

Effect of Sodium-Glucose Cotransporter Type 2 Inhibitors on Clinical Outcomes in Patients With Cardiovascular Disease: A Meta-Analysis of Randomized Controlled Trials

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Abstract

Background

Controlled studies and observational studies have shown that sodium-glucose cotransporter type 2 inhibitors (SGLT-2s) are beneficial to the mortality of patients with heart failure (HF). However, it is unclear whether SGLT-2s can benefit patients with other cardiovascular diseases. Here, we conducted a systematic review and meta-analysis to determine the clinical benefits of SGLT-2s in cardiovascular patients with or without diabetes.

Methods

We searched PubMed, EMBASE, Cochrane Library, Web of Science databases, and ClinicalTrials.gov databases for randomised controlled trials written in English from inception until November 1, 2020. Two reviewers independently identified randomised controlled trials comparing the effects of SGLT-2s in patients with cardiovascular disease with or without diabetes. Primary outcomes were all-cause mortality, cardiovascular mortality, and hospitalisation for heart failure. Secondary outcomes were major adverse events from cardiovascular, metabolic, renal, and infectious diseases. The effects of SGLT-2s were evaluated using RevMan5.3 software. The Cochrane risk of bias tool was used to assess study quality.

Results

We identified 10 randomised controlled trials (24500 patients in the SGLT-2 group and 17960 patients in the placebo group). Meta-analysis showed that SGLT-2 treatment significantly reduced all-cause mortality, cardiovascular mortality, and hospitalisation for heart failure (HHF) in patients with cardiovascular disease (all-cause mortality relative risk [RR]: 0.86; 95% confidence interval [CI]: 0.80–0.91; $P < 0.00001$; $I^2 = 11\%$; cardiovascular mortality RR: 0.85; 95% CI: 0.79–0.92; $P < 0.0001$; $I^2 = 35\%$; HHF RR: 0.69; 95% CI: 0.64–0.81; $P < 0.00001$; $I^2 = 0\%$). In patients with heart failure, mortality and HHF after SGLT-2 treatment for heart failure with reduced ejection fraction were significantly reduced, whereas heart failure with preserved ejection fraction did not differ compared with placebo treatment. Moreover, SGLT-2s induced a lower incidence of renal damage and myocardial infarction than the placebo group; however, the risk of infection, amputation, volume depletion, and diabetic ketoacidosis was higher.

Conclusions

In this exploratory analysis, SGLT-2s had significant clinical effects in the treatment of patients with cardiovascular disease and had significant benefits in terms of renal function and myocardial infarction, but were associated with increased risk of infection, ketoacidosis, amputation, and volume depletion.

Background

The prevalence of cardiovascular disease is increasing, and cardiovascular disease has remained the leading cause of morbidity and mortality worldwide for the last 20 years. Cardiovascular diseases include

myocardial infarction, stroke, atherosclerotic cardiovascular diseases, hypertension, atrial fibrillation, and heart failure. Among them, myocardial infarction and stroke are the main causes of complications and death in patients with diabetes mellitus[1]. Among patients with cardiovascular disease, those with type 2 diabetes (T2DM) comprise a higher-risk subgroup, and T2DM has been shown to be an independent risk factor. Long-lasting diabetes is often complicated by atherosclerosis, heart failure, and chronic kidney disease. Therefore, for patients with heart failure or chronic kidney disease combined with diabetes, mortality and hospitalisation for heart failure (HHF) are greatly increased. Many recent clinical studies have shown that sodium-glucose cotransporter type 2 inhibitors (SGLT-2s) show very good clinical effects in patients with T2DM and cardiovascular diseases [2, 3]. Diabetes mellitus is not the only cause of cardiovascular disease, and cardiovascular disease from other causes is associated with a higher risk of poor prognosis. Therefore, any drug needs to be evaluated for efficacy and safety in a wide range of patients with cardiovascular diseases, regardless of the presence of T2DM as a comorbidity.

SGLT-2s are a new class of medicines for the treatment of T2DM. Inhibiting the expression of SGLT-2 protein in the renal tubules of the kidneys, which reduces the reabsorption of glucose in the kidneys, increases the excretion of glucose in the urine and reduces the level of glucose in the blood plasma[4, 5]. Currently, eight SGLT-2s (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, luseogliflozin, ipragliflozin, sotagliflozin, and tofogliflozin) have been approved worldwide for the treatment of T2DM, either as monotherapy or in combination with other hypoglycaemic drugs. In addition, SGLT-2s have been shown to reduce cardiovascular risk events, including lowering blood pressure, improving weight loss, lowering haemoglobin A1c levels, reducing myocardial infarction, reducing stroke, and reducing cardiovascular death in people with T2DM [6, 7]. In the last 5 years, large randomised controlled trials in patients with T2DM have shown that SGLT-2s improve cardiovascular and renal outcomes, particularly outcomes of patients with heart failure [8, 9]. AstraZeneca's dapagliflozin has been approved in the European Union for the treatment of adult patients with symptomatic heart failure with reduced ejection fraction (HFrEF), regardless of whether the patients had T2DM [10]. However, it is still unclear whether the clinical benefits of SGLT-2s can be extended to all patients with cardiovascular diseases.

Therefore, in this study, we conducted a meta-analysis of the clinical outcomes of SGLT-2s in patients with cardiovascular diseases, with or without T2DM, and explored the relationships among clinical efficacy, the heart failure subtype, and the SGLT-2 type.

Materials And Methods

Data sources and search strategy

Eligible studies were identified by searching PubMed, EMBASE, Cochrane Library, Web of Science, and ClinicalTrials.gov databases. Searches were conducted by two study investigators independently by the end of November 1, 2020. Search keywords included "cardiovascular disease +", "CVD", "cardiovascular death", "cardiovascular mortality", "coronary artery disease", "CAD", "heart failure", "HF", "myocardial infarction", "stroke", "+", "atrial fibrillation", "SGLT-2", and "sodium-glucose co-transporter 2 inhibitors". The

search strategies are detailed in Multimedia Appendix 1. The search was restricted to human studies. References for the identified studies were also retrieved to identify studies that may be eligible. Only articles written in English were considered. There were no restrictions on the publication date.

Inclusion and exclusion criteria

Eligible patients included patients with cardiovascular disease, with or without T2DM. Patients with other age-related comorbidities were not excluded. Patients in the intervention group were treated with SGLT-2s (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, luseogliflozin, ipragliflozin, sotagliflozin, and tofogliflozin) for a period of time. Patients who received a placebo or drugs other than SGLT-2s were used as controls. The primary outcomes were all-cause mortality, cardiovascular death, and HHF. The secondary outcomes were adverse cardiovascular reactions, adverse reactions in endocrine, renal side adverse reactions, infection, and other adverse reactions.

