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Effects of SGLT2 inhibitors on cardiovascular and renal outcomes in type 2 diabetes

A meta-analysis with trial sequential analysis

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Abstract

Background: It is unclear whether there are false positive or negative results in the effects of sodium-glucose transporter 2 (SGLT2) inhibitors on various cardiovascular and renal outcomes in patients with type 2 diabetes. We aimed to explore this issue by a meta-analysis with trial sequential analysis.

Methods: We included randomized trials evaluating the effects of SGLT2 inhibitors on cardiorenal endpoints in type 2 diabetic patients. Eight endpoints evaluated in the study were fatal or nonfatal myocardial infarction (MI), fatal or nonfatal stroke, major adverse cardiovascular events (MACE), cardiovascular death or hospitalization for heart failure (CVD or HHF), all-cause death (ACD), cardiovascular death (CVD), hospitalization for heart failure (HHF), and kidney function progression (KFP). Meta-analysis and trial sequential analysis was conducted for each endpoint.

Results: Seven randomized trials of SGLT2 inhibitors were included for pooled analysis. Compared with placebo, SGLT2 inhibitors significantly reduced the risk of MACE (HR 0.89, 95% confidence interval [CI] 0.84–0.94), MI (HR 0.91, 95% CI 0.84–0.99), CVD (HR 0.86, 95% CI 0.79–0.93), CVD or HHF (HR 0.77, 95% CI 0.73–0.82), HHF (HR 0.67, 95% CI 0.62–0.74), KFP (HR 0.63, 95% CI 0.56–0.70), and ACD (HR 0.88, 95% CI 0.83–0.94), whereas SGLT2 inhibitors did not have significant effects on stroke (HR 0.98, 95% CI 0.88–1.09). Trial sequential analyses for MI and stroke showed that cumulative Z curve did not cross trial sequential monitoring boundary and required information size, whereas those for the other 6 endpoints showed that cumulative Z curve crossed trial sequential monitoring boundary and/or required information size.

Conclusions: Compared with placebo, SGLT2 inhibitors conclusively reduce the risk of MACE, CVD or HHF, ACD, CVD, HHF, and KFP in patients with type 2 diabetes, whereas the effects of SGLT2 inhibitors on MI and stroke are not conclusive and need to be further assessed in future studies with the adequate sample size to reject or accept the effect size.

Abbreviations: ACD = all-cause death, APIS = a priori information size, CI = confidence interval, CVD = cardiovascular death, CVD or HHF = cardiovascular death or hospitalization for heart failure, HHF = hospitalization for heart failure, HR = hazard ratio, KFP = kidney function progression, MACE = major adverse cardiovascular events, MI = myocardial infarction, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, RCTs = randomized controlled trials, SGLT2 = sodium-glucose transporter 2.

Keywords: cardiorenal events, death, SGLT2 inhibitors, type 2 diabetes

1. Introduction

Previous meta-analyses[1–3] have revealed that sodium-glucose transporter 2 (SGLT2) inhibitors vs placebo can significantly reduce the incidence of various cardiovascular and renal events except stroke in patients with type 2 diabetes. Although these meta-analyses[1–3] have greater sample size than individual randomized trials have, it is unclear whether the sample size of these meta-analyses[1–3] is adequate to accept or reject the effect size. Thus, there might be false positive or false negative results in the findings from prior meta-analyses.[1–3]

Conventional meta-analysis (equivalent to interim analysis of a single trial) might be subjected to type I error due to the repetitive testing of cumulative data. To overcome this weakness, trial sequential analysis was developed in order to confirm the results of traditional meta-analysis, to ensure that the sample size is adequate to reject or accept the effect size, and to determine the adequate sample size required by any future trial before a meta-analysis is deemed conclusive.[4] Thus, conducting trial sequential analysis is a good way to examine whether the findings from prior meta-analyses are the false positive or negative results or not.

Moreover, the published meta-analyses[1–3] assessing the effects of SGLT2 inhibitors on cardiorenal endpoints in patients

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The authors have no conflicts of interests to disclose.

Supplemental Digital Content is available for this article.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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with type 2 diabetes failed to include 3 new randomized trials[5–7] of SGLT2 inhibitors. Thus, we carried out this study to assess the effects of SGLT2 inhibitors on 8 cardiovascular and renal outcomes in patients with type 2 diabetes by meta-analysis of all relevant randomized trials including 3 recent ones,[5–7] and more importantly, to identify whether the effects of SGLT2 inhibitors on different cardiorenal outcomes are conclusive or not by trial sequential analysis.

