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ORIGINAL RESEARCH

Comparison of Effectiveness Among Different Sodium-Glucose Cotransoporter-2 Inhibitors According to Underlying Conditions: A Network Meta-Analysis of Randomized Controlled Trials

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BACKGROUND: To investigate the individual profile of each SGLT2 (sodium-glucose cotransoporter-2) inhibitor in patients with different backgrounds.

METHODS AND RESULTS: This study included 21 placebo-controlled randomized controlled trials with a total of 96 196 participants, investigating empagliflozin, ertugliflozin, dapagliflozin, canagliflozin, and sotagliflozin. The primary efficacy end point was the composite of cardiovascular death and hospitalizations for heart failure. The secondary efficacy end points were all-cause death, cardiovascular death, hospitalizations for heart failure, kidney disease progression, and acute kidney injury. We conducted subgroup analyses based on the underlying comorbidities, including diabetes and chronic kidney disease. Safety end points were also assessed among SGLT2 inhibitors in the overall cohort. In the overall cohort, there were no significant differences in the primary efficacy outcome among the SGLT2 inhibitors, while empagliflozin (hazard ratio [HR], 0.70 [95% CI, 0.53–0.92]) and dapagliflozin (HR, 0.73 [95% CI, 0.56–0.96]) were associated with lower risk of acute kidney injury than sotagliflozin. The presence or absence of diabetes did not alter the results. In patients with chronic kidney disease, there were no differences in the efficacy outcomes among SGLT2 inhibitors, while in patients without chronic kidney disease, empagliflozin was associated with lower risk of the primary outcome compared with ertugliflozin (HR, 0.77 [95% CI, 0.60–0.98]). For safety outcomes, no significant differences were observed in amputation, urinary tract infection, genital infection, hypoglycemia, and diabetic ketoacidosis.

CONCLUSIONS: The differences in reducing cardiovascular and kidney outcomes as well as safety profiles across SGLT2 inhibitors were not consistently significant, although empagliflozin might be preferred in patients without chronic kidney disease. Further investigations are needed to better understand the mechanism and clinical effectiveness of each SGLT2 inhibitor in certain populations.

Key Words: CKD ■ cardiovascular death or hospitalizations for HF ■ diabetes ■ network meta-analysis ■ SGLT2 inhibitors

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CLINICAL PERSPECTIVE

What Is New?

- This network meta-analysis of 21 randomized controlled trials involving 96 196 patients with different backgrounds showed no consistent evidence that a particular sodium-glucose cotransoporter-2 inhibitor was superior to other agents, while empagliflozin showed comparatively large effects in reducing cardiovascular outcomes in patients without underlying chronic kidney disease.

What Are the Clinical Implications?

- Clinicians may be reassured that there was no evidence that a particular sodium-glucose cotransoporter-2 inhibitor was consistently more efficacious than other agents in reducing cardiovascular or renal events, although empagliflozin might potentially be preferred in patients without chronic kidney disease.

Nonstandard Abbreviations and Acronyms

AKI	acute kidney injury
CANVAS	Canagliflozin Cardiovascular Assessment Study
CREDENCE	Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation
EMPA-REG OUTCOME	BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
SGLT2	sodium-glucose cotransoporter-2
VERTIS CV	Cardiovascular Outcomes Following Ertugliflozin Treatment in Type 2 Diabetes Mellitus Participants With Vascular Disease

SGLT2 (sodium-glucose cotransporter-2) inhibitors were initially introduced as a class of antihyperglycemic medications for patients with diabetes.[1] In addition to their fundamental role as diabetic agents, such as lowering glycated hemoglobin, body weight, and blood pressure, they have demonstrated promising effects in reducing cardiovascular and renal outcomes among patients with diabetes across numerous randomized controlled trials (RCTs).[2–5]

Furthermore, a growing body of evidence shows that SGLT2 inhibitors can reduce cardiovascular and renal events regardless of the presence of diabetes, baseline kidney function, and left ventricular ejection fraction.[6–15] Recent meta-analyses of large RCTs showed the consistent effect of SGLT2 inhibitors in reducing the risks of composite renal outcome, acute kidney injury (AKI), the composite of cardiovascular death and hospitalizations for heart failure (HF), cardiovascular death, all-cause death, and hospitalizations for HF across the included population. These findings supported the use of SGLT2 inhibitors in patients with HF or chronic kidney disease (CKD), irrespective of the diabetic status or the kidney disease causes.[11,16]