Data extraction and quality assessment

The included studies reported all-cause mortality, cardiovascular mortality, and HHF. All literature titles and abstracts were initially screened for relevance to exclude studies that were not meaningful to our research by two reviewers. Drs. Zheng and Dai independently analysed the full text and extracted data from selected studies; divergence was settled by discussion and consensus or by third-party arbitration. The risk assessment tool for Cochrane bias was used, and the included randomised controlled trials (RCTs) were assessed according to the literature assessment criteria in the Cochrane Systematic Review Manual[11].

Data synthesis and analysis

Meta-analyses were conducted using Cochrane's Review Manager (RevMan) version 5.3 (The Cochrane Collaboration, Copenhagen, Denmark) and R programming language, version 3.6.3 (R Foundation for Statistical Computing, Guangzhou, China). We used the associated relative risk (RR) with 95% confidence intervals (CIs) to evaluate clinical outcomes (efficacy and safety) in patients with cardiovascular disease receiving standard treatment with or without SGLT-2s. We assessed whether the results of the included studies were consistent. Chi-square tests were used to assess heterogeneity, and I^2 was used for quantitative analysis. Values of $P \geq 0.05$ and $I^2 \leq 50\%$ were not considered to represent heterogeneity, and fixed-effect models were used. In contrast, $P < 0.05$ and $I^2 > 50\%$ indicated significant heterogeneity among the different studies. Sensitivity analysis was performed by successively deleting each study and reanalysing the dataset for all remaining studies. Publication bias was assessed using funnel plots and Egger's tests. P values less than 0.05 (two-tailed) were considered statistically significant, and we did not adjust for multiple testing.

Results

Search results

In total, 7351 articles were retrieved from PubMed, EMBASE, Cochrane Library, and Web of Science databases, and 108 articles were retrieved from ClinicalTrials.gov. After removing duplicate studies, the remaining 5763 articles were screened. After reading 33 eligible full-text articles, 23 were excluded, and 10 studies (total of 42682 participants) met our inclusion criteria[12–21]. The systematic search results are presented in Fig. 1. HF patient data from cardiovascular outcome trials were available from published post-hoc studies[22, 23].

Basic characteristics and quality evaluation of the literature

In total, 42682 patients were included in 10 RCTs (25108 patients in the intervention group and 18574 patients in the control group). The detailed baseline characteristics of each study are presented in Table S1. Quality evaluation was conducted using the Cochrane systematic evaluation method, and the included studies had a low risk of overall bias, as shown in Figure S1.

Primary outcomes

The summarised outcomes of our meta-analysis are presented in Table S2. To evaluate the primary outcomes, 10 trials were included in the meta-analysis. Estimates of primary outcomes for all-cause mortality, cardiovascular mortality, and hospitalisation for heart failure are shown in Figs. 2–4.

All-cause mortality

All 10 articles contained all-cause mortality outcomes, with a total of 43682 patients (25108 in the SGLT-2 group and 18574 in the placebo group; RR: 0.86; 95% CI: 0.80–0.91; $P < 0.00001$; $I^2 = 0\%$; Fig. 2).

Cardiovascular mortality

Nine articles contained outcomes of cardiovascular death (24933 in the SGLT-2 group and 18421 in the placebo group). Subgroup analysis showed that cardiovascular death was significantly lower in patients using SGLT-2s than in the placebo group (RR: 0.85; 95% CI: 0.79–0.92; $P < 0.0001$; $I^2 = 26\%$; Fig. 3).

HHF

Nine articles included outcomes for HHF (24959 in the SGLT-2 group and 18436 in the placebo group). Meta-analysis showed that HHF was significantly lower in patients using SGLT-2 than in the placebo group (RR: 0.69; 95% CI: 0.64–0.74; $P < 0.00001$; $I^2 = 0\%$; Fig. 4)

Secondary outcomes

Adverse cardiovascular outcomes

There were five studies with adverse cardiovascular events, including four with myocardial infarction. The five studies included 28983 patients (17753 in the SGLT-2 group and 11230 in the placebo group). Meta-analysis results showed that the incidence of myocardial infarction was significantly lower in patients

receiving SGLT-2 inhibitors than in those receiving a placebo (RR: 0.90; 95% CI: 0.82–0.99; $P = 0.03$; $I^2 = 32\%$). Five studies with stroke outcomes included 29248 patients (17869 in the SGLT-2 group and 11379 in the placebo group). Meta-analysis results indicated that there were no significant differences in the incidence of stroke between patients treated with SGLT-2 inhibitors and those treated with a placebo (RR: 0.98; 95% CI: 0.86–1.11; $P = 0.72$; $I^2 = 21\%$; Fig. 5).

Adverse endocrine outcomes

In total, 30719 patients (18645 in the SGLT-2 group and 12074 in the placebo group) were included in the six studies on hypoglycaemia outcomes. Meta-analysis results showed that there were no significant differences in the incidence of hypoglycaemia between patients using SGLT-2s and those using the placebo (RR: 1.00; 95% CI: 0.96–1.05; $P = 0.87$; $I^2 = 8\%$).

Additionally, 34796 patients (20674 in the SGLT-2 group and 14122 in the placebo group) were included in six studies of outcomes related to diabetic ketoacidosis. Meta-analysis results showed that the incidence of diabetic ketoacidosis in patients treated with SGLT-2s was significantly higher than that in patients treated with a placebo (RR: 3.65; 95% CI: 1.83–7.27; $P = 0.0002$; $I^2 = 0\%$; Fig. 6).

Adverse renal outcomes

In the four trials, there were no significant differences in compound outcomes of acute renal failure between the SGLT-2 and placebo groups (RR: 1.00; 95% CI: 0.90–1.11; $P = 0.99$; $I^2 = 84\%$). Sensitivity analysis was performed by sequentially deleting each study and reanalysing the datasets for all remaining studies (RR: 0.99, 95% CI: 0.90–1.10, $P = 0.96$; $I^2 = 80.8\%$; Table S3). In total, 35124 patients with acute renal injury were included in seven articles (20850 in the SGLT-2 group and 14274 in the placebo group). Meta-analysis results showed that the incidence of acute renal injury in patients treated with SGLT-2s was significantly lower than that in patients treated with a placebo (RR: 0.80; 95% CI: 0.68–0.93; $P = 0.004$; $I^2 = 0\%$; Fig. 7).

Adverse infection outcomes

Outcomes of infection, including urinary tract infection, male genital infection, and female genital infection, were evaluated. The results suggested that the incidence of infection in patients treated with SGLT-2s was significantly higher than that in patients treated with a placebo ($P < 0.05$). The results of urinary tract infection were assessed in four articles, which included a total of 25720 patients (16146 in the SGLT-2 group and 9574 in the placebo group). Meta-analysis results showed that the incidence of urinary tract infection in patients treated with SGLT-2 inhibitors was significantly higher than that in patients treated with a placebo (RR: 1.08; 95% CI: 1.01–1.15; $P = 0.02$; $I^2 = 39\%$).