2. Methods

According to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement,[8] we conducted this study by performing meta-analysis and trial sequential analysis. The PRISMA checklist for this study is presented in Table S1 (Supplemental Content, which is the PRISMA checklist, http://links.lww.com/MD/F880).

2.1. Inclusion criteria and risk of bias assessment

We applied the detailed search strategies (see Table S2, Supplemental Content, which shows the search strategies in detail, http://links.lww.com/MD/F881) to search Embase and PubMed from the creation date of the 2 online databases to January 8, 2021. Original studies eligible for inclusion were randomized controlled trials (RCTs) assessing the effect of any SGLT2 inhibitor versus placebo on cardiorenal endpoints in patients with type 2 diabetes. This meta-analysis study measured 8 cardiorenal and mortality endpoints, which consisted of fatal or nonfatal myocardial infarction (MI), fatal or nonfatal stroke, major adverse cardiovascular events (MACE), cardiovascular death or hospitalization for heart failure (CVD or HHF), all-cause death (ACD), cardiovascular death (CVD), hospitalization for heart failure (HHF), and kidney function progression (KFP).

Two authors independently completed the work assignments before data analysis, which contained study selection, data extraction, and risk of bias assessment. Having a discussion with a third author would address all the disagreements between them as for those above assignments. Risk of bias assessment for included RCTs was done based on the Cochrane risk of bias assessment tool.[9]

2.2. Statistical analysis

We performed meta-analysis by using the data of hazard ratios (HRs) and 95% confidence intervals (CIs) deriving from original studies included in this meta-analysis study. Statistical heterogeneity was measured by I^2 statistic. $I^2 > 50\%$ means substantial heterogeneity, and in that case pooled analysis would be done with the random-effects model. Otherwise, pooled analysis would be done with the fixed-effects model. As for pooled treatment effects, $P \leq .05$ or the 95% CIs of pooled HRs not including 1.0 denotes statistical significance.

Trial sequential analysis was conducted for each of the 8 outcomes of interest, with calculation of the required information size to detect 10% relative risk reduction of various endpoints in the SGLT2 inhibitor group with power of 80% and alpha of 5%. The required information size was calculated with the method of a priori information size (APIS). The data of the overall average survival rate as for various outcomes used for calculating the required information size were derived from the corresponding data of the placebo group in the DECLARE–TIMI 58 trial[10] since this trial[10] had the greatest sample size and the longest follow-up duration which insured the accuracy of those data. We completed all statistical analyses using the Stata software (version 15.1), with meta-analyses conducted by the command of "metan" and trial sequential analyses conducted by the command of "metacumbounds".

2.3. Ethical statement

The data analyzed in this study were extracted from previously published studies, and thus ethical approval was not necessary.

3. Results

The complete process of study selection is presented in Figure S1 (Supplemental Content, which is the flow diagram of study selection, http://links.lww.com/MD/F878). Ultimately, we included 7 RCTs[5–7,10–13] for pooled analysis. The 7 trials included in this study consisted of the VERTIS CV trial[5] assessing ertugliflozin, the SCORED trial[6] and the SOLOIST-WHF trial[7] assessing sotagliflozin, the DECLARE–TIMI 58 trial[10] assessing dapagliflozin, the EMPA-REG OUTCOME trial[11] assessing empagliflozin, and the CREDENCE trial,[12] and the CANVAS Program trial[13] assessing canagliflozin. The SCORED trial[6] enrolled patients with type 2 diabetes and chronic kidney disease, the SOLOIST-WHF trial[7] enrolled patients with type 2 diabetes and worsening heart failure, and the later 5 trials[5,10–13] enrolled patients with type 2 diabetes regardless of with/without chronic kidney disease or heart failure. The included RCTs involved a total of 58783 patients with type 2 diabetes, and all of the trials were with the low risk of bias (see Fig. S2, Supplemental Content, which shows the quality assessment results for included RCTs,

Table 1

Characteristics of included studies.

