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Cardiovascular Safety, Long-Term Noncardiovascular Safety, and Efficacy of Sodium–Glucose Cotransporter 2 Inhibitors in Patients With Type 2 Diabetes Mellitus: A Systemic Review and Meta-Analysis With Trial Sequential Analysis

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***Background*—**The cardiovascular and long-term noncardiovascular safety and efficacy of SGLT2 (sodium–glucose cotransporter 2) inhibitors have not been well documented.

***Methods and Results*—**For cardiovascular outcomes, we performed a meta-analysis with trial sequential analysis of randomized controlled trials and adjusted observational studies, each with a minimum of 26 weeks and 2000 patient-years of follow-up. For long-term noncardiovascular safety and efficacy outcome analyses, we included only randomized controlled trials with at least 2 years and 1000 patient-years of follow-up. Five studies with 351 476 patients were included in cardiovascular outcomes analysis. Meta-analyses showed that SGLT2 inhibitors significantly reduced the risks of major adverse cardiac events (hazard ratio [HR]: 0.80; 95% confidence interval [CI], 0.69–0.92; P=0.002), all-cause mortality (HR: 0.67; 95% CI, 0.54–0.84; P<0.001), cardiovascular mortality (HR: 0.77; 95% CI, 0.60–0.98; P=0.03), nonfatal myocardial infarction (HR: 0.86; 95% CI, 0.76–0.98; P=0.02), hospitalization for heart failure (HR: 0.62; 95% CI, 0.55–0.69; P<0.001), and progression of albuminuria (HR: 0.68; 95% CI, 0.58–0.81; P<0.001). No significant difference in nonfatal stroke was found. Analyses limited to randomized controlled trials showed similar findings. Trial sequential analysis provided firm evidence of a 20% reduction in major adverse cardiac events, all-cause mortality, and hospitalization for heart failure with SGLT2 inhibitors, but evidence remains inconclusive for cardiovascular mortality. Nine randomized controlled trials contributed to long-term noncardiovascular and efficacy analyses. SGLT2 inhibitors reduced incidence of hypoglycemia and acute kidney injury but increased the risks of urinary tract and genital infections.

***Conclusions*—**SGLT2 inhibitors showed remarkable cardiovascular- and renal-protective effects and good long-term noncardiovascular safety with sustained efficacy. **(*J Am Heart Assoc*. 2018;7:e007165. DOI: 10.1161/JAHA.117.007165.)**

Key Words: cardiovascular disease • meta-analysis • observational study • randomized controlled trial • SGLT2 (sodium–glucose cotransporter 2) inhibitor • trial sequential analysis

Type 2 diabetes mellitus (DM) is a systemic disease associated with an increased risk of cardiovascular complications.[1] Previous studies emphasized the glucose-lowering effects of antihyperglycemic drugs but often did not evaluate their ability to reduce the long-term complications of DM.[2] The past decade has witnessed increasingly available treatments for DM. The beneficial effect on microvascular complications is well established for glycemic control, but the effect on macrovascular outcomes remains unclear.[3,4] In contrast, concern has been raised about the cardiovascular safety of antihyperglycemic drugs, since rosiglitazone was shown to increase risk of myocardial infarction (MI) and heart

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Accompanying Tables S1 through S4 and Figures S1 through S17 are available at http://jaha.ahajournals.org/content/7/2/e007165/DC1/embed/inline-supplementary-material-1.pdf

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Clinical Perspective

What Is New?

- Meta-analyses with >350 000 patients revealed that SGLT2 (sodium–glucose cotransporter 2) inhibitors significantly reduced the risks of major adverse cardiac events, all-cause mortality, cardiovascular mortality, nonfatal myocardial infarction, hospitalization for heart failure, and progression of albuminuria.
- Trial sequential analyses provided firm evidence of a 20% reduction in major adverse cardiac events, all-cause mortality, and hospitalization for heart failure with SGLT2 inhibitors, but evidence remains inconclusive for cardiovascular mortality.
- At long-term follow-up, SGLT2 inhibitors reduced incidence of hypoglycemia and acute kidney injury but increased risks of urinary tract and genital infections.

What Are the Clinical Implications?

- SGLT2 inhibitors showed remarkable cardiovascular- and renal-protective effects and good long-term noncardiovascular safety with sustained efficacy and should be strongly considered in type 2 diabetes mellitus patients with established or high risk of cardiovascular disease.

failure.[5,6] This finding promoted the design of a body of randomized trials to determine the long-term cardiovascular safety of each individual antihyperglycemic drug.[7,8]

SGLT2 (sodium–glucose cotransporter 2) inhibitors are a novel class of agents that lower glucose by inhibiting renal glucose reabsorption, a mechanism independent of insulin.[9] Previous efficacy trials established the favorable effects of SGLT2 inhibitors on a variety of markers of vascular risk, including glucose concentrations, body weight, and blood pressure.[10] Nevertheless, questions remain regarding the ability of SGLT2 inhibitors to affect the risk of cardiovascular outcomes. Recent publication of several large randomized controlled trials (RCTs) reported the cardiovascular effect of SGLT2 inhibitors; however, results on rare individual end points such as all-cause death were not consistent (hazard ratios [HRs], EMPA-REG OUTCOME [BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients] trial: 0.68 [95% confidence interval (CI), 0.57–0.82]; CANVAS [Canagliflozin Cardiovascular Assessment Study] trial: 0.84 [95% CI, 0.70–1.01]; CANVAS-R [A Study of the Effects of Canagliflozin (JNJ-28431754) on Renal Endpoints in Adult Participants With Type 2 Diabetes Mellitus] trial: 0.92 [95% CI, 0.70–1.21]) and cardiovascular death (HRs, EMPA-REG OUTCOME trial: 0.62 [95% CI, 0.49–0.77]; CANVAS trial: 0.88 [95% CI, 0.70–1.10]; CANVAS-R trial: 0.86 [95% CI, 0.61–1.22]).[11,12] Meanwhile, the long-term noncardiovascular safety of SGLT2 inhibitors has not been fully documented. In this context, we performed a meta-analysis of RCTs and observational studies to determine the cardiovascular and long-term noncardiovascular safety of SGLT2 inhibitors and performed trial sequential analysis (TSA) to reduce type I error in meta-analysis to confirm and determine whether conclusions from meta-analyses were conclusive.[13] We also evaluated all long-term efficacy of SGLT2 inhibitors.

Methods

The data that support the findings of this study are available from Dr Xin-Lin Zhang on reasonable request (xinlzhang0807@gmail.com). We conducted the meta-analysis in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (PRISMA checklist).[14]

Data Sources and Searches

We searched Medline, the Cochrane Central Register of Controlled Trials, and Embase from inception to November 20, 2017, without language restrictions. The following keywords were used: *sodium–glucose cotransporter 2* and individual drug names. We also manually checked reference lists of the identified reports and relevant reviews to identify potentially eligible articles.

Study Selection

Two reviewers (X.-L.Z. and Q.-Q.Z.) independently assessed the eligibility of studies. We performed 2-part analyses. For cardiovascular outcomes, we included RCTs and adjusted observational studies with a minimum of 26 weeks and 2000 patient-years of follow-up. For long-term noncardiovascular safety and efficacy outcome analyses, we included only RCTs with at least 2 years and 1000 patient-years of follow-up. All studies had to have head-to-head comparison of an SGLT2 inhibitor with placebo or other glucose-lowering drug in patients with type 2 DM. Studies included in the cardiovascular outcome analysis had to have cardiovascular outcomes predefined and independently adjudicated and to report at least 1 of our selected cardiovascular outcomes. Discrepancies, if any, were resolved by consensus by a third independent investigator (Y.-H.C.). We excluded animal studies, review studies, studies that were not randomized, and studies with short-term follow-up and limited participants.

Outcome Measures

The primary end point was major adverse cardiac events (MACE), defined as a composite of death from cardiovascular

causes, nonfatal MI, or nonfatal stroke. Other end points included all-cause and cardiovascular death, nonfatal MI, nonfatal stroke, hospitalization for heart failure, hospitalization for heart failure and cardiovascular death, and renal microvascular outcome. We also included noncardiovascular safety outcomes and efficacy outcomes in the analysis.

Data Extraction and Quality Assessment

Prespecified data elements were extracted by 2 investigators (X.-L.Z. and Q.-Q.Z.) from each trial. The following items were recorded: registry number; treatment groups; study sample size; length of follow-up; and patient characteristics including age, sex, duration of DM, baseline HbA1c levels, and body mass index. We also recorded outcome event rates for analysis. Disagreements were resolved by a third reviewer (L.K.). Two reviewers (Q.-Q.Z. and L.K.) independently evaluated the potential risk of bias of each trial according to the Cochrane Collaboration guidelines[15] and rated the quality of observational study using the Newcastle–Ottawa Scale.[16]

Data Synthesis and Statistical Analysis

HRs and odds ratios (ORs) were used as summary statistics for binary variables, whereas weighted mean differences (WMDs) were effect estimates for continuous variables. The HR with a 95% CI for each end point was directly extracted from each study. Pooled analyses were calculated with fixed-effect models (Mantel–Haenszel method) or random-effect models (DerSimonian–Laird method) according to the extent of heterogeneity, with the other model as a complement.[17] Heterogeneity was assessed with the I^2 statistic and the χ^2-based Q test.[18] A cutoff value of P=0.10 suggests significant heterogeneity. For all outcomes in which ORs were used as the estimates, rates of event in patient-years were used rather than number of events alone because the length of follow-up of each trial varied. If there were no outcome events in one of the treatment groups, we applied the treatment arm continuity correction (the reciprocal value of the opposite treatment group size).[19] To test the robustness of the findings for cardiovascular outcomes, we performed subgroup analysis confined to RCTs. Publication bias was assessed by performing Begg and Egger tests. No evidence of publication bias was detected. For the effect estimate, a 2-tailed P value <0.05 was considered statistically significant. Meta-analyses were done by using Stata software version 12.0 (StataCorp).

TSA could reduce type I error because it combines estimation of required information size with adjusted threshold for statistical significance.[13,20,21] TSA was performed for cardiovascular outcomes by anticipating a 20% relative risk reduction, an overall 5% risk of type I error, and a statistical test power of 80%.

Results

Study Selection and Characteristics

Of 3236 citations initially identified, 164 were retrieved for full-text evaluation and 11 studies met inclusion criteria (Figure S1).[11,12,22–30] For cardiovascular outcomes analysis, 3 RCTs[11,12,22] and 2 observational studies[23,24] were included with 351 476 patients and median follow-up of 3.1 years. Nine RCTs contributed to the analysis of long-term noncardiovascular safety and efficacy of SGLT2 inhibitors, with a medium follow-up of 2 years.[11,12,22,25–30] All trials were carried out with patients who had type 2 DM. Empagliflozin was used in 2 trials,[11,29] canagliflozin was used in 4 trials,[12,26,27] and dapagliflozin was used in 3 trials[25,28,30]; the 2 observational studies involved various SGLT2 inhibitors.[23,24] All studies were multicenter, performed across multiple countries. When reported, the mean age enrolled in all included trials ranged from 54 to 64 years, the percentage of men ranged from 49% to 72%, the mean duration of DM ranged from 5.8 to 13.7 years, and the mean HbA1c level ranged from 7.7% to 8.5%. Detailed baseline characteristics of each trial are presented in Table 1. The inclusion and exclusion criteria and primary and secondary end points of each study are presented in Table S1. All studies had good quality (Tables S2 and S3).

Cardiovascular Outcomes

Major adverse cardiovascular events

Treatment with SGLT2 inhibitors resulted in a statistically significant reduction in MACE compared with placebo (HR: 0.80; 95% CI, 0.69–0.92; P=0.002; Figure 1). Considerable heterogeneity was detected (I^2=73.3%). Analyses limited to RCTs showed similar findings (HR: 0.86; 95% CI, 0.78–0.95; P=0.002). TSA of MACE showed that although the pooled sample size did not exceed the estimated required information size; the cumulative z curve crossed both the conventional boundary and the trial sequential monitoring boundary (Figure 2), indicating that firm evidence of a 20% reduction in MACE with SGLT2 inhibitors compared with control treatments. Largely consistent results for MACE were found across a number of subgroup analyses (Table S4).

Total and cardiovascular mortality

SGLT2 inhibitors were associated with a statistically significant reduction in all-cause mortality in SGLT2 inhibitors (HR: 0.67; 95% CI, 0.54–0.84; P<0.001; Figure 3, top). Considerable heterogeneity was found (I^2=85.7%). Analyses limited to RCTs showed similar findings (HR: 0.79; 95% CI, 0.6–0.95; P=0.009). In TSA, the cumulative results crossed the traditional boundary and the trial sequential monitoring boundary,

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Table 1. Baseline Characteristics of Included Trials

Trial	Identifier	SLGT2 Inhibitor	Comparator	Year	FU, y	No.	Age, y	Male, %	White, %	Diabetes Mellitus Duration, y	BMI, kg/m^2	CAD, %	PAD	HbA1c, %	eGFR, mL/min/1.73 m^2	SBP, mm Hg	Insulin, %
EMPA-REG OUTCOME[11,22]	NCT01131676	Empagliflozin	Placebo	2015	3.1	7020	63.1	71.5	72.4	NA	30.6	75.6	20.8	8.07	74	135.5	48.2
CANVAS[12]	NCT01032629	Canagliflozin	Placebo	2017	5.7	4330	62.4	66.1	73.4	13.4	32.1	54.8	15.9	8.2	77.2	136.3	50.2
CANVAS-R[12]	NCT01989754	Canagliflozin	Placebo	2017	2.1	5812	64	62.8	82	13.7	31.9	57.6	24.5	8.3	75.9	136.9	50.3
CVD-REAL[23]	NCT02993614	Mixed	Non-SGLT2i	2017	0.75	309 056	56.9	55.5	NA	NA	NA	13.1	3.4	NA	NA	NA	29.4
EASEL[24]	NA	Mixed	Non-SGLT2i	2017	1.6	25 258	65.8	55.9	35.2	5.6	NA	14.7	15.8	NA	NA	NA	19.7
Bailey et al[25]	NCT00528879	Dapagliflozin	Placebo	2013	2	546	53.7	55	NA	5.8	31.8	NA	NA	8.1	NA	127.7	NA
Bode et al[26]	NCT01106651	Canagliflozin	Placebo	2015	2	714	63.6	55.5	77.3	11.7	31.6	NA	NA	7.7	77.5	NA	32.8
Leiter et al[27]	NCT00968812	Canagliflozin	Glimepiride	2015	2	1450	56.2	52.1	67.4	6.6	31.0	NA	NA	7.8	90.2	130.0	NA
Del Prato et al[28]	NCT00660907	Dapagliflozin	Glipizide	2015	4	814	58.1	55.3	NA	6.1	31.7	NA	NA	7.7	89.5	132.8	NA
Ridderstrale et al[29]	NCT01167881	Empagliflozin	Glimepiride	2014	2	1549	55.7	54.0	67	NA	30.3	NA	NA	7.92	88.1	133.5	NA
Wilding et al[30]	NCT00673231	Dapagliflozin	Placebo	2014	2	800	58.8	49.2	96.4	5.9	33.1	16.6	10.4	8.47	NA	NA	73.7

BMI indicates body mass index; CAD, coronary artery disease; CANVAS, Canagliflozin Cardiovascular Assessment Study trial; CVD-REAL, the Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT-2 Inhibitors study; EASEL, the evidence for cardiovascular outcomes with sodium glucose co-transporter 2 inhibitors in the real world study; eGFR, estimated glomerular filtration rate; EMPA-REG OUTCOME, BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; FU, follow-up; NA, not available; PAD, peripheral artery disease; SBP, systolic blood pressure; SGLT2, sodium–glucose cotransporter 2; SGLT2i, sodium–glucose cotransporter 2 inhibitor.

