Effects of SGLT2 inhibitors on cardiovascular death and all-cause death in patients with type 2 diabetes and chronic kidney disease: an updated meta-analysis including the SCORED trial

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Abstract

Background: The effects of sodium-glucose transporter 2 (SGLT2) inhibitors on cardiovascular death (CV death) and all-cause death (AC death) in patients with type 2 diabetes (T2D) and chronic kidney disease (CKD) are currently under intensive investigation. We intended to conduct an updated meta-analysis including the SCORED trial to evaluate the effects of SGLT2 inhibitors on death and cardiorenal events in this vulnerable population.

Methods: Cardiorenal outcome trials of SGLT2 inhibitors were included. Primary outcomes were CV death and AC death, while secondary outcomes were hospitalization for heart failure (HHF), myocardial infarction (MI), CKD progression, cardiovascular death or hospitalization for heart failure (CV death or HHF), major adverse cardiovascular events (MACE), and stroke. Meta-analysis was conducted for each outcome.

Results: Eight trials were included for meta-analysis. Compared with placebo, SGLT2 inhibitors significantly lowered the risk of CV death (HR = 0.86, 95% CI = 0.75–0.98), AC death (HR = 0.87, 95% CI = 0.79–0.96), HHF (HR = 0.64, 95% CI = 0.56–0.74), MI (HR = 0.76, 95% CI = 0.65–0.89), CKD progression (HR = 0.62, 95% CI = 0.54–0.72), and CV death or HHF (HR = 0.73, 95% CI = 0.67–0.80). No heterogeneity existed in the above meta-analyses (all I^2 values = 0%), whereas moderate heterogeneity existed in the meta-analyses for MACE and stroke (I^2 = 31.6% and 44.5%, respectively).

Conclusions: Our findings suggest that SGLT2 inhibitors versus placebo significantly lower death, heart failure, renal failure, and MI events in patients with T2D and CKD. Head-to-head trials are needed to examine the possible differences in the effects of various gliflozins on MACE and stroke.

Introduction

Three relevant meta-analysis studies[1–3] have demonstrated that sodium-glucose transporter 2 (SGLT2) inhibitors are superior to placebo in lowering mortality and cardiorenal events among patients with type 2 diabetes (T2D), while three others[4–6] have demonstrated that SGLT2 inhibitors are superior to placebo and glucagon-like peptide-1 receptor agonists (GLP-1 RAs) in lowering

cardiovascular or renal composite outcomes among patients with T2D and chronic kidney disease (CKD). However, the three meta-analyses[4–6] conducted in patients with T2D and CKD have failed to reveal significant effects of SGLT2 inhibitors versus comparator on cardiovascular death (CV death) and all-cause death (AC death) due to the limited statistical power for the death outcomes.

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Recently, a large randomized trial named SCORED[7] has been published and designed to evaluate the cardiorenal efficacy of sotagliflozin in patients with T2D and CKD, which provides new evidence of gliflozins for the treatment of concomitant T2D and CKD. Although the SCORED trial is powered to evaluate the effect of sotagliflozin on heart failure (HF) composite outcome and also reveals a significant reduction with sotagliflozin versus placebo in this outcome, this trial does not have sufficient power to evaluate the effects of sotagliflozin on mortality endpoints such as CV death and AC death. Sotagliflozin is a dual SGLT1 and SGLT2 inhibitor. The cardiovascular benefits of SGLT2 inhibitors have been confirmed by large outcome trials. Conversely, it is not clear what clinical benefits were derived through the inhibition of SGLT1 with sotagliflozin therapy in two sotagliflozin trials.[7,8]

Moreover, Salah *et al.*[9] identified that the estimators for the cardiovascular benefits of sotagliflozin versus placebo were similar with those of SGLT2 inhibitors versus placebo, and therefore concluded that, as for treatment with sotagliflozin, the cardiovascular benefits might be almost attributable to the inhibition of SGLT2, while the potential incremental efficacy of SGLT1 inhibition remains to be explored. Thus, we sought to evaluate the effects of SGLT2 inhibitors on various cardiorenal and death outcomes, including CV death and AC death, in patients with concomitant T2D and CKD, by implementing an updated meta-analysis incorporating relevant trials including the latest SCORED trial[7] assessing sotagliflozin.