Study name	Study type	Median follow-up (years)	Participants	Mean age (years)	Women (%)	Intervention	Comparator	History of cardiovascular disease (%)	History of heart failure (%)	eGFR <60 ml/min/1.73 m^2 (%)
EMPA-REG OUTCOME	RCT	3.1	7020	63.1	2004 (28.5)	Empagliflozin, 10 or 25 mg	Placebo	7020 (100.0)	706 (10.1)	1818 (25.9)
CANVAS Program	RCT	2.4	10142	63.3	3633 (35.8)	Canagliflozin, 100 or 300 mg	Placebo	6656 (65.6)	1461 (14.4)	2039 (20.1)
DECLARE–TIMI 58	RCT	4.2	17160	63.9	6422 (37.4)	Dapagliflozin, 10 mg	Placebo	6974 (40.6)	1724 (10.0)	1270 (7.4)
CREDENCE	RCT	2.6	4401	63.0	1494 (33.9)	Canagliflozin, 100 mg	Placebo	2223 (50.5)	652 (14.8)	2631 (59.8)
VERTIS CV	RCT	3.0	8246	64.0	2477 (30.0)	Ertugliflozin, 5 or 15 mg	Placebo	8246 (100.0)	1958 (23.7)	1807 (21.9)
SOLOIST-WHF	RCT	0.8	1222	70.0	412 (33.7)	Sotagliflozin, 200–400 mg	Placebo	1222 (100.0)	1222 (100.0)	854 (69.9)
SCORED	RCT	1.3	10584	69.0	4754 (44.9)	Sotagliflozin, 200–400 mg	Placebo	9381 (88.7)	3283 (31.0)	10584 (100.0)

eGFR = estimated glomerular filtration rate, RCT = randomized controlled trial.

http://links.lww.com/MD/F879). The baseline characteristics of included studies are detailed in Table 1. The median duration of follow-up ranged from 0.8 to 4.2 years, mean age ranged from 63 to 70 years, and the female proportion of participants ranged from 28.5% to 44.9%. Participants from each study were type 2 diabetes patients with a certain proportion of cardiovascular disease and/or renal disease. The original data of this meta-analysis study are given in Table S3 (Supplemental Content, which presents the original data analyzed in this study, http://links.lww.com/MD/F882).

3.1. Traditional meta-analyses

Compared with placebo, SGLT2 inhibitors significantly reduced the risk of MACE (HR 0.89, 95% CI 0.84–0.94; $I^2=0\%$; P for drug effect <.001) (Fig. 1), MI (HR 0.91, 95% CI 0.84–0.99; $I^2=0\%$; P for drug effect=.034) (Fig. 2), CVD (HR 0.86, 95% CI 0.79–0.93; $I^2=47.6\%$; P for drug effect <.001) (Fig. 3), CVD or HHF (HR 0.77, 95% CI 0.73–0.82; $I^2=29.8\%$; P for drug effect <.001) (Fig. 4), HHF (HR 0.67, 95% CI 0.62–0.74; $I^2=0\%$; P for drug effect <.001) (Fig. 5), KFP (HR 0.63, 95% CI 0.56–0.70; $I^2=36.8\%$; P for drug effect <.001) (Fig. 6), and ACD (HR 0.88,

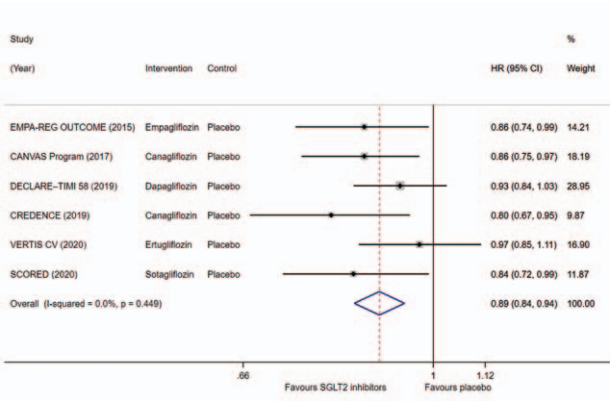

Figure 1. Meta-analysis of the effect of SGLT2 inhibitors on major adverse cardiovascular events in patients with type 2 diabetes. CI = confidence interval, HR = hazard ratio, SGLT2 = sodium-glucose transporter 2.