Nonetheless, because the existing RCTs compared SGLT2 inhibitors with placebo, the hierarchical assessment of superiority among SGLT2 inhibitors has not yet been ascertained. Limited data from a retrospective cohort study suggested that dapagliflozin, compared with empagliflozin, was associated with lower risk of HF in patients with diabetes.[17] Although a few network meta-analyses reported almost similar efficacy profiles across SGLT2 inhibitors for cardiorenal outcomes in patients with or without diabetes and those with CKD or HF,[18–20] comprehensive assessments according to various patient backgrounds are yet to be determined.

Moreover, it is essential to consider the safety profile of each SGLT2 inhibitor when selecting a specific agent within the class. However, proper selection remains uncertain without the comparative safety evidence. Because adverse events of SGLT2 inhibitors, such as genital infection, urinary tract infection (UTI), and hypovolemia, can lead to treatment discontinuation,[21,22] the comparative safety profiles should be investigated.

To address these important knowledge gaps, in this network meta-analysis, we aimed to pool various populations (ie, with or without diabetes, with or without CKD, and HF phenotype: HF with reduced ejection fraction [HFrEF] or HF with preserved ejection fraction [HFpEF]) from previous RCTs and indirectly compare the efficacy and safety of each SGLT2 inhibitor, with potential important clinical implications in specific agent selection according to diabetes, CKD, or HF phenotypes.

METHODS

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (Table S1)[23] and was registered to the Prospective Register of Systematic Reviews (CRD42023403810). Ethics exemption/institutional review board approval was granted. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Eligibility Criteria

The inclusion criteria were the following: (1) a study published in a peer-reviewed journal; (2) a double-blinded RCT or a subgroup analysis of the RCT comparing an SGLT2 inhibitor with a placebo; (3) the study involved adults (aged ≥18 years); (4) the study duration was at least 3 months; (5) the study investigated outcomes of interest (listed below); (6) sample size ≥500 patients (to minimize the potential risk of distorted estimation due to publication bias and lower methodological quality of small studies).[11,24]

Information Sources and Data Collection Process

MEDLINE, EMBASE, and CENTRAL databases were searched with a medical librarian from database inception to August 31, 2023, to identify all published studies that investigated SGLT2 inhibitors. The search strategy is shown in Tables S2 through S4. Two authors (R.K. and A.W.) independently extracted studies meeting the inclusion criteria and assessed the risk of bias using the Cochrane Collaboration Risk of Bias 2.0 tool.[25] Any discrepancies were resolved through consensus.

Outcomes

The primary efficacy outcome was the composite of cardiovascular death and hospitalizations for HF. The secondary efficacy outcomes were all-cause death, cardiovascular death, hospitalizations for HF, kidney disease progression (defined as a sustained decrease of estimated glomerular filtration rate ≥50% from randomization [definitions in different subgroups are available in Table S5]) and AKI (defined by the specific Medical Dictionary for Regulatory Activities Preferred Term, when possible). The safety outcomes were limb amputation, fractures (definitions available in Table S6), hypoglycemia, diabetic ketoacidosis, orthostatic hypotension, UTI, and genital infections.

Statistical Analysis

We extracted hazard ratios (HRs) and 95% CIs from published articles whenever possible, while risk ratios (RRs) and SEs were estimated on the basis of the number of events and participants in each study when HRs were unavailable.[11,26] The HRs (or risk ratios) were synthesized using the "netmeta" 4.2.1 package (R Foundation for Statistical Computing, Vienna, Austria) with a random-effects model.[27,28] We assessed the heterogeneity between studies in each outcome using Q-statistics, τ, and I^2.[29] Q-statistics showed whether the observed heterogeneity was statistically significant, while I^2 was interpreted as follows: 0% to 40%, might not be important; 30% to 60%, may represent moderate heterogeneity; 50% to 90%, may represent substantial heterogeneity; 75% to 100%, considerable heterogeneity.[30] Publication bias was evaluated with funnel plots and Egger's test.[31]

