events, we added a 0.5 for correction.[28] Heterogeneity was assessed with the I^2 statistic. Funnel plots and Egger's and Begg's tests were used to assess for publication bias when at least 10 studies were available for an outcome.[29]

We used subgroup analyses to evaluate medication class effects for comparisons of SGLT2Is vs. other anti-hyperglycemic medications. All analyses were performed using SAS version 9.4 software.

RESULTS

Search Results

From the initial 39,396 articles identified from our literature search, 50 articles[1S–50S] describing 39 trials and 112,128 patients were included in our analysis (eFigure 1). All non-English articles included were written in Chinese, and a native Chinese-speaking co-author (WW) extracted data from these articles. Among the included trials, 28 trials (median follow up duration = 76 weeks) compared SGLT2I vs. placebo (eTable 5) and 12 trials (median follow up duration = 52 weeks) compared SGLT2I vs. other anti-hyperglycemic medications (eTable 6). The other anti-hyperglycemic medication in these trials was metformin in one trial, a dipeptidyl peptidase-4 inhibitor (DPP4I) in six trials, and a sulfonylurea in five trials (eTable 6). One trial compared an SGLT2I with both placebo and another anti-hyperglycemic medication.[13S]

For the placebo-controlled trials, study patients tended to be between 50 and 70 years old, male, of white race, and obese (with a BMI between 30 and 35 kg/m^2), and have a baseline HbA_{1c} between 7.5 and 8.5% (eTables 7 and 8). Duration of T2D varied across trials, although most enrolled patients with T2D for more than 5 years. Ten of the 28 trials required participants to have high risk for or pre-existing ASCVD (eTable 7).

Patient characteristics for the trials comparing an SGLT2I to another anti-hyperglycemic medication were similar to the placebo-controlled trials (eTable 9). None of these trials with an active comparison group required patients to be high risk for or have pre-existing ASCVD at trial entry.

Risk of bias assessments for individual studies arranged by outcome are available in eTables 10–22. Table 1 summarizes the quality of evidence across trials. In general, the overall confidence in the estimated effect for the seven pre-specified outcomes was moderate or high for placebo-controlled trials. In trials comparing an SGLT2I to another anti-hyperglycemic medication, a small sample size led to lower overall confidence in the estimated effects, particularly for the outcomes of MI, stroke, and renal events. We observed no publication bias for any of these outcomes regardless of comparison (eFigures 2–5).

Cardiovascular Risk Factors

SGLT2Is reduced HbA_{1c} when compared to both placebo (MD = −0.55%, 95% CI −0.62 to −0.49, I^2 = 89%) (Fig. 1A) and other anti-hyperglycemic medications (−0.11%, −0.21 to −0.01, I^2 = 81%) (eFigure 7A) (eTable 23). SGLT2Is additionally led to lower weight (vs. placebo, −2.02 kg, −2.22 to −1.82, I^2 = 69%; vs. other anti-hyperglycemic medications, −3.85 kg, −4.51 to −3.19, I^2 = 92%) (Fig. 1B and eFigure 7B) and SBP (vs. placebo, −3.62 mmHg, −4.22 to −3.01, I^2 = 63%; vs. other anti-hyperglycemic medications, −4.37 mmHg, −5.21 to −3.53, I^2 = 52%) (Fig. 1C and eFigure 7C). SGLT2Is decreased eGFR when compared to placebo (−1.41 mL/min/1.73m^2, −1.98 to −0.84, I^2 = 26%) (eFigure 6B) but attenuated a decline in eGFR when compared to other anti-hyperglycemic medications (2.63 mL/min/1.73m^2, 1.15 to 4.11, I^2 = 54%) (eFigure 7D). Small absolute increases in both HDL and LDL were also observed (eFigures 6C, 6D, 7E, 7F).

