Systematic Review and Meta-Analysis

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Gliflozins for the prevention of stroke in diabetes and cardiorenal diseases

A meta-analysis of cardiovascular outcome trials

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Abstract

Background: Individual randomized trials are not powered to assess the relationship between use of sodium–glucose transporter 2 inhibitors and risk of stroke. We sought to explore this issue by a meta-analysis incorporating relevant trials including several latest trials.

Methods: Cardiovascular outcome trials of gliflozins were included. Primary outcome was stroke, while secondary outcome was major adverse cardiovascular events (MACE), which was a composite of stroke, myocardial infarction, or cardiovascular death. Meta-analysis was conducted stratified by with/without chronic kidney disease (CKD), with/without heart failure (HF), and with/without atherosclerotic cardiovascular disease (ASCVD), and stratified by different gliflozins.

Results: We included 9 trials in this meta-analysis. Compared with placebo, gliflozins significantly lowered stroke (hazard ratio [HR] 0.68, 95% confidence interval [CI] 0.55–0.84) and MACE (HR 0.77, 95% CI 0.69–0.86) in type 2 diabetes (T2D) patients with CKD, but did not significantly affect stroke (HR 1.00, 95% CI 0.86–1.16) and MACE (HR 0.94, 95% CI 0.86–1.02) in T2D patients without CKD. Gliflozins had no significant effects on the stroke risk (HR 0.94, 95% CI 0.82–1.07) in T2D patients regardless of HF status ($P_{subgroup}$ = .684) and ASCVD status ($P_{subgroup}$ = .915), but significantly lowered MACE (HR 0.89, 95% CI 0.83–0.96) in T2D patients regardless of HF status ($P_{subgroup}$ = .428) and ASCVD status ($P_{subgroup}$ = .423). Canagliflozin (HR 0.84, 95% CI 0.69–1.01) showed the trend of a reduction in the stroke risk versus placebo, and sotagliflozin (HR 0.73, 95% CI 0.54–0.98) significantly lowered the stroke risk; whereas the other 3 gliflozins did not significantly affect that risk. Ertugliflozin (HR 0.97, 95% CI 0.85–1.11) had no significant effects on the MACE risk, whereas the other 4 gliflozins significantly lowered that risk.

Conclusions: Gliflozins, especially canagliflozin and sotagliflozin, should be recommended in T2D patients with CKD to prevent stroke. Most gliflozins lower the risk of MACE in T2D patients regardless of HF status and ASCVD status, whereas ertugliflozin is not observed to lower that risk.

Abbreviations: ASCVD = atherosclerotic cardiovascular disease, CI = confidence interval, CKD = chronic kidney disease, HF = heart failure, HR = hazard ratio, MACE = major adverse cardiovascular events, SGLT2 = sodium–glucose transporter 2, T2D = type 2 diabetes.

Keywords: atherosclerotic cardiovascular disease, chronic kidney disease, heart failure, sodium–glucose transporter 2 inhibitors, stoke, type 2 diabetes

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

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1. Introduction

Large randomized trials assessing the cardiovascular efficacy of sodium–glucose transporter 2 (SGLT2) inhibitors are powered to evaluate 2 cardiovascular composite outcomes. One is major adverse cardiovascular events (MACE) which is a composite of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes; and the other is a composite of hospitalization for heart failure (HF) or death from cardiovascular causes. Unfortunately, those individual cardiovascular trials are not powered to assess whether use of SGLT2 inhibitors is associated with an increased risk of stroke or not. There have been several relevant meta-analyses[1–3] already published aiming to explore this issue, of which all did not reveal a significant association between use of gliflozins and occurrence of stroke. Moreover, these published studies[1–3] of meta-analysis failed to have the statistical power to assess the efficacy of gliflozins in preventing stroke among various subgroups of patients with type 2 diabetes (T2D).

Nowadays, the new evidence from relevant randomized trials, such as the SOLOIST-WHF trial,[4] the SCORED trial,[5] and the VERTIS CV trial,[6] is available. The SOLOIST-WHF trial[4] adds the more evidence of gliflozins used in the subgroup of T2D patients with HF, the SCORED trial[5] adds that of gliflozins used in the subgroup of T2D patients with chronic kidney disease (CKD), and the VERTIS CV trial[6] adds that of gliflozins used in the subgroup of T2D patients with atherosclerotic cardiovascular disease (ASCVD).

Thus, we sought to evaluate the efficacy of gliflozins in preventing stroke among various T2D subgroups, by performing a meta-analysis with subgroup analyses stratified by the existence of concomitant disease or not. Moreover, we sought to evaluate the heterogeneity in the efficacy of different gliflozins, by performing an additional subgroup analysis stratified by type of gliflozins.

2. Methods

This study of meta-analysis is reported according to the preferred reporting items for systematic reviews and meta-analyses statement.[7] The corresponding preferred reporting items for systematic reviews and meta-analyses checklist is available.

2.1. Search strategy and inclusion criteria

Corresponding retrieval strategies (Table S1, Supplemental Digital Content, http://links.lww.com/MD2/A491, which shows the search strategies) respectively for the Embase and PubMed databases were used to search relevant literatures from the database start date to January 27, 2021. In this meta-analysis study, we included those randomized trials which were designed to assess the efficacy of any gliflozin compared to placebo in preventing cardiovascular and cerebrovascular outcomes among T2D or non-T2D patients. The primary outcome for this meta-analysis was stroke, which included fatal stroke and nonfatal stroke in terms of seriousness, and included ischemic stroke and hemorrhagic stroke in terms of type. The secondary outcome was MACE, which was a composite of stroke, myocardial infarction, or cardiovascular death.

2.2. Study selection, quality assessment and data extraction

Two authors independently completed these essential works for meta-analysis. A third author with rich experience in systematic reviews with meta-analyses addressed the disagreements between them. Quality assessment for included trials was according to the Cochrane risk of bias assessment tool.[8] The data extracted from included trials contained type of study, patient characteristics, type of intervention, type of control, outcome data in various subgroups stratified by T2D with/without CKD, T2D with/without HF, and T2D with/without ASCVD. Patients with an estimated glomerular filtration rate value of < 60 mL/min/1.73 m^2 were considered as patients with CKD.[9] Outcome data were reflected by hazard ratios (HRs) and 95% confidence intervals (CIs) of gliflozins versus control.

