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ORIGINAL ARTICLE

Comparison of cardiovascular outcomes of new antihyperglycemic agents in Type 2 Diabetes Mellitus: a meta-analysis

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Abstract

Aims The study aims to provide comprehensive evidence for the selection of agents in type 2 diabetes mellitus (T2DM) patients with cardiovascular risk and summarize the lasted evidence for the cardiovascular effects of sodium glucose cotransporter-2 inhibitor (SGLT2i) in patients with heart failure (HF).

Methods and results Several online databases were searched. All studies that explored the cardiovascular effects of SGLT2i or glucagon-like peptide 1 receptor agonist (GLP1-RA) were screened and reviewed. A total of 38 studies were included. Compared with GLP1-RA, the use of SGLT2i significantly reduced the risk of cardiovascular death [risk ratio (RR) = 0.59; 95% confidence interval (CI), 0.44–0.58], hospitalization of heart failure (HHF) (RR = 0.77; 95% CI, 0.74–0.80), death from any cause (RR = 0.64; 95% CI, 0.60–0.68), and myocardial infarction (MI) (RR = 0.81; 95% CI, 0.76–0.87). However, SGLT2i significantly increased the risk of stroke (RR = 1.10; 95% CI, 1.04–1.17). Compared with the control group, SGLT2i treatment reduced the risk of cardiovascular death by 14% (RR = 0.86; 95% CI, 0.79–0.94), HHF by 25%, and death from any cause by 9% in patients with HF, regardless of diabetes status.

Conclusions SGLT2i is associated with a lower risk of cardiovascular death, HHF, death from any cause, and MI in patients with T2DM compared with GLP1-RA. In addition, SGLT2i brought more benefits with respect to the effects of cardiovascular death, HHF, and death from any cause in patients with HF, regardless of diabetes status.

Keywords Cardiovascular outcomes; Sodium glucose cotransporter-2 inhibitor; Glucagon-like peptide 1 receptor agonist; Type 2 diabetes; Heart failure

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Introduction

Major adverse cardiovascular events (MACE) are the most common morbidity and mortality in patients with type 2 diabetes mellitus (T2DM).[1] Numerous cardiovascular outcome trials have provided evidence that sodium glucose cotransporter-2 inhibitor (SGLT2i) reduced MACE rates in T2DM patients. It was reported that SGLT2i exerted protective effects against hospitalization of heart failure (HHF) compared with metformin.[2] Compared with placebo, SGLT2i presented significant beneficial effects on HHF, death from any cause, and MACE in patients with T2DM.[3] Compared with dipeptidyl peptidase-4 inhibitor, SGLT2i brings more benefits with respect to cardiovascular outcomes and risk factors.[4] Similar to SGLT2i, glucagon-like peptide 1 receptor agonist (GLP1-RA) is a new class of glucose-lowering drug and also presents benefits for MACE and HHF.[5] However, SGLT2i and GLP1-RA demonstrated several differences with respect to the types of cardiovascular events they present. According to previous network meta-analyses, SGLT2i exerts much of its protective effects against HHF, while GLP1-RA mostly tackles non-fatal stroke.[6,7] Recently, a head-to-head comparison of the effects on cardiovascular outcomes between SGLT2i and GLP1-RA has been addressed. However, contradictory conclusions were

observed. It was revealed that SGLT2i displayed neutral effects on all components of MACE compared with GLP1-RA.[8] Another study revealed that SGLT2i was more effective than GLP1-RA in improving cardiovascular outcomes,[9] while an Italian cohort study demonstrated that GLP1-RA was superior to SGLT2i in improving cardiovascular outcomes.[10] However, the utility of previous meta-analyses is limited because they indirectly assessed the comparative effects of SGLT2i and GLP1-RA due to a lack of head-to-head trials. In order to provide a more comprehensive conclusion and a basis for the selection of agents for T2DM patients, we firstly collected the latest available data for the meta-analysis to do a head-to-head comparison of the cardiovascular effects between SGLT2i and GLP1-RA.