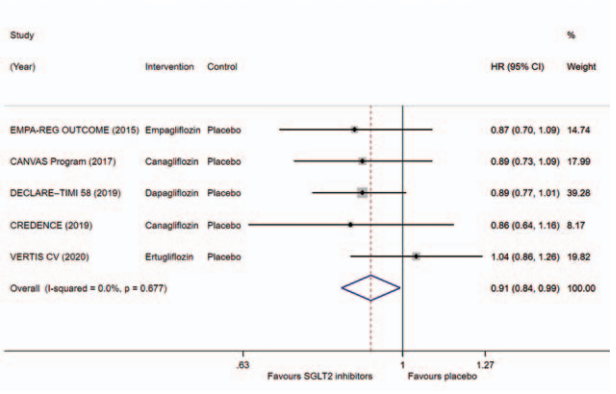

Figure 2. Meta-analysis of the effect of SGLT2 inhibitors on myocardial infarction in patients with type 2 diabetes. CI = confidence interval, HR = hazard ratio, SGLT2 = sodium-glucose transporter 2.

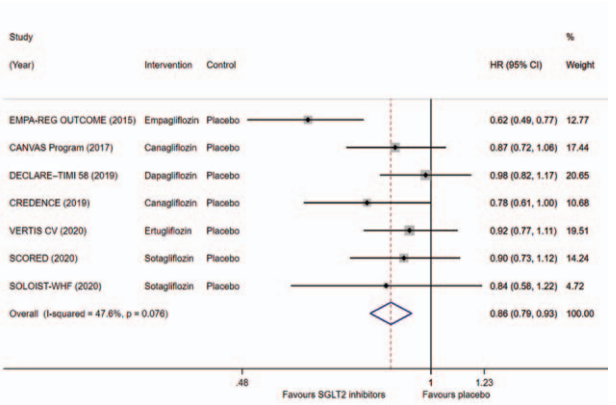

Figure 3. Meta-analysis of the effect of SGLT2 inhibitors on cardiovascular death in patients with type 2 diabetes. CI = confidence interval, HR = hazard ratio, SGLT2 = sodium-glucose transporter 2.

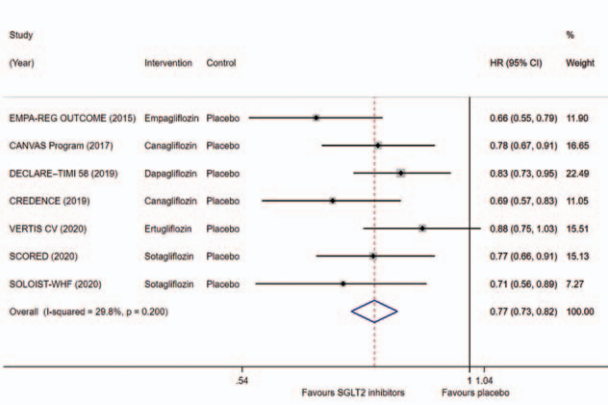

Figure 4. Meta-analysis of the effect of SGLT2 inhibitors on cardiovascular death or hospitalization for heart failure in patients with type 2 diabetes. CI = confidence interval, HR = hazard ratio, SGLT2 = sodium-glucose transporter 2.

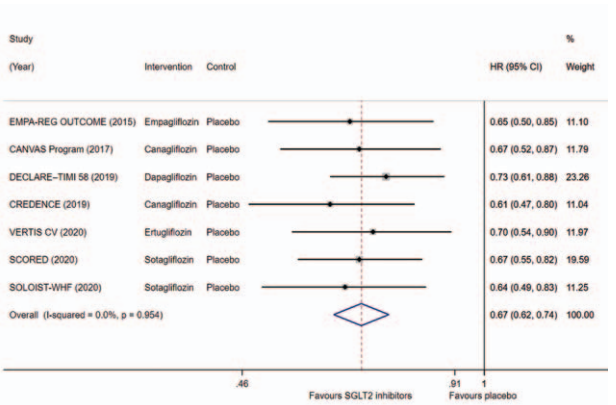

Figure 5. Meta-analysis of the effect of SGLT2 inhibitors on hospitalization for heart failure in patients with type 2 diabetes. CI = confidence interval, HR = hazard ratio, SGLT2 = sodium-glucose transporter 2.