2.3. Statistical analysis

We conducted meta-analysis using the fixed-effects model with the inverse variance method. I^2 statistic was computed to evaluate heterogeneity. Substantial heterogeneity was considered as an I^2 value of $>50\%$. Subgroup analysis was performed according to with/without CKD, with/without HF, and with/without ASCVD, and according to different gliflozins. We examined subgroup differences by Cochran Q test. This test with a P value of $<.05$ denotes statistical significance. All statistical analyses were done using the Stata/MP software (version 16.0).

2.4. Ethical statement

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

3. Results

3.1. Characteristics of included studies

After reviewing 208 potentially eligible full-text articles, we identified 13 articles[4–6,9–18] reporting a total of 9 randomized trials used for meta-analysis. The whole process of study selection is shown in Figure S1, Supplemental Digital Content, http://links.lww.com/MD2/A488 (which is the flow diagram of study selection). The 9 trials included in meta-analysis consisted of EMPA-REG OUTCOME[10,11] assessing empagliflozin in T2D and ASCVD, CANVAS Program[9,12,13] assessing canagliflozin in T2D, DECLARE–TIMI 58[14] assessing dapagliflozin in T2D, CREDENCE[15,16] assessing canagliflozin in T2D and nephropathy, VERTIS CV[6] assessing ertugliflozin in T2D and ASCVD, DAPA-HF[17] assessing dapagliflozin in HF, DAPA-CKD[18] assessing dapagliflozin in CKD, SOLOIST-WHF[4] assessing sotagliflozin in T2D and HF, and SCORED[5] assessing sotagliflozin in T2D and CKD. All the included trials were with the low risk of bias, as is suggested in Figure S2, Supplemental Digital Content, http://links.lww.com/MD2/A489 (which shows the quality assessment results of included studies). As is shown in Table S2, Supplemental Digital Content, http://links.lww.com/MD2/A492 (which shows the characteristics of included studies), each trial enrolled more than 1000 participants, and had a relatively long duration of follow-up with the minimum of 0.8 years and the maximum of 4.2 years, while participants in each trial had different proportions of CKD, HF, and ASCVD. All the data extracted from included articles are given in Table S3, Supplemental Digital Content, http://links.lww.com/MD2/A493 (which provides the original data extracted from included articles).

3.2. Meta-analyses on stroke

Figure 1 presents the effect of gliflozins on stroke in T2D patients according to CKD status. Gliflozins significantly

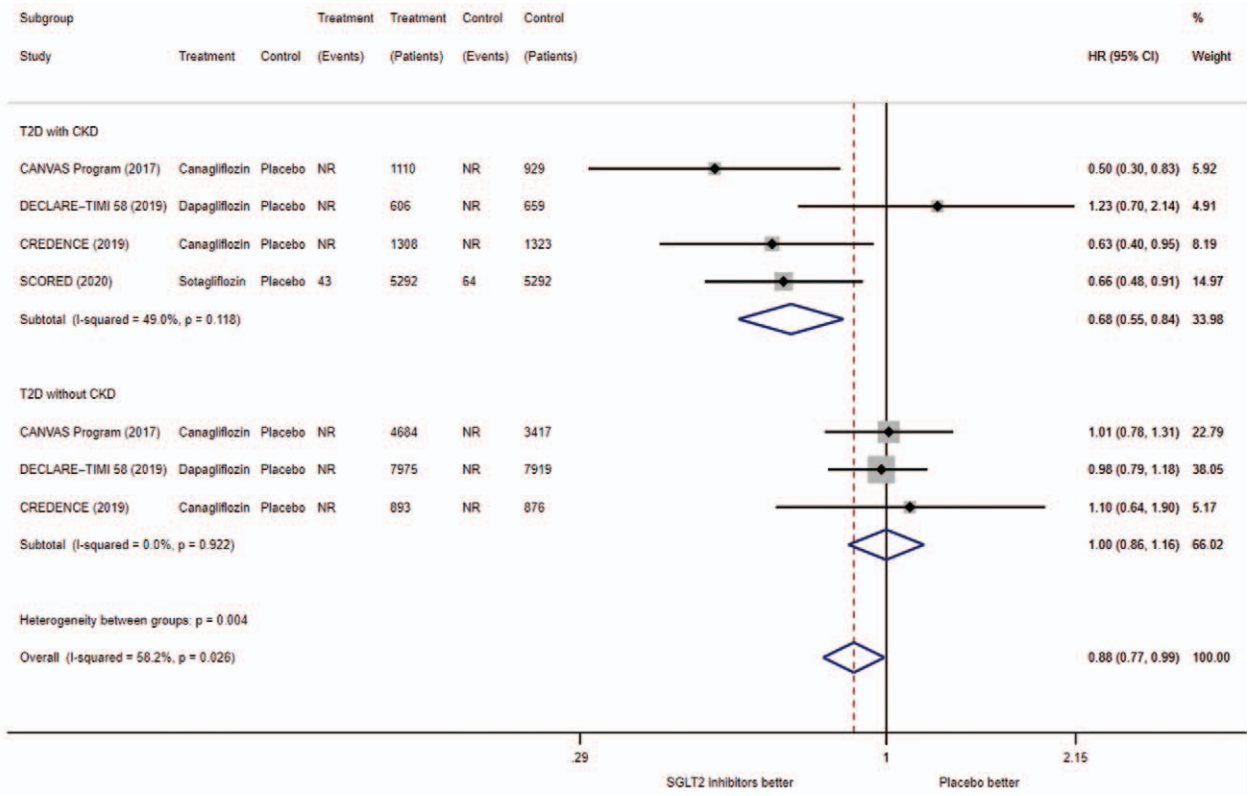

Figure 1. Meta-analysis of the effect of gliflozins on stroke in T2D patients according to CKD status. CI = confidence interval, CKD = chronic kidney disease, HR = hazard ratio, NR = not reported in original articles, SGLT2 = sodium–glucose transporter 2, T2D = type 2 diabetes.