Results of male and female genital infections were included in the three articles, which involved a total of 25400 patients (15975 in the SGLT-2 group and 9425 in the placebo group). Meta-analysis results showed that the incidence of male and female genital infections in patients treated with SGLT-2s was

significantly higher than that in patients treated with a placebo (male: RR: 3.35; 95% CI: 2.90–3.87; $P < 0.00001$; $I^2 = 0\%$; female: RR: 3.85; 95% CI: 3.43–4.32; $P < 0.00001$; $I^2 = 0\%$; Fig. 8).

Others

Five articles containing fracture outcomes included 34533 patients (20543 in the SGLT-2 group and 13990 in the placebo group). Meta-analysis results showed that there were no significant differences in fracture incidence between patients treated with SGLT-2s and those treated with a placebo (RR: 1.11; 95% CI: 0.99–1.23; $P = 0.08$; $I^2 = 24\%$).

Four articles included outcomes of amputation involving 27513 patients (15856 in the SGLT-2 group and 11657 in the placebo group). Meta-analysis results showed that the incidence of amputation in patients treated with SGLT-2s was significantly higher than that in patients treated with a placebo (RR: 1.42; 95% CI: 1.18–1.71; $P = 0.0002$; $I^2 = 32\%$).

Six articles included outcomes of volume depletion in 30719 patients (18645 in the SGLT-2 group and 12074 in the placebo group). Meta-analysis results showed that the volume depletion of patients treated with a placebo was significantly lower than that of patients treated with SGLT-2s (RR: 1.22; 95% CI: 1.11–1.33; $P < 0.0001$; $I^2 = 45\%$; Fig. 9).

Subgroup analysis

Detailed forest plots displaying subgroup analyses are presented in the Supporting Information. For all outcomes in the overall cardiovascular disease population, no subgroup effect was observed upon stratification by T2DM status (Figs. S2–S4). In a subgroup analysis of heart failure types, there were no significant differences in all-cause mortality, cardiovascular mortality, or HHF between the SGLT-2 and placebo groups among patients with heart failure with preserved ejection fraction (HFpEF; Figs. S5–S7). SGLT-2s reduced all-cause mortality, cardiovascular mortality, and HHF largely independent of drug type, with the exception of ertugliflozin and sotagliflozin (Figs. S8–S10). In terms of safety, only the subgroup analysis of ketoacidosis and acute renal injury was performed because of the limited number of included trials. In terms of ketoacidosis, canagliflozin and ertugliflozin showed significant differences compared with the placebo group, whereas the other drugs showed no significant differences. There were no significant differences in acute renal failure between patients administered dapagliflozin, canagliflozin, or ertugliflozin and patients administered a placebo (Fig. S11). Empagliflozin significantly reduced the number of acute renal failure events (Fig. S12).

Sensitivity analysis results

Sensitivity analysis was performed to compare all-cause mortality by sequentially removing one study at a time and observing the exaggerated effect this had on the overall results. As shown in Fig. 10, after each study was excluded, the pooled RR of the remaining included studies was approximately 0.87, with

no significant change, suggesting that the results of this meta-analysis were stable and reliable. Removing any study did not affect the overall results (Fig. 10).

Publication bias

Using funnel plots drawn by Review Manager 5.3, we visually assessed the publication bias of all-cause mortality (Egger's test $P=0.3638$, 95% CI -0.662–0.669). All evidence suggested that the probability of publication bias was low. Funnel plots were not generated for other comparisons because fewer than 10 studies were included (Fig. 11).

Discussion

To the best of our knowledge, this is the first study comparing SGLT-2s with a placebo in comprehensive outcomes of primary efficacy and adverse events in cardiovascular diseases in patients with and without T2DM. Cardiovascular diseases include various conditions, such as common coronary artery disease, hypertension, dyslipidaemia, congenital heart disease, valvular disease, and arrhythmia. Accordingly, cardiovascular diseases are a serious threat to human health worldwide. Cardiovascular outcomes, survival, and prognosis in patients with cardiovascular diseases are relatively poor. In a previous meta-analysis, SGLT-2 treatment of patients with T2DM significantly reduced all-cause mortality, cardiovascular mortality, HHF, risk of HF, and renal failure [24–28]. Moreover, among participants with established cardiovascular disease, regardless of the presence or absence of T2DM, SGLT-2s significantly reduce mortality and major adverse cardiovascular events (MACEs) compared with the placebo, and the benefit for the prevention and treatment of HF and renal disease is consistent with that of earlier meta-analyses[29]. The same results were observed in the HFrEF population; however, there were no significant differences in patients with HFpEF and no significant differences between the two groups for most adverse events. The results for the risk of infection, amputation, and hypovolemia should be interpreted with caution.

SGLT-2s were superior to the placebo or other glucose-lowering drugs in terms of the pooled primary efficacy outcomes, including all-cause mortality, cardiovascular mortality, HHF, and renal benefits from EMPA-REG OUTCOME[12, 30], CANVAS-R[13, 31], CANVAS [32, 33], CREDENCE[34, 35], DECLARE-TIMI 58[36, 37], and VERTIS-CV trials [20, 38]. In the EMPA-REG OUTCOME trial, all eligible patients had established cardiovascular disease, and empagliflozin reduced the risk of all-cause mortality by 32%, cardiovascular mortality by 38%, and HHF by 35% compared with the placebo. At the same time, the study confirmed that the dose of empagliflozin did not affect the hazard ratios of cardiovascular outcomes. In the CANVAS and CANVAS-R trials, treatment resulted in reductions of 49% for all-cause mortality, 47% for cardiovascular mortality, 30% for HHF, and 22% for major adverse cardiovascular events. Patients in the canagliflozin group had a lower risk of cardiovascular mortality, HHF, and renal failure than those in the placebo group at a median follow-up of 2.62 years in the CREDENCE trial. In the DECLARE-TIMI 58 trial, dapagliflozin appeared to robustly reduce the risk of cardiovascular mortality or HHF and MACEs in patients with T2DM and previous myocardial infarction. In the VERTIS-CV trial

involving patients with T2DM and established atherosclerotic cardiovascular disease, ertugliflozin was shown to be noninferior to the placebo with MACEs. However, the incidence of cardiovascular mortality or HHF did not differ significantly between the two groups. Owing to the diverse properties of different drugs, we cannot exclude the possibility that differences among the agents in this class may result in real differences in clinical outcomes. It is also possible that the effects of individuals are similar because the confidence interval of VERTIS CV overlaps with that of previous trials. Owing to limited literature on the HFpEF population, the role of SGLT-2s in patients with HFpEF remains unclear. In current research on HFpEF, only the subgroup analyses in the DECLARE-TIMI 58 and VERTIS-CV trials suggested a potential impact on HHF or cardiovascular mortality. Two ongoing clinical trials in patients with HFpEF will provide further evidence of its efficacy (NCT03057951 and NCT01297257).