In parallel, experimental evidence emerged suggesting that SGLT2i plays a cardioprotective role dependent on blood glucose level.[11,12] Therefore, recent trials have also focused on the cardiovascular effects of SGLT2i in patients with heart failure (HF), regardless of diabetes status. The EMPEROR-Reduced trial proved that no significant difference in cardiovascular death was found between the SGLT2i and placebo groups in patients with HF, but SGLT2i treatment was closely associated with a lower incidence of HHF.[13] In contrast, the DAPA-HF trial demonstrated that SGLT2i significantly reduced the risk of cardiovascular death among patients with HF.[14] Thus, based on previous contradictory conclusions, we present the meta-analysis to explore the pooled overall effectiveness of SGLT2i in patients with HF, aiming to provide further insight into the data on SGLT2i's cardiovascular benefits.

Methods

The study was registered in PROSPERO, with Registration No. CRD42023423524.

Search strategy

Studies published in the PubMed, Web of Science, EMBASE, the Cochrane Library, and China National Knowledge Infrastructure before or on 13 August 2023 were searched using the following search terms: 'diabetes', 'diabetes mellitus', 'heart failure', 'sodium glucose co-transporter 2 inhibitor', 'SGLT-2 inhibitor', 'dapaliflozin', 'empagliflozin', 'ipragliflozin', 'canagliflozin', 'glucagon-like peptide-1 receptor agonists', 'GLP-1RA', 'liraglutide', 'dulaglutide', 'exenatide', 'lixisenatide', 'semaglutide', and 'albiglutide', alone or in combination, without language restriction.

Inclusion and exclusion criteria

The following inclusion criteria were applied: (i) type of participants: patients (≥18 years old) in each study who were diagnosed with HF or T2DM and (ii) type of study: all studies that compared the effects of SGLT2i and GLP1-RA as monotherapy or combination therapy with other hypoglycaemic drugs on cardiovascular outcomes and all studies that provide information with respect to cardiovascular outcomes of HF patients divided into the SGLT2i and placebo groups. Exclusion criteria include (i) study design: reviews, comments, letters, case reports, and abstracts; (ii) type of participants: animals, patients <18 years old, and pregnant women; and (iii) insufficient information concerning evaluation rates.

Outcomes

The primary outcomes evaluated in this study were cardiovascular death, HHF, death from any cause, myocardial infarction (MI), and stroke. The secondary outcome included a change in the level (relative to baseline) of haemoglobin A1c (HbA1c), systolic blood pressure (SBP), diastolic blood pressure (DBP), lipid indices [high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides], and body mass index (BMI).

Study selection

After eliminating duplicates, the remaining identified trials were reviewed by two independent investigators to confirm that they fulfilled the inclusion criteria. The full text of articles would be retrieved and carefully reviewed by three investigators if they thought the titles or abstracts were potentially useful. When discrepancies occurred between investigators, all authors would evaluate the results and reach the final decision. Finally, the relevant studies in the reference lists were screened and assessed in the same manner.

Data extraction

A predefined data extraction form was applied, and two authors independently extracted data. The extracted data included the last name of the first author, geographical region, sample size (*N*), percentage of male patients (%), mean age (years), portion of different drug use, primary outcomes, and research type. The Newcastle–Ottawa scale (NOS) was employed to assess the quality of the included retrospective studies. The NOS score of 1–3, 4–6, and 7–9 presented low,

intermediate, and high quality, respectively. We used the Cochrane risk of bias tools to assess the quality of randomized controlled trials (RCTs). All disagreements were resolved through discussion.