Methods

This study was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[10] The study protocol for this meta-analysis had been successfully registered in the INPLASY website before the study selection began, and is available as a free download from https://inplasy.com/inplasy-2021-2-0023/.

Search strategies and inclusion/exclusion criteria

We utilized the corresponding search strategies (Supplemental Table S1 in Appendix 1) respectively for the two online databases of PubMed and Embase) to search relevant original studies. The time range of literature retrieval was from the start date of databases to 6 February 2021. Original studies included in this meta-analysis were randomized placebo-controlled trials which were designed to evaluate the efficacy of any SGLT2 inhibitor on mortality or cardiorenal endpoints in patients with T2D and CKD, or were designed to evaluate that efficacy in patients with T2D or CKD and reported the data regarding that efficacy in the subgroup of patients with T2D and CKD.

Outcomes of interest

Two primary outcomes for this meta-analysis were CV death and AC death, while six secondary outcomes were hospitalization for heart failure (HHF), fatal and nonfatal myocardial infarction (MI), CKD progression, cardiovascular death or hospitalization for heart failure (CV death or HHF), major adverse cardiovascular events (MACE), and fatal and nonfatal stroke. CKD was defined as estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2.[11] The three composite outcomes of CKD progression, CV death or HHF, and MACE were defined in detail in the prior study protocol. MACE was defined as a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke; which was consistent across included trials. Conversely, the definitions of CKD progression and composite HF outcome were similar but slightly different across included trials; which are detailed in Supplemental Appendix 1 (p 3).

Study selection, data extraction and risk of bias assessment

Two authors independently performed study selection according to the inclusion criteria. After that, they independently assessed the risk of bias of included trials and extracted the prespecified data from included trials. The prespecified data to be extracted are detailed in the prior study protocol. Based on the Cochrane risk of bias assessment tool,[12] we assessed the bias risk of included studies in terms of the following seven aspects: risk of selection bias (in regard to random sequence generation), risk of selection bias (in regard to allocation concealment), risk of performance bias (in regard to blinding of participants and personnel), risk of reporting bias (in regard to selective reporting), risk of detection bias (in regard to blinding of outcome assessment), risk of attrition bias (in regard to incomplete outcome

data), and risk of other bias. Discrepancies between them were addressed by discussion, or arbitration by another experienced author.

Statistical analysis

We utilized hazard ratios (HRs) and 95% confidence intervals (CIs) as reported in included studies to conduct meta-analysis. I^2 statistic was computed to evaluate statistical heterogeneity. If $I^2 > 50\%$ (it means substantial heterogeneity), meta-analysis would be conducted with the random-effects model. Otherwise, meta-analysis would be conducted with the fixed-effects model. Funnel plots and Egger tests were done to detect whether there was publication bias or not. $p < 0.05$ for effect size or from Egger test denotes the statistically significant drug effect or publication bias. We did all statistical analyses in the Stata/ MP software (version 16.0).

Results

Patient characteristics of included trials

After study selection (Supplemental Figure S1 in Appendix 1), we ultimately included 8 randomized trials[7,8,11,13–17] in this meta-analysis, and all the 8 trials were with low risk of bias (Supplemental Figure S2 in Appendix 1). The included trials were the trials of SCORED,[7] SOLOIST-WHF,[8] DAPA-CKD,[13] VERTIS CV,[14] CREDENCE,[15] DECLARE–TIMI 58,[16] CANVAS Program,[11] and EMPA-REG OUTCOME.[17] All of the participants the SCORED trial[7] enrolled were patients with T2D and CKD; whereas the participants the SOLOIST-WHF trial[8] enrolled were patients with T2D and HF, those the DAPA-CKD trial[13] enrolled were patients with CKD, and those the other five trials,[11,14–17] enrolled were patients with T2D. Thus, to accurately conduct meta-analysis, we extracted the data of all the participants from the SCORED trial[7] whereas we only extracted the data of the subgroup of patients with T2D and CKD from the other seven trials.[8,11,13–17] All the data that were used for pooled analysis in this meta-analysis and were extracted from included trials are provided in Supplemental Appendix 2.