We further performed subgroup analyses for the efficacy outcomes according to the presence and absence of diabetes, CKD (defined as estimated glomerular filtration rate <60 mL/min per 1.73 m^2), and HF phenotype (HFrEF or HFpEF) to examine the different effects of SGLT2 inhibitors in specific populations. We conducted sensitivity analyses. First, to ensure the robustness of the benefit of empagliflozin, we excluded the EMPA-REG OUTCOME (BI 10773 [Empagliflozin] Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) trial because it reported larger effect sizes of empagliflozin in the composite of cardiovascular death and hospitalizations for HF, cardiovascular death, and all-cause death, than other trials. Second, we excluded the VERTIS CV (Cardiovascular Outcomes Following Ertugliflozin Treatment in Type 2 Diabetes Mellitus Participants With Vascular Disease) trial because it was the only trial investigating ertugliflozin, which could lead to unstable effect estimations.[32]

RESULTS

We identified 2124 reports through the initial database search and retrieved 86 full-text articles after removing 34 items on the basis of the title and abstract. We excluded studies investigating <500 patients, non–placebo controlled, with <3 months of follow-up, or outcome of interest unavailable. Finally, 21 RCTs were included in the analysis (Figure S1).

Baseline characteristics are summarized in Table S7, and outcomes in each study are summarized in Tables S8 and S9. We identified 8 trials investigating dapagliflozin, 6 trials for empagliflozin, 3 trials for canagliflozin, 3 trials for sotagliflozin, and 1 trial for ertugliflozin (Figure 1). Overall, 51 964 participants were randomly assigned to SGLT2 inhibitors, and 44 232 were randomly assigned to placebo. The median follow-up periods ranged from 3 months to 4.2 years. Overall, the risks of bias in almost all the included studies were rated as low (Figure S2). Publication bias was

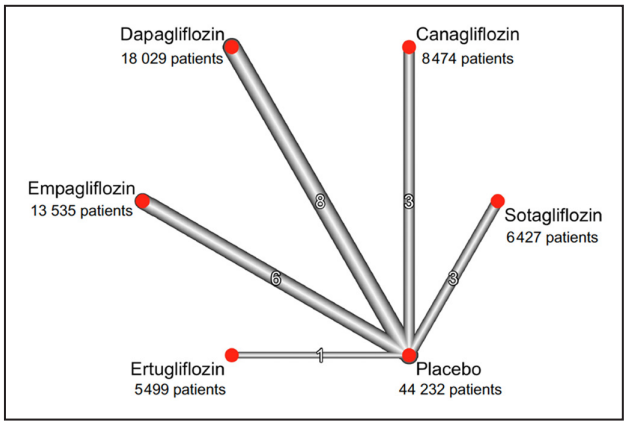

Figure 1. Network diagram of the included trials.
Line widths are proportional to the number of trials comparing the corresponding pair of treatments.

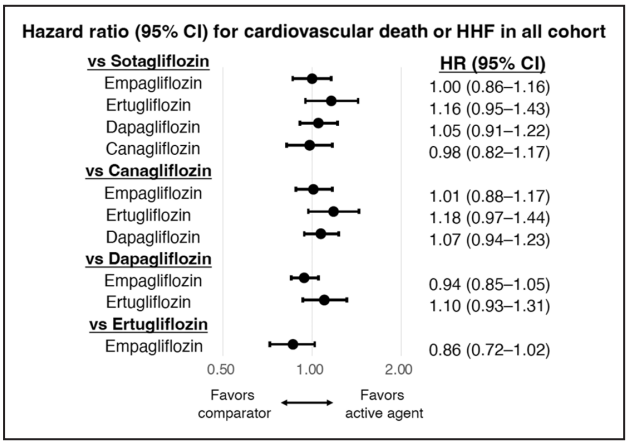

Figure 2. Forest plots for the composite of cardiovascular death or HHF in all cohorts.
Q-statistics, 8.12 (P=0.52); τ, 0; I^2, 0%. HHF indicates hospitalizations for heart failure; and HR, hazard ratio.

not suggested for the studied outcomes (Figures S3 and S4).