Statistical analysis

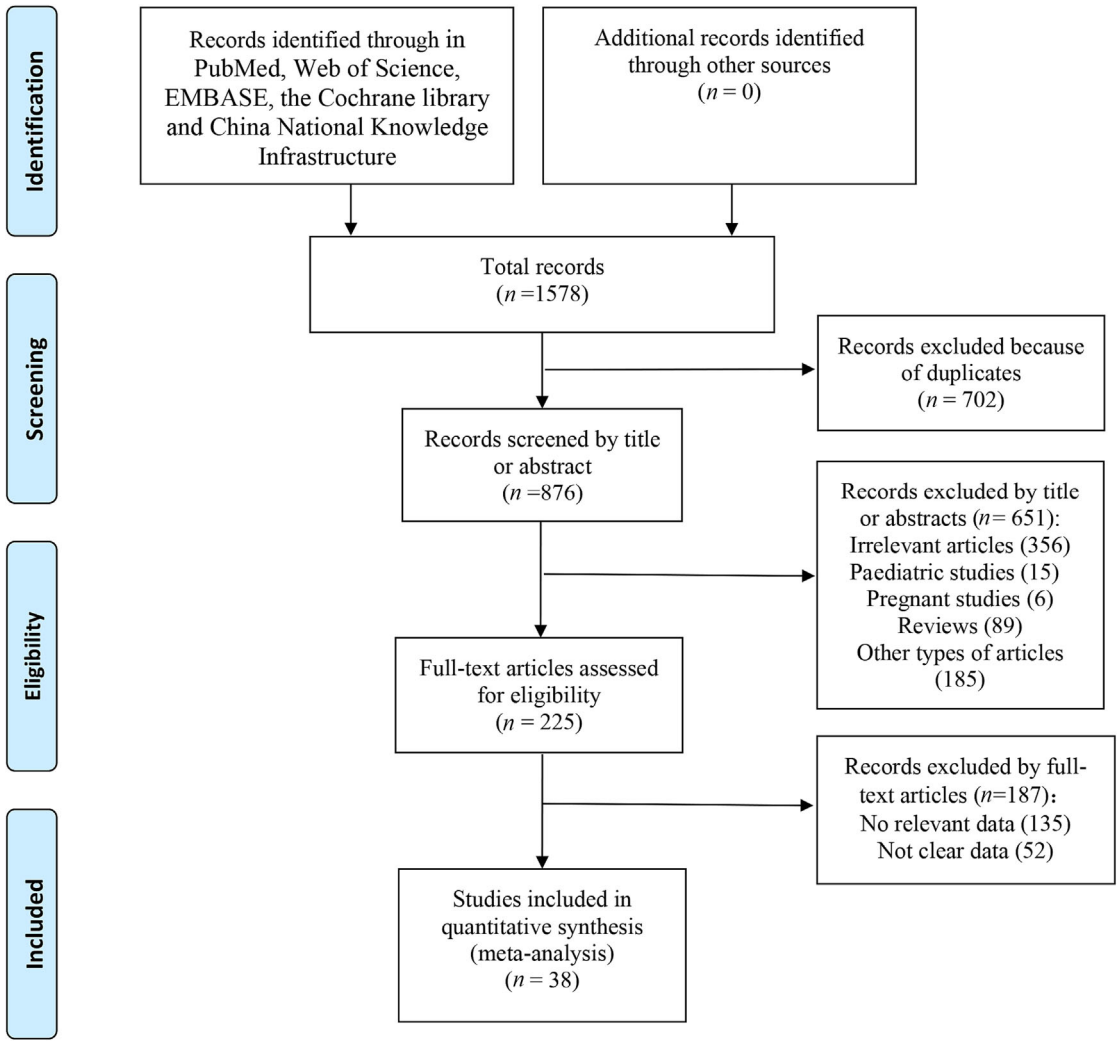
We employed risk ratio (RR) and weighted mean difference (WMD) to compare dichotomous variables and continuous variables, respectively. All results are reported with 95% confidence intervals (CIs). Fixed-effect models were conducted to pool the effect estimates of the outcomes, while random-effect models were used if significant heterogeneity was detected. I^2 was used to estimate heterogeneity, and $I^2 > 50\%$ was considered significant. The possible publication bias of outcome was presented by Egger's test and Begg's test ($P < 0.10$). The sensitivity analyses were conducted by removing one study at a time to observe the effect estimate of the outcomes. We completed all statistical analysis with STATA 12.0 statistical software (STATA Corporation, College Station, Texas, USA).