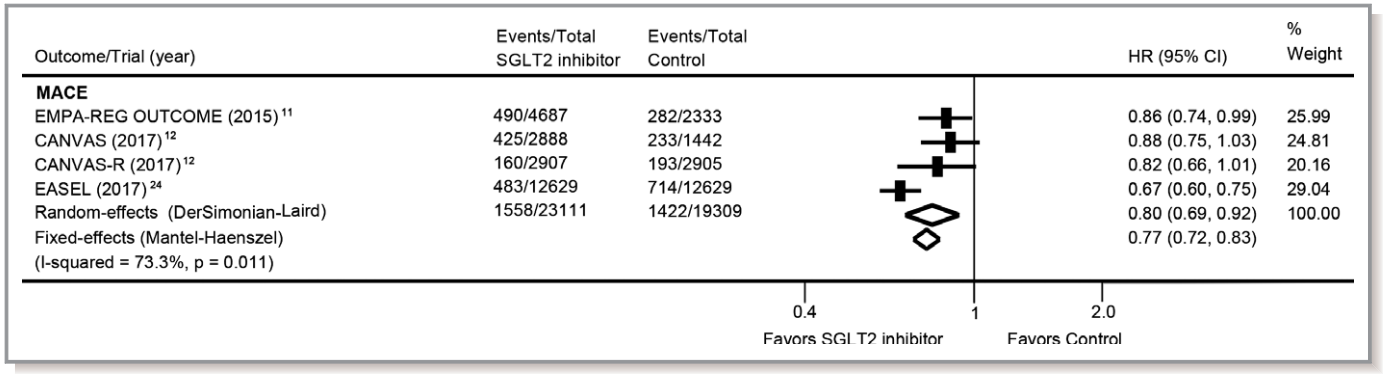

Figure 1. Effects of SGLT2 inhibitors on MACE. CI indicates confidence interval; CANVAS, Canagliflozin Cardiovascular Assessment Study trial; EASEL, the evidence for cardiovascular outcomes with sodium glucose co-transporter 2 inhibitors in the real world study; EMPA-REG OUTCOME, BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; HR, hazard ratio; MACE, major adverse cardiovascular event; SGLT2, sodium–glucose cotransporter 2.

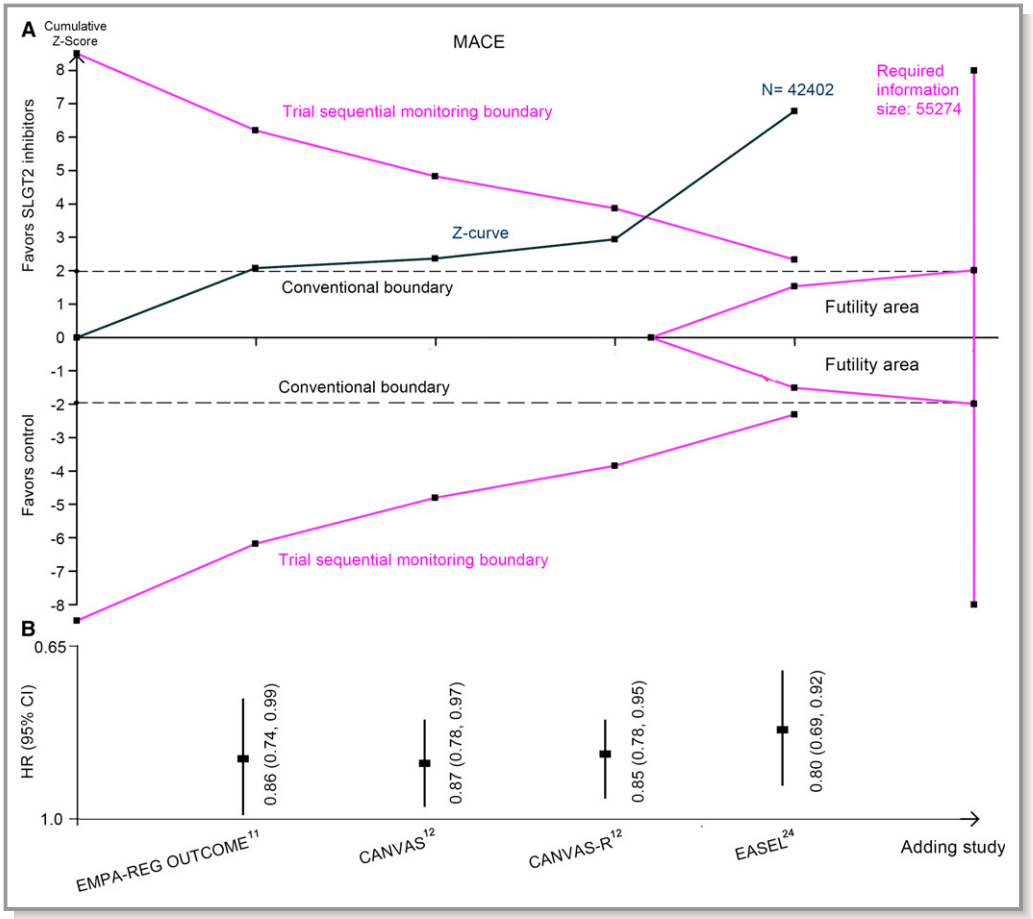

Figure 2. A, Trial sequential analysis for MACE in patients receiving SGLT2 inhibitors vs control. B, Funnel plots showing the trajectory of the overall point estimates and the evolution of their corresponding precision as each study enters the meta-analysis. CI indicates confidence interval; CANVAS, Canagliflozin Cardiovascular Assessment Study trial; EASEL, the evidence for cardiovascular outcomes with sodium glucose co-transporter 2 inhibitors in the real world study; EMPA-REG OUTCOME, BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; HR, hazard ratio; MACE, major adverse cardiovascular event; SGLT2, sodium–glucose cotransporter 2.

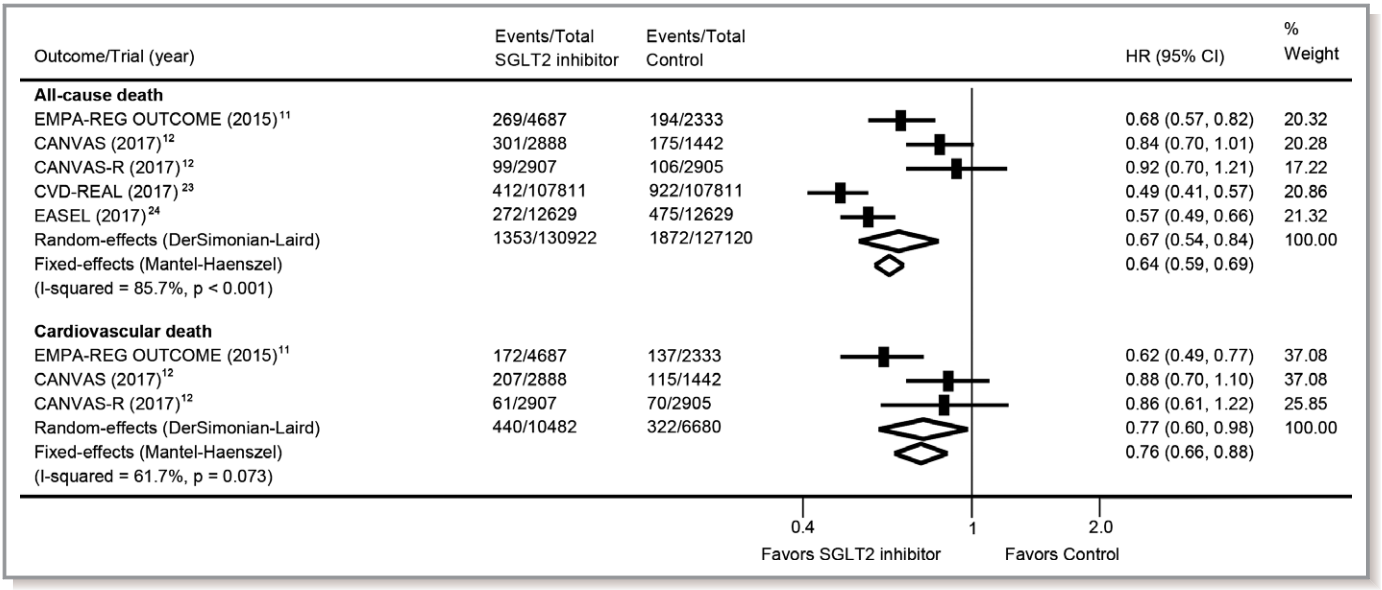

Figure 3. Effects of SGLT2 inhibitors on all-cause death (top) and cardiovascular death (bottom). CI indicates confidence interval; CANVAS, Canagliflozin Cardiovascular Assessment Study trial; CVD-REAL, the Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT-2 Inhibitors study; EASEL, the evidence for cardiovascular outcomes with sodium glucose co-transporter 2 inhibitors in the real world study; EMPA-REG OUTCOME, BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; HR, hazard ratio; SGLT2, sodium–glucose cotransporter 2.

suggesting firm evidence of a 20% reduction in all-cause mortality with SGLT2 inhibitors compared with control treatments (Figure 4).

There was a statistically significant reduction in cardiovascular mortality with the use of SGLT2 inhibitors (HR: 0.77; 95% CI, 0.60–0.98; P=0.033; Figure 3, bottom). Significant heterogeneity was detected (I^2=61.7%). In TSA, the z curve crossed the conventional boundary but did not cross the monitoring boundary, indicating that a 20% reduction in cardiovascular mortality with SGLT2 inhibitors was inconclusive and that additional evidence is needed to confirm the finding (Figure S2).

Nonfatal MI and nonfatal stroke

Meta-analysis showed a statistically significant reduction in incidence of nonfatal MI in patients assigned to SGLT2 inhibitors than those assigned to placebo (HR: 0.86; 95% CI, 0.76–0.98; P=0.02; Figure 5, top). TSA showed that the cumulative z curve did not cross the trial sequential monitoring boundary before reaching the required information size, suggesting evidence of <20% relative risk reduction for nonfatal MI (Figure S3). There was no statistically significant difference in rates of nonfatal stroke (HR: 0.96; 95% CI, 0.82–1.12; P=0.67; Figure 5, bottom). The cumulative z curve did not cross the conventional boundary, although the required information size was reached, suggesting that there was not a 20% relative risk reduction for nonfatal stroke (Figure S4). We did not find significant heterogeneity across these trials in either comparison (I^2=0 and 32.2%, respectively).

Hospitalization for heart failure and cardiovascular death

SGLT2 inhibitors were associated with a statistically significant reduction in incidence of hospitalization for heart failure compared with control (HR: 0.62; 95% CI, 0.55–0.69; P<0.001; Figure 6, top). Analyses limited to RCTs showed similar findings for this outcome (HR: 0.66; 95% CI, 0.55–0.80; P<0.001). SGLT2 inhibitors also reduced the risk for the composite end point of hospitalization for heart failure and cardiovascular death (HR: 0.64; 95% CI, 0.55–0.74; P<0.001; Figure 6, bottom); a similar finding was observed in RCTs (HR: 0.72; 95% CI, 0.63–0.84; P<0.001). TSA of hospitalization for heart failure showed that the pooled sample size exceeded the estimated RIS, and the cumulative z curve crossed both the conventional boundary and the trial sequential monitoring boundary, indicating firm evidence of a 20% reduction in risk for hospitalization for heart failure with SGLT2 inhibitors compared with control treatments (Figure S5).

Renal microvascular outcome

SGLT2 inhibitors showed a benefit with respect to the progression of albuminuria (HR: 0.68; 95% CI, 0.58–0.81; P<0.001; Figure 7). Significant heterogeneity was detected across trials (I^2=80.5%). In TSA, the cumulative value crossed the traditional boundary and the trial sequential monitoring

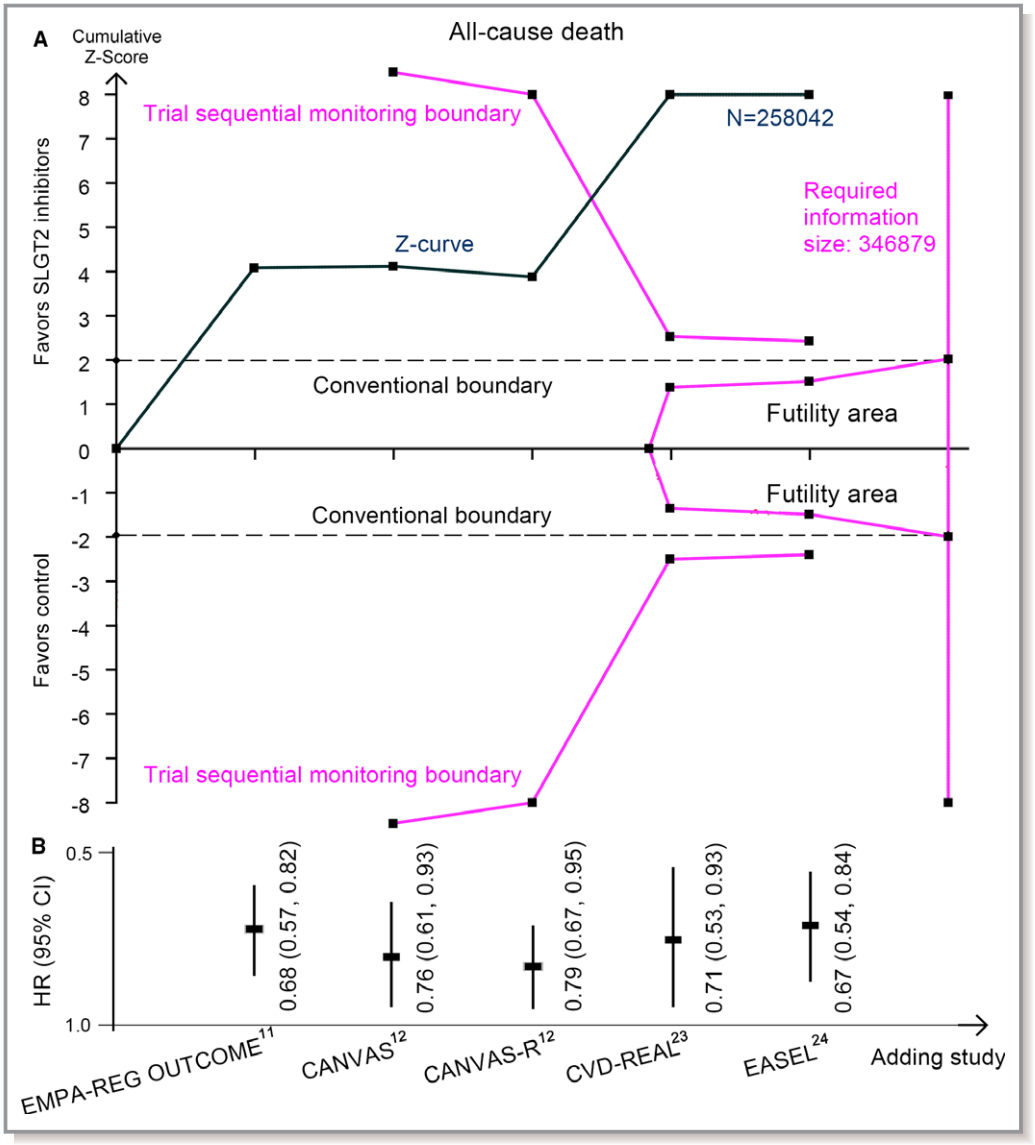

Figure 4. A, Trial sequential analysis for all-cause death in patients receiving SGLT2 inhibitors vs control. B, Funnel plots showing the trajectory of the overall point estimates and the evolution of their corresponding precision as each study enters the meta-analysis. CI indicates confidence interval; CANVAS, Canagliflozin Cardiovascular Assessment Study trial; CVD-REAL, the Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT-2 Inhibitors study; EASEL, the evidence for cardiovascular outcomes with sodium glucose co-transporter 2 inhibitors in the real world study; EMPA-REG OUTCOME, BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; HR, hazard ratio; SGLT2, sodium–glucose cotransporter 2.

boundary, indicating firm evidence of a 20% reduction in risk of progression of albuminuria with SGLT2 inhibitors compared with control treatments (Figure S6).