Overall Cohort

Significant differences between the 5 SGLT2 inhibitors were not observed for the composite of cardiovascular death and hospitalizations for HF (Figure 2, Table S10), all-cause death (Table S10), cardiovascular death (Table S11), hospitalizations for HF (Table S11), and kidney disease progression (Table S12). However, empagliflozin (HR, 0.70 [95% CI, 0.53–0.92]) and dapagliflozin (HR, 0.73 [95% CI, 0.56–0.96]) were associated with lower risks of AKI compared with sotagliflozin (Table S12).

Subgroups According to Underlying Diabetes

In patients with diabetes (Figure 3; Tables S13 through S15), while significant differences were not observed for the primary outcome, all-cause death, cardiovascular death, hospitalizations for HF, and kidney disease progression, empagliflozin (HR, 0.75 [95% CI, 0.55–1.00]) and dapagliflozin (HR, 0.75 [95% CI, 0.57–1.00]) were associated with lower risks of AKI compared with sotagliflozin.

In patients without diabetes (Figure 3; Tables S16 through S18), there were no differences between the SGLT2 inhibitors in each outcome tested, although empagliflozin and dapagliflozin were the only agents for those patients without diabetes among included studies.

Subgroups According to Underlying CKD

In patients with CKD (Figure 4; Tables S19 through S21), there were no differences between the SGLT2 inhibitors in the risks of the studied efficacy outcomes.

In patients without CKD (Figure 4; Tables S22 through S24), empagliflozin was associated with a lower risk of the primary outcome compared with ertugliflozin (HR, 0.77 [95% CI, 0.60–0.98]), lower risk of all-cause death compared with dapagliflozin (HR, 0.72 [95% CI, 0.52–0.99]), and lower risk of cardiovascular

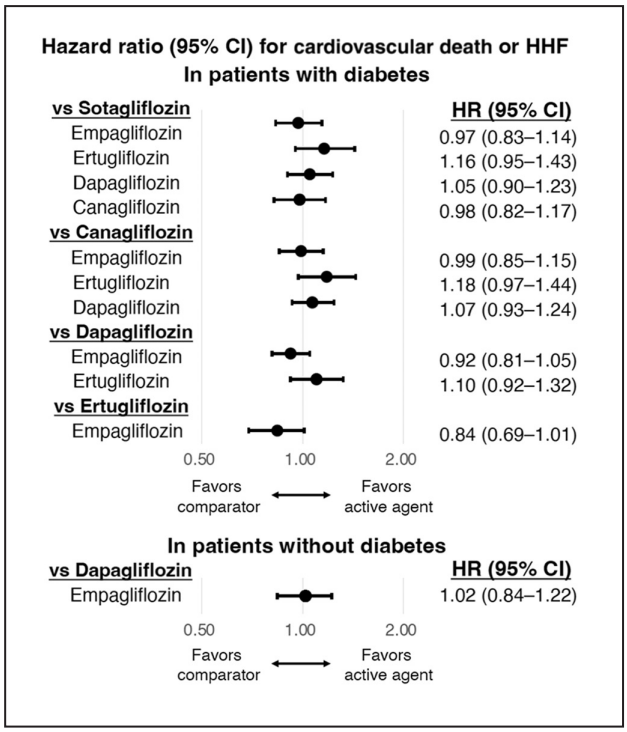

Figure 3. Forest plots for the composite of cardiovascular death or HHF in patients with/without diabetes.
For patients with diabetes: Q-statistics, 6.69 (P=0.57); τ, 0; I^2, 0%. For patients without diabetes: Q-statistics, 2.27 (P=0.69); τ, 0; I^2, 0%. HHF indicates hospitalizations for heart failure; and HR, hazard ratio.