lowered the stroke risk versus placebo in T2D patients with CKD (HR 0.68, 95% CI 0.55–0.84; $I^2 = 49.0\%$), but did not in T2D patients without CKD (HR 1.00, 95% CI 0.86–1.16; $I^2 = 0\%$). CKD status significantly affected the effect of gliflozins on stroke in T2D patients ($P_{subgroup} = .004$). Figure 2 presents the effect of gliflozins on stroke in T2D patients according to HF status. Gliflozins had no significant effects on the stroke risk versus placebo in T2D patients (HR 0.94, 95% CI 0.82–1.07; $I^2 = 0\%$) regardless of HF status ($P_{subgroup} = .684$). Figure 3 presents the effect of gliflozins on stroke in T2D patients according to ASCVD status. Gliflozins had no significant effects on the stroke risk versus placebo in T2D patients (HR 0.98, 95% CI 0.88–1.10; $I^2 = 6.9\%$) regardless of ASCVD status ($P_{subgroup} = .915$). Figure 4 shows that CKD status did not significantly affect the effect of gliflozins on stroke in T2D patients with ASCVD ($P_{subgroup} = .210$), while the wide 95% CIs of HRs suggested the lack of power. Figure 5 presents the effect of different gliflozins on stroke. Canagliflozin (HR 0.84, 95% CI 0.69–1.01; $I^2 = 0\%$) showed the trend of a reduction in the stroke risk versus placebo, and sotagliflozin (HR 0.73, 95% CI 0.54–0.98; $I^2 = 66.5\%$) significantly lowered the stroke risk; whereas empagliflozin (HR 1.18, 95% CI 0.89–1.56; $I^2 = 0\%$), dapagliflozin (HR 0.99, 95% CI 0.84–1.16; $I^2 = 0\%$) and ertugliflozin (HR 1.06, 95% CI 0.82–1.37; $I^2 = 0\%$) had no significant effects on the stroke risk. The subgroup effect according to different gliflozins almost reached statistical significance ($P_{subgroup} = .096$).

3.3. Meta-analyses on MACE

Figure 6 presents the effect of gliflozins on MACE in T2D patients according to CKD status. Gliflozins significantly lowered the MACE risk versus placebo in T2D patients with CKD (HR 0.77, 95% CI 0.69–0.86; $I^2 = 0\%$), but did not in T2D patients without CKD (HR 0.94, 95% CI 0.86–1.02; $I^2 = 0\%$). CKD status significantly affected the effect of gliflozins on MACE in T2D patients ($P_{subgroup} = .005$). Figure 7 presents the effect of gliflozins on MACE in T2D patients according to HF status. Gliflozins significantly lowered the MACE risk versus placebo in T2D patients (HR 0.89, 95% CI 0.83–0.96; $I^2 = 0\%$) regardless of HF status ($P_{subgroup} = .428$). Figure 8 presents the effect of gliflozins on MACE in T2D patients according to ASCVD status. Gliflozins significantly lowered the MACE risk versus placebo in T2D patients (HR 0.90, 95% CI 0.84–0.95; $I^2 = 19.5\%$) regardless of ASCVD status ($P_{subgroup} = .423$). Figure 9 shows that CKD status did not significantly affect the effect of gliflozins on MACE in T2D patients with ASCVD ($P_{subgroup} = .429$), while the wide 95% CIs of HRs suggested the lack of power. Figure 10 presents the effect of different gliflozins on MACE. Empagliflozin (HR 0.86, 95% CI 0.74–0.99; $I^2 = 0\%$), canagliflozin (HR 0.84, 95% CI 0.76–0.93; $I^2 = 0\%$), dapagliflozin (HR 0.90, 95% CI 0.83–0.97; $I^2 = 0\%$), and sotagliflozin (HR 0.81, 95% CI 0.70–0.95; $I^2 = 53.9\%$) significantly lowered the MACE risk versus placebo; whereas ertugliflozin (HR 0.97, 95% CI 0.85–1.11; $I^2 = 0\%$) had no significant effects on the MACE risk. The subgroup effect according to different gliflozins was not statistically significant