Noncardiovascular Safety Outcomes

Nine trials comprising 23 035 patients contributed to the analysis of noncardiovascular safety (Table 2). Pooled analysis showed that serious adverse events (OR: 0.90; 95% CI, 0.81–1.00; P=0.05; Figure S7), hypoglycemia (OR: 0.48; 95% CI, 0.28–0.82; P=0.008; Figure S8), and acute kidney injury (OR: 0.80; 95% CI, 0.67–0.96; P=0.014; Figure S9) were less common among patients receiving SGLT2 inhibitors than controls. However, there was a higher risk of genital infection with SGLT2 inhibitors than with controls in both female patients (OR: 3.17; 95% CI, 2.15–4.68; P<0.001; Figure S10) and male patients (OR: 3.61; 95% CI, 3.10–4.19; P<0.001; Figure S11). SGLT2 inhibitors were also associated with a higher incidence

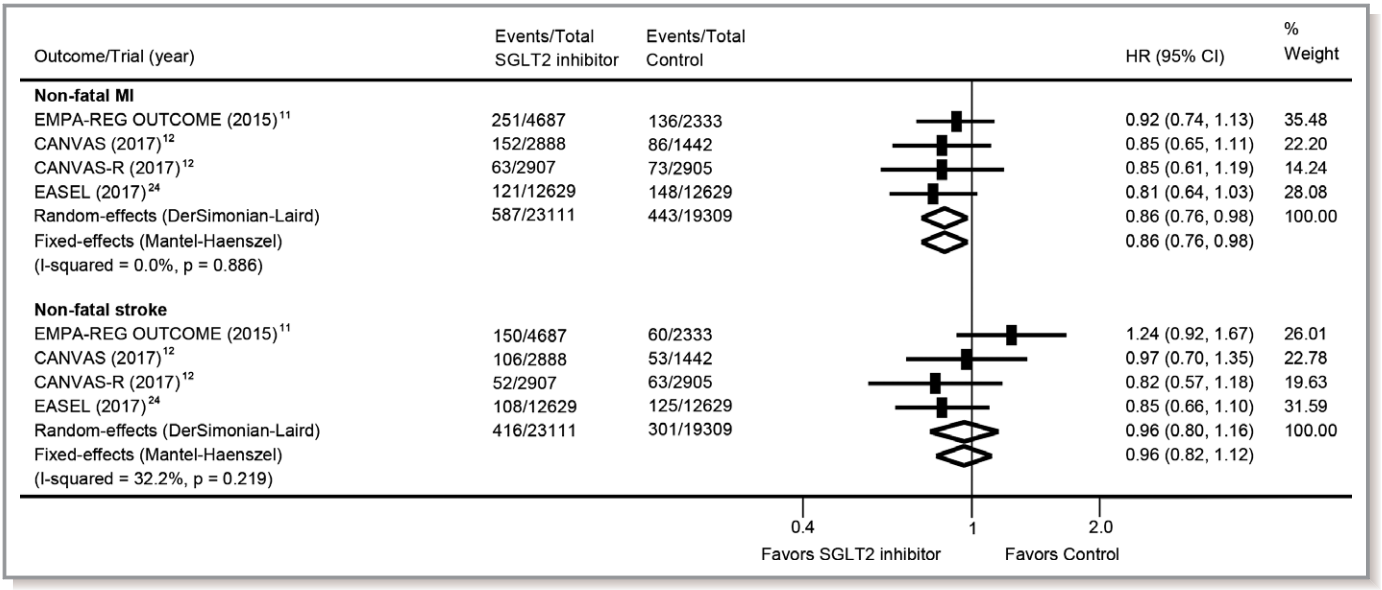

Figure 5. Effects of SGLT2 inhibitors on nonfatal MI (top) and nonfatal stroke (bottom). CI indicates confidence interval; CANVAS, Canagliflozin Cardiovascular Assessment Study trial; EASEL, the evidence for cardiovascular outcomes with sodium glucose co-transporter 2 inhibitors in the real world study; EMPA-REG OUTCOME, BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; HR, hazard ratio; MI, myocardial infarction; SGLT2, sodium–glucose cotransporter 2.

of urinary tract infection (OR: 1.15; 95% CI, 1.00–1.33; P=0.047; Figure S12) and volume depletion (OR: 1.28; 95% CI, 1.11–1.46; P<0.001; Figure S13). The risks of diabetic ketoacidosis (DKA), thromboembolic events, and bone fracture (Figure S14) and of hyperkalemia and adverse events leading to discontinuation (Figure S15) were similar in the 2 groups.

Efficacy Outcomes

SGLT2 inhibitors significantly reduced HbA1c levels compared with controls, with a WMD of −0.39% (95% CI, −0.52 to −0.26; Figure 8 and Table 3). SGLT2 inhibitors also significantly reduced fasting blood glucose (WMD: −0.71 mmol/L; 95%

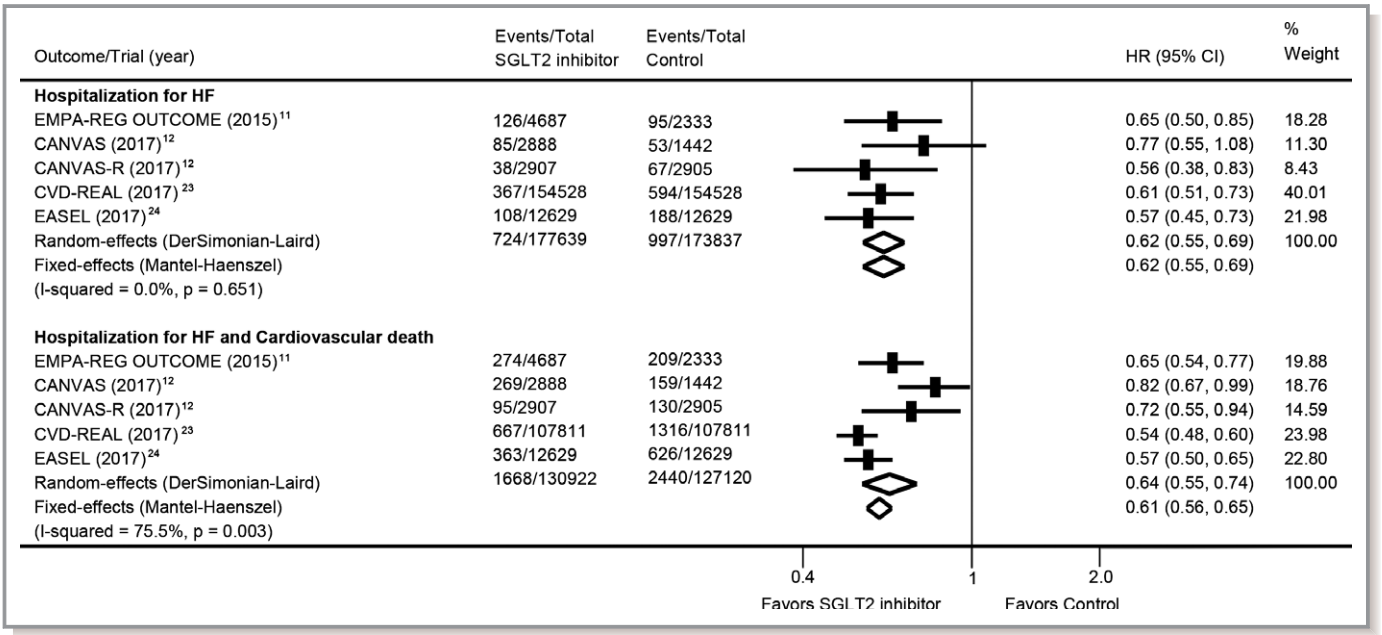

Figure 6. Effects of SGLT2 inhibitors on hospitalization for HF (top) and the composite of hospitalization for HF and cardiovascular death (bottom). CI indicates confidence interval; CANVAS, Canagliflozin Cardiovascular Assessment Study trial; CVD-REAL, the Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT-2 Inhibitors study; EASEL, the evidence for cardiovascular outcomes with sodium glucose co-transporter 2 inhibitors in the real world study; EMPA-REG OUTCOME, BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; HF, heart failure; HR, hazard ratio; SGLT2, sodium–glucose cotransporter 2.

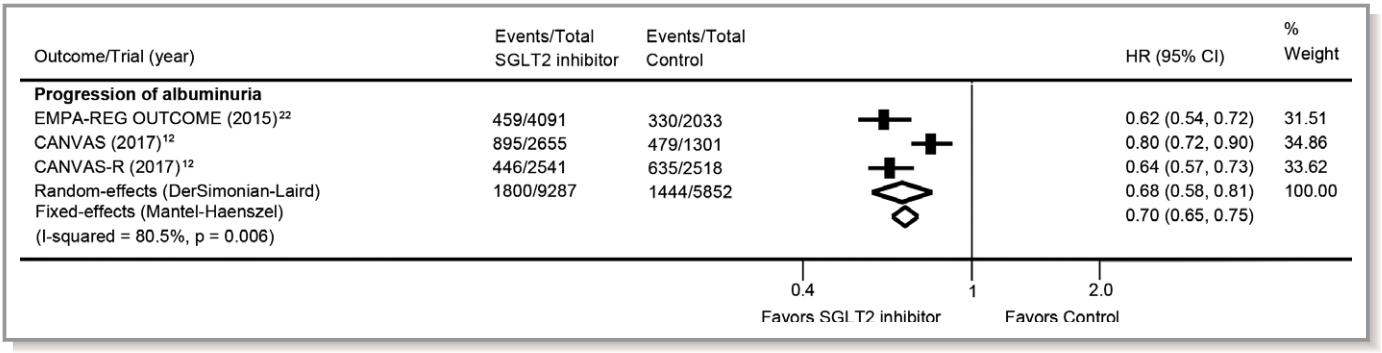

Figure 7. Effects of SGLT2 inhibitors on progression of albuminuria. CI indicates confidence interval; CANVAS, Canagliflozin Cardiovascular Assessment Study trial; EMPA-REG OUTCOME, BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; HR, hazard ratio; SGLT2, sodium–glucose cotransporter 2.

CI, −0.88 to −0.55; Figure S16), body weight (WMD: −2.90 kg; 95% CI, −3.72 to −2.07; Figure S17), systolic blood pressure (WMD: −3.84 mm Hg; 95% CI, −4.70 to −2.98) and diastolic blood pressure (WMD: −1.03 mm Hg; 95% CI, −1.78 to −0.28). SGLT2 inhibitors slightly increased levels of low-density lipoprotein cholesterol (WMD: 0.09 mmol/L; 95% CI, 0.03–0.14) and high-density lipoprotein cholesterol (WMD: 0.10 mmol/L; 95% CI, 0.04–0.15). Subgroup analysis based on type of SGLT2 inhibitor showed largely similar findings.

Discussion

The study had several main findings. First, meta-analyses for cardiovascular outcomes analysis with 351 476 patients showed that SGLT2 inhibitors were associated with a statistically significant reduction in risk of MACE, all-cause mortality, cardiovascular mortality, nonfatal MI, and hospitalization for heart failure. Second, TSA provided firm evidence of a 20% reduction in MACE, all-cause mortality, and hospitalization for heart failure with SGLT2 inhibitors compared with control treatments, but evidence remain inconclusive for cardiovascular mortality. Third, SGLT2 inhibitors were also associated with a significant reduction in progression of albuminuria. Fourth, there was no significant difference in risk of nonfatal stroke. Fifth, SGLT2 inhibitors significantly reduced incidence of hypoglycemia and acute kidney injury but were associated with higher incidence of urinary tract infection and higher risk of genital infection in both female and male patients. Sixth, SGLT2 inhibitors showed sustained reduction in HbA1c levels and a number of other metabolic risk factors.

Comparisons With Other Meta-Analyses

When we searched PubMed for other relevant meta-analyses, we found 3 that analyzed cardiovascular outcomes of SGLT2 inhibitors.[31–33] In all cases, the prior meta-analyses were limited to RCTs, primarily to evaluate the glucose-lowering effects of SGLT2 inhibitors (except the EMPA-REG OUTCOME trial) but not the cardiovascular safety outcomes. In these trials, cardiovascular outcomes were not predefined and independently adjudicated, and thus detection bias was not negligible. In addition, as acknowledged by the authors of these prior meta-analyses at the time of publication, these trials (except the EMPA-REG OUTCOME trial) included a relatively small number of cardiovascular events, which could substantially limit their conclusions. Sensitively analyses excluding the EMPA-REG OUTCOME trial yielded different conclusions from the overall analyses in these prior meta-analyses and showed no benefit in reducing all-cause mortality and MACE. In contrast, our meta-analysis is based on substantially more mature data regarding the number of cardiovascular events, with the addition of the recently published CANVAS and CANVAS-R trials, along with reports from the large-scale, propensity score–matching CVD-REAL and EASEL studies, all with the primary aim of assessing cardiovascular outcomes. These updated studies allow for more robust assessment of the potential benefits of SGLT2 inhibitors on cardiovascular outcomes. Indeed, our overall and sensitivity analyses generated very similar results, confirming the robustness of our findings.

The included trials in prior meta-analyses had a wide range of follow-up durations, although those were not taken into account in the analyses. It is hard to determine the extent of effects that the lack of adjustment of follow-up would have on outcome estimation; however, it is clear that the precision of effect estimates would be compromised. In contrast, for cardiovascular outcomes analysis, we extracted HRs from each trial and directly pooled HRs with their CIs. We chose HRs because they allow harmonization of the time-period variability across studies. For noncardiovascular outcomes for which an HR was not reported, we used the rate of events in patient-years rather than the number of events alone to control for durations of follow-up. Another methodological

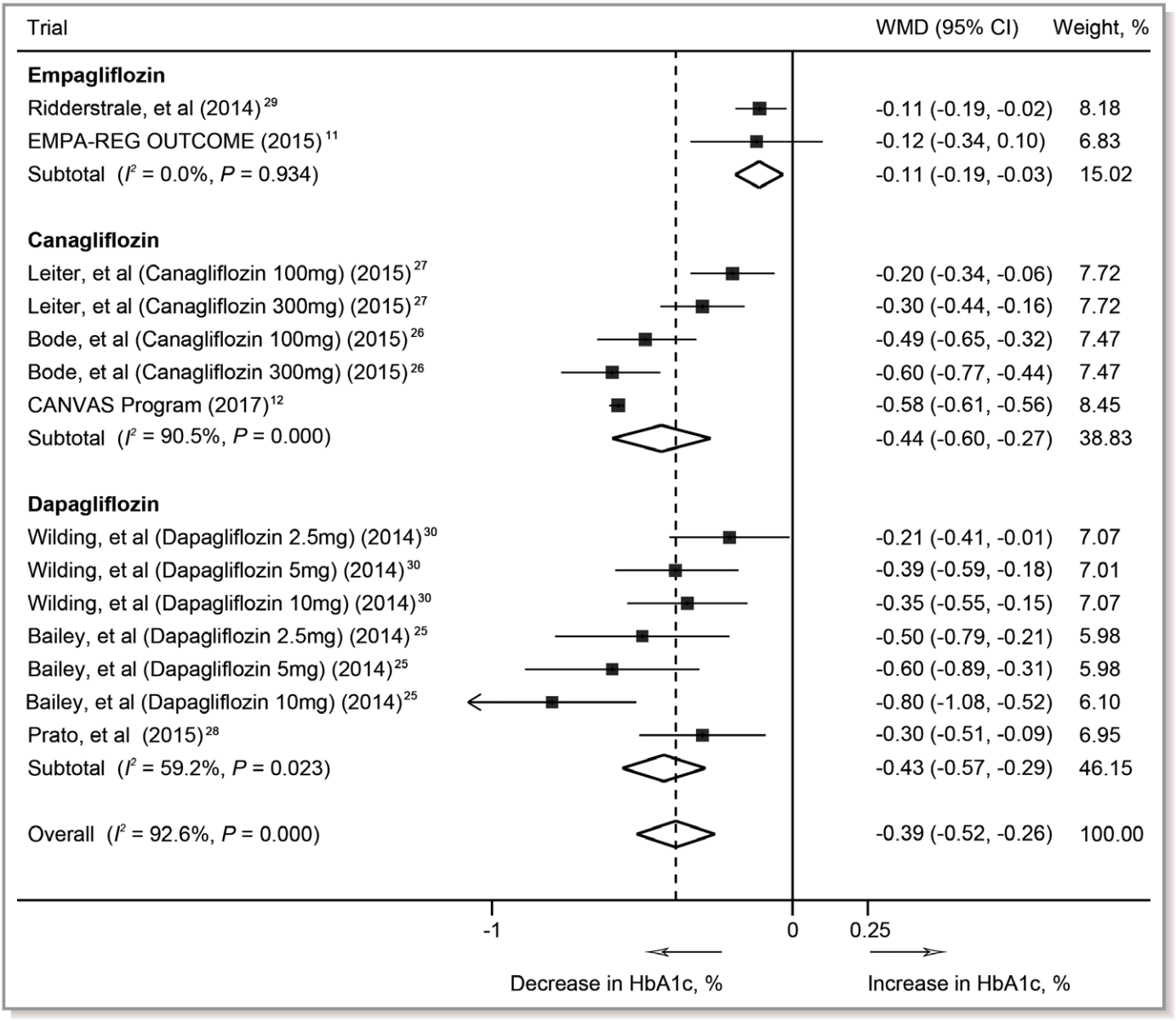

Figure 8. Meta-analyses of effects of SGLT2 inhibitors vs control on HbA1c levels. CI indicates confidence interval; CANVAS, Canagliflozin Cardiovascular Assessment Study trial; EMPA-REG OUTCOME, BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; SGLT2, sodium–glucose cotransporter 2; WMD, weighted mean difference.

strength of our study is the performance of TSA to determine whether conclusions drawn from meta-analyses were in fact conclusive.

Because of the methodological differences, our findings were also different from those of prior meta-analyses. We provided firm evidence that showed no difference in incidence of nonfatal stroke between SGLT2 inhibitors and controls, whereas the other meta-analysis showed an increased risk of nonfatal stroke associated with patients receiving SGLT2 inhibitors. For outcomes with the same direction of results between our and others' analyses, the magnitude of benefits was also considerably different. For instance, we suggested a moderate reduction in risk for cardiovascular death associated with SGLT2 inhibitors (HR: 0.77; 95% CI, 0.60–0.98), whereas other meta-analyses suggested a much more remarkable reduction (OR: 0.63; 95% CI, 0.51–0.77). Differences also existed in estimates of noncardiovascular outcomes, and all other meta-analyses did not evaluate long-term renal microvascular safety and efficacy of SGLT2 inhibitors.