In terms of safety, three available studies showed neutral effects on myocardial infarction and stroke in patients receiving SGLT-2s [39–41]. In an RCT and a nationwide cohort study, the results showed no increased risk of hypoglycaemia with SGLT-2 monotherapy [42, 43]; however, SGLT-2s were associated with approximately twice the risk of diabetic ketoacidosis as DPP4 inhibitors [44]. Accordingly, clinicians should be cautious when combining SGLT-2s with other hypoglycaemic drugs. SGLT-2s reduced the risk of dialysis, transplantation, or death due to kidney disease in individuals with T2DM, with or without basic renal disease, and provided protection against acute kidney injury[45–47]. The use of SGLT-2s was not associated with an increased risk of fracture and amputation compared with other antidiabetics [44, 48–50]. Volume depletion is another major concern, not consistent with recent studies, which showed significant differences between SGLT-2s and other oral hypoglycaemic agents in volume depletion events[51–53], perhaps because of individualised dosing of SGLT-2s. Other potential side effects include urinary tract infection and male/female genital infection, which may be attributed to the selective inhibition of renal proximal tubule glucose reabsorption by SGLT-2s. According to the United States Food and Drug Administration, all manufacturers are required to add a warning of potential infection to the prescribing information and patient medication guide for all SGLT-2s in 2018. Although these adverse events should not mask the overall cardio-renal benefits of SGLT-2s [54–56], individuals at risk of these complications should be monitored closely, and treatment should be reconsidered or discontinued if such complications occur.

Our study had some limitations. First, confounding factors, such as age, sex, regionalism, baseline haemoglobin A1c, estimated glomerular filtration rate, and exposure to cardiovascular disease-related drugs, as well as drug combinations and other potential factors, were difficult to control. Second, articles published in languages other than English were excluded. Third, few RCTs of certain SGLT-2 drugs in the HFpEF population have been published. Finally, this meta-analysis may be underpowered for comparison of long-term adverse events between SGLT-2s and the placebo owing to the different durations of follow up for the included RCTs. Therefore, additional studies are required to confirm our findings.

Conclusion

This meta-analysis showed that initiation of SGLT-2s was associated with substantially lower all-cause/cardiovascular mortality and lower HHF in patients with cardiovascular disease and in both diabetic and nondiabetic patients. However, no benefit was observed in patients with HFpEF. SGLT-2s increased the risk of amputation, infection, volume depletion, and diabetic ketoacidosis, but slowed the decline in renal function and myocardial infarction adverse outcomes compared with a placebo. These findings have important implications for the future direction of SGLT-2 therapy in cardiovascular disease research, but more studies are needed to determine the mechanism of SGLT-2s in cardiovascular disease treatment, as well as large RCTs to demonstrate the clinical efficacy of SGLT-2s in a specific cardiovascular disease.

Abbreviations

T2DM: type 2 diabetes; HHF: hospitalisation for heart failure; SGLT-2: sodium-glucose cotransporter type 2 inhibitor; HFrEF: heart failure with reduced ejection fraction; HFpEF: heart failure with preserved ejection fraction; RCT: randomised controlled trial; RR: relative risk; MACE: major adverse cardiovascular event.

Declarations

Acknowledgements

None.

Authors' contributions

CYZ conceived the meta-analysis. CYZ and HFD developed the research strategy and provided statistical expertise. HFD drafted the manuscript. All Authors contributed to the development of the selection criteria, risk of bias assessment strategy, and data extraction criteria. All Authors read, provided feedback, and approved the final manuscript.

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Availability of data and materials

Not applicable.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

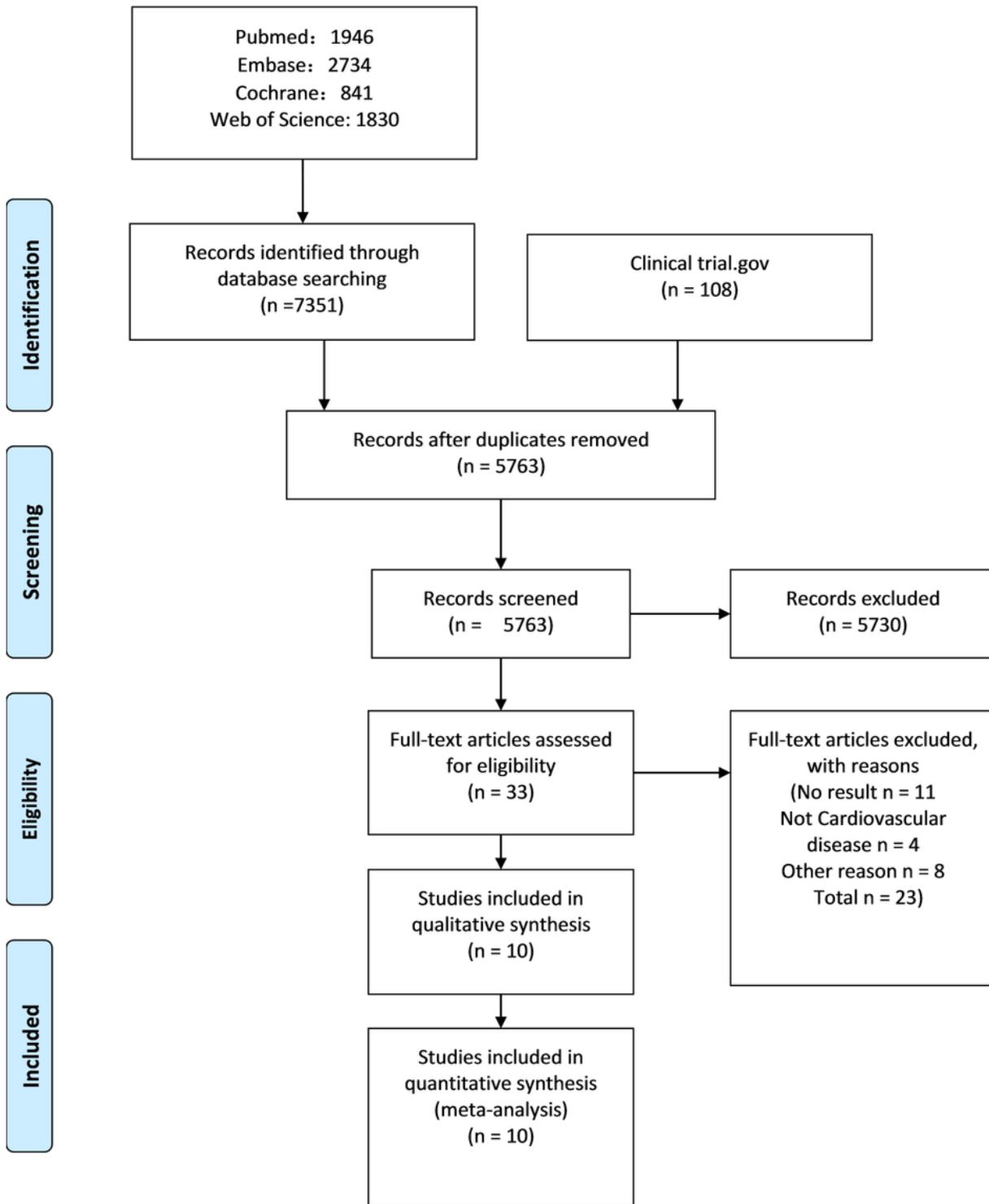


Figure 1

Literature screening and selection flow chart.