Results

Selection of included studies and study characteristics

A total of 1578 relevant articles were screened by searching several online databases. The review and selection process of the included trials in the study is presented in *Figure 1*. Finally, 38 studies were identified in the meta-analysis, whose

Figure 1 PRISMA diagram of study selection.



characteristics are summarized in Supporting Information, *Tables S1* and *S2*.[8–10,13–47] Among these studies, 19 were RCTs, 18 were retrospective studies, and the last one was a prospective study. Twenty-four trials focused on the comparison of SGLT2i with GLP1-RA in patients with T2DM, while 14 studies discussed the effect of SGLT2i on cardiovascular outcomes in patients with HF. The results of the quality assessment are estimated in Supporting Information, *Tables S1* and *S3*.

Effects of sodium glucose cotransporter-2 inhibitor and glucagon-like peptide 1 receptor agonist on cardiovascular outcomes in type 2 diabetes mellitus patients

The use of SGLT2i significantly reduced the risk of cardiovascular death compared with GLP1-RA (RR = 0.59; 95% CI, 0.53–0.65). The SGLT2i group also lowered the risk of HHF by 23% (RR = 0.77; 95% CI, 0.74–0.80). As high heterogeneity was detected in these two outcomes, subgroup analyses were undertaken based on sample size. Heterogeneity was significantly decreased in 'small size' subgroups, and results were consistent between different groups (*Figure 2*). Furthermore, SGLT2i significantly reduced the risks of death from any cause (RR = 0.64; 95% CI, 0.60–0.68) and MI (RR = 0.81; 95% CI, 0.76–0.87) (*Figure 2*). A significant difference was observed in the risk of stroke (RR = 1.10; 95% CI, 1.04–1.17) among patients treated with SGLT2i and GLP1-RA (*Figure 3*). The pooled result showed that the effect of SGLT2i and GLP1-RA treatments on HbA1c is similar (WMD = 0.33%; 95% CI, −0.03% to 0.69%). However, SGLT2i brought benefits with respect to the SBP (WMD = −2.0 mmHg; 95% CI, −2.08 to −1.92 mmHg) and DBP (WMD = −2.00 mmHg; 95% CI, −2.07 to −1.93 mmHg) (*Figure 3*). No significant difference was observed in BMI or blood lipids, including HDL-C, LDL-C, and triglycerides, between the SGLT2i and GLP1-RA treatments (Supporting Information, *Figure S1*).

Effects of sodium glucose cotransporter-2 inhibitor on cardiovascular outcomes in patients with heart failure

Compared with the control group, SGLT2i treatment reduced the risk of cardiovascular death by 14% (RR = 0.86; 95% CI, 0.79–0.94) in patients with HF. The use of SGLT2i was closely associated with a lower incidence of HHF (RR = 0.75; 95% CI,

Figure 2 Meta-analysis of cardiovascular effects on (A) cardiovascular death, (B) hospitalization of heart failure (HHF), (C) death from any cause, and (D) myocardial infarction (MI) of sodium glucose cotransporter-2 inhibitor and glucagon-like peptide 1 receptor agonist in type 2 diabetes mellitus patients. CI, confidence interval; RR, risk ratio.