Implications for Clinical Practice

The US Food and Drug Administration (FDA) requires that a good cardiovascular safety has to be established before of

Table 2. Noncardiovascular Safety Outcomes

Safety Outcomes	Patients, N	OR (95% CI)	*P* Value	I^2, %
Serious adverse event	23 031	0.90 (0.81–1.00)	0.05	51.7
Leading to discontinuation	23 031	1.00 (0.93–1.08)	0.99	15.4
Hypoglycemia	17 219	0.48 (0.28–0.82)	0.008	98.0
Urinary tract infection	17 219	1.15 (1.00–1.33)	0.047	43.6
Male genital infection	14 647	3.61 (3.10–4.19)	<0.001	26.5
Female genital infection	6419	3.17 (2.15–4.68)	<0.001	68.1
Volume depletion	16 405	1.28 (1.11–1.46)	<0.001	37.4
Acute kidney injury	13 510	0.80 (0.67–0.96)	0.014	0
Bone fracture	19 421	1.14 (0.86–1.52)	0.36	64.4
Diabetic ketoacidosis	17 162	1.96 (0.77–4.98)	0.16	0
Thromboembolic event	17 162	0.88 (0.61–1.28)	0.50	0
Hyperkalemia	11 350	1.21 (0.77–1.91)	0.41	81.7

CI indicates confidence interval; OR, odds ratio.

any anti-hyperglycemic drug being adopted into clinical practice.[34] This statement was first raised by the poor cardiovascular performance of rosiglitazone, which was reported to increase the risk for heart failure and MI.[5,6] Cardiovascular concern has also been raised regarding DPP4 (dipeptidyl peptidase 4) inhibitors taken as a class,[35] and particularly for saxagliptin,[36] regarding the risk of admission to the hospital for heart failure. In this context, however, we found that SGLT2 inhibitors did not increase the risk of any but instead reduced the risk of a range of cardiovascular outcomes, including individual mortality outcomes. It should to be noted that a large portion of the patients with type 2 DM also had high cardiovascular risk. These patients were treated at baseline for other cardiovascular risk factors; treatment included antihypertensive, low-density lipoprotein cholesterol–lowering, and anticoagulant/antiplatelet therapies. They achieved excellent control of associated cardiovascular risk factors at trial entry, and control was sustained throughout the study duration.

The observation of remarkable cardiovascular and renal protective benefits of SGLT2 inhibitors on the basis of excellent conventional treatments has important clinical implications for cardiologists in managing patients with cardiovascular disease and type 2 DM. First, these findings well documented the cardiovascular safety of SGLT2 inhibitors and provided strong support for the clinical use of these drugs, either as alternative therapy or as adjuncts to metformin, other oral antiglycemic agents, or insulin.[37] Second, our findings strongly supported a new concept that was previously ignored by most cardiologists[38]: Selective glucose-lowering treatment with SLGT2 inhibitors—for example, blood pressure-lowering treatment with the use of renin–angiotensin–aldosterone system inhibitors or β-blockers, lipid-lowering therapy with statins or ezetimibe or PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors, and anticoagulant treatment with acetylsalicylic acid—could significantly improve the cardiovascular outcomes of diabetic patients with established CVD or with high cardiovascular risk.[39,40] Many patients with coronary heart disease have concomitant DM. Previous guidelines in cardiology did not make a recommendation on the selection of antihyperglycemic drugs in this population.[39,40] However, based on current evidence, antihyperglycemic drugs should be chosen with preference in patients with CVD and type 2 DM, with strong recommendation for use of antidiabetic drugs that improve cardiovascular outcomes, such as SGLT2 inhibitors and several GLP-1 (glucagon-like peptide 1) receptor agonists.[41,42] Our analyses, together with those trials, provide strong evidence and could help cardiologists select the preferred glucose-lowering drugs before guideline revision, which is expected in the next few years.

Our analysis supports the cardiovascular benefits of SGLT2 inhibitors as a class effect. It is noteworthy that risk reduction for cardiovascular events was achieved primarily by reducing the risk of the development or progression of heart failure. The mechanisms of cardiovascular protection associated with SGLT2 inhibitors are not clear but are considered multidimensional, which has been discussed elsewhere.[43,44] It may involve hemodynamic effects (reductions in blood pressure and intravascular volume, osmotic diuresis), metabolic effects (cardiac fuel energetics and hormonal effects; eg, increased glucagon release), and cardiac ion handing.[9,44] The effects on cardiac ion handing are complex, and several mechanisms have been proposed, such as inhibition of the sodium–hydrogen exchanger, interaction between SGLT1 (sodium–glucose cotransporter 1) or SMIT1 (sodium–myoinositol

Table 3. Efficacy Outcomes

Outcome	Subgroup	Patients, N	WMD (95% CI)	*P* Value	I^2, %
HbA1c, %	Overall	23 043	−0.39 (−0.52 to −0.26)	<0.001	92.6
	Empagliflozin	8569	−0.11 (−0.19 to −0.03)	0.006	0
	Canagliflozin	12 306	−0.44 (−0.60 to −0.27)	<0.001	90.5
	Dapagliflozin	2168	−0.43 (−0.57 to −0.29)	<0.001	59.2
Body weight, kg	Overall	23 043	−2.90 (−3.72 to −2.07)	<0.001	97.1
	Empagliflozin	8569	−2.02 (−5.01 to 0.97)	0.185	98.2
	Canagliflozin	12 306	−3.06 (−4.52 to −1.60)	<0.001	98.5
	Dapagliflozin	2168	−3.19 (−3.68 to −2.70)	<0.001	32.2
FBG, mmol/L	Overall	5881	−0.71 (−0.88 to −0.55)	<0.001	58.2
	Empagliflozin	1549	−0.69 (−0.87 to −0.51)	<0.001	NA
	Canagliflozin	2164	−0.89 (−1.25 to −0.53)	<0.001	83.5
	Dapagliflozin	2168	−0.59 (−0.79 to −0.39)	<0.001	9.1
SBP, mm Hg	Overall	22 235	−3.84 (−4.70 to −2.98)	<0.001	78.2
	Empagliflozin	8569	−3.27 (−5.37 to −1.17)	0.002	91.6
	Canagliflozin	12 306	−4.79 (−5.86 to −3.71)	<0.001	68.4
	Dapagliflozin	1360	−2.59 (−4.07 to −1.12)	0.001	0
DBP, mm Hg	Overall	19 971	−1.03 (−1.78 to −0.28)	0.007	83.3
	Empagliflozin	8569	−0.86 (−2.93 to 1.21)	0.414	94
	Canagliflozin	10 856	−1.62 (−2.24 to −1.00)	<0.001	38.4
	Dapagliflozin	546	0.09 (−1.05 to 1.23)	0.88	0
LDL-C, mmol/L	Overall	18 684	0.09 (0.03–0.14)	0.001	52
	Empagliflozin	7020	0.04 (0–0.08)	0.073	0
	Canagliflozin	10 856	0.12 (0.09–0.15)	<0.001	0
	Dapagliflozin	808	2.35 (−6.21 to 10.92)	0.59	67.1
HDL-C, mmol/L	Overall	18 684	0.10 (0.04–0.15)	<0.001	87.1
	Empagliflozin	7020	0.65 (−0.04 to 1.34)	0.063	52.3
	Canagliflozin	10 856	0.09 (0.04–0.14)	0.001	93.1
	Dapagliflozin	808	2.55 (−2.57 to 7.68)	0.328	27.3

CI indicates confidence interval; DBP, diastolic blood pressure; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; WMD, weighted mean difference.

cotransporter 1) and gp91phox NADPH oxidase, and the inhibition of SGLT-induced intracellular sodium and calcium accumulation.[45,46]

Noncardiovascular Safety of SGLT2 Inhibitors

In our analysis, confirmed hypoglycemic adverse events were significantly less common in patients receiving SGLT2 inhibitors, despite the greater reduction in HbA1c concentration that was achieved. This finding may be related to the self-limiting nature of this mode of action: Efficacy decreases as hyperglycemia lessens.[47] In line with previous reports, SGLT2 inhibitors were associated with increased risks of genital infections. The risk was similar in female and male patients in our study, which was a bit different from a previous study that showed a greater risk for women than for men.[48] In addition, an increase risk of urinary tract infection was observed in our analysis. All of these infections were generally mild to moderate in intensity, were easy to treat, and rarely led to discontinuation. SGLT2 inhibitors increased the risk of volume depletion-related events, a result that may be related to their effect of osmotic diuresis of glucose and sodium.[10] Previously, some trials indicated that SGLT2 inhibitors might have adverse effects on the risk of bone fractures[49]; however, this was not confirmed in our meta-analysis of nearly 20 000 patients. We showed that SGLT2 inhibitors reduced the incidence of acute

kidney injury, and this observation was confirmed in a large propensity score–matched cohort study.[50]

The development of DKA has been a source of concern for patients receiving SGLT2 inhibitors. This concern was initially raised about off-label use of SGLT2 inhibitors in patients with type 1 DM.[51,52] Later in 2015, based on first-year postmarketing surveillance reporting of 20 DKA cases, the FDA issued a statement warning that SGLT2 inhibitors might increase the risk of DKA.[53] Using a large claims database of commercially insured patients in the United States that included 38 045 patients each receiving an SGLT2 inhibitor or DDP4 inhibitor after propensity score matching (including a total of 81 ketoacidosis events), Fralick and colleagues confirmed that SGLT2 inhibitors were associated with ≈2-fold increase in developing ketoacidosis (HR: 2.2; 95% CI, 1.4–3.6).[54] Similarly, Blau and colleagues searched the FDA Adverse Event Reporting System (FAERS) for reports of acidosis in patients treated with SGLT2 inhibitors and identified 259 reports of acidosis (including 192 reports of ketoacidosis).[55] The estimated overall risk of developing acidosis was ≈14-fold higher for SGLT2 inhibitors compared with DDP4 inhibitors based on 477 reports of acidosis and 71 reports of ketoacidosis. Analysis limited to type 2 DM showed a ≈7-fold increased risk of acidosis associated with SGLT2 inhibitors.[55] Nevertheless, currently published cardiovascular outcome RCTs did not detect a significant difference in DKA incidence; however, it should be noted that these 2 RCTs involved a limited number of ketoacidosis events (5 cases for the EMPA-REG OUTCOME and 18 cases for CANVAS).[11,12] Although DKA in the setting of SGLT2 inhibitor therapy is unusual,[56,57] adjunctive point-of-care home ketone monitoring should be considered in a subset of high-risk patients because DKA related to SGLT2 inhibitors can present with lower blood glucose levels.[10]

Pooled data from the CANVAS and CANVAS-R trials revealed an unexpected ≈2-fold higher incidence of lower limb amputation associated with canagliflozin (6.3 versus 3.4 participants per 1000 patient-years), corresponding to a number needed to harm of ≈300.[12,58] A pharmacovigilance analysis using FAERS confirmed that use of canagliflozin might be associated with an increased risk of amputations.[59] On the basis of these data, the FDA has added a "black box warning" regarding amputations with canagliflozin,[58] although inconsistent findings were found in a much larger retrospective real-world study involving 63 845 new users each receiving canagliflozin or non–SGLT2 inhibitor agents (196 amputation events).[60] The European Medicines Agency's Pharmacovigilance Risk Assessment Committee warns that the risk of amputation may also apply to other SGLT2 inhibitors to highlight the importance of routine preventative foot care because amputation has a large negative impact on patient clinical course,[61] although no data are available to date supporting this generalization.[62] Indeed, in the pharmacovigilance analysis mentioned, increase of amputation risk was not observed in patients receiving dapagliflozin or empagliflozin.[59] Whether the risk is specific to canagliflozin or is a class effect of SGLT2 inhibitors remains to be understood. It is very likely that the EMPA-REG OUTCOME trial of empagliflozin will be reassessed because primary analysis of this trial did not systematically include adequate data on amputation.[11] The ongoing DECLARE (Dapagliflozin Effect on Cardiovascular Events) trial, a large-scale cardiovascular outcomes trial of dapagliflozin that is now required to systematically collect amputation data, will shed light on this debate.

Limitations

We acknowledge several limitations. First, the results were analyzed for study-level data but not for patient-level data; individual patient-level data could improve the accuracy of the findings. Second, we could not rule out potential publication bias even though statistical evaluation did not suggest significant publication bias. Third, considerable heterogeneity was detected in the analyses of several outcomes and may be due to the differences in trial populations, baseline comorbidities, and treatment regimens. In these cases, data were pooled with random-effects models. Fourth, most patients enrolled were white; therefore, caution should be used in generalizing the findings to other populations.

Conclusions

Our meta-analysis provides robust reassurance regarding the cardiovascular and long-term noncardiovascular safety of SGLT2 inhibitors, with sustained efficacy in reducing a range of markers of vascular risk. SGLT2 inhibitors showed remarkable cardiovascular and renal protective benefits and might be considered as preferred for type 2 DM patients with established or high risk for CVD.

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Disclosures

None.

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Supplemental Material

Table S1. Primary and secondary endpoints, inclusion and exclusion criteria of included randomized controlled trials.

Trial	Primary endpoint	Secondary endpoint	Inclusion Criteria	Exclusion criteria
EMPA-REG OUTCOME[1 2]	Composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.	Primary outcome plus hospitalization for unstable angina; individual endpoint	Type 2 diabetes adults (≥18 years of age) with a body-mass index of 45 or less and an estimated glomerular filtration rate (eGFR) of at least 30 ml per minute per 1.73 m2 of body-surface area, had established cardiovascular disease and had received no glucose-lowering agents for at least 12 weeks before randomization and had a glycated hemoglobin level of at least 7.0% and no more than 9.0% or had received stable glucose-lowering therapy for at least 12 weeks before randomization and had a glycated hemoglobin level of at least 7.0% and no more than 10.0%	Uncontrolled hyperglycemia with glucose >240 mg/dL after an overnight fast during placebo run-in and confirmed by a second measurement, Indication of liver disease, Estimated glomerular filtration rate <30 ml/min/1.73 m2, etc.
CANVAS[3]	Composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.	Death from any cause, death from cardiovascular causes, progression of albuminuria, and the composite of death from cardiovascular causes and hospitalization for heart failure	Type 2 diabetes (glycated hemoglobin level, ≥7.0% and ≤10.5%) and were either 30 years of age or older with a history of symptomatic atherosclerotic cardiovascular disease or 50 years of age or older with two or more of the following risk factors for cardiovascular disease: duration of diabetes of at least 10 years, systolic blood pressure higher than 140 mm Hg while they were receiving one or more antihypertensive agents, current smoking, microalbuminuria or macroalbuminuria, or high-density lipoprotein (HDL) cholesterol level of less than 1 mmol per liter (38.7 mg per deciliter). Participants were required to have an estimated glomerular filtration rate (eGFR) at entry of more than 30 ml per minute per 1.73 m2 of body-surface area	History of diabetic ketoacidosis, type 1 diabetes, pancreas or beta-cell transplantation, or diabetes secondary to pancreatitis or pancreatectomy.
CANVAS-R[3]	Similar to CANVAS	Similar to CANVAS	Similar to CANVAS	Similar to CANVAS
EASEL[4]	The composite of all-cause mortality	A composite of all-cause mortality, nonfatal MI, and	Patients with T2DM were required to have 1 year of observation prior to the index date, with established CVD and	Patients with T1DM, secondary diabetes, missing sex data prior to the index date were excluded from this study.