Meta-analyses

Figure 1 shows the results of meta-analysis on CV death (including 5 trials involving 18299 patients with T2D and CKD), AC death (including 6 trials involving 21205 patients with T2D and CKD), HHF (including 5 trials involving 18299 patients with T2D and CKD), and MI (including 5 trials involving 18299 patients with T2D and CKD). Compared with placebo, SGLT2 inhibitors significantly lowered the risk of CV death (HR = 0.86, 95% CI = 0.75–0.98; $I^2 = 0\%$; p for effect size = 0.028) (Figure 1(a)), AC death (HR = 0.87, 95% CI = 0.79–0.96; $I^2 = 0\%$; p for effect size = 0.008) (Figure 1(b)), HHF (HR = 0.64, 95% CI = 0.56–0.74; $I^2 = 0\%$; p for effect size < 0.001) (Figure 1(c)), and MI (HR = 0.76, 95% CI = 0.65–0.89; $I^2 = 0\%$; p for effect size = 0.001) (Figure 1(d)). Figure 2 shows the results of meta-analysis on CKD progression (including 6 trials involving 21205 patients with T2D and CKD), CV death or HHF (including 8 trials involving 23864 patients with T2D and CKD), MACE (including 6 trials involving 20104 patients with T2D and CKD), and stroke (including 5 trials involving 18299 patients with T2D and CKD). Compared with placebo, SGLT2 inhibitors significantly lowered the risk of CKD progression (HR = 0.62, 95% CI = 0.54–0.72; $I^2 = 0\%$; p for effect size < 0.001) (Figure 2(a)), CV death or HHF (HR = 0.73, 95% CI = 0.67–0.80; $I^2 = 0\%$; p for effect size < 0.001) (Figure 2(b)), MACE (HR = 0.84, 95% CI = 0.77–0.92; $I^2 = 31.6\%$; p for effect size < 0.001) (Figure 2(c)), and stroke (HR = 0.72, 95% CI = 0.59–0.87; $I^2 = 44.5\%$; p for effect size = 0.001) (Figure 2(d)).

Detection of publication bias

Publication bias was not observed in the meta-analysis for any of the 8 outcomes: CV death (P from Egger test = 0.743), AC death (P from Egger test = 0.148), HHF (P from Egger test = 0.364), MI (P from Egger test = 0.458), CKD progression (P from Egger test = 0.175), CV death or HHF (P from Egger test = 0.388), MACE (P from Egger test = 0.690), and stroke (P from Egger test = 0.509). The detailed results of publication bias detection are presented in Supplemental Figures S3-S10 in Appendix 1.