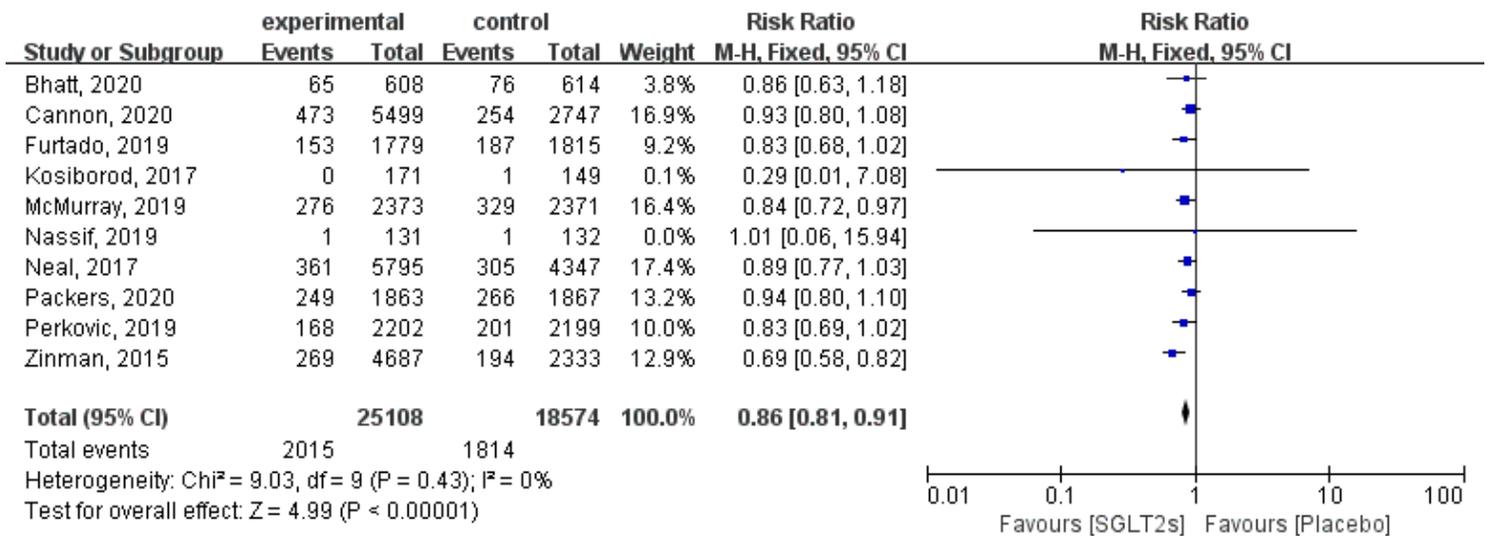


Figure 2

Forest plot of meta-analysis for the comparison of all-cause mortality between the SGLT-2 and placebo groups.

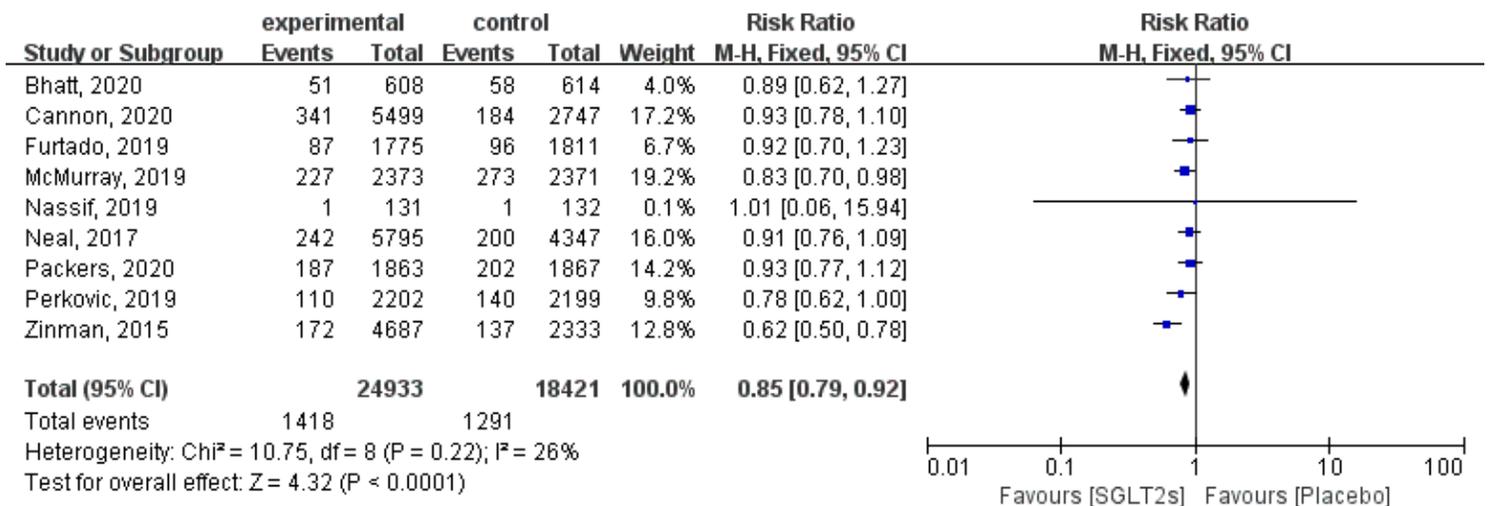


Figure 3

Forest plot of meta-analysis for the comparison of cardiovascular death between the SGLT-2 and placebo groups.