	and hospitalization for heart failure	nonfatal stroke, as well as the individual component of the composite endpoints	were new users of SGLT2i or new users of non-SGLT2i AHA on top of standard care therapy.	
CVD-REAL[5]	Hospital admissions for heart failure	All-cause death; and composite of hospital admissions for heart failure or all-cause death	Patients with T2D that were newly started on either SGLT-2i or newly started on other glucose lowering drugs were selected from each dataset beginning on the date of first prescription or pharmacy dispensation of an SGLT-2i or a new other glucose lowering drugs in each of the country.	Patients with Type 1 or gestational diabetes were excluded.
Wilding, et al[6]	Change from baseline in HbA1c	Change in total body weight, calculated mean daily insulin dose; proportion of patients with calculated mean daily insulin dose reduction≥10% from baseline.	Aged 18–80 whose T2DM was inadequately controlled (HbA1c 7.5–10.5%) on a stable dose of insulin at ≥30 units/day for at least 8 weeks with or without up to two OADs	•Type 1 Diabetes •Treatment with more than two additional oral antidiabetic drugs •Moderate and severe renal (kidney) failure or dysfunction
Ridderstrale, et al[7]	Change from baseline in HbA1c	The occurrence of confirmed hypoglycaemic adverse events, and changes from baseline in bodyweight, systolic blood pressure, and	Adults (aged ≥18 years) with type 2 diabetes, BMI less than or equal to 45 kg/m², and HbA1c concentrations of 7–10%, receiving an unchanged dose of metformin immediate release (≥1500 mg/day, maximum tolerated dose, or maximum dose according to the local label) for at least 12 weeks before randomisation	eGFR of less than 60 mL/min per 1·73 m², blood glucose concentration greater than 13·3 mmol/L after an overnight fast, and use of antidiabetes drugs other than metformin immediate release any time during the 12 weeks before randomisation

		diastolic blood pressure at weeks 52 and 104		
Bailey, et al[8]	Change from baseline in HbA1c	Change from baseline in fasting plasma glucose (FPG), and body weight, etc	Aged 18–77 years, had type 2 diabetes, HbA1c 7–10%, C-peptide concentration 0·34 nmol/L or more, body-mass index 45 kg/m² or less, and were taking a stable dose of metformin (≥1500 mg per day) for at least 8 weeks before enrolment.	Serum creatinine 133 μmol/L or more for men or 124 μmol/L or more for women; urine albumin/creatinine ratio more than 203·4 mg/mmol; aspartate aminotransferase or alanine aminotransferase more than three times the upper limit of normal, etc.
Prato, et al[9]	Change from baseline in HbA1c	Change in A1C, FPG, and systolic and diastolic BP; percentage change in body weight and fasting plasma lipids	•Type 2 Diabetes •Treated with oral anti-diabetic drug therapy (therapy including Metformin for at least 8 weeks prior to enrolment) •HbA1c >6.5% and </=10%	•Type 1 Diabetes •Insulin therapy within one year of enrolment •Renal (kidney) failure or dysfunction
Leiter, et al[10]	Change from baseline in HbA1c	Change in A1C, FPG, and systolic and diastolic BP; percentage change in body weight and fasting plasma lipids	Men and women ≥18 and ≤80 years of age with type 2 diabetes and A1C ≥7.0% (53mmol/mol) and ≤9.5% (80 mmol/mol) whose conditions were stable while receiving metformin therapy (≥2,000 mg/day, or≥1,500 mg/day if unable to tolerate a higher dose) for ≥10 weeks.	Repeated fasting plasma glucose (FPG) or self-monitored blood glucose (SMBG) measurements of ≥15.0 mmol/L (270 mg/dL) during the pretreatment phase; a history of type 1 diabetes; a history of more than one severe hypoglycemia episode within 6 months before screening; estimated glomerular filtration rate (eGFR) ,55 mL/min/1.73 m 2 (or ,60mL/min/1.73 m2.

Bode, et al[11]	Change from baseline in HbA1c	The proportion of patients reaching HbA1c <7.0 and<6.5%, change from baseline in fasting plasma glucose (FPG), etc.	Men and women aged 55–80 years with T2DM, who had HbA1c≥7.0 to≤10.0% at screening, and were either not on AHA therapy or on a stable regimen of AHA(s) as monotherapy or combination therapy.	History of diabetic ketoacidosis, type 1 diabetes mellitus (T1DM), pancreas or beta cell transplantation, or diabetes secondary to pancreatitis or pancreatectomy, or a severe hypoglycemic episode within 6 months before screening

Table S2. Risk of bias of included randomized controlled trials.

Trial	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
EMPA-REG OUTCOME[1 2]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
CANVAS[3]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
CANVAS-R[3]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Bailey, et al[8]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Bode, et al[11]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Leiter, et al[10]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Prato, et al[9]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Ridderstrale, et al[7]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Wilding, et al[6]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

Table S3. Study quality of included comparative observational studies using the Newcastle-Ottawa scale.

Author/Study	Year	Study quality (Newcastle-Ottawa Scale)			
		Selection	Comparability	Outcome/exposure	Total score
CVD-REAL[5]	2017	****	**	***	9
EASEL[4]	2017	****	**	***	9

Table S4. Subgroup analyses for MACE.

Subgroup	HR (95% CI)	*P* value
Age		
< 65 y	0.963 (0.837, 1.108)	0.601
≥ 65 y	0.758 (0.666, 0.864)	0
Sex		
Male	0.864 (0.773, 0.967)	0.011
Female	0.836 (0.696, 1.005)	0.056
Race		
White	0.856 (0.769, 0.952)	0.004
Asian	0.844 (0.537, 1.327)	0.463
Black	0.847 (0.264, 2.714)	0.78
Glycated hemoglobin		
<8.0-8.5%	0.839 (0.682, 1.033)	0.099
≥8.0-8.5%	0.937 (0.664, 1.323)	0.713
BMI		
<30kg/m2	0.847 (0.65, 1.104)	0.22
≥30kg/m2	0.871 (0.706, 1.076)	0.2
Blood pressure		
SBP ≥140mmHg and/or DBP ≥90mmHg	0.836 (0.726, 0.963)	0.013
SBP <140mmHg and DBP <90mmHg	0.884 (0.778, 1.005)	0.061
eGFR		
≥90mL/min/1.73m2	0.943 (0.726, 1.225)	0.661
60 to <90mL/min/1.73m2	0.858 (0.69, 1.067)	0.169
<60mL/min/1.73m2	0.785 (0.627, 0.982)	0.034
History of cardiovascular disease		
Yes	0.843 (0.756, 0.939)	0.002
No	0.876 (0.709, 1.081)	0.217
Insulin use		
Yes	0.88 (0.775, 1.001)	0.052
No	0.831 (0.719, 0.959)	0.012
RAAS inhibitor use		
Yes	0.88 (0.79, 0.98)	0.02
No	0.77 (0.621, 0.955)	0.017
Beta-blocker use		
Yes	0.784 (0.697, 0.883)	0

No	0.84 (0.693, 1.017)	0.074
Statin use		
Yes	0.857 (0.766, 0.959)	0.007
No	0.859 (0.711, 1.039)	0.117
Antithrombotic use		
Yes	0.87 (0.782, 0.968)	0.011
No	0.811 (0.651, 1.011)	0.063
Diuretic use		
Yes	0.758 (0.572, 1.004)	0.054
No	0.965 (0.726, 1.282)	0.803

DBP, diastolic blood pressure; RAAS, renin–angiotensin–aldosterone system; SBP, systolic blood pressure.

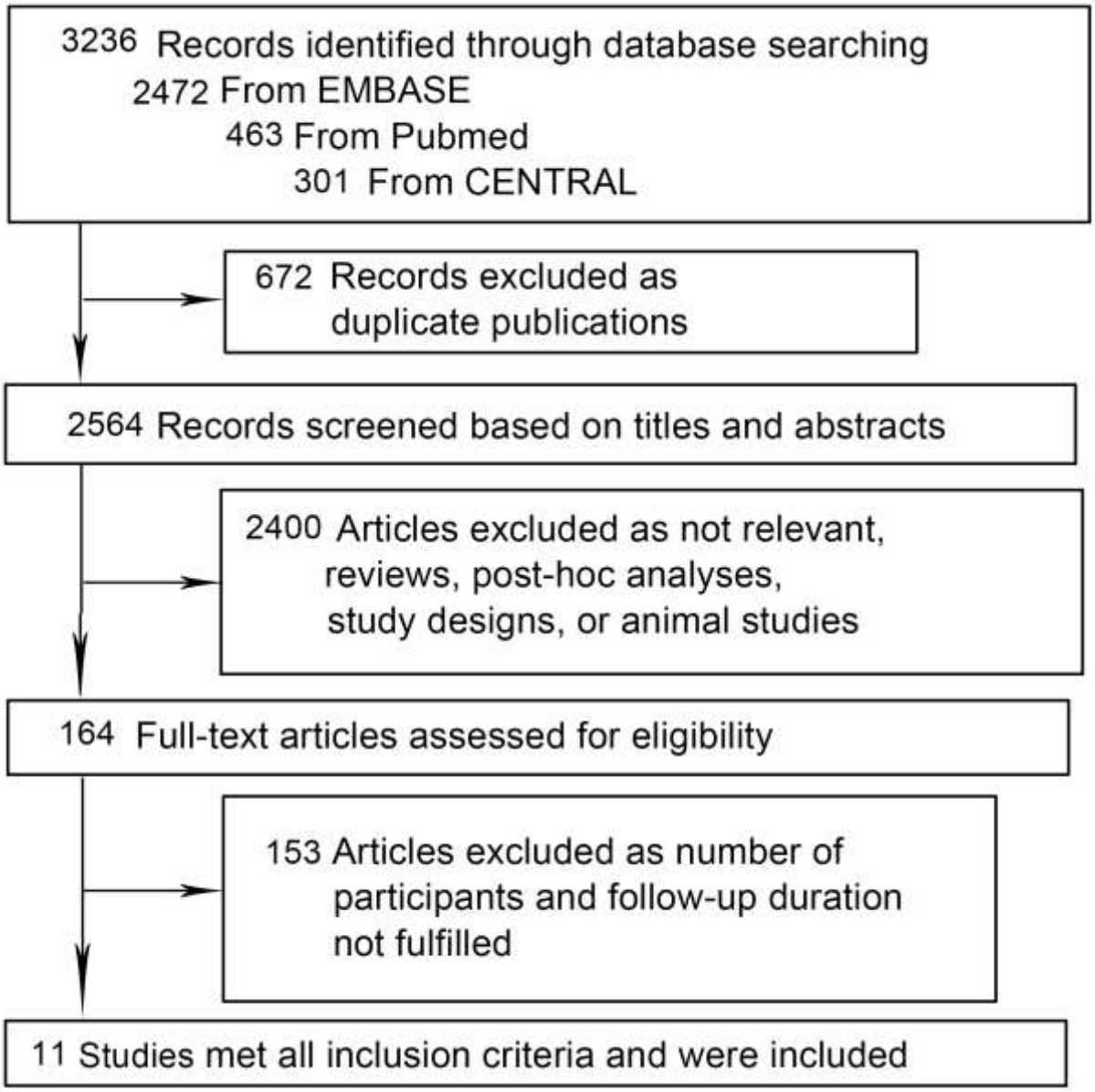

Figure S1. Flow diagram of study selection.

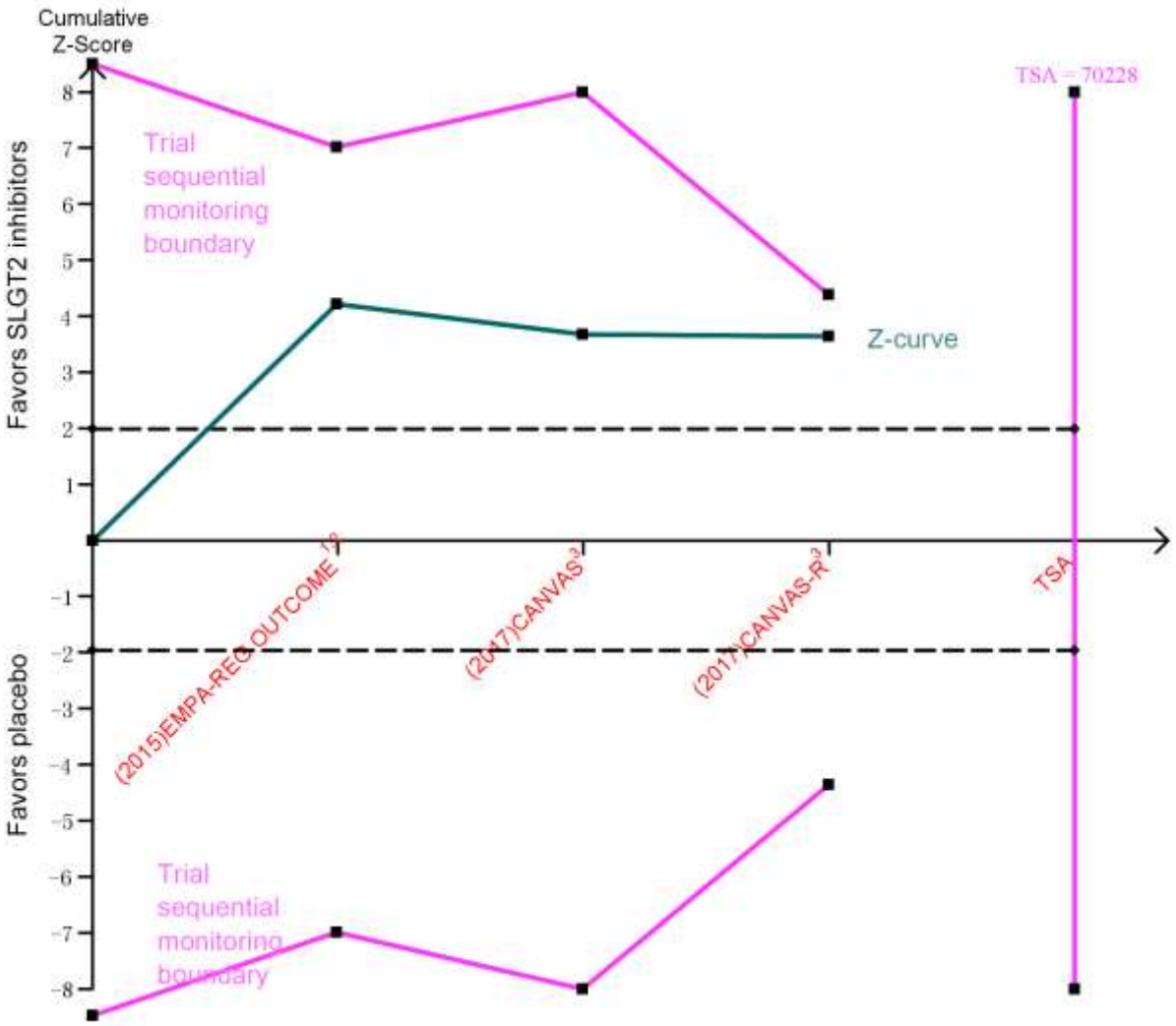

Figure S2. Trial sequential analysis for cardiovascular death in patients receiving SGLT2 inhibitors versus control.

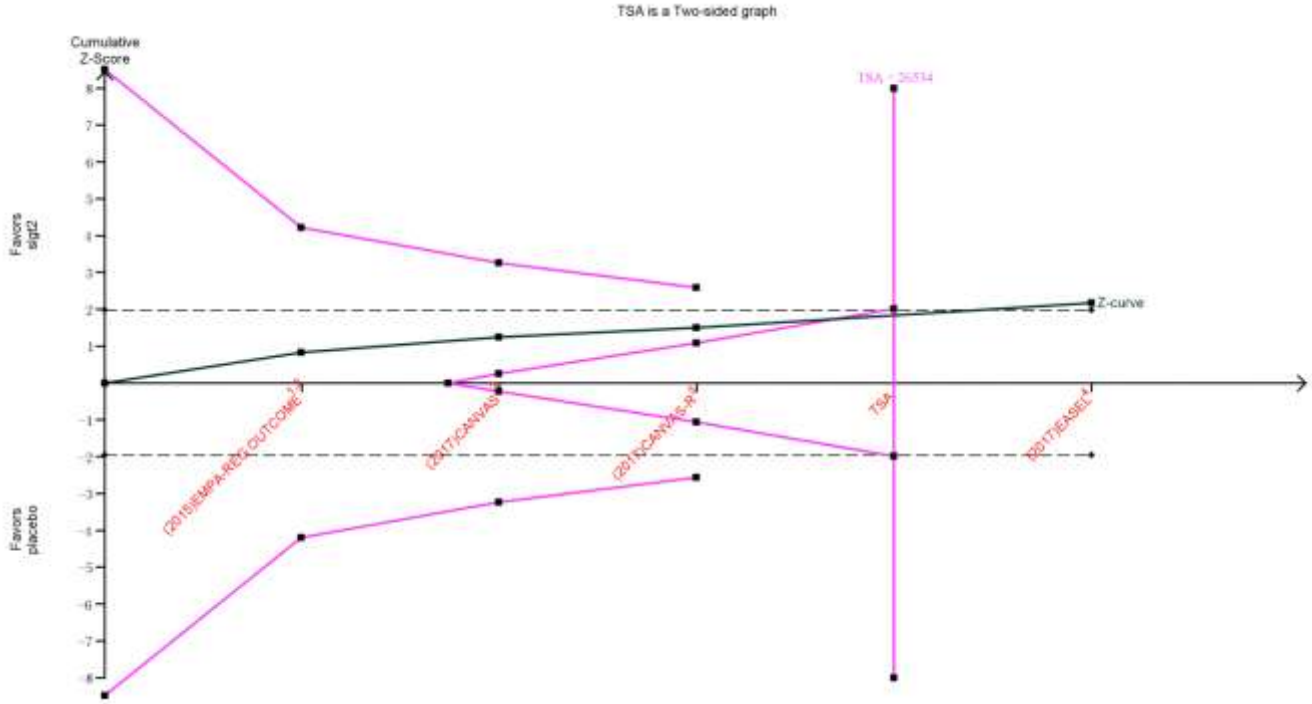

Figure S3. Trial sequential analysis for nonfatal myocardial infarction in patients receiving SGLT2 inhibitors versus control.