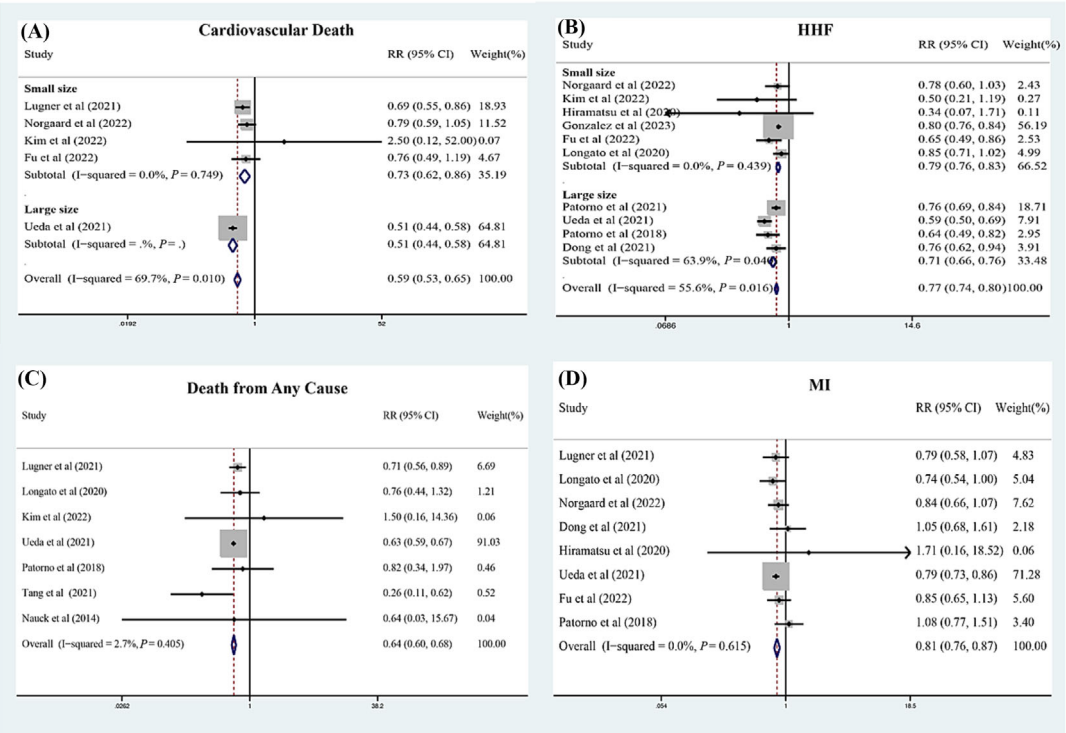
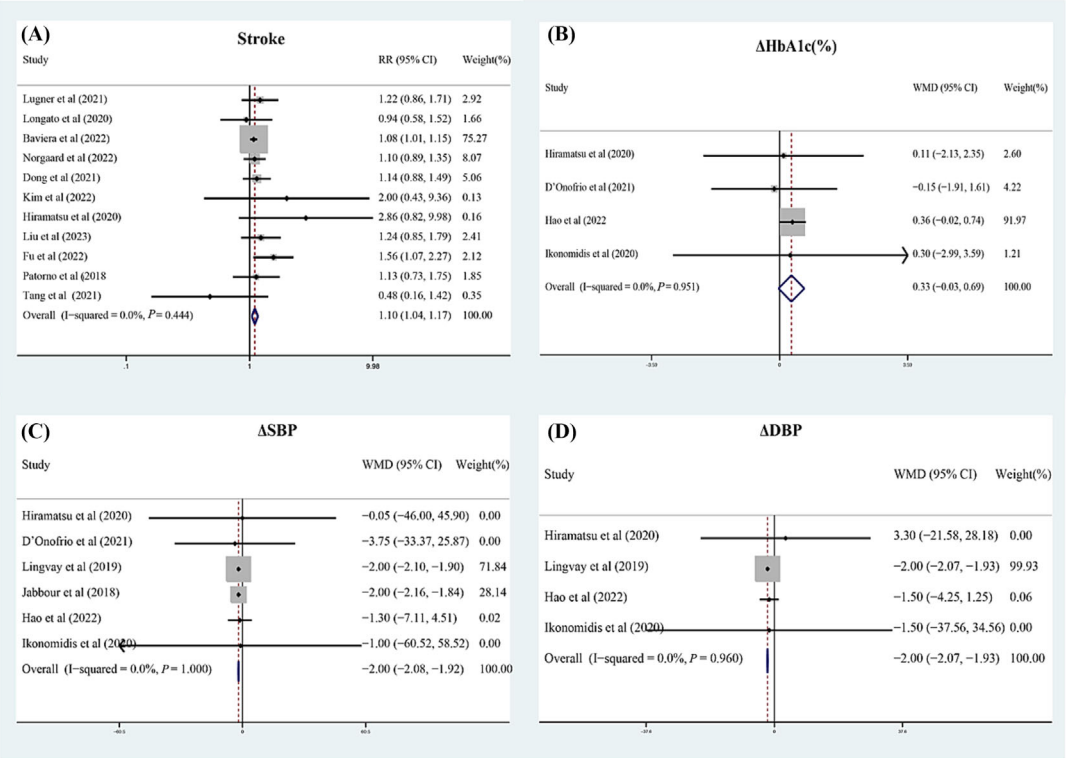


Figure 3 Meta-analysis of cardiovascular effects on (A) stroke, (B) haemoglobin A1c (HbA1c), (C) systolic blood pressure (SBP), and (D) diastolic blood pressure (DBP) of sodium glucose cotransporter-2 inhibitor and glucagon-like peptide 1 receptor agonist in type 2 diabetes mellitus patients. CI, confidence interval; RR, risk ratio; WMD, weighted mean difference.