Microvascular and Macrovascular Outcomes

Compared to placebo, SGLT2Is decreased the risk of the 3-component MACE outcome (RR = 0.89, 0.83 to 0.95, I^2 = 0%) (eFigure 8A) (eTable 23). Additionally, lower risks of MI (0.90, 0.82 to 1.00, I^2 = 0%) (eFigure 8B) and heart failure (0.70, 0.62 to 0.78, I^2 = 0%) (eFigure 8C) were observed with SGLT2Is. No differences in stroke or any renal event were detected (eFigures 8D and 8E). No differences in any microvascular or macrovascular outcomes were observed between SGLT2Is and other anti-hyperglycemic medications (eFigure 9); however, the numbers of trials and patients available for these comparisons were limited (e.g., there was only one trial that included MACE as an outcome) (eTable 23).

Mortality

SGLT2Is reduced mortality compared to placebo (RR = 0.87, 0.80 to 0.94, I^2 = 0%) (eFigure 8F). No difference in mortality

Table 1 GRADE Evidence of SGLT2Is on Glycated Hemoglobin, Mortality, Macrovascular Outcomes, Any Renal Outcome, and Genital Yeast Infections

	Summary of findings		GRADE quality assessment					
	No. of participants (studies)	Effect (RR/MD)	Risk of bias[a]	Inconsistency	Indirectness	Imprecision[d]	Publication bias	Quality of evidence
SGLT2I vs. Placebo								
HbA_{1c} (%)	44,959 (27)[1S, 3S–24S, 26S–34S]	−0.55 (−0.62 to −0.49)	High (due to attrition)	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	++++ High
All-cause mortality	45,101 (26)[1S, 3S–19S, 21S–24S, 26S–34S]	0.87 (0.80 to 0.94)	High (due to attrition)	Serious inconsistency (because of inconsistency in relative effects[b])	No serious indirectness	No serious imprecision	Undetected	+++ Moderate
3-Component MACE	36,378 (4)[3S–5S, 7S–8S, 16S–18S]	0.89 (0.83 to 0.95)	High (due to attrition)	No serious inconsistency	Serious indirectness (because indirectness of the population[c])	No serious imprecision	Undetected	+++ Moderate
Any myocardial infarction	33,457 (6)[3S–4S, 6S–8S, 16S–18S, 22S, 24S]	0.90 (0.82 to 1.00)	High (due to attrition)	No serious inconsistency	Serious indirectness (because indirectness of the population[c])	No serious imprecision	Undetected	+++ Moderate
Stroke	33,178 (5)[3S–4S, 7S–8S, 16S–18S, 24S, 30S]	0.98 (0.86 to 1.12)	High (due to attrition)	No serious inconsistency	Serious indirectness (because indirectness of the population[c])	No serious imprecision	Undetected	+++ Moderate
Any renal event	40,882 (15)[3S–9S, 16S–18S, 21S–24S, 26S, 29S, 30S–31S, 33S]	0.96 (0.73 to 1.27)	High (due to attrition and reporting)	Serious inconsistency (because of inconsistency in relative effects[b])	No serious indirectness	No serious imprecision	Undetected	+++ Moderate
Any genital yeast infection	35,072 (26)[1S–2S, 5S–19S, 21S–24S, 26S–34S]	4.00 (3.10 to 5.15)	High (due to attrition and reporting)	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	+++ Moderate
SGLT2I vs. Other Anti-hyperglycemic Medication								
HbA_{1c} (%)	7433 (10)[13S, 27S, 35S–39S, 41S–42S, 44S–50S]	−0.11 (−0.21 to −0.01)	High (due to attrition)	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	++++ High
All-cause mortality	7376 (11)[13S, 27S, 35S–38S, 40S–50S]	1.04 (0.53 to 2.06)	High (due to attrition)	No serious inconsistency	No serious indirectness	Serious imprecision (because impression of relative effect)	Undetected	+++ Moderate
Any myocardial infarction	2363 (2)[41S–42S, 44S–46S]	0.52 (0.04 to 6.25)	High (due to attrition)	No serious inconsistency	Serious indirectness (because indirectness of the background medication[c])	Serious imprecision (because impression in OIS criterion and relative effect)	Undetected	++ Low
Stroke	2044 (2)[41S–42S, 48S]	1.01 (0.11 to 9.68)	Moderate	Serious inconsistency (because of inconsistency in relative effects[b])	No serious indirectness	Serious imprecision (because impression in OIS criterion and relative effect)	Undetected	++ Low