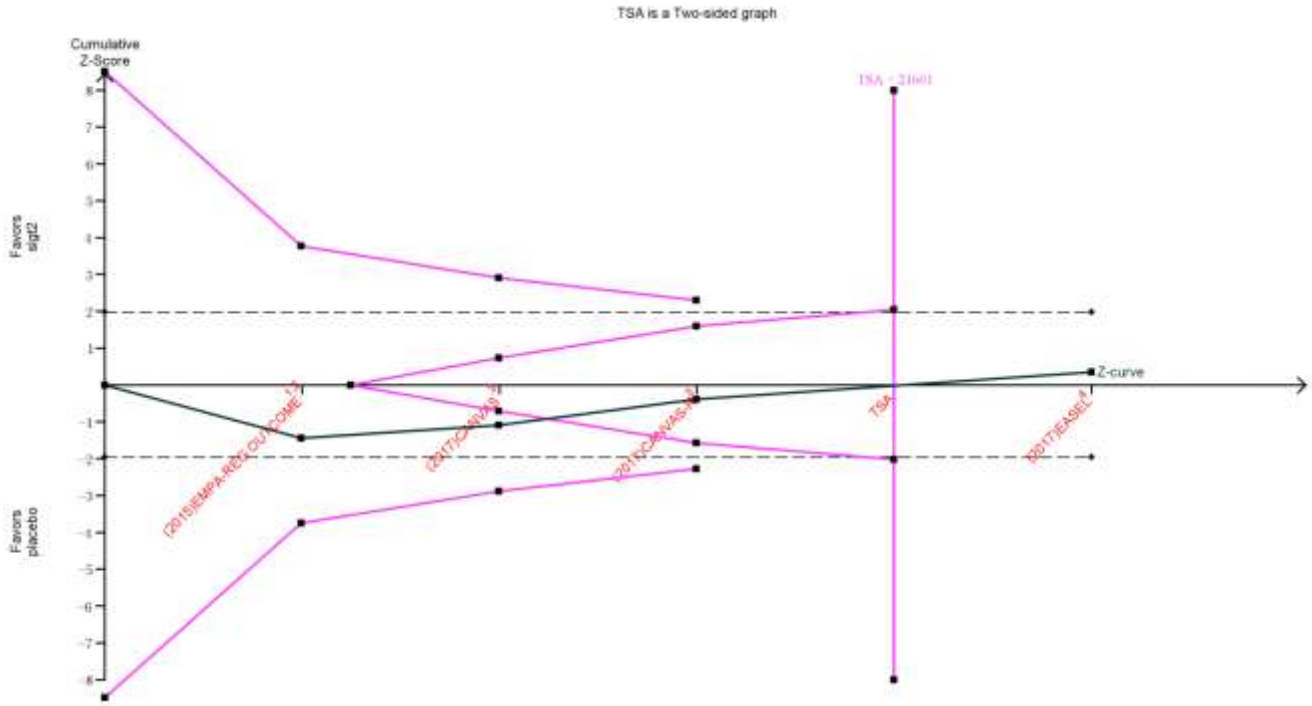

Figure S4. Trial sequential analysis for nonfatal stroke in patients receiving SGLT2 inhibitors versus control.

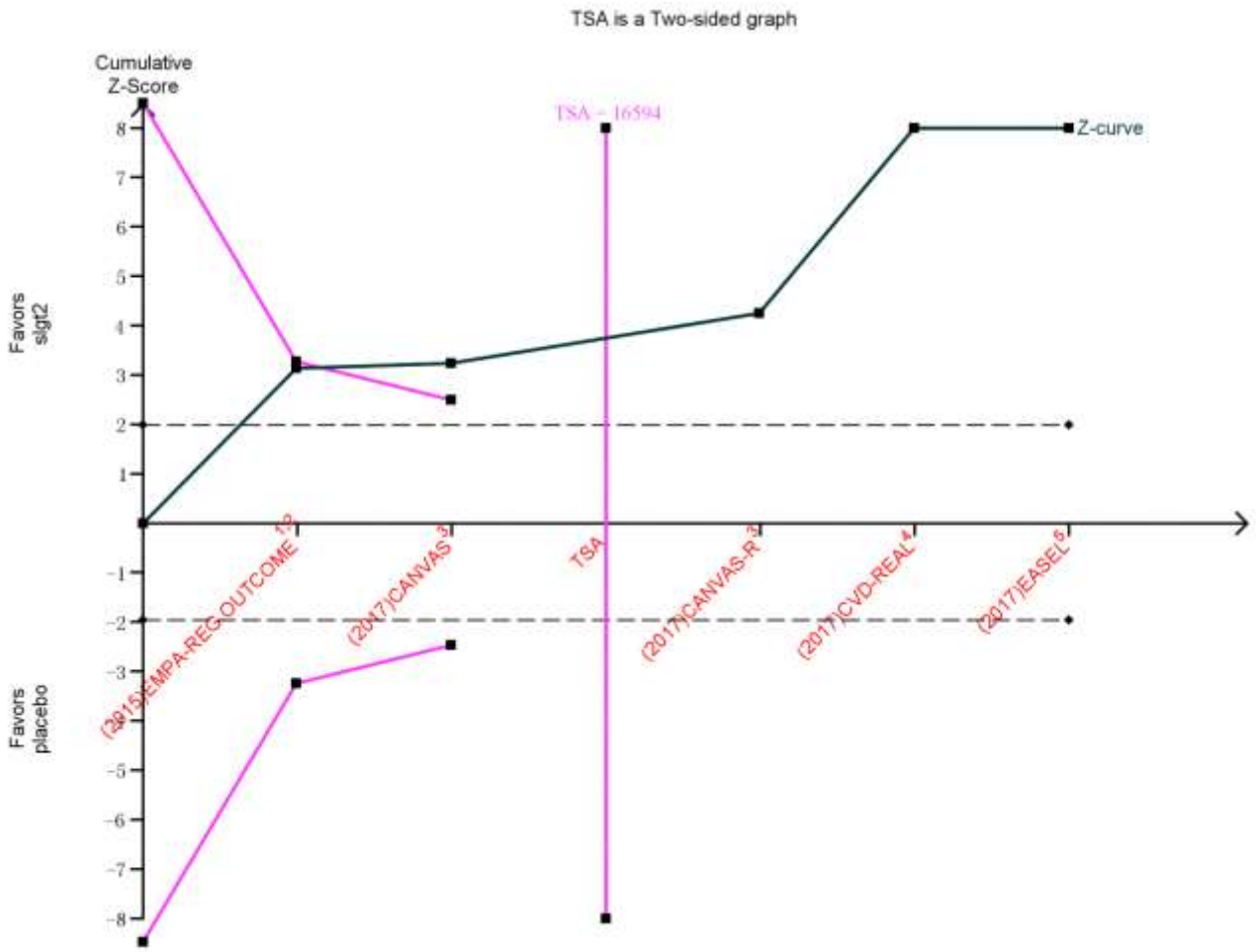

Figure S5. Trial sequential analysis for hospitalization for heart failure in patients receiving SGLT2 inhibitors versus control.

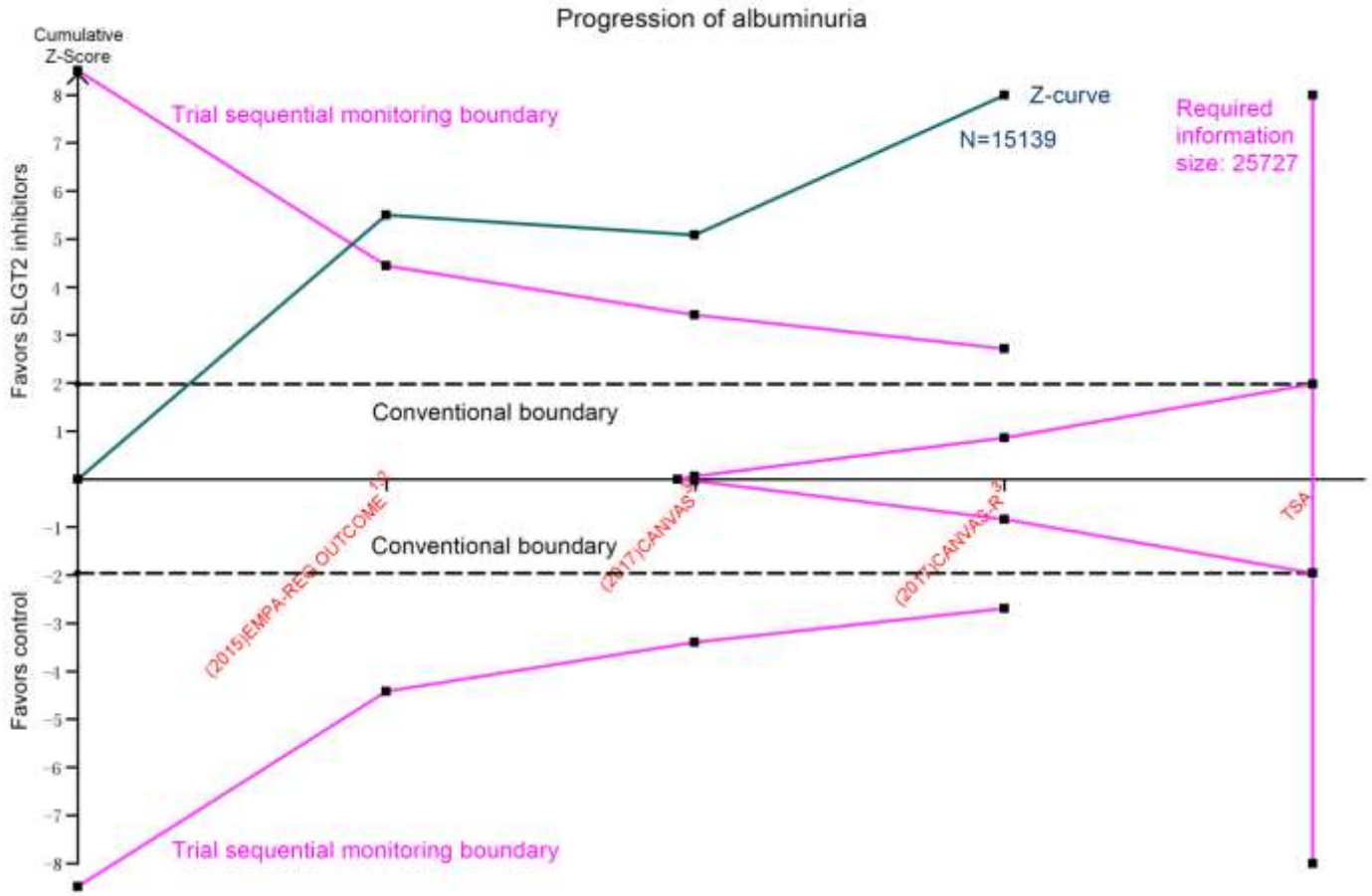

Figure S6. Trial sequential analysis for progression for albuminuria in patients receiving SGLT2 inhibitors versus control.

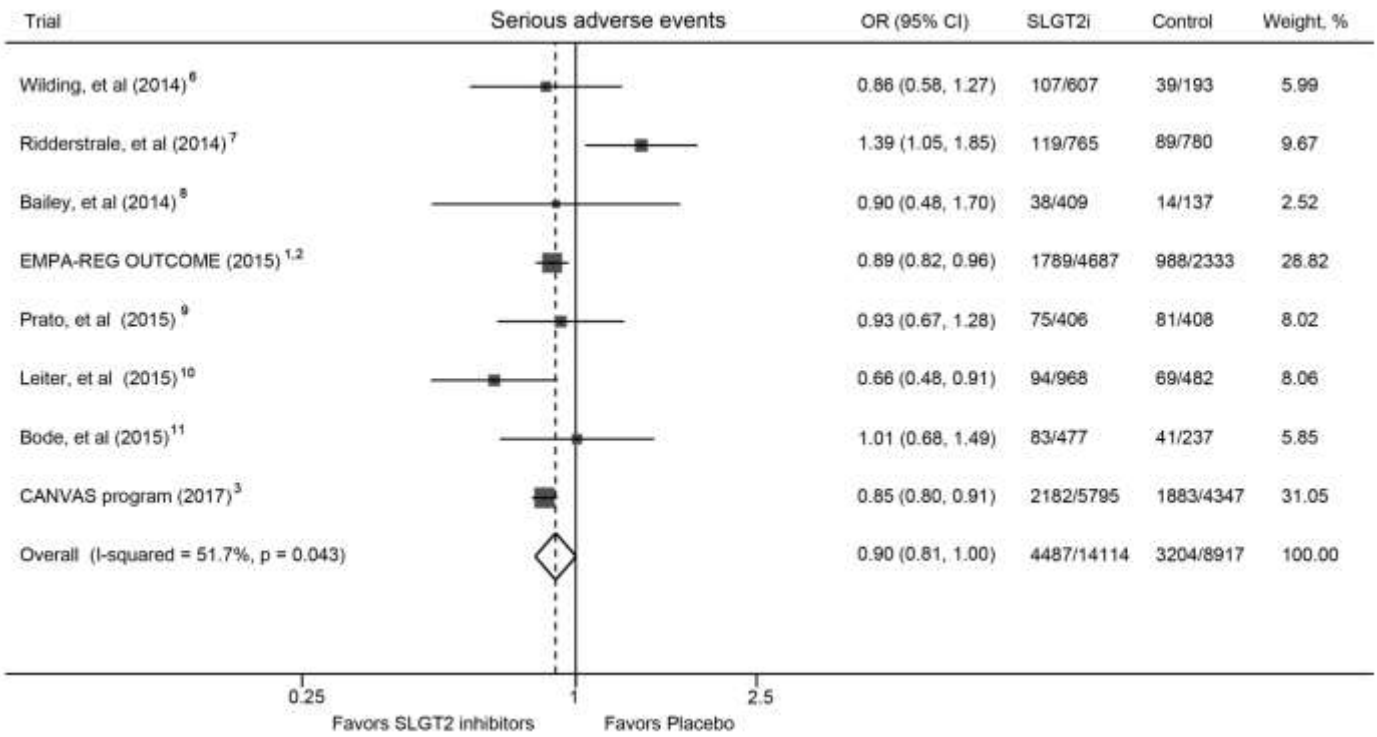

Figure S7. Pooled risk for serious adverse events in patients who received SGLT2 inhibitors versus control from randomized controlled trials.