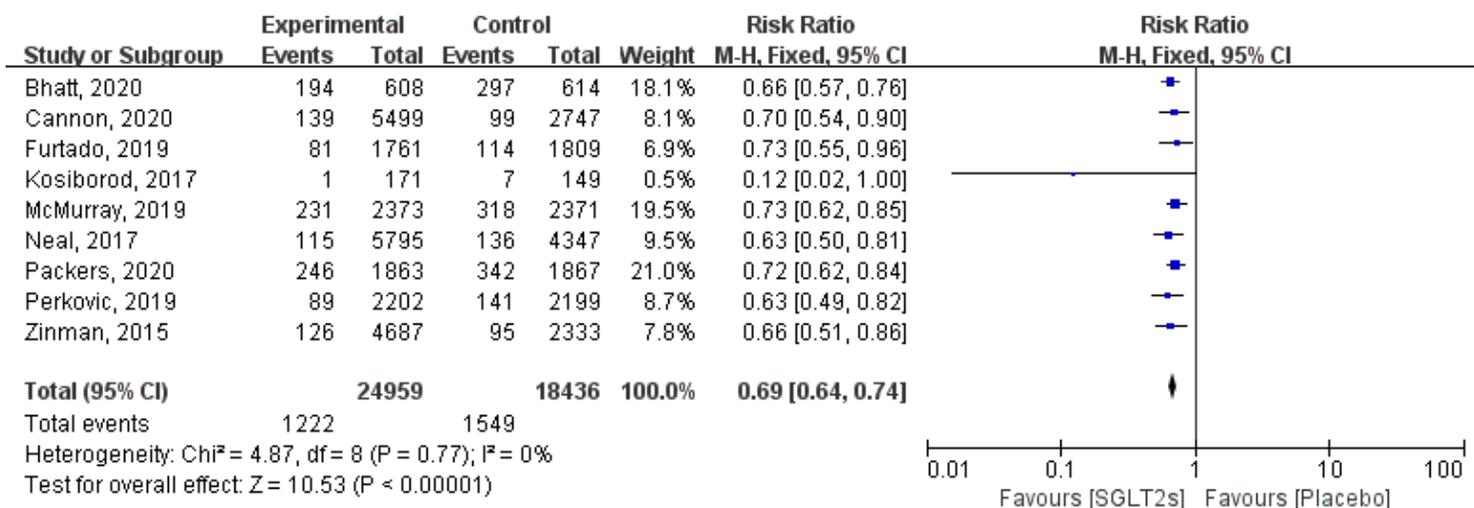


Figure 4

Forest plot of meta-analysis for the comparison of HHF between the SGLT-2 and placebo groups.

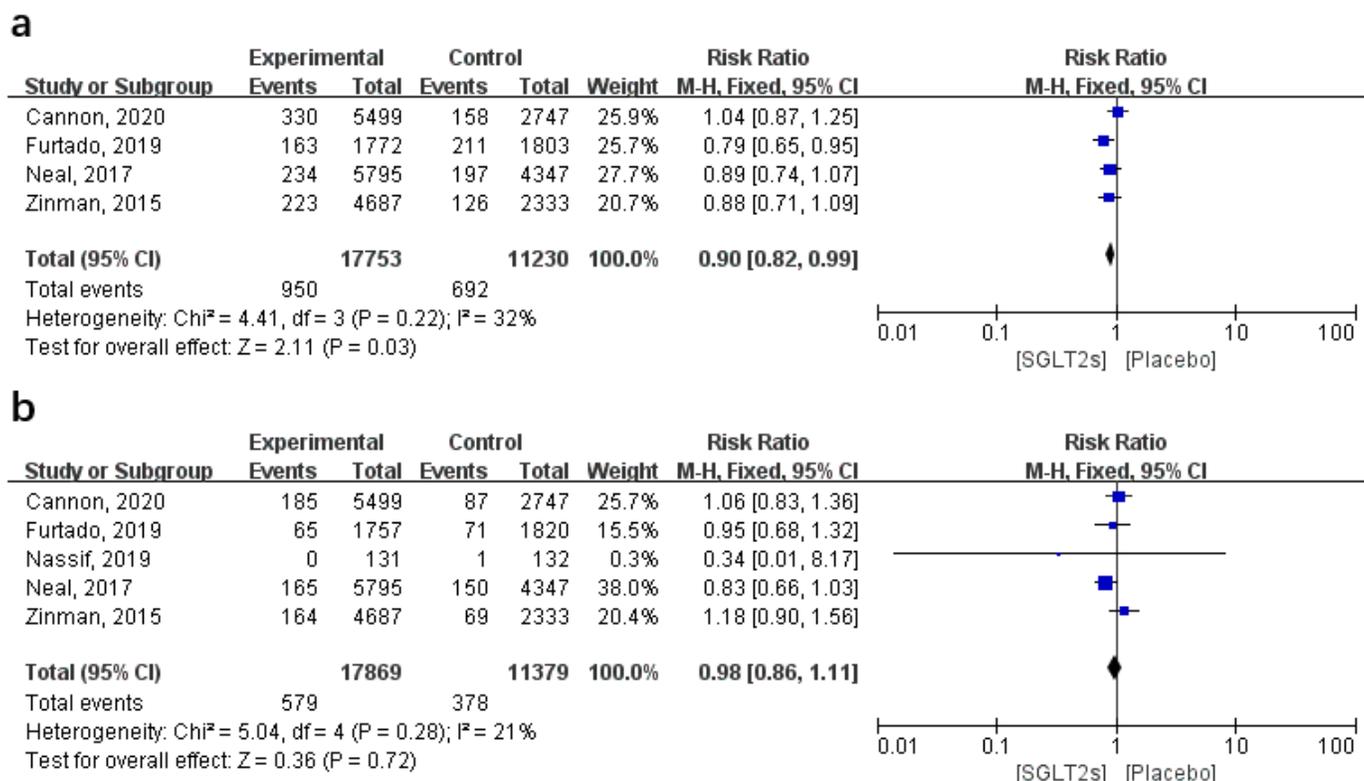


Figure 5

Forest plot of meta-analysis for the comparison of adverse cardiovascular events between SGLT-2 and placebo groups. (a) Myocardial infarction adverse outcomes, (b) stroke adverse outcomes.