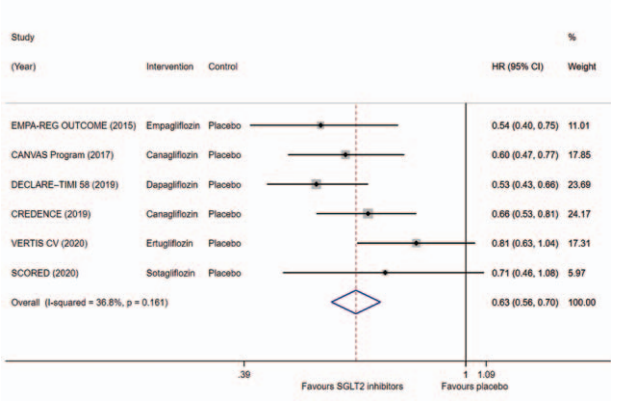

Figure 6. Meta-analysis of the effect of SGLT2 inhibitors on kidney function progression in patients with type 2 diabetes. CI = confidence interval, HR = hazard ratio, SGLT2 = sodium-glucose transporter 2.

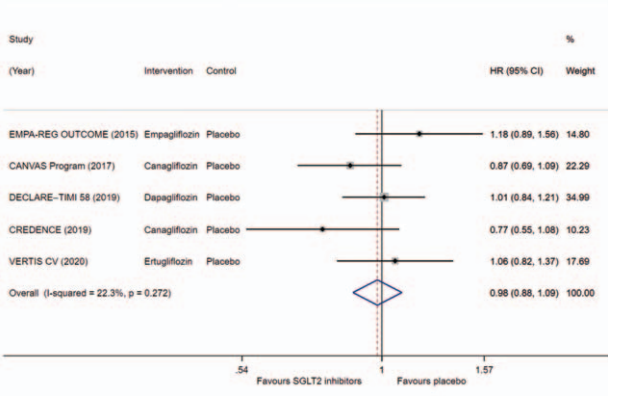

Figure 8. Meta-analysis of the effect of SGLT2 inhibitors on stroke in patients with type 2 diabetes. CI = confidence interval, HR = hazard ratio, SGLT2 = sodium-glucose transporter 2.

95% CI 0.83–0.94; I^2=47.0%; *P* for drug effect <.001) (Fig. 7). SGLT2 inhibitors versus placebo did not significantly reduce the risk of stroke (HR 0.98, 95% CI 0.88–1.09; I^2=22.3%; *P* for drug effect=.723) (Fig. 8).

3.2. Trial sequential analyses

Trial sequential analysis for MI (Fig. 9) shows that cumulative Z curve crosses traditional boundary of statistical significance, but does not cross trial sequential monitoring boundary, and does not reach required information size [a priori information size (APIS= *55558*)]. Cumulative Z curve crossed traditional boundary of statistical significance, suggesting the result of meta-analysis for MI was positive. Cumulative Z curve did not reach required information size and did not cross trial sequential monitoring boundary, suggesting the sample size of meta-analysis for MI was not sufficient while the meta-analysis result was not conclusive. Thus, the significant effect of SGLT2 inhibitors on MI revealed by meta-analysis might be a false positive result.

Trial sequential analysis for stroke (Fig. 10) shows that cumulative Z curve does not cross traditional boundary of statistical significance and trial sequential monitoring boundary,

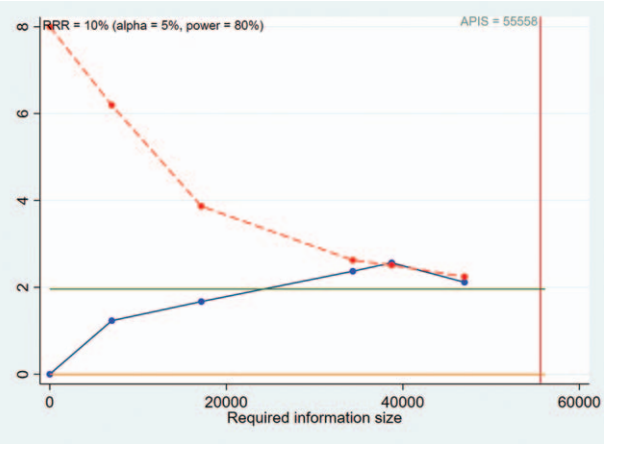

Figure 9. Trial sequential analysis for myocardial infarction. APIS = a priori information size, RRR = relative risk reduction.