Table 1 (continued)

	Summary of findings		GRADE quality assessment					
	No. of participants (studies)	Effect (RR/MD)	Risk of bias[a]	Inconsistency	Indirectness	Imprecision[d]	Publication bias	Quality of evidence
Any renal event	4823 (5)[27S, 37S–39S, 41S–42S, 44S–46S, 49S–50S]	1.22 (0.72 to 2.07)	High (due to attrition)	Serious inconsistency (because of inconsistency in relative effects[b])	Serious indirectness (because indirectness of the background medication[c])	Serious imprecision (because impression of relative effect)	Undetected	+ very low
Any genital yeast Infection	7258 (11)[13S, 27S, 35S–46S, 48S–50S]	5.38 (3.86 to 7.49)	High (due to attrition)	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	+ + + + High

Abbreviations: *HbA$_{1c}$*, glycated hemoglobin; *MACE*, major adverse cardiovascular event

[a] Detailed review of evidence found in eTables 12–24. Overall risk of bias was determined as follows: If all five domains had low bias, then overall bias was low. If more than 60% of domains had some concern, then overall bias was high. If less than 60% of domains had some concern, then overall bias was some concern. If more than 20% of domains had high bias, then overall bias was high

[b] Used I^2 and forest plots (75% of study effects in the same direction) to determine inconsistency

[c] Studies required (1) pre-existing cardiovascular disease (CVD); (2) pre-existing CVD or older age and high CVD risk; (3) enrolled 70% patients with CVD

[d] Optimal information size (OIS) at relative risk reduction (RRR) 20%, α 0.05, and β 0.2

was seen between SGLT2Is and other anti-hyperglycemic medications (1.04, 0.53 to 2.06, $I^2 = 0\%$) (eFigure 9E).

Adverse Events

Compared to both placebo and other anti-hyperglycemic medications, SGLT2Is increased the risk of genital yeast infections (RR = 4.00, 3.10 to 5.15; 5.38, 3.86 to 7.49, respectively) (Fig. 2 and eFigure 9F). This increase was similar in both men (3.67, 2.67 to 5.04 vs placebo; 5.11, 2.61 to 10.01 vs. other anti-hyperglycemic medications) and women (3.36, 2.62 to 4.32 vs. placebo; 4.26, 3.16 to 5.74 vs. other anti-hyperglycemic medications) (eTable 23). When compared to placebo, SGLT2Is increased the risk of DKA (2.37, 1.39 to 4.02) but decreased the risk of severe hypoglycemia (0.76, 0.60 to 0.97). Compared to another anti-hyperglycemic class, SGLT2Is decreased the risk of any hypoglycemic event (0.45, 0.22 to 0.91). No differences in rates of UTIs or fractures were observed for either comparison (eTable 23).

Subgroup Analyses

The characteristics of the trials included in each subgroup analysis are available in eTable 24 and results are in eTable 25. Results were limited to three outcomes (HbA1c, SBP, and any hypoglycemia) and two drug classes (SUs and DPP4Is) due to the small number of trials that met our inclusion criteria and were largely consistent with overall results.

DISCUSSION

In trials of at least 52 weeks' duration, SGLT2Is reduced several cardiovascular risk factors (except for LDL cholesterol which was slightly increased), reduced macrovascular outcomes, and reduced mortality, compared to placebo. Compared to other anti-hyperglycemic medications, SGLT2Is reduced cardiovascular risk factors. However, insufficient data were available to conclude the effects of SGLT2Is compared to other anti-hyperglycemic medications for longer-term outcomes, including microvascular outcomes, macrovascular outcomes, or mortality. Approximately, a fourfold increased risk of genital yeast infections was observed with SGLT2Is in both comparisons and for men and women.