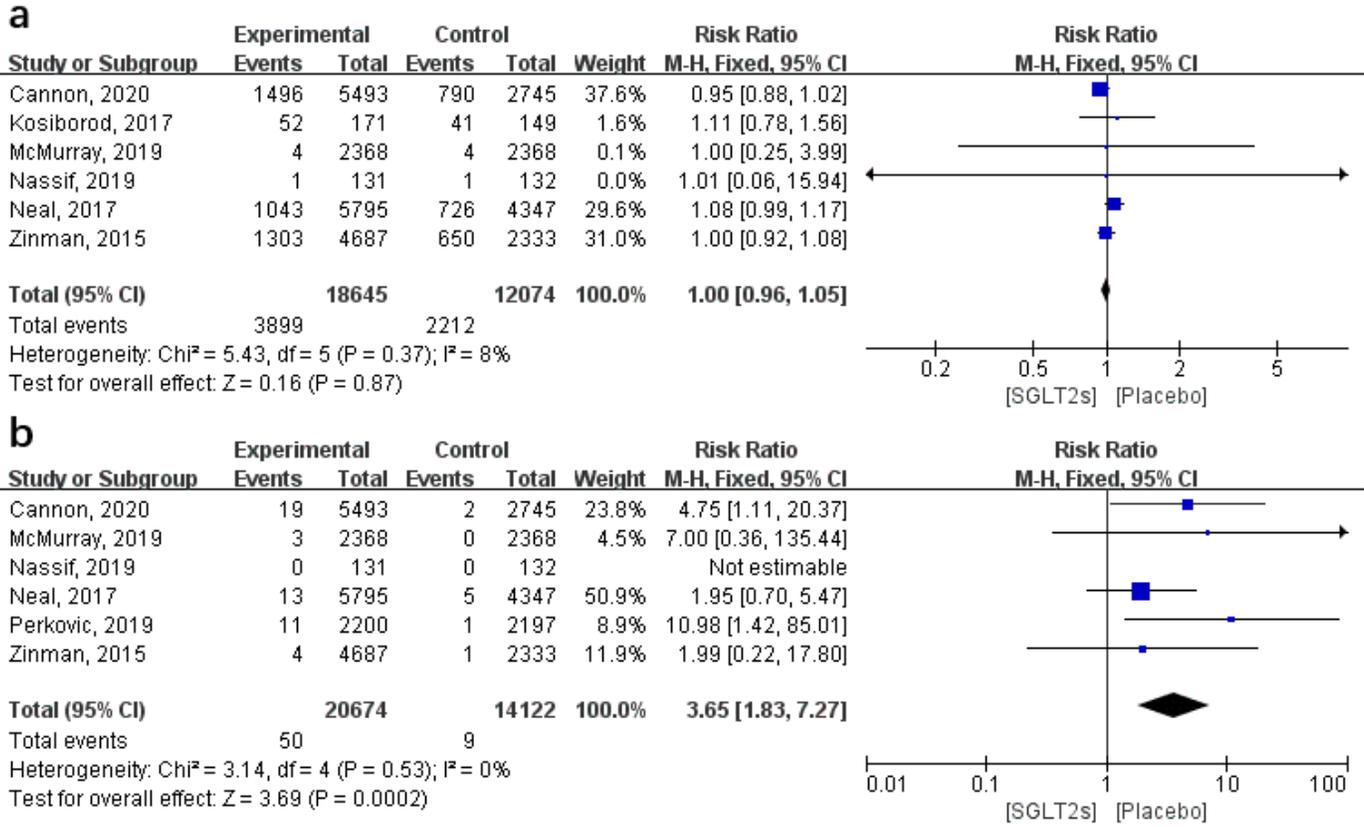


Figure 6

Forest plot of meta-analysis for the comparison of adverse endocrine events between the SGLT-2 and placebo groups. (a) Hypoglycaemia adverse outcomes, (b) diabetic ketoacidosis adverse outcomes.

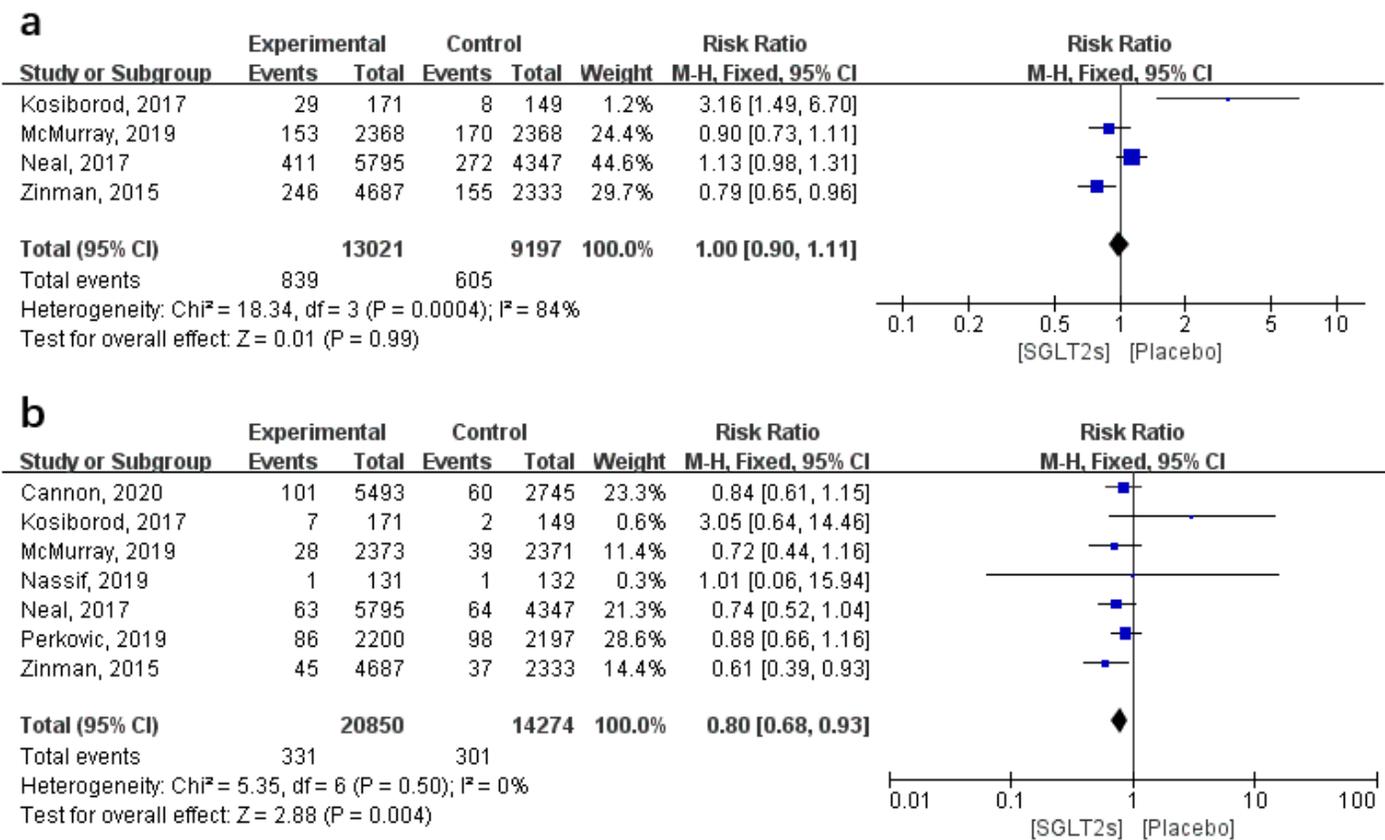


Figure 7

Forest plot of meta-analysis for the comparison of adverse renal events between the SGLT-2 and placebo groups. (a) Acute renal failure, (b) acute renal injury.