Discussion

This meta-analysis is the first to incorporate the latest SCORED trial[7] and evaluate the effects of SGLT2 inhibitors on CV death and AC death as well as six other cardiorenal endpoints in patients with concomitant T2D and CKD. Accordingly,
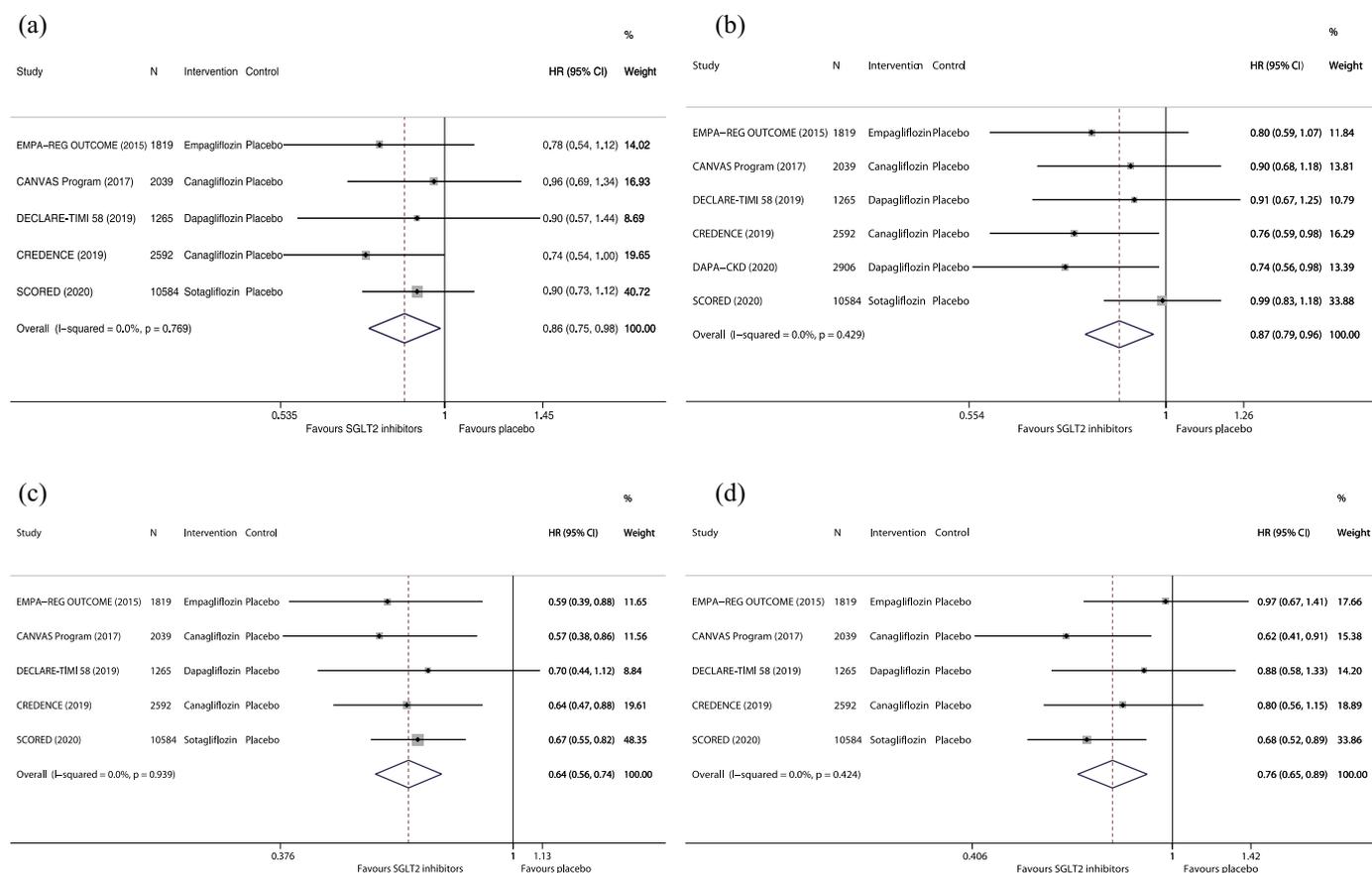
Figure 1. Effects of SGLT2 inhibitors on CV death (a), AC death (b), HHF (c), and MI (d) in patients with T2D and CKD.
AC death, all-cause death; CI, confidence interval; CKD, chronic kidney disease; CV death, cardiovascular death; HHF, hospitalization for heart failure; HR, hazard ratio; MI, myocardial infarction; SGLT2, sodium-glucose transporter 2; T2D, type 2 diabetes.

this study produces the key findings that compared with placebo SGLT2 inhibitors lowered CV death by 14% (HR: 0.86), AC death by 13% (HR: 0.87), HHF by 36% (HR: 0.64), MI by 24% (HR: 0.76), CKD progression by 38% (HR: 0.62), CV death or HHF by 27% (HR: 0.73), MACE by 16% (HR: 0.84), and stroke by 28% (HR: 0.72).

A meta-analysis[4] identified that SGLT2 inhibitors lowered MI by 22%, HHF by 39%, and MACE by 20% in patients with T2D and CKD, but did not significantly affect the occurrence of CV death and stroke. One other meta-analysis[5] identified that SGLT2 inhibitors lowered MACE by 19%, MI by 23%, HHF by 39%, and CKD progression by 29% in patients with T2D and CKD; but did not significantly affect the occurrence of CV death, AC death, and stroke. The nonsignificant effects of SGLT2 inhibitors on death and stroke events revealed in the above two studies[4,5] are closely associated with the lack of

statistical power due to failing to include the SCORED trial. Moreover, another meta-analysis[6] identified that SGLT2 inhibitors were more effective than placebo in lowering MACE and renal composite outcome among patients with T2D and CKD, and more effective than GLP-1 RAs in lowering renal composite outcome; but failed to evaluate any mortality outcome such as CV death and AC death. Oppositely, our meta-analysis identified SGLT2 inhibitors with the reduced risks of these two mortality endpoints in this vulnerable population.