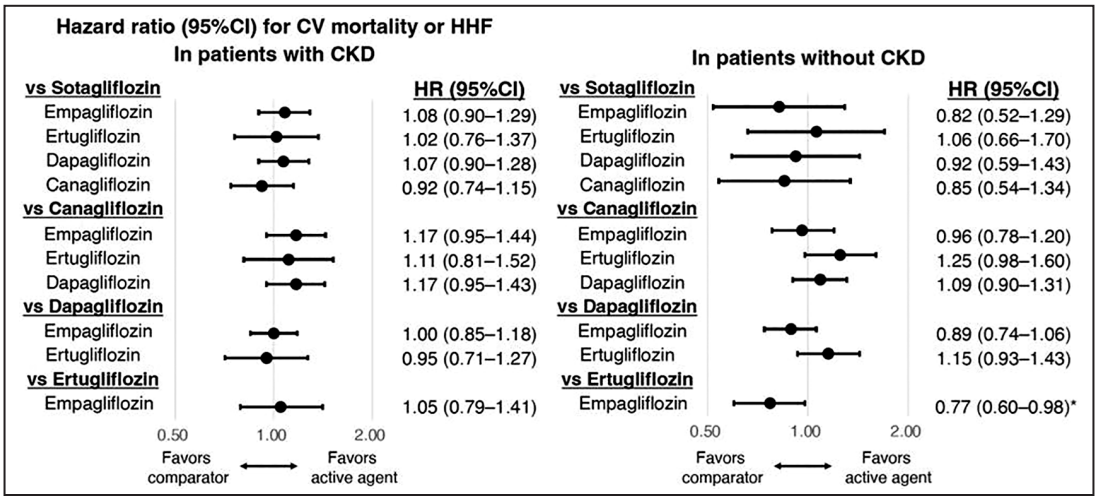

Figure 4. Forest plots for the composite of cardiovascular death or HHF in patients with/without CKD.
*Denotes the statistical significance. For patients with CKD: Q-statistics, 4.08 (P=0.54); τ, 0; I^2, 0%. For patients without CKD: Q-statistics, 4.14 (P=0.39); τ, 0.02; I^2, 3.4%. HHF indicates hospitalizations for heart failure; and HR, hazard ratio.

death compared with dapagliflozin (HR, 0.59 [95% CI, 0.39–0.89]) and canagliflozin (HR, 0.62 [95% CI, 0.40–0.96]).

Subgroups According to HF Phenotype

There were no differences between the SGLT2 inhibitors in the risk of the studied efficacy outcomes in patients with HFrEF or HFpEF (Tables S25 through S30).

Sensitivity Analysis

According to the analysis excluding the EMPA-REG OUTCOME trial, a similar pattern was observed for all the cardiovascular outcomes studied in the overall cohort and patients with diabetes (Tables S31). In patients with CKD, however, canagliflozin was associated with lower risk of hospitalizations for HF compared with empagliflozin (HR, 0.71 [95% CI, 0.54–0.95]). In patients without CKD, ertugliflozin was associated with higher risk of cardiovascular death or hospitalizations for heart failure than empagliflozin (HR, 1.30 [95% CI, 1.02–1.66]), and dapagliflozin was associated with higher risk of hospitalization for HF than empagliflozin (HR, 1.31 [95% CI, 1.01–1.70]). The analysis excluding the VERTIS-CV trial showed a similar result as the principal analyses (Tables S32).

Safety Outcomes

No significant differences between the SGLT2 inhibitors were observed in the risk of limb amputation, fractures, hypoglycemia, diabetic ketoacidosis, UTI, and genital infections (Figures S5 through S10), whereas ertugliflozin and empagliflozin were associated with higher risks of orthostatic hypotension than canagliflozin (Figure S11). Empagliflozin was also associated with a higher risk of orthostatic hypotension than dapagliflozin.

DISCUSSION

In this network meta-analysis of 21 RCTs, we found that all SGLT2 inhibitors have generally equivalent efficacy profiles for cardiovascular and kidney outcomes, as well as safety profiles, although patients without CKD may benefit from empagliflozin. Taken together, our findings may guide clinicians in selecting an optimal agent on the basis of each patient's individual background.

Comparison of Efficacy Among SGLT2 Inhibitors for the Overall Population

The cardio- and renoprotective effects of SGLT2 inhibitors have been established as a class effect,[11] and their clinical benefits in patients with diabetes in comparison with other glucose-lowering agents, such as dipeptidyl peptidase-4 inhibitors and glucagon-like peptide-1 receptor agonists, have been investigated.[33] In our study, we observed no differences between the 5 SGLT2 inhibitors in the risk of the primary outcome, all-cause death, cardiovascular death, hospitalizations for HF, and kidney disease progression in the overall cohort.