0.70–0.80). A significantly lower incidence of death from any cause (RR = 0.91; 95% CI, 0.86–0.97) was observed among HF patients treated with SGLT2i (*Figure 4*).

Furthermore, we assessed the cardiovascular effects of SGLT2i in HF patients with or without diabetes. Similar results were found in HF patients with diabetes (*Figure 4*). SGLT2i treatment lowered the risk of cardiovascular death by 14% (RR = 0.86; 95% CI, 0.76–0.97). Patients treated with SGLT2i were more likely to have a low risk of HHF (RR = 0.71; 95% CI, 0.66–0.76). In addition, the use of SGLT2i was closely associated with a lower incidence of death from any cause (RR = 0.78; 95% CI, 0.68–0.91). The effects of SGLT2i on cardiovascular outcomes in HF patients without diabetes are presented in Supporting Information, *Figure S2*.

Publication bias and sensitivity analysis

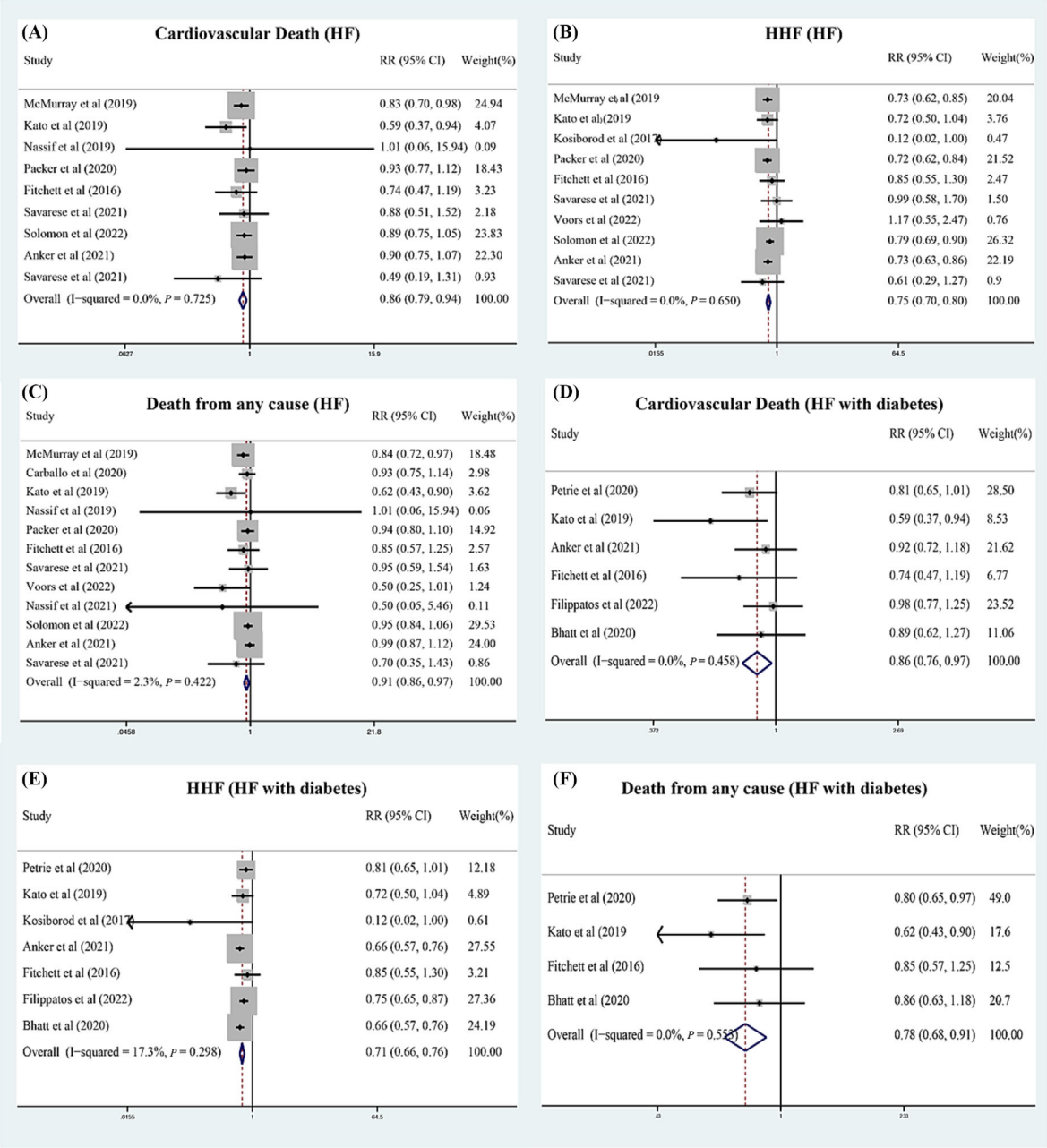
No significant publication bias was noted in the study (Supporting Information, *Table S4*). Sensitivity analysis revealed no meaningful differences in the outcomes except for the pooled results of cardiovascular death in patients with HF and diabetes.