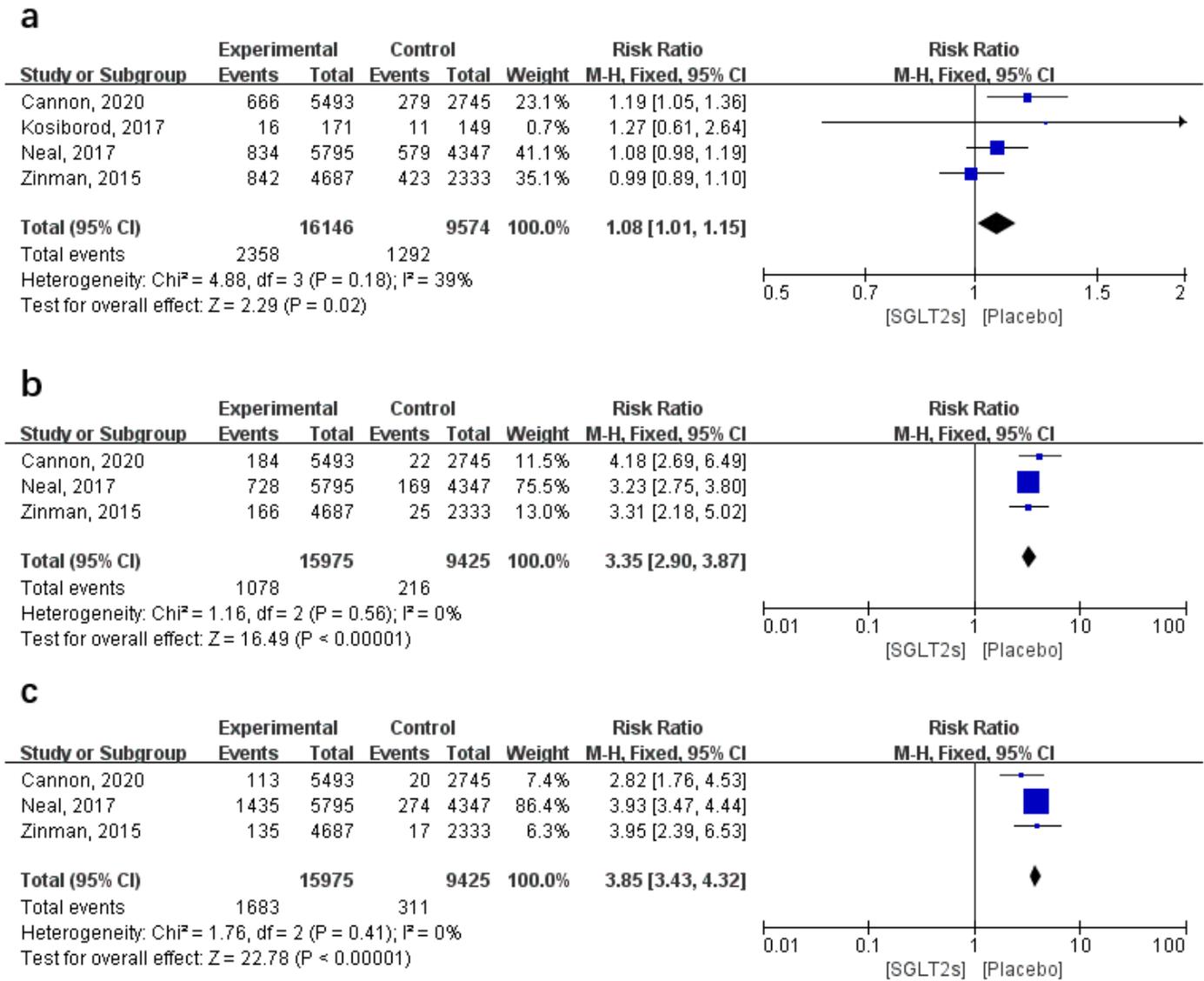


Figure 8

Forest plot of meta-analysis for the comparison of infection adverse events between the SGLT-2 and placebo groups. (a) Urinary tract infection adverse outcomes, (b) male genital infection adverse outcomes, (c) female genital infection adverse outcomes.

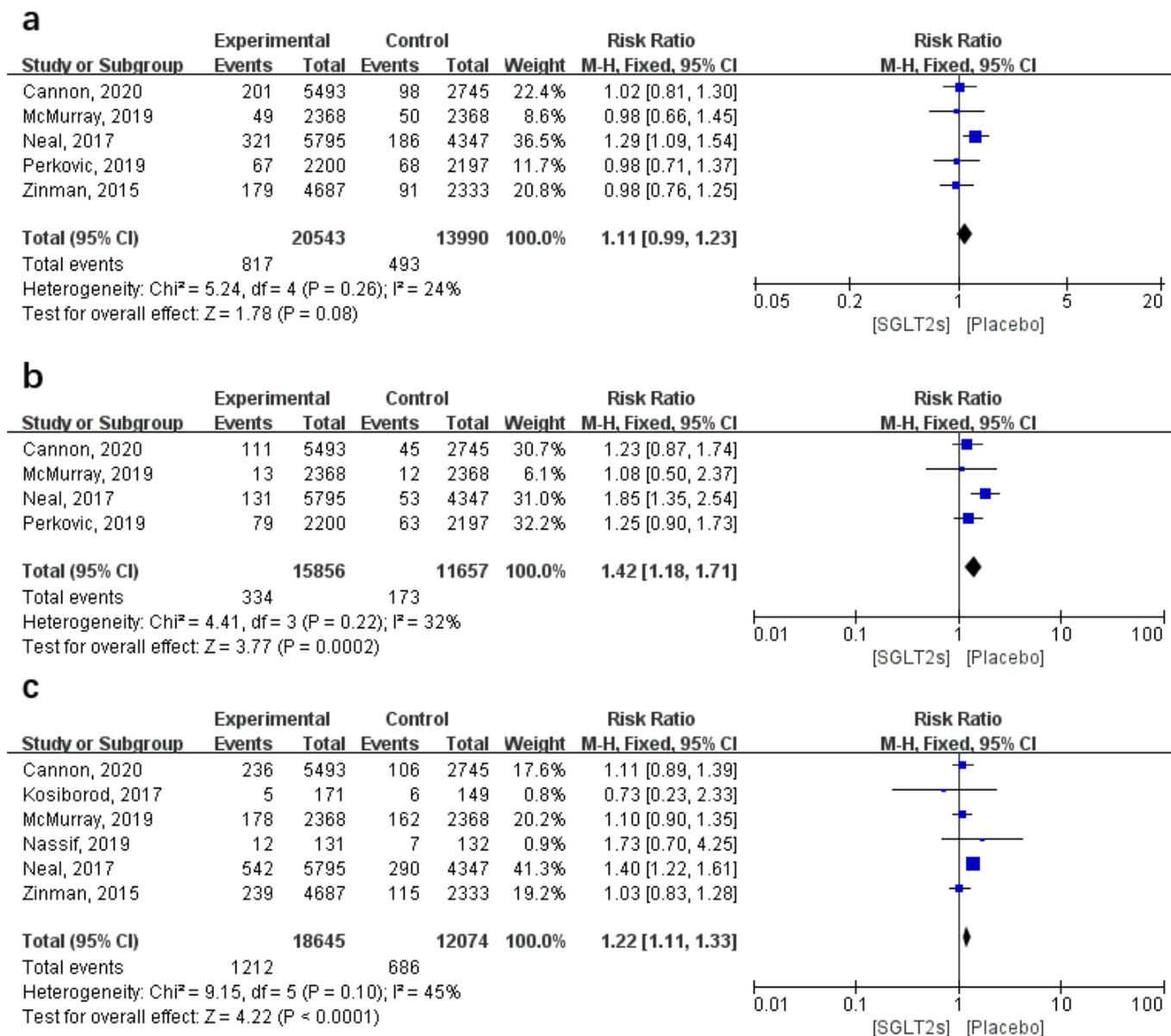


Figure 9

Forest plot of meta-analysis for the comparison of other adverse events between the SGLT-2 and placebo groups. (a) Fracture adverse outcomes, (b) amputation adverse outcomes, (c) volume depletion adverse outcomes.

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