While significant attention has been paid to the large CV outcome trials, our study reveals the sparsity of evidence on the effectiveness of SGLT2Is compared to other anti-hyperglycemic medications in longer-term randomized controlled trials. At best, modest data were available to allow for reasonable effect estimations of SGLT2Is on cardiovascular risk factors compared to other anti-hyperglycemic medications. It is plausible that reductions in cardiovascular risk factors could lead to reductions in microvascular outcomes, macrovascular outcomes, or mortality with longer follow-up. However, the excitement for the findings in the SGLT2I CV

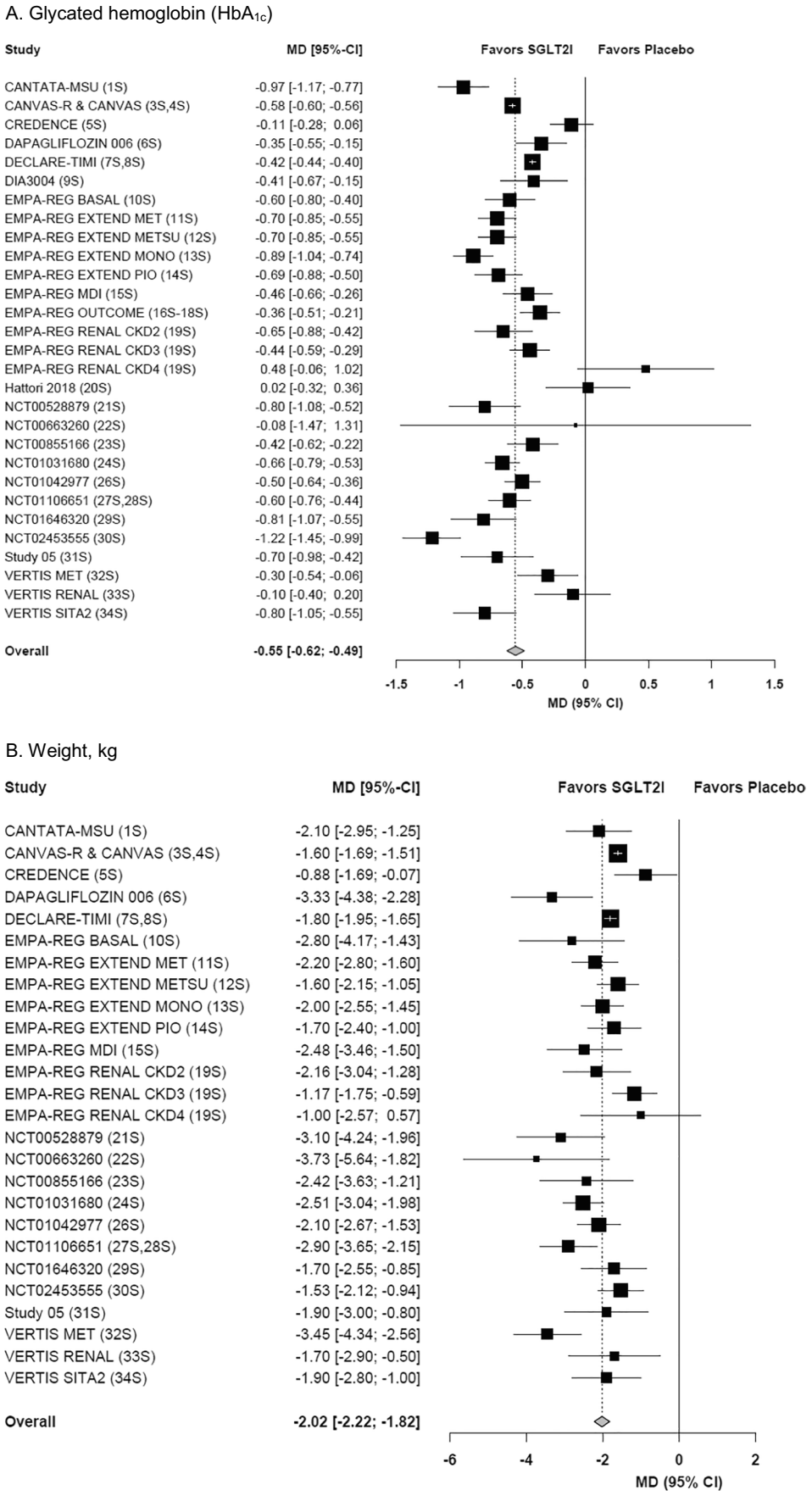
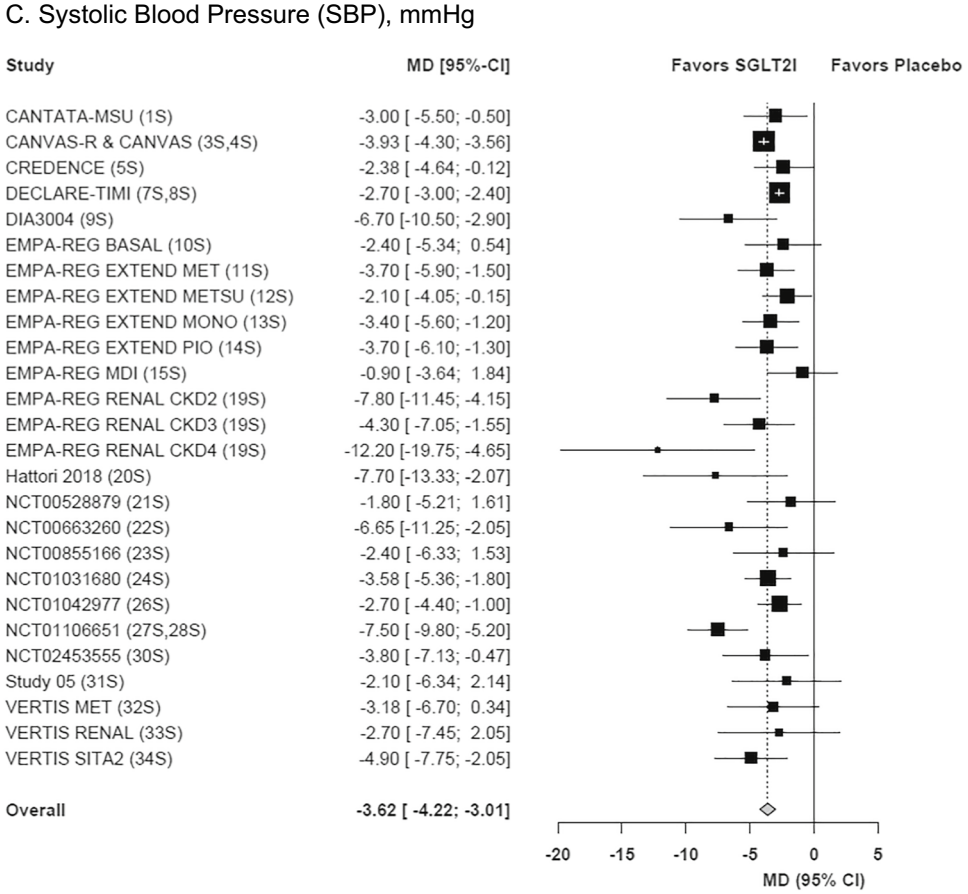


Fig. 1 Forest plots of cardiovascular risk factor effects for SGLT2I vs. placebo

Fig. 1 (continued)



outcome trials has been the identification of lower CV event rates and not their effects on cardiovascular risk factors.