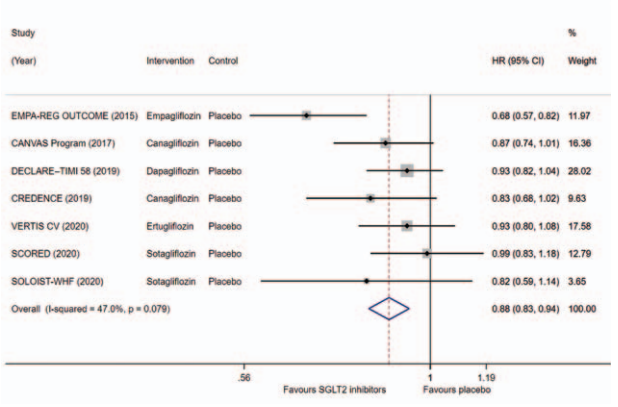

Figure 7. Meta-analysis of the effect of SGLT2 inhibitors on all-cause death in patients with type 2 diabetes. CI = confidence interval, HR = hazard ratio, SGLT2 = sodium-glucose transporter 2.

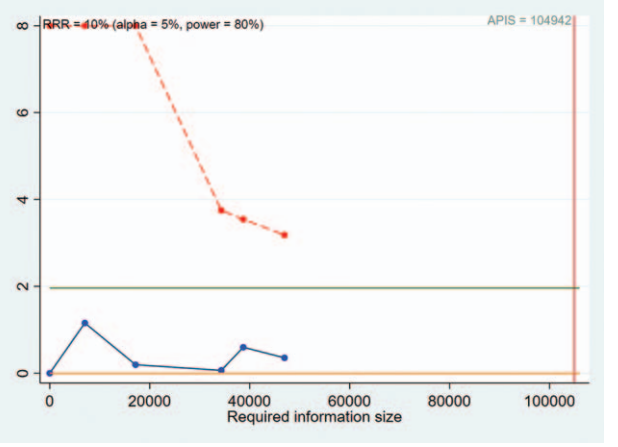

Figure 10. Trial sequential analysis for stroke. APIS = a priori information size, RRR = relative risk reduction.

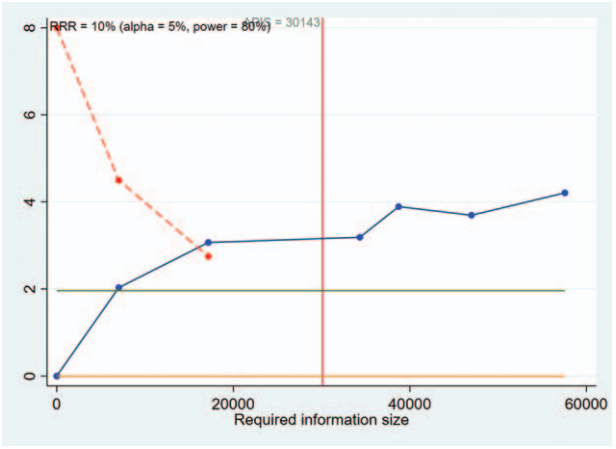

Figure 11. Trial sequential analysis for major adverse cardiovascular events. APIS = a priori information size, RRR = relative risk reduction.

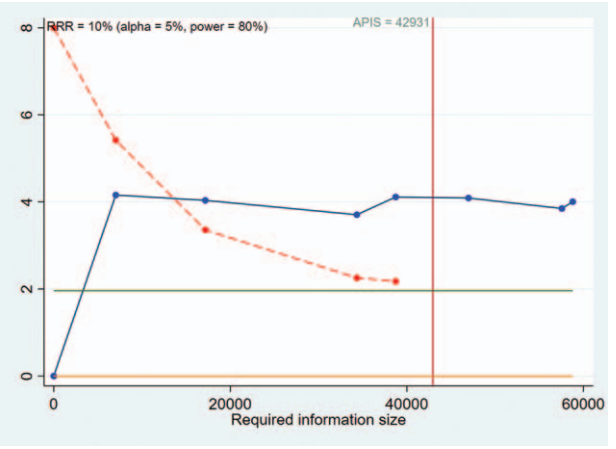

Figure 13. Trial sequential analysis for all-cause death. APIS = a priori information size, RRR = relative risk reduction.

and does not reach required information size (APIS = 104942). Cumulative Z curve did not cross traditional boundary of statistical significance, suggesting the result of meta-analysis for stroke was negative. Cumulative Z curve did not reach required information size and did not cross trial sequential monitoring boundary, suggesting the sample size of meta-analysis for stroke was not sufficient while the meta-analysis result was not conclusive. Thus, the nonsignificant effect of SGLT2 inhibitors on stroke revealed by meta-analysis might be a false negative result.