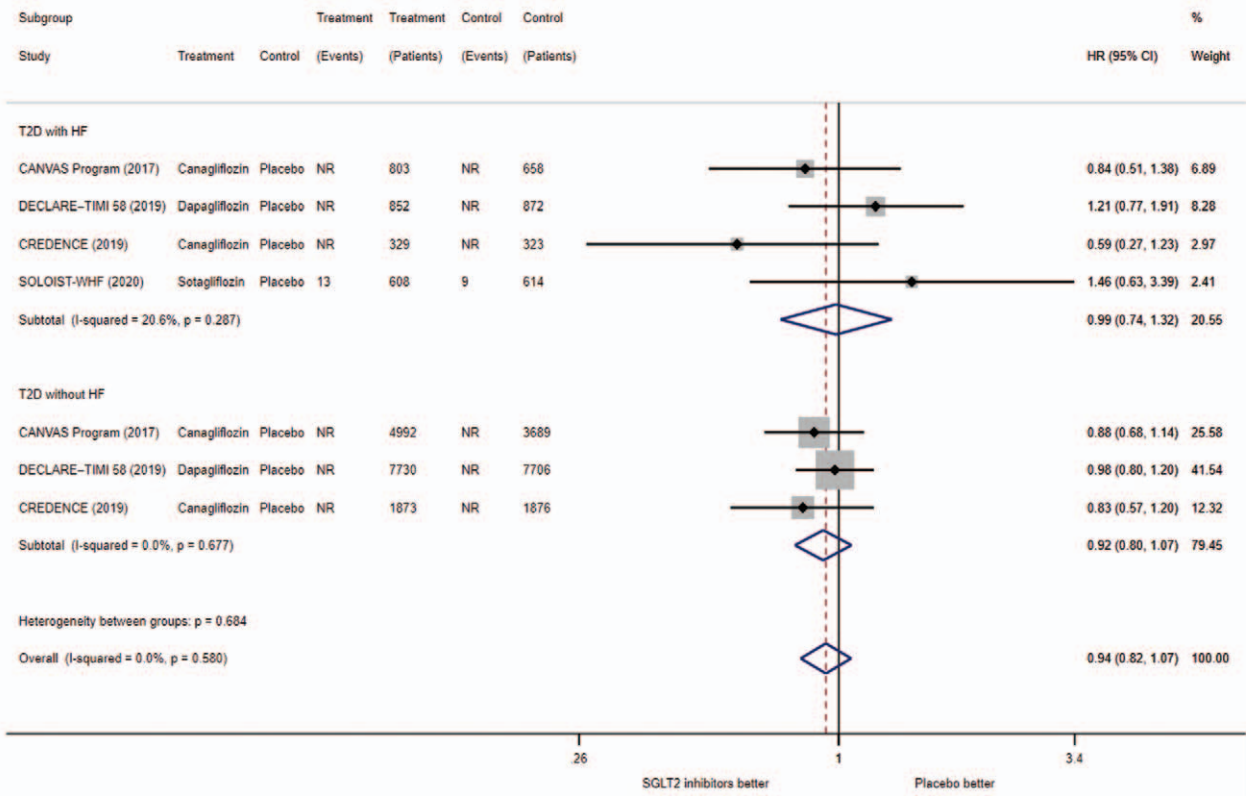

Figure 2. Meta-analysis of the effect of gliflozins on stroke in T2D patients according to HF status. CI = confidence interval, HF = heart failure, HR = hazard ratio, NR = not reported in original articles, SGLT2 = sodium–glucose transporter 2, T2D = type 2 diabetes.

($P_{subgroup}$ = .362), which was associated with the lack of power as suggested by the wide 95% CIs of HRs.

3.4. Test for publication bias

Figures S3 to S12, Supplemental Digital Content, http://links.lww.com/MD2/A490 (which are funnel plots including Egger test results) did not reveal any publication bias in all the meta-analyses conducted in this study.

4. Discussion

By performing this meta-analysis incorporating the data from all the relevant cardiovascular outcome trials of gliflozins including the 2 recent trials of SOLOIST-WHF[4] and SCORED,[5] we evaluated the effects of different gliflozins on stroke and MACE in different subgroups defined by T2D with/without CKD, T2D with/without HF, and T2D with/without ASCVD. Accordingly, we produced the 3 key findings.

First, gliflozins significantly lowered the stroke risk versus placebo in T2D patients with CKD (HR 0.68, 95% CI 0.55–0.84) but did not in T2D patients without CKD (HR 1.00, 95% CI 0.86–1.16), with the significant subgroup difference ($P_{subgroup}$ = .004). Gliflozins did not have significant effects on the stroke risk in T2D patients with/without HF, and in those with/without ASCVD. Three previous meta-analyses[1–3] showed that SGLT2 inhibitors were not associated with an increased risk of stroke in overall T2D patients, and failed to explore the possible subgroup effects according to CKD status, HF status, or ASCVD status since the available data were limited at that time. Fortunately, our meta-analysis examined the existence of these subgroup effects or not, and identified the significant efficacy of gliflozins in lowering stroke among patients with T2D and CKD. This finding will guide gliflozins to be used in that special population to prevent stroke.

Second, gliflozins significantly lowered the MACE risk versus placebo in T2D patients with CKD (HR 0.77, 95% CI 0.69–0.86) but did not in T2D patients without CKD (HR 0.94, 95% CI 0.86–1.02), with the significant subgroup difference ($P_{subgroup}$ = .005). Similarly, Giugliano et al[19] identified that the benefit of SGLT2 inhibitors on MACE increased in more severe kidney disease. Meanwhile, our study also revealed that gliflozins significantly lowered the MACE risk in T2D patients independent of HF status ($P_{subgroup}$ = .428) and ASCVD status ($P_{subgroup}$ = .423). On the contrary, 2 previous meta-analyses[2,20] showed a significant reduction with SGLT2 inhibitors in MACE among T2D patients with ASCVD but a nonsignificant effect of SGLT2 inhibitors on MACE among T2D patients without ASCVD. This point should be updated because our study incorporated the more data such as those from the trials of VERTIS CV[6] and CREDENCE[15] compared to the previous 2 studies.[2,20]

Third, the results of meta-analysis stratified by different gliflozins revealed the more possibility of the superiority of canagliflozin and sotagliflozin over 3 other gliflozins (ie, empagliflozin, dapagliflozin, and ertugliflozin) in lowering stroke, and that of 4 gliflozins (ie, empagliflozin, canagliflozin, dapagliflozin, and sotagliflozin) over ertugliflozin in lowering MACE. This finding will guide specific gliflozins to be used for the prevention of stroke and/or MACE.