Regarding the microvascular and macrovascular outcomes data available for this systematic review, we observed high rates of imprecision, indirectness, and inconsistency when comparing SGLT2Is to other anti-hyperglycemic medications. Limited sample size likely contributed to these findings, as only 2 to 5 trials and a few thousand patients were available for analyses for these outcomes. Since in clinical practice the major decision is selection of one anti-hyperglycemic medication over another, and SGLT2Is are often expensive or inaccessible compared to other medications,[30] additional prospective trials comparing SGLT2Is to other medications are needed.

Similar to previous, narrower meta-analyses, we observed that SGLT2Is reduced mortality, 3-component MACE, and MI compared to placebo. These findings provide reassurance that the beneficial effects of SGLT2Is are durable for at least 1 year and help support their prioritized use in current international guideline recommendations.[31]

Additionally, we found that SGLT2Is increased the risk of genital yeast infections compared to both placebo and other anti-hyperglycemic medications. This finding existed in both women and men, and their risks were similar. SGLT2Is also increased the risk of DKA, which has previously been well described.[32] However, SGLT2Is did not increase the risk for UTIs, despite the potential increased risk of UTIs from induced glucosuria. This finding was consistent with a prior meta-analysis of SGLT2Is.[33] SGLT2Is also decreased the risk of serious hypoglycemia, likely due to the decreased need to add other medications that increase the risk of hypoglycemia.

Our meta-analysis has several limitations. First, we excluded observational studies because they are prone to bias and a large number of clinical trials have been conducted; however, observational studies may be necessary to evaluate the effectiveness of SGLT2Is vs. other anti-hyperglycemic medications. Results from observational studies have generally been positive with suggestions that SGLT2Is may reduce the risk for heart failure, major kidney events, and cardiovascular mortality,[34–36] although many important outcomes have not been examined to date. Second, we chose to limit the quality assessment to seven pre-specified outcomes. While this may limit the ability to interpret some of the results, we prioritized quality assessments for the outcomes that would most impact the clinical decision of prescribing an SGLT2I to patients with T2D. Third, we combined all anti-hyperglycemic medications into one comparator group; however, we investigated comparisons between different classes of medications in subgroup analyses when possible.