Wang *et al.*[18] carried out a meta-analysis based on those trials enrolling T2D patients and performed a subgroup analysis by grouping included trials into the subgroup of T2D with CKD and the subgroup of T2D without CKD according to mean eGFR < 60 mL/min/1.73 m^2 or not. Although the authors revealed a significant reduction with SGLT2 inhibitors (risk ratio = 0.82,
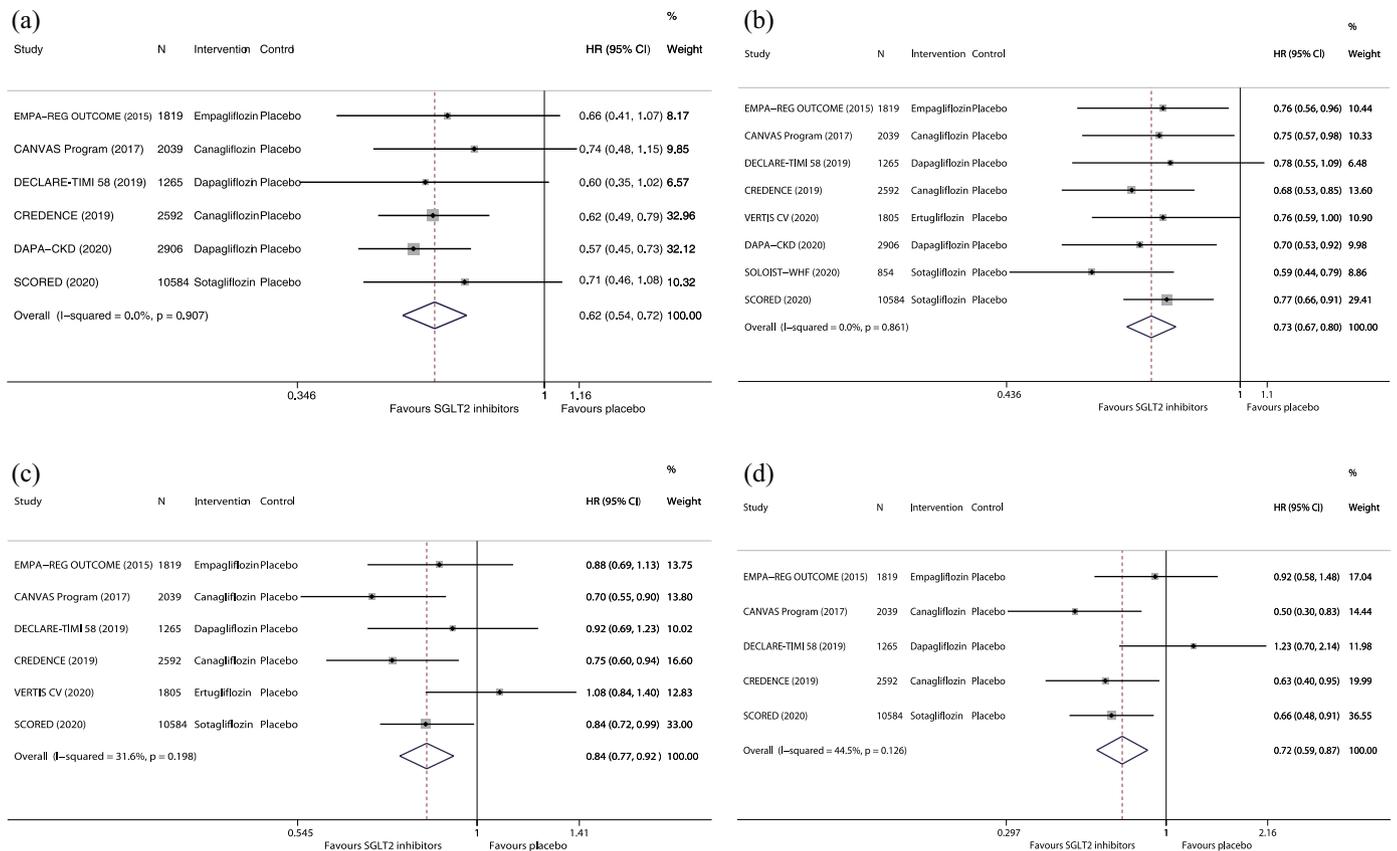
Figure 2. Effects of SGLT2 inhibitors on CKD progression (a), CV death or HHF (b), MACE (c), and stroke (d) in patients with T2D and CKD.
CI, confidence interval; CV death or HHF, cardiovascular death or hospitalization for heart failure; CKD, chronic kidney disease; HR, hazard ratio; MACE, major adverse cardiovascular events; SGLT2, sodium-glucose transporter 2; T2D, type 2 diabetes.