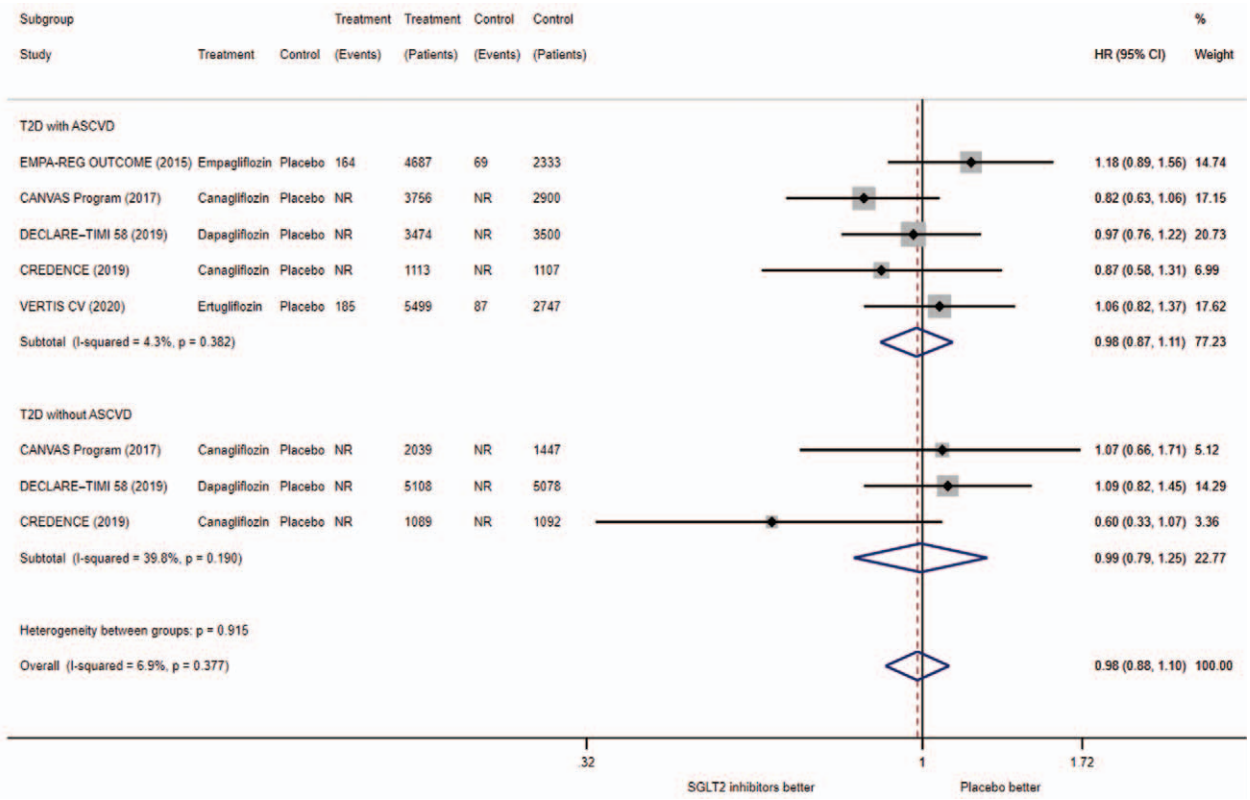

Figure 3. Meta-analysis of the effect of gliflozins on stroke in T2D patients according to ASCVD status. ASCVD = atherosclerotic cardiovascular disease, CI = confidence interval, HR = hazard ratio, NR = not reported in original articles, SGLT2 = sodium–glucose transporter 2, T2D = type 2 diabetes.

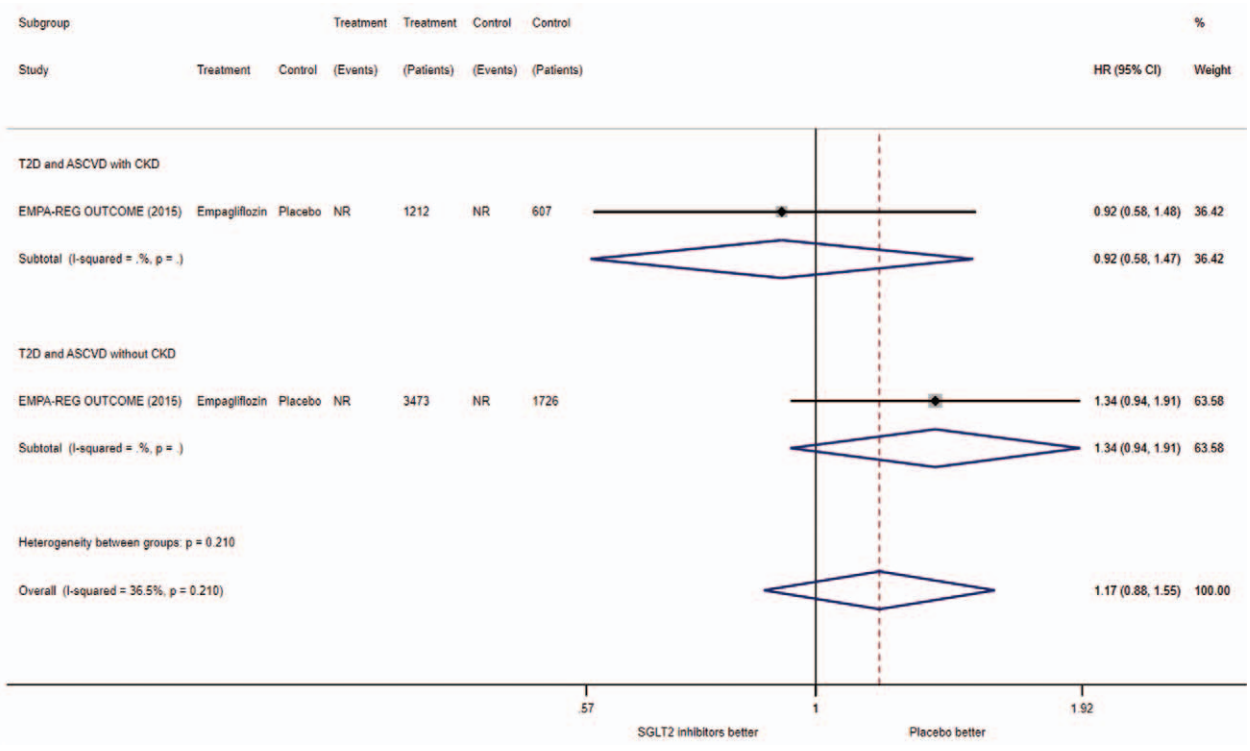

Figure 4. Meta-analysis of the effect of gliflozins on stroke in T2D patients with ASCVD according to CKD status. ASCVD = atherosclerotic cardiovascular disease, CI = confidence interval, CKD = chronic kidney disease, HR = hazard ratio, NR = not reported in original articles, SGLT2 = sodium–glucose transporter 2, T2D = type 2 diabetes.