Regarding AKI, empagliflozin and dapagliflozin were associated with lower risk than sotagliflozin in the overall population. While SGLT2 inhibitors

can hypothetically lead to AKI due to hypovolemia, excessive decrease in intraglomerular pressure, and renal medullary hypoxia,[34,35] studies reported that SGLT2 inhibitors could actually be associated with lower risks of AKI compared with placebo, dipeptidyl peptidase-4 inhibitors, and glucagon-like peptide-1 receptor agonists,[36,37] although the mechanism remains unclear. A possible explanation for the reno-protective effect of SGLT2 inhibitors is the reduction in kidney oxygen consumption.[38] Another potential explanation includes the attenuations in intraglomerular pressure and kidney inflammatory reactions.[39–41] While SGLT2 is mainly expressed in the kidney, SGLT1 is expressed in the brush border of the small intestine, late renal proximal tubule, heart, and brain.[42] SGLT1 inhibition blocks glucose absorption at the brush border of the small intestinal epithelium,[42] which may contribute to diarrhea and possibly lead to AKI. Indeed, sotagliflozin was associated with higher incidences of diarrhea compared with placebo in previous trials,[43–45] whereas increased incidence of diarrhea was not reported in trials of other SGLT2 inhibitors. Such increased risk of AKI in sotagliflozin may dilute the preventive effect of SGLT2 blockade, compared with more SGLT2-selective agents.

Comparison of Efficacy Among SGLT2 Inhibitors for Patients With/Without Diabetes

While several studies have indicated the superior efficacy on cardiovascular death and all-cause death of empagliflozin over dapagliflozin and canagliflozin in patients with diabetes,[46,47] previous network meta-analysis reported no significant differences in efficacy profiles across SGLT2 inhibitors in patients with diabetes.[18] Our updated meta-analysis with large trials also did not show the significant benefits of an agent over the others, except for empagliflozin and dapagliflozin versus sotagliflozin for AKI, as mentioned above. As for patients without diabetes, despite the growing evidence of the benefits of SGLT2 inhibitors,[16] interclass comparisons among SGLT2 inhibitors were lacking. Our network meta-analysis included patients without diabetes and showed that empagliflozin and dapagliflozin had equivalent efficacy in reducing cardiovascular and kidney events in this population as well. While there were no significant differences in the studied outcomes between empagliflozin and dapagliflozin, dapagliflozin showed consistently lower HRs than empagliflozin in patients without diabetes. Because other SGLT2 inhibitors have not been evaluated in patients without diabetes, future investigations on this population are warranted.

Comparison of Efficacy Among SGLT2 Inhibitors for Patients With/Without CKD

Although SGLT2 inhibitors were shown to have efficacy on cardiovascular and renal outcomes in patients with and without CKD,[48] there is limited evidence investigating the efficacy of each SGLT2 inhibitor on the basis of a patient's kidney function. One network meta-analysis investigating patients with CKD revealed no significant difference in the composite of cardiorenal outcomes among dapagliflozin, sotagliflozin, and canagliflozin.[19] While our study also showed no significant differences in efficacy among empagliflozin, ertugliflozin, dapagliflozin, sotagliflozin, and canagliflozin in patients with CKD, empagliflozin was associated with a lower risk of cardiovascular outcomes when compared with dapagliflozin, canagliflozin, and ertugliflozin, in patients without CKD. The sensitivity analyses also showed the superiority of empagliflozin over ertugliflozin in the primary outcome. However, because the EMPA-REG OUTCOME trial was the only trial reporting cardiovascular death and all-cause death in patients without CKD, we were unable to confirm the superiority of empagliflozin for cardiovascular death and all-cause death in patients without CKD. The possible explanation for the favorable efficacy of empagliflozin in patients without CKD compared with patients with CKD is the high selectivity for SGLT2.[49] Because the effect of SGLT2 inhibition can be attenuated by impaired kidney function,[39] its consistently lowest HRs for cardiovascular outcomes in patients without CKD is reasonable. However, further studies are needed to confirm this hypothesis.