Trial sequential analyses for MACE (Fig. 11), CVD or HHF (Fig. 12) and ACD (Fig. 13) show that cumulative Z curve crosses traditional boundary of statistical significance, trial sequential monitoring boundary, and required information size (APIS = 30143, 48853, and 42931, respectively). Cumulative Z curve crossed traditional boundary of statistical significance, suggesting these meta-analysis results were positive. Cumulative Z curve crossed required information size and trial sequential monitoring boundary, suggesting the sample size of these meta-analyses was sufficient while the corresponding results were conclusive. Thus,

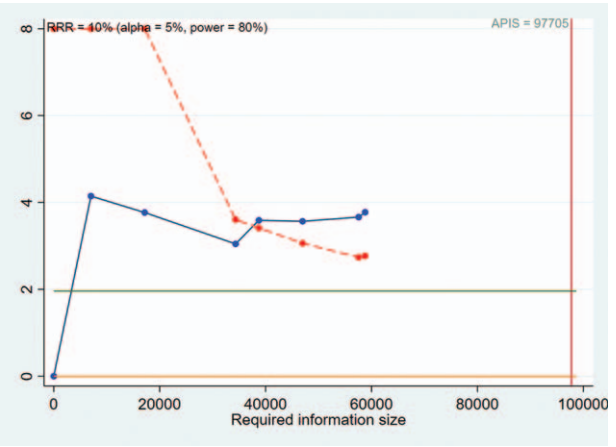

Figure 14. Trial sequential analysis for cardiovascular death. APIS = a priori information size, RRR = relative risk reduction.

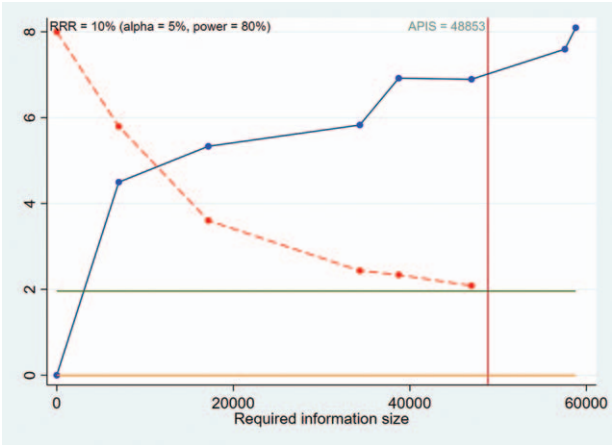

Figure 12. Trial sequential analysis for cardiovascular death or hospitalization for heart failure. APIS = a priori information size, RRR = relative risk reduction.

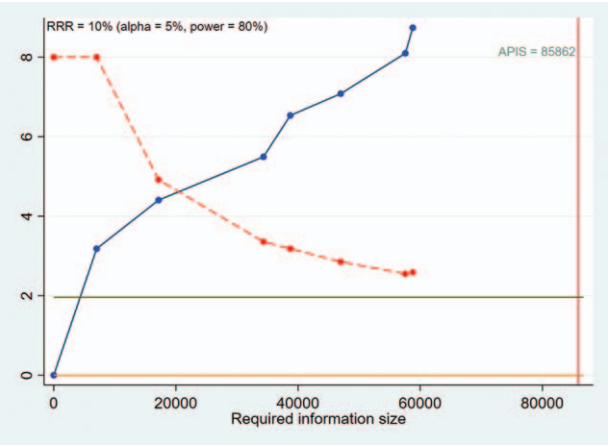

Figure 15. Trial sequential analysis for hospitalization for heart failure. APIS = a priori information size, RRR = relative risk reduction.