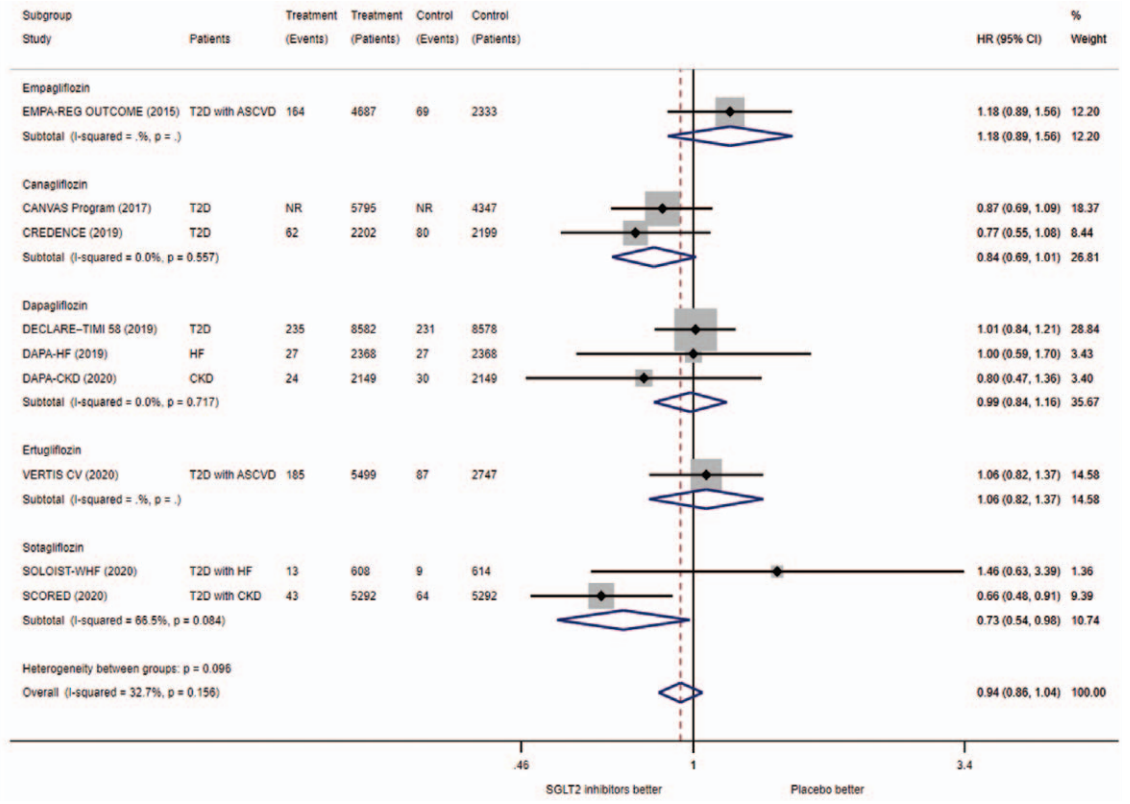

Figure 5. Meta-analysis of the effect of different gliflozins on stroke. ASCVD = atherosclerotic cardiovascular disease, CI = confidence interval, CKD = chronic kidney disease, HF = heart failure, HR = hazard ratio, NR = not reported in original articles, SGLT2 = sodium–glucose transporter 2, T2D = type 2 diabetes.

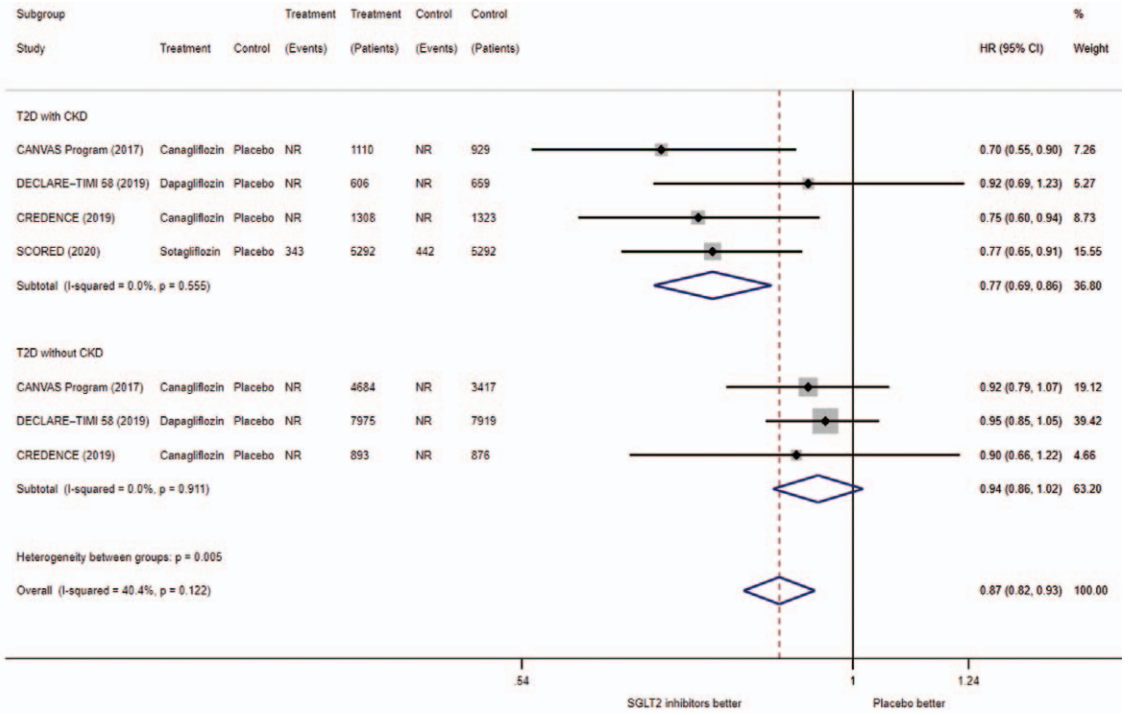

Figure 6. Meta-analysis of the effect of gliflozins on MACE in T2D patients according to CKD status. CI = confidence interval, CKD = chronic kidney disease, HR = hazard ratio, MACE = major adverse cardiovascular events, NR = not reported in original articles, SGLT2 = sodium–glucose transporter 2, T2D = type 2 diabetes.