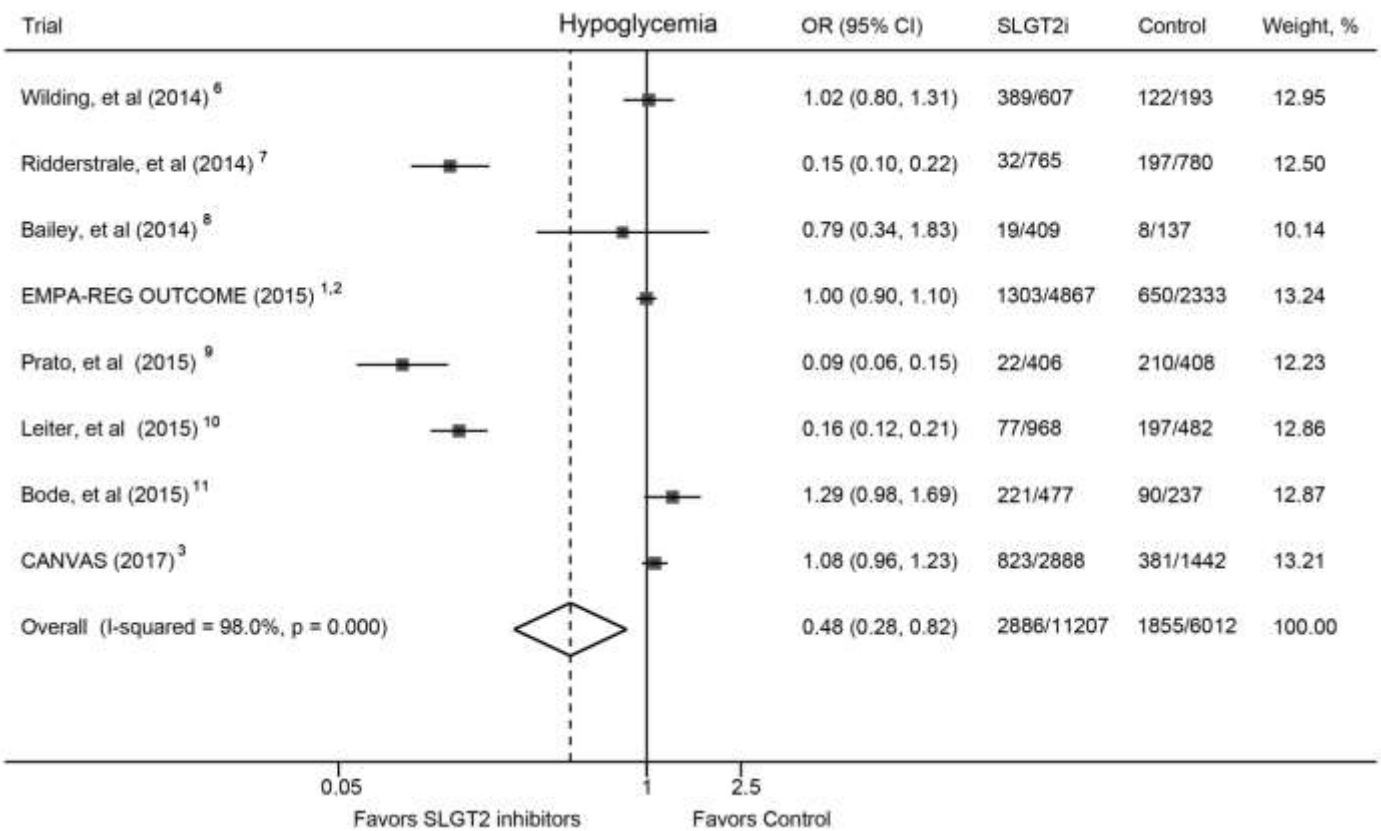

Figure S8. Pooled risk for hypoglycemia in patients who received SGLT2 inhibitors versus control from randomized controlled trials.

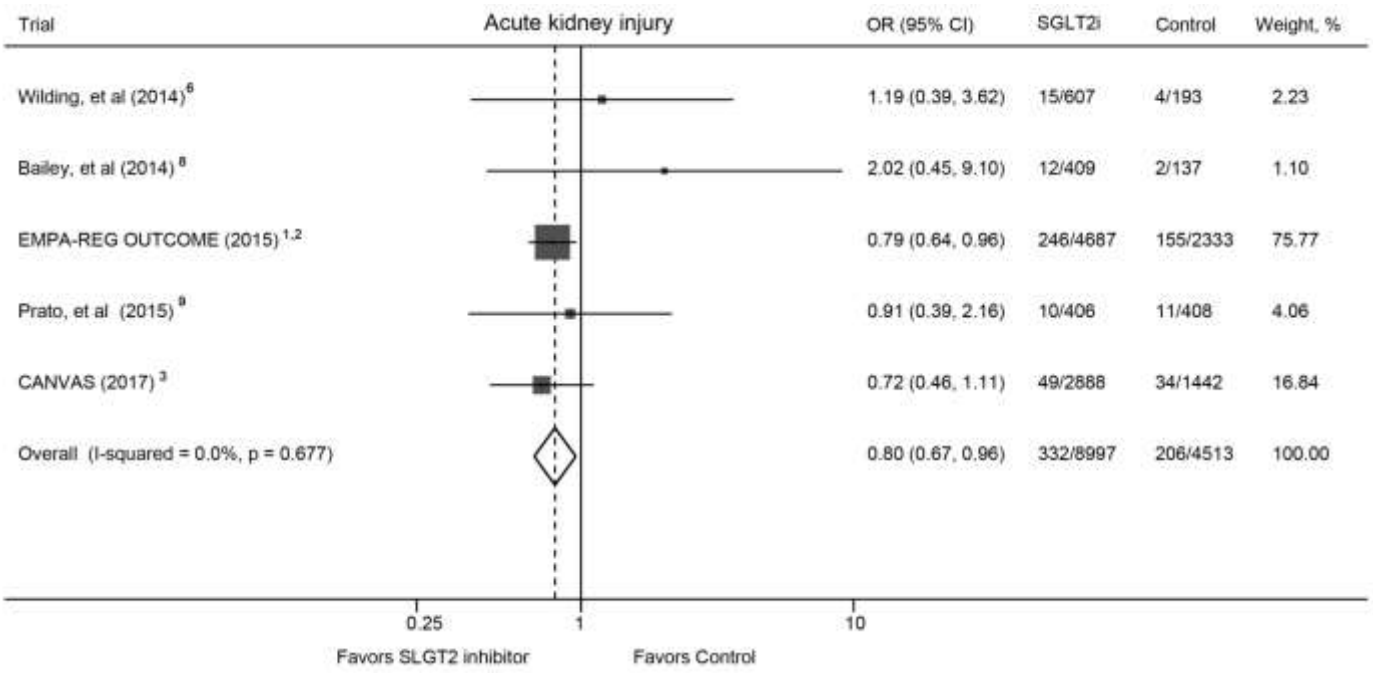

Figure S9. Pooled risk for acute kidney injury in patients who received SGLT2 inhibitors versus control from randomized controlled trials.

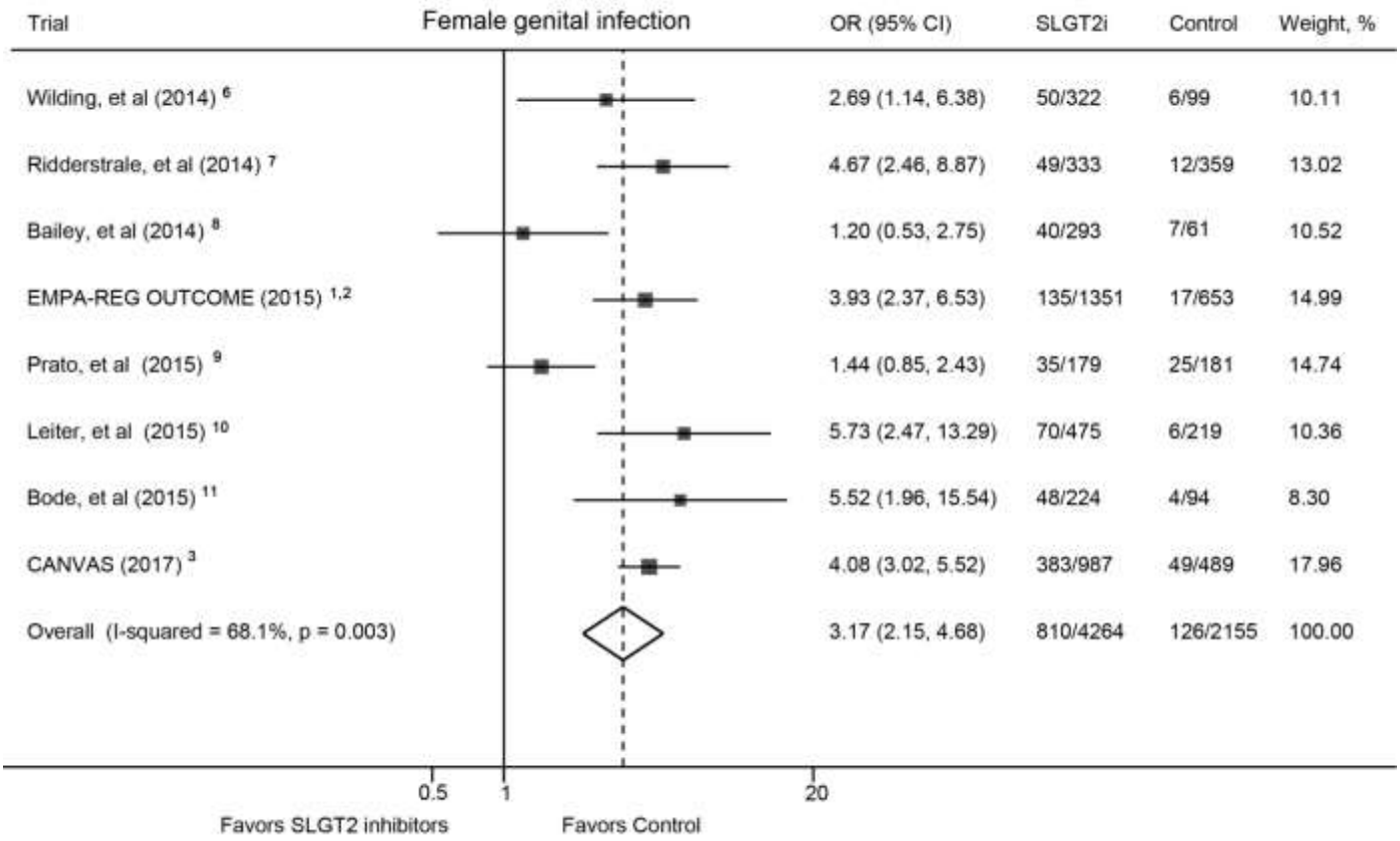

Figure S10. Pooled risk for female genital infection in patients who received SGLT2 inhibitors versus control from randomized controlled trials.

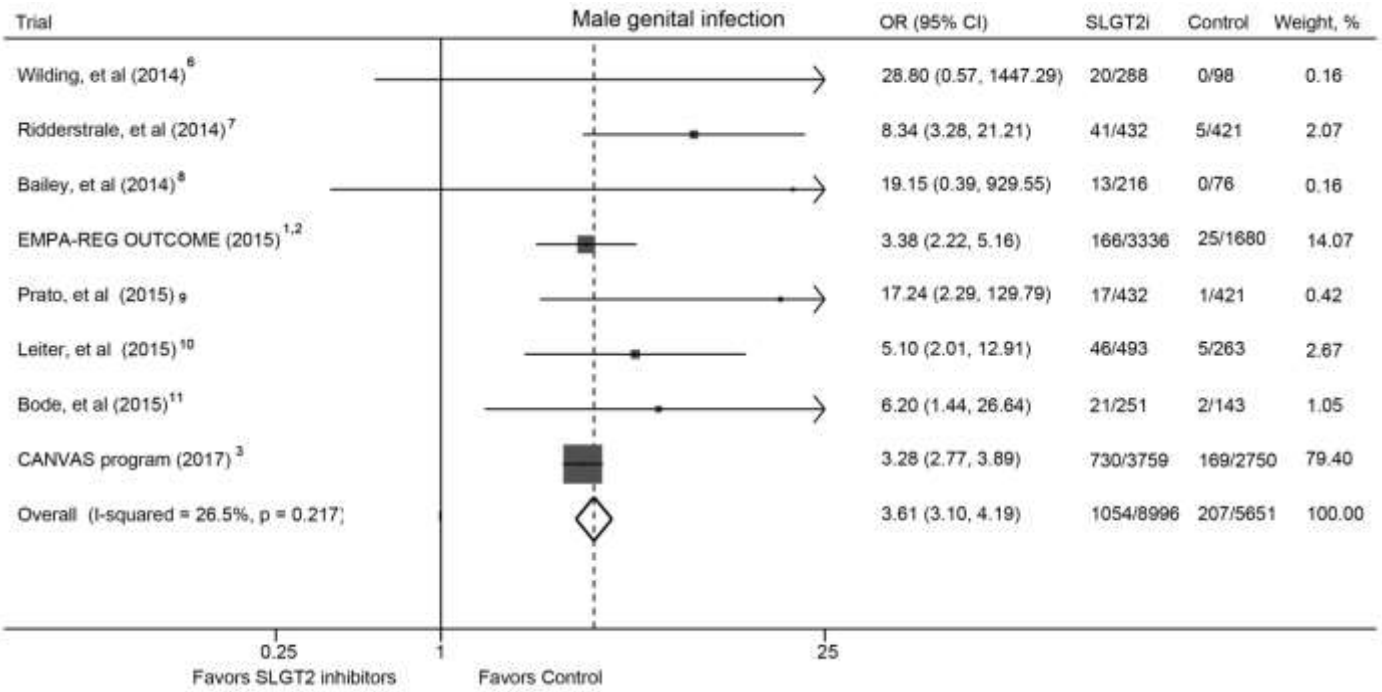

Figure S11. Pooled risk for male genital infection in patients who received SGLT2 inhibitors versus control from randomized controlled trials.

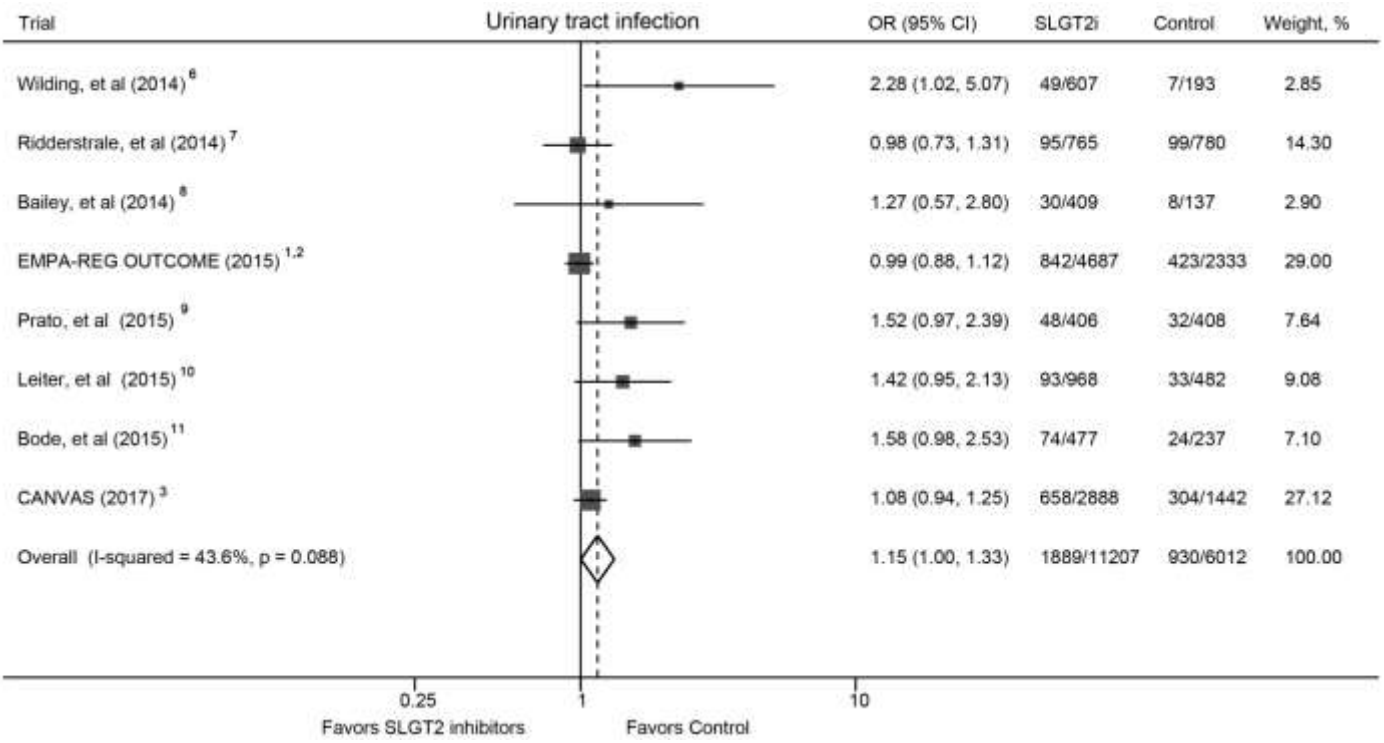

Figure S12. Pooled risk for urinary tract infection in patients who received SGLT2 inhibitors versus control from randomized controlled trials.