Discussion

In the meta-analysis, data from 38 trials were assessed, and we draw the following conclusions. Compared with GLP1-RA, SGLT2i was more likely to reduce the risk of cardiovascular death, HHF, death from any cause, and MI in patients with T2DM. SGLT2i brought more benefits with respect to the control of SBP and DBP. However, the incidence of stroke was increased in the SGLT2i treatment group. In addition, compared with the control group, SGLT2i treatment reduced the risk of cardiovascular death, HHF, and death from any cause in patients with HF, regardless of glucose level.

SGLT2 works in the proximal renal tubule, reabsorbing the majority of filtered glucose. An enhanced expression of SGLT is noticed in T2DM patients; therefore, SGLT2i enhances glycosuria and reduces hyperglycaemia by inhibiting SGLT2 independently of insulin.[48] Cardiovascular benefits of SGLT2i in patients with T2DM have been demonstrated in large clinical trials comparing SGLT2i with placebo. EMPA-REG displayed that the SGLT2i group had a lower rate of cardiovascular death, HHF, and death from any cause.[3] The CANVAS trial also demonstrated that the rate of cardiovascular causes, HHF, non-fatal MI, and non-fatal stroke, was lower with SGLT2i treatment.[49] However, the DECLARE-TIMI 58 trial

Figure 4 Meta-analysis of cardiovascular effects on (A, D) cardiovascular death, (B, E) hospitalization of heart failure (HHF), and (C, F) death from any cause of sodium glucose cotransporter-2 inhibitor and placebo in heart failure (HF) patients. CI, confidence interval; RR, risk ratio.



posted opposite results.[50] No significant difference in the MACE in the SGLT2i group was observed except for HHF. The consistent evidence led us to hypothesize that SGLT2i may be effective as an HF treatment regardless of T2DM status. The DAPA-HF trail demonstrated that treatment with SGLT2i was associated with a lower risk of cardiovascular death, HHF, and death from any cause.[14] The EMPEROR-Reduced trial proved that SGLT2i markedly reduced the risk of HHF and cardiovascular death. No significant beneficial effects on death from any cause were detected.[13] The DELIVER trial[38] and the EMPEROR-Preserved trial[51] also reached contradictory conclusions due to the HF subtype.