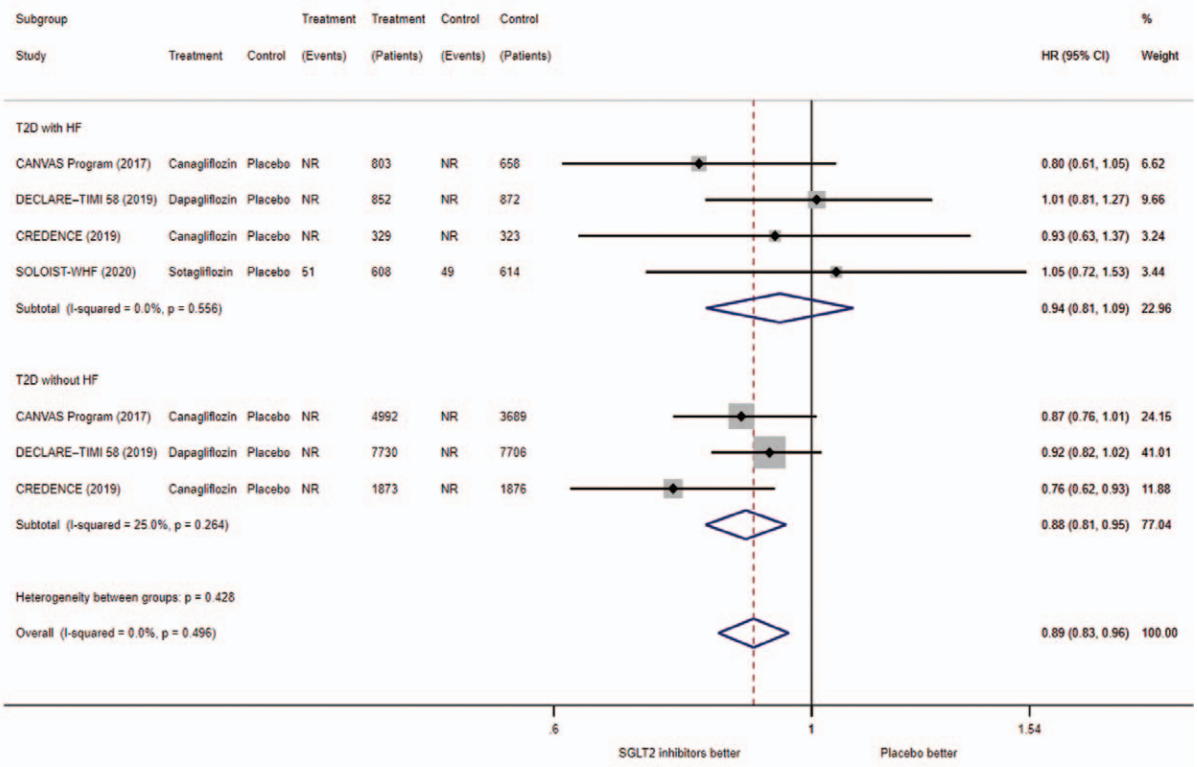

Figure 7. Meta-analysis of the effect of gliflozins on MACE in T2D patients according to HF status. CI = confidence interval, HF = heart failure, HR = hazard ratio, MACE = major adverse cardiovascular events, NR = not reported in original articles, SGLT2 = sodium–glucose transporter 2, T2D = type 2 diabetes.

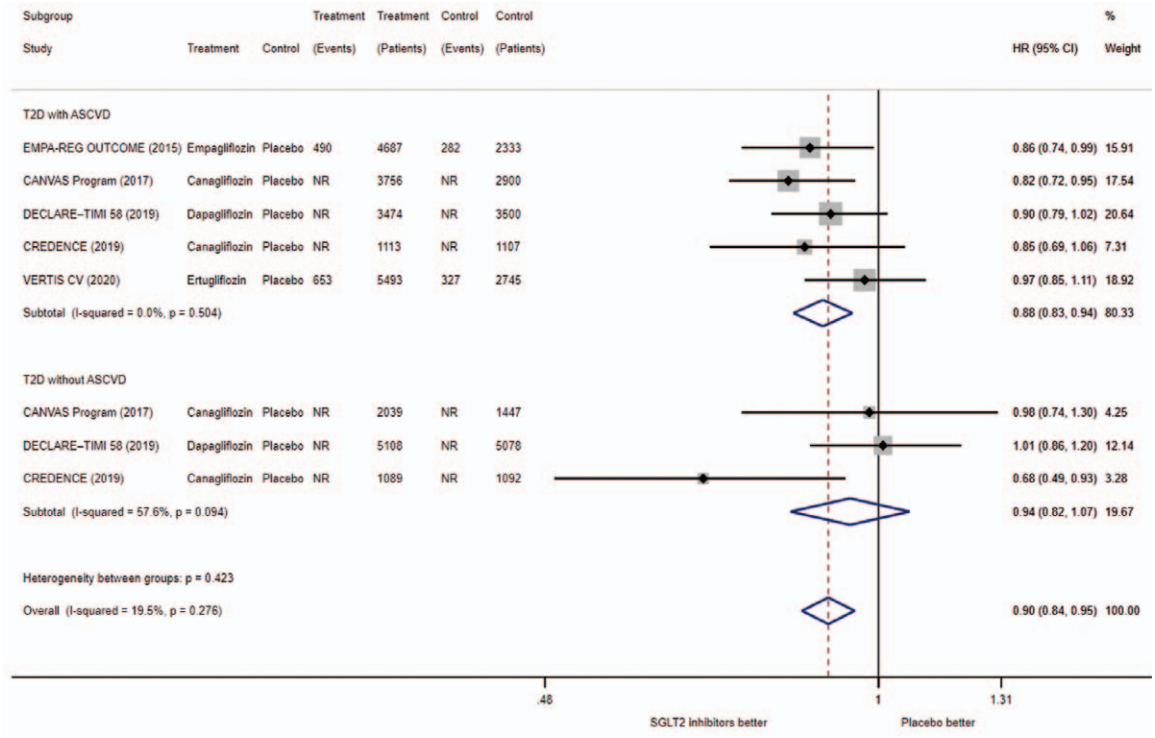

Figure 8. Meta-analysis of the effect of gliflozins on MACE in T2D patients according to ASCVD status. ASCVD = atherosclerotic cardiovascular disease, CI = confidence interval, HR = hazard ratio, MACE = major adverse cardiovascular events, NR = not reported in original articles, SGLT2 = sodium–glucose transporter 2, T2D = type 2 diabetes.

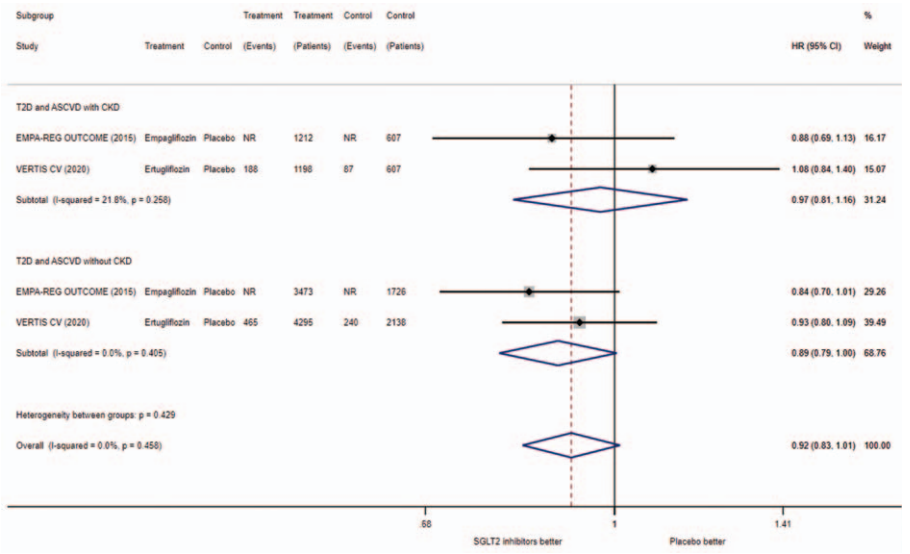

Figure 9. Meta-analysis of the effect of gliflozins on MACE in T2D patients with ASCVD according to CKD status. ASCVD = atherosclerotic cardiovascular disease, CI = confidence interval, CKD = chronic kidney disease, HR = hazard ratio, MACE = major adverse cardiovascular events, NR = not reported in original articles, SGLT2 = sodium–glucose transporter 2, T2D = type 2 diabetes.