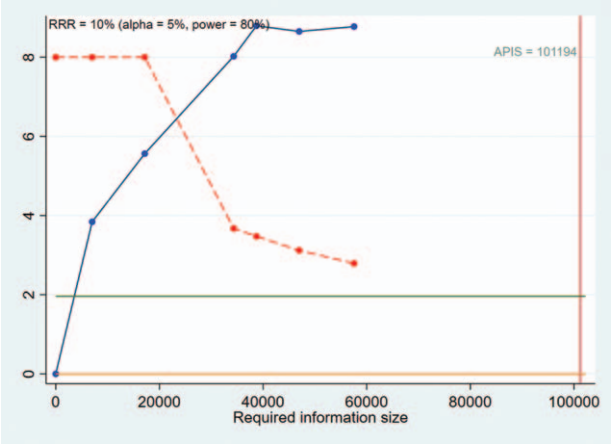

Figure 16. Trial sequential analysis for kidney function progression. APIS = a priori information size, RRR = relative risk reduction.

SGLT2 inhibitors conclusively reduced the risk of MACE, CVD or HHF, and ACD.

Trial sequential analyses for CVD (Fig. 14), HHF (Fig. 15), and KFP (Fig. 16) show that cumulative Z curve crosses traditional boundary of statistical significance and trial sequential monitoring boundary, but does not reach required information size (APIS = 97705, 85862, and 101194, respectively). Cumulative Z curve crossed traditional boundary of statistical significance, suggesting these meta-analysis results were positive. Cumulative Z curve did not reach required information size but crossed trial sequential monitoring boundary, suggesting the corresponding results were conclusive although the sample size of these meta-analyses was not completely sufficient. Thus, the significant effects of SGLT2 inhibitors on CVD, HHF and KFP revealed by meta-analysis were true positive results.

4. Discussion

This meta-analysis is the first study in which trial sequential analysis was used to identify potentially false positive and false negative results among the effects of SGLT2 inhibitors on 8 cardiovascular and renal outcomes in patients with type 2 diabetes. On the other hand, this meta-analysis is an up-to-date meta-analysis in terms of evaluating the effects of SGLT2 inhibitors on cardiorenal outcomes in type 2 diabetic patients due to 3 recently-published RCTs[5–7] of SGLT2 inhibitors being considered in the study. Accordingly, this study produces the following 3 findings.

First, meta-analyses revealed that SGLT2 inhibitors significantly reduced the risk of 7 cardiorenal outcomes (i.e., MI, MACE, CVD or HHF, ACD, CVD, HHF, and KFP) compared with placebo whereas SGLT2 inhibitors did not have significant effects on the occurrence of stroke. This finding is similar with that in 3 prior meta-analyses.[1–3]

Second, trial sequential analyses revealed that the significant effects of SGLT2 inhibitors on MACE, CVD or HHF, ACD, CVD, HHF, and KFP were conclusive. It means that there is no need to perform another updated meta-analysis evaluating the effects of SGLT2 inhibitors on the above 6 cardiorenal endpoints in type 2 diabetic patients. Therefore, this finding will further support SGLT2 inhibitors used for prevention of these cardiorenal endpoints in type 2 diabetes, as recommended in the latest consensus report.[14]

Third, trial sequential analyses also revealed that the significant effect of SGLT2 inhibitors on MI might be a false positive result, while the nonsignificant effect of SGLT2 inhibitors on stroke might be a false negative result. It suggests that before we can make firm conclusions about the effects of SGLT2 inhibitors on MI and stroke in type 2 diabetes, there is a need for an updated meta-analysis with the adequate sample size to reject or accept the effect size, or a need for future studies which enroll type 2 diabetic patients at high risk of developing MI or stroke.

In conclusion, compared with placebo, SGLT2 inhibitors conclusively reduce the risk of MACE, CVD or HHF, ACD, CVD, HHF, and KFP in patients with type 2 diabetes, whereas the effects of SGLT2 inhibitors on MI and stroke are not conclusive and need to be further assessed in future studies with the adequate sample size to reject or accept the effect size.

Author contributions

Conceptualization: Mei Qiu.
Data curation: Mei Qiu, Liangliang Ding, Hairong Zhou.
Formal analysis: Liangliang Ding.
Validation: Mei Qiu, Hairong Zhou.
Writing – original draft: Mei Qiu.
Writing – review & editing: Liangliang Ding, Hairong Zhou.

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