GLP1-RA mimics the function of GLP-1 and binds G-protein receptors expressed on the pancreatic beta cells, suppressing the release of glucagon from the pancreatic beta cells in a glucose-dependent manner.[52] Cardiovascular efficacy of

GLP1-RA has been explored in several large clinical trials among T2DM patients. In the ELIXA trial, GLP1-RA did not significantly alter the rate of MACE of GLP1-RA compared with placebo,[53] and consistent results were observed in the SUSTAIN-6 trial.[54] However, the LEADER trial suggests that GLP1-RA was superior to placebo for reducing the risk of cardiovascular death and all-cause death, with no significant difference in HHF.[55] Similar results were detected in the Harmony Outcomes trial[56] and the REWIND trial.[57] A meta-analysis summarized the comprehensive results of RCTs and the significant reduction of MACE, cardiovascular death, stroke, MI, all-cause death, and HF.[5] Based on previous comprehensive evidence, GLP1-RA was recommended as a first-line treatment in T2DM patients with high-risk or established cardiovascular disease.

Recently, a head-to-head comparison of the effects on cardiovascular outcomes between SGLT2i and GLP1-RA has been addressed. However, contradictory conclusions were observed. It is still unclear whether using one drug over the other yields differences in cardiovascular outcomes, and comprehensive conclusions are necessary. A previous meta-analysis evaluated the effects of SGLT2i and GLP1-RA, but the study just compared the absolute benefits of these drugs with placebo, respectively. SGLT2i brought more benefits with respect to HHF in the study, which was consistent with our study and another meta-analysis.[6,7] Zelniker *et al*.[7] also compared the effects of SGLT2i and GLP1-RA for the prevention of MACE in T2DM patients. Similarly, no direct comparison was performed. Therefore, our meta-analysis firstly and directly compares the effects of SGLT2i and GLP1-RA on cardiovascular outcomes.

According to the pooled results of our meta-analysis, SGLT2i was superior to GLP1-RA for reducing the rate of cardiovascular death, HHF, and MI in patients with T2DM. In addition, compared with the control group, SGLT2i treatment reduced the risk of cardiovascular death, HHF, and death from any cause in patients with HF. All these results suggested the significant cardiovascular benefits of SGLT2i in patients with HF, regardless of T2DM status. Mechanisms explaining the cardiovascular efficacy of SGLT2i are not completely understood but are a topic of intensive investigation. SGLT2i treatment was associated with a reduction in extracellular volume, explaining the reduction in SBP and DBP,[58] which was consistent with our study. SGLT2i activates voltage-gated potassium channels and protein kinase G and induces vasodilatation, resulting in improved endothelial function and arterial stiffness.[59] Improvements in cardiac energy metabolism and bioenergetics are another hypothesis. β-Hydroxybutyrate induced by SGLT2i is an energy-efficient 'superfuel', and it offers an alternative and less expensive myocardial fuel source, resulting in improved cardiac metabolism.[60] SGLT2i also mediates a reduction in plasma uric acid level, which is associated with cardiovascular complications.[61] Another postulated mechanism is decreasing myocardial intracellular sodium concentration by inhibiting the Na^+/H^+ exchanger 1 isoform in the cardiomyocyte, leading to a decrease in intracellular calcium and an increase in mitochondrial calcium.[62] Increased myocardial intracellular sodium is an early hallmark of HF, while increased mitochondrial calcium prevents HF.[63]

Limitations

There are several potential limitations to address. First, there was a difference in the duration of follow-up between trials. Second, most trials comparing the effects of SGLT2i and GLP1-RA are retrospective studies, but the quality of these trials is high. Finally, the effects of other agents cannot be excluded.

Conclusions

SGLT2i is associated with a lower risk of cardiovascular death, HHF, death from any cause, and MI in patients with T2DM compared with GLP1-RA. In addition, SGLT2i brought more benefits with respect to the effects of cardiovascular death, HHF, and death from any cause in patients with HF, regardless of diabetes status. Our findings provide comprehensive evidence for the selection of agents in T2DM patients with cardiovascular risk and summarize the lasted evidence for the cardiovascular effects of SGLT2i in patients with HF.

Acknowledgements

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Conflict of interest

None declared.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Study characteristics of included studies comparing SGLT2i and GLP1-RA in patients with T2DM.

Table S2. Study characteristics of included studies comparing SGLT2i and placebo in HF patients regardless of diabetes status.

Table S3. Quality assessment of included RCTs.

Table S4. Publication bias of cardiovascular outcomes.

Figure S1. Supporting information.

Figure S2. Supporting information.

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