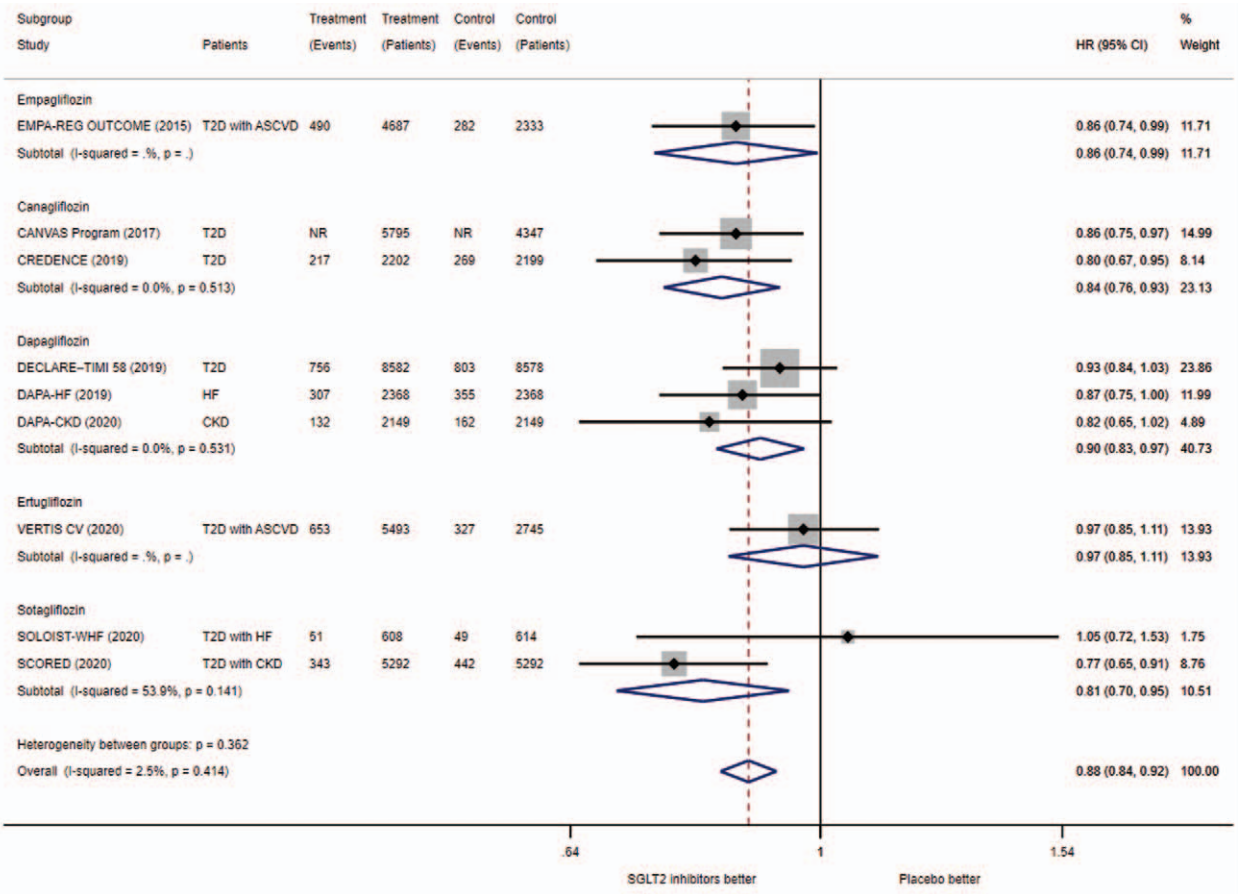

Figure 10. Meta-analysis of the effect of different gliflozins on MACE. ASCVD = atherosclerotic cardiovascular disease, CI = confidence interval, CKD = chronic kidney disease, HF = heart failure, HR = hazard ratio, MACE = major adverse cardiovascular events, NR = not reported in original articles, SGLT2 = sodium–glucose transporter 2, T2D = type 2 diabetes.

This study has 3 main weaknesses. First, substantial heterogeneity was found in a few of the subgroups evaluated in the study. It needs to be further clarified. Second, insufficient statistical power was found in the meta-analysis for the subgroup of T2D and ASCVD patients with CKD and that of T2D and ASCVD patients without CKD. Future studies are required to perform more detailed analysis in more specific subgroups such as the above 2 subgroups. Third, we assessed the total stoke risk in patients treated by gliflozins but failed to assess the risks of different types of strokes. Fourth, individual patient data are needed to confirm the effect of gliflozins on stroke by conducting the multi-factor analysis in which various confounding factors such as history of stroke are adjusted, and to explore the effect of gliflozins on stroke in patients with history of stroke and those without history of stroke. Last, we failed to assess the effect of hypertension status at baseline on the efficacy of gliflozins. Further studies assessing the above issues are clinically meaningful. Conversely, 2 of the strengths of this study are all the included studies with high quality and no publication bias observed in all the meta-analyses conducted this study.

In conclusion, gliflozins, especially canagliflozin and sotagliflozin, should be recommended in T2D patients with CKD to prevent stroke. Most gliflozins lower the risk of MACE in T2D patients regardless of HF status and ASCVD status, whereas ertugliflozin is not observed to lower that risk.

Author contributions

Conceptualization: Mei Qiu.
Data curation: Mei Qiu, Liang-Liang Ding, Ze-Lin Zhan.
Formal analysis: Jia-Nan Huang.
Validation: Li-Min Zhao, Jie Ning.
Writing – original draft: Li-Min Zhao.
Writing – review & editing: Jie Ning.

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