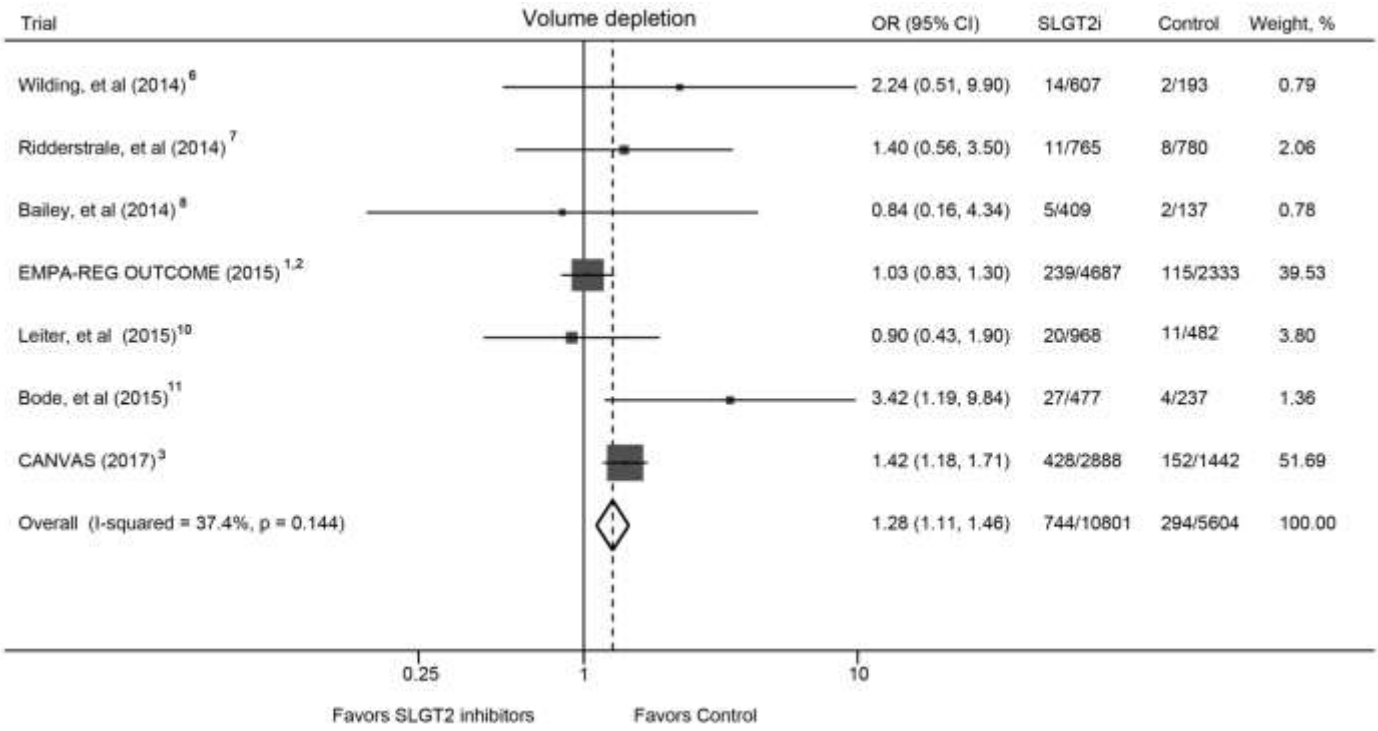

Figure S13. Pooled risk for volume depletion in patients who received SGLT2 inhibitors versus control from randomized controlled trials.

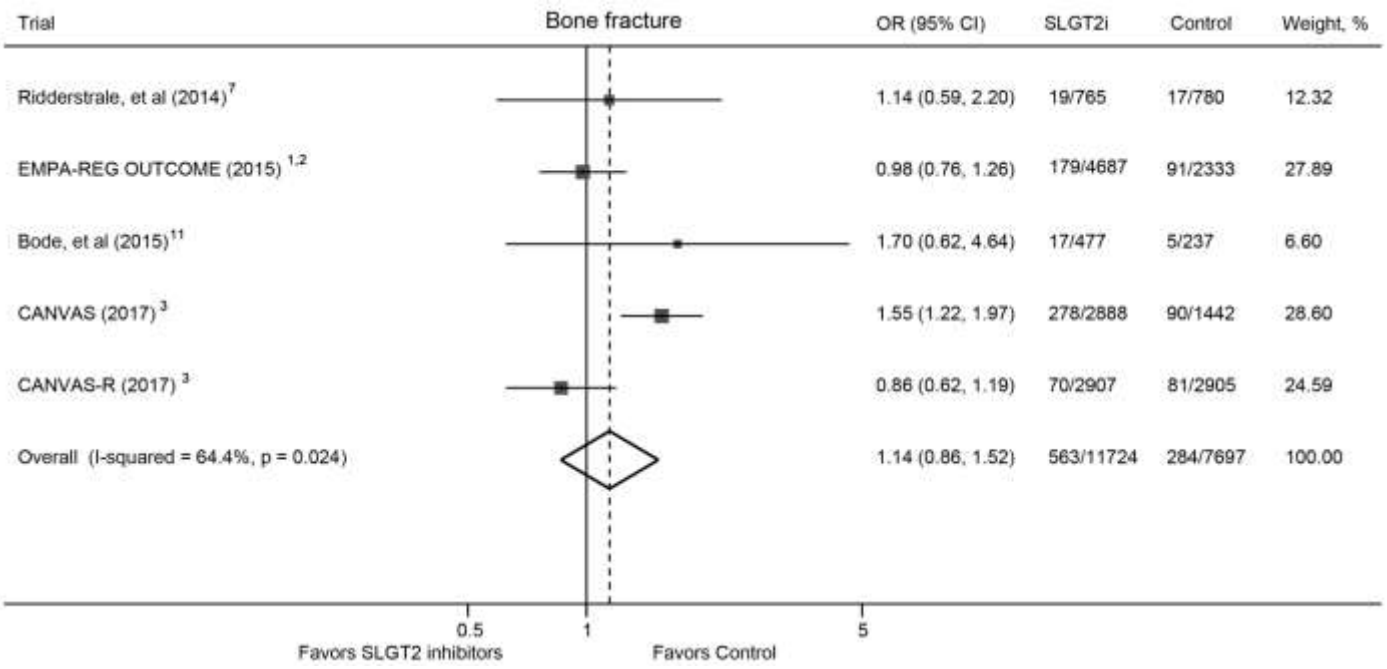

Figure S14. Pooled risk for bone fracture in patients who received SGLT2 inhibitors versus control from randomized controlled trials.

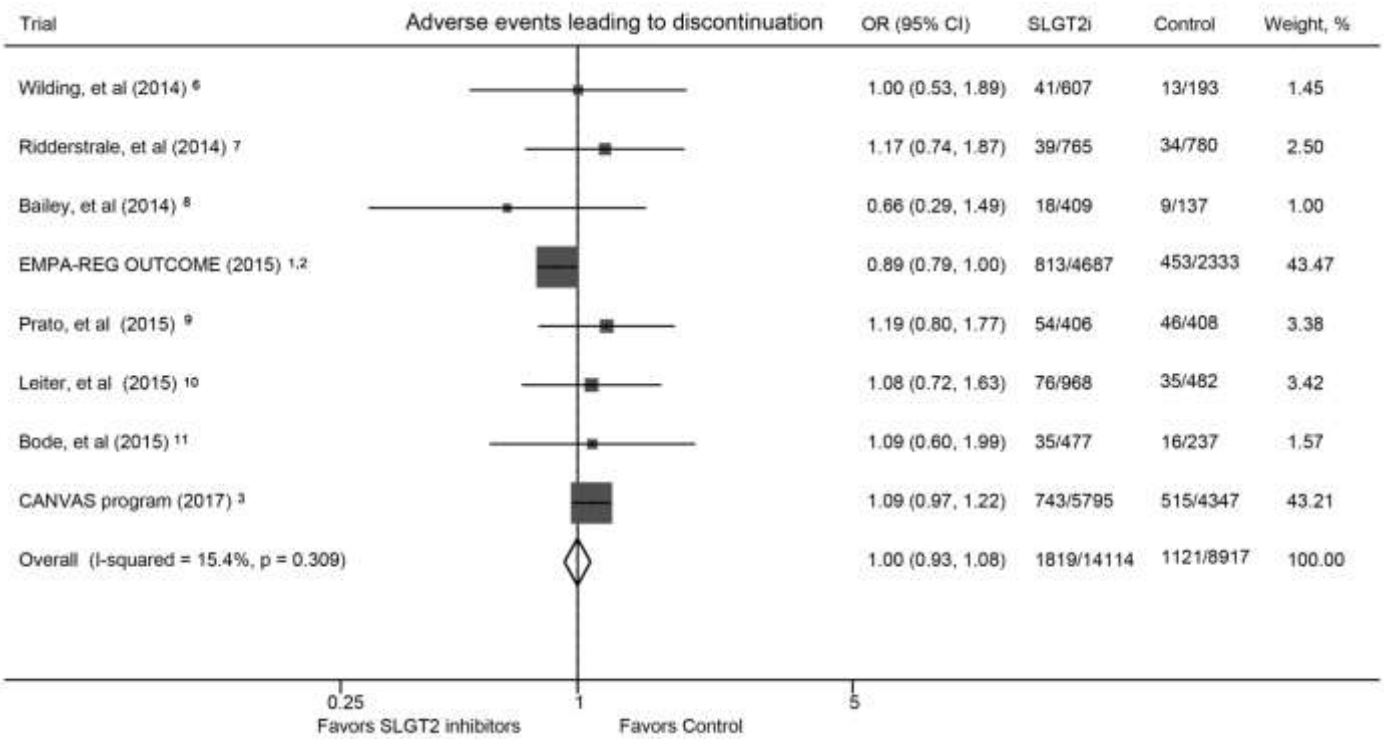

Figure S15. Pooled risk for adverse events leading to discontinuation in patients who received SGLT2 inhibitors versus control from randomized controlled trials.

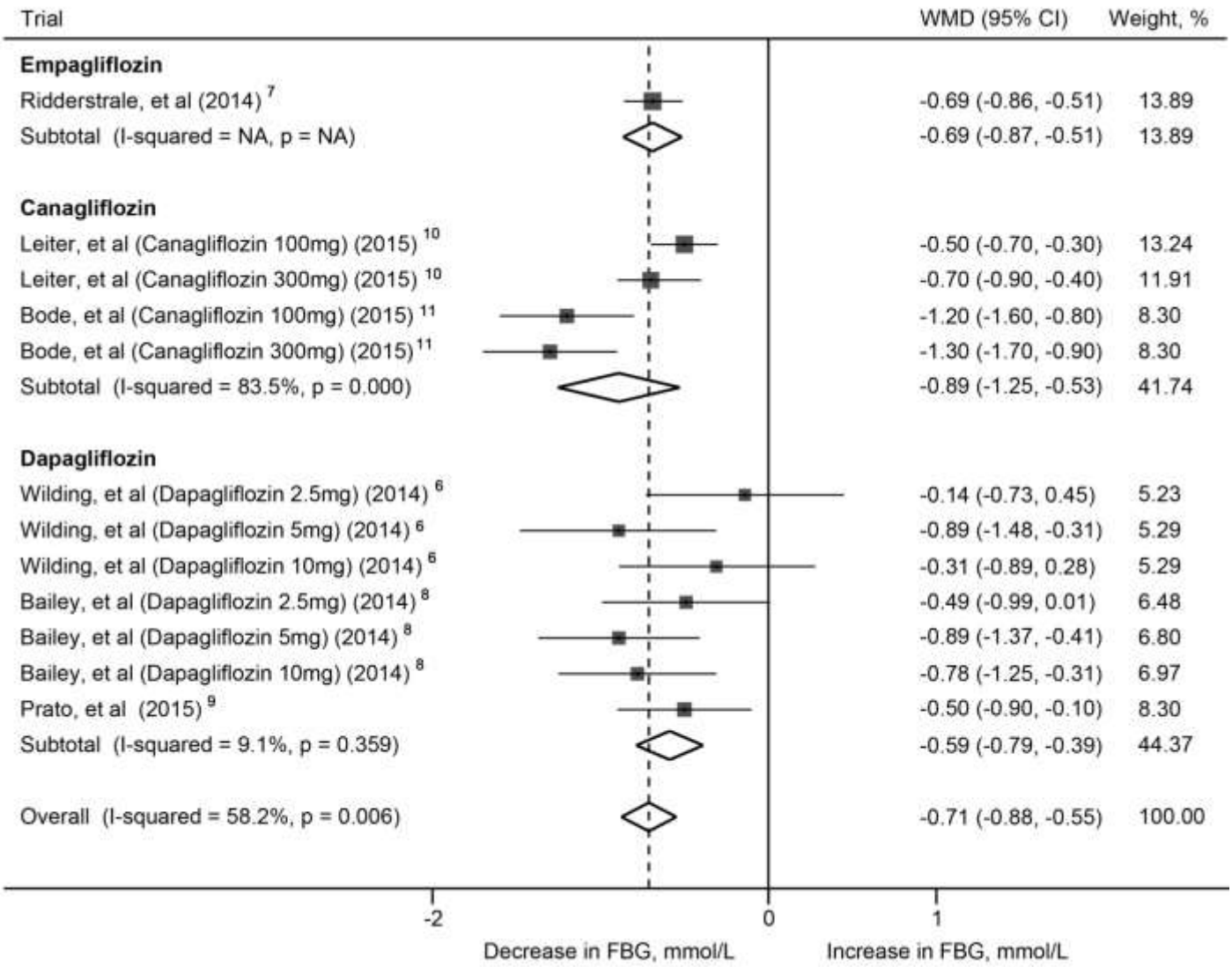

Figure S16. Meta-analyses of effects of SGLT2 inhibitors versus control on fasting blood glucose.

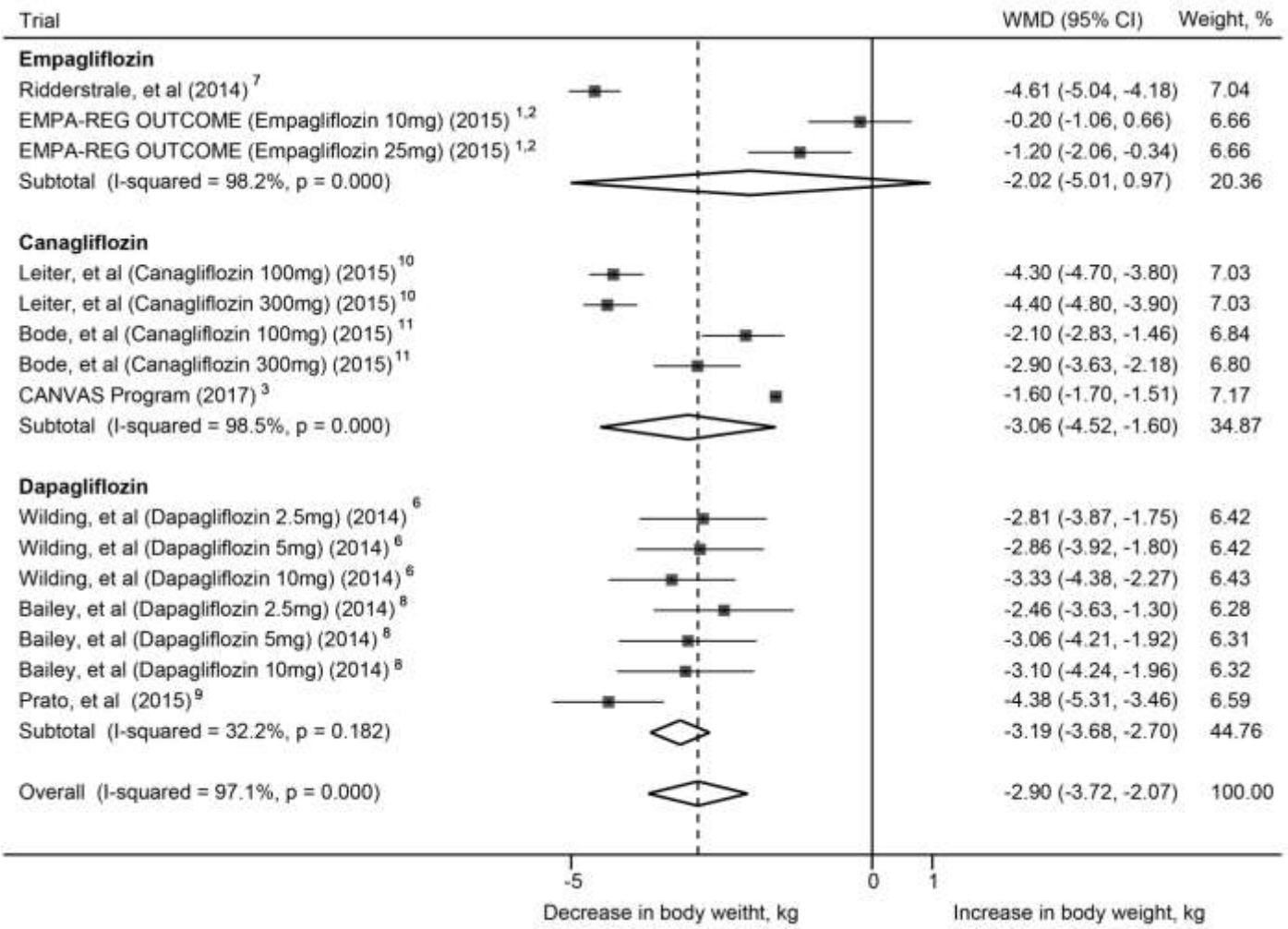

Figure S17. Meta-analyses of effects of SGLT2 inhibitors versus control on body weight

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