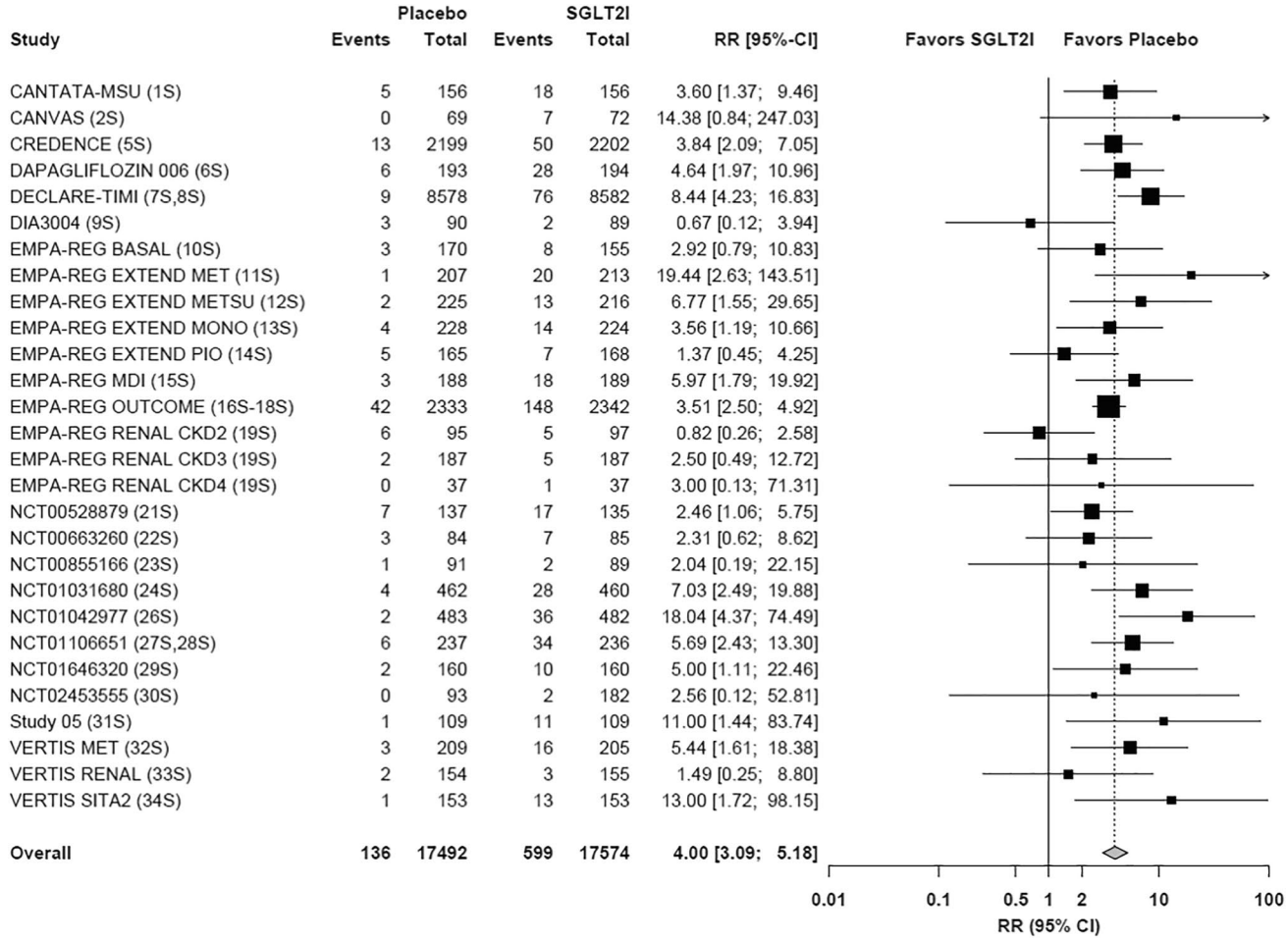


Fig. 2 Forest plot of genital yeast infections for SGLT2I vs. placebo

CONCLUSIONS

Our systematic review and meta-analysis comprehensively evaluated the longer-term effects of SGLT2Is compared to placebo and other anti-hyperglycemic medications. We found that SGLT2Is improved multiple cardiovascular risk factors, MI, heart failure, and mortality, compared to placebo; compared to other anti-hyperglycemic medications, SGLT2Is reduced cardiovascular risk factors. SGLT2Is increased the risk of genital yeast infections for both comparisons and for men and women. Inadequate data was available to compare SGLT2Is to other anti-hyperglycemic medications for microvascular outcomes, macrovascular outcomes, or mortality. These results help inform shared decision-making discussions regarding the benefits and risks in prescribing SGLT2Is for patients with T2D.

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Author Contribution *JTA is the guarantor of this work and had access to the data, designed the study, analyzed and interpreted the data, and drafted the manuscript. NL had access to the data, designed the study, analyzed and interpreted data, critically reviewed/edited the manuscript, and obtained funding for the study. EMS, WW, MF, AK, and MRS had access to the data, contributed to the design, analyzed and interpreted data, and reviewed/edited the manuscript. SB, NMM, ESH, LHP, ANW, CCT, MZ, VGP, and ELT contributed to the design and data interpretation, and reviewed/edited the manuscript. KG, SJ, and BB contributed to the design and critically reviewed/edited the manuscript.*

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Declarations

Conflict of Interest: *The authors declare no competing interests. VGP disclosed paid consultantships from Humana and Vizient. ANW disclosed a paid consultantship from Takeda. ESH declared stock options in Merck, Abbvie, and Amgen. JTA, EMS, WW, MF, AK, MRS, SB, NMM, LHP, CCT, MZ, ELT, KG, BB, SJ, and NL report no conflicts of interest, financial or otherwise.*

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