95% CI = 0.67–0.99) versus placebo in AC death among the subgroup of T2D with CKD, the grouping criterion according to the mean value of eGFR could lead to a certain proportion of patients with eGFR ≥ 60 mL/min/1.73 m^2 being included in the CKD subgroup meanwhile those with eGFR < 60 mL/min/1.73 m^2 being included in the non-CKD subgroup. Compared to Wang *et al.*'s[18] meta-analysis, our meta-analysis does not have this shortcoming, and produces a more accurate estimated value regarding the effect of SGLT2 inhibitors on AC death in patients with T2D and CKD by including more new randomized trials.

Our meta-analysis incorporated the cardiorenal outcome trials of five kinds of gliflozins, which consisted of four kinds of SGLT2 inhibitors (i.e. ertugliflozin, canagliflozin, dapagliflozin, and empagliflozin) and a dual SGLT1 and SGLT2 inhibitor (namely, sotagliflozin). In the results of

meta-analysis for two primary outcomes (i.e. CV death, and AC death) and most of the secondary outcomes (i.e. HHF, MI, CKD progression, and CV death or HHF), there was not any heterogeneity found (all I^2 values = 0%). This suggests the sufficient similarity between SGLT2 inhibitors and the dual SGLT1/SGLT2 inhibitor sotagliflozin in the efficacy of lowering mortality, HF, renal failure, and MI events among patients with T2D and CKD, and also suggests that the differences in the definitions of composite renal and HF outcomes across included trials did not significantly bias the estimators derived from meta-analysis on these two outcomes. On the contrary, in the meta-analyses for the two secondary outcomes of MACE and stroke there was moderate heterogeneity found (I^2 = 31.6% and 44.5%, respectively). This may suggest that nonnegligible differences exist among different gliflozins as for preventing MACE and stroke in patients with T2D and CKD. This assumption is, to some extent,

supported by the following findings from previous studies: a network meta-analysis[19] revealed the significant superiority of canagliflozin (versus empagliflozin: HR = 0.71, 95% CI = 0.51–0.99) over empagliflozin in lowering stroke among T2D patients. Meanwhile, a traditional meta-analysis[20] showed that canagliflozin and sotagliflozin significantly lowered the risk of total stroke in patients with T2D and impaired renal function, whereas dapagliflozin and empagliflozin did not have significant effects on that risk. Moreover, SGLT2 inhibitors were not considered to have a class effect as for reducing MACE.[21] However, the possible differences in the effects of various gliflozins on MACE and stroke still need to be examined by head-to-head trials comparing one SGLT2 inhibitor to another.

This study has two main limitations: first, we failed to assess the efficacy of gliflozins in patients without T2D because we focused on patients with T2D and CKD. Accordingly, future studies assessing the cardiorenal benefits of gliflozins in patients without T2D are of clinical interest. Second, we evaluated the effects of gliflozins on death and cardiorenal outcomes in patients with T2D and CKD while CKD was defined as eGFR < 60 mL/min/1.73 m², but failed to evaluate those in more specific subgroups such as the subgroup of patients with T2D and eGFR < 45 or 30 mL/min/1.73 m². Conversely, this study has two main strengths: all the trials included in this meta-analysis were high-quality studies, as there was no publication bias observed in the meta-analyses for all the outcomes evaluated in this study.

In conclusion, compared with placebo, our findings suggest that SGLT2 inhibitors, including the dual SGLT1/SGLT2 inhibitor sotagliflozin, significantly lower death, HF, renal failure, and MI events in patients with T2D and CKD. Head-to-head trials comparing one SGLT2 inhibitor to another are urgently needed to examine the possible differences in the effects of various gliflozins on MACE and stroke.

Author contributions
ZL-M contributed to data curation and formal analysis and wrote the original draft, ZZ-L contributed to data curation and formal analysis and wrote the review & editing, QM contributed to conceptualization and data curation and validation and wrote the review & editing.

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Supplemental material
Supplemental material for this article is available online.

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