Comparison of Efficacy Among SGLT2 Inhibitors for Patients With HFrEF/HFpEF

A previous meta-analysis showed that SGLT2 inhibitors reduced the risk of cardiovascular death and hospitalization for HF irrespective of HF phenotype.[50] In our study, dapagliflozin showed the lowest point estimate for the primary outcome, all-cause or cardiovascular death, and kidney disease progression in patients with HFrEF (though not statistically significant), while there was no such pattern in patients with HFpEF. These findings were somewhat inconsistent with the previous meta-analyses that reported reduced HF events in patients with a history of HF who received sotagliflozin, compared with those who received dapagliflozin, empagliflozin, or ertugliflozin.[20,51] This discordance probably resulted from the differences in the included studies. We only included large trials involving >500 patients to stablize estimation of the effects of each agent while also including substudies of previously published trials that focused on HF status. In contrast, the previous

meta-analysis included relatively small trials[51] or did not include relatively new trials and substudies of previously published trials.[20] Nevertheless, our findings corroborated another study that suggested the potential higher efficacy of dapagliflozin compared with sotagliflozin, empagliflozin, canagliflozin, and ertugliflozin in patients with HF.[18] Because data on HF phenotype for the outcome of interest were not comprehensively available, especially for the trials of sotagliflozin and canagliflozin, the interpretation of our study results is limited. Given that SGLT2 inhibitors have been considered an essential element in the treatment of patients with HFrEF and HFpEF, future studies focusing on HF phenotype will provide additional insights.

Safety Comparisons Among SGLT2 Inhibitors

Previous studies suggested that SGLT2 inhibitors are associated with a range of adverse events,[11,52] which can negatively affect the quality of life of SGLT2 inhibitor users and can lead to treatment discontinuation.[21,22] Our findings were consistent with a previous study that showed that genital infection was a common adverse event associated with the use of SGLT2 inhibitors.[16] However, among the studied SGLT2 inhibitors, sotagliflozin was associated with the lowest point estimate of genital infections, which was also in line with another meta-analysis.[53] In the presentstudy, whereas a similar pattern was seen, it did not reach statistical significance.[42]

It has been controversial whether SGLT2 inhibitors increase the risk of limb amputation. The CANVAS (Canagliflozin Cardiovascular Assessment Study) program, including 2 large RCTs investigating canagliflozin in 2017, reported that canagliflozin might increase the risk of amputation compared with placebo.[3] In contrast, the CREDENCE (Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation) trial in 2019 reported no increases in amputations among patients receiving canagliflozin compared with placebo, which was consistent with other clinical trials of another SGLT2 inhibitor.[54] Observational studies also reported no significant increases in amputations with the use of canagliflozin.[55,56] In 2020, the US Food and Drug Administration removed the boxed warning about the risk of amputation for canagliflozin based on its benefits on cardiovascular and renal diseases and lower incidences of amputations than previously described. In our study, despite the highest point estimate of canagliflozin, there were no significant differences in effect size between the SGLT2 inhibitors, which means that the current study cannot recommend one agent over another in terms of the risk of limb amputation.

Limitations

This study has several limitations. First, our study was a trial-level meta-analysis without individual-level data. Therefore, more detailed analysis based on concurrent comorbidities other than those investigated in this study (eg, body mass index, baseline glycated hemoglobin level, concomitant use of other glucose-lowering agents, phenotypes of HF, and kidney disease causes) could not be performed, although some studies showed that neither baseline glycated hemoglobin level nor kidney disease affects the overall efficacy of SGLT2 inhibitors.[11,57] Second, we included only placebo-controlled trials because there were no head-to-head RCTs directly comparing SGLT2 inhibitors, meaning that all the effect estimates in our study were solely based on the magnitude observed in each RCT in comparison with placebo. In addition, our study did not take into account the other glucose-lowering agents, such as glucagon-like peptide-1 receptor agonists or dipeptidyl peptidase-4 inhibitors, because the aim of our study was to explore the efficacy and safety profiles of different SGLT2 inhibitors in various populations, including those without diabetes. Therefore, our analysis could not assess the between-design inconsistency, as the built network was only connected through placebo, which can possibly undermine the robustness of direct and indirect comparisons.[58] Nevertheless, to the best of our knowledge, this is the first report that pooled and compared the effect of each SGLT2 inhibitor in different populations. Third, although we have combined the same agent into 1 group, the dose of each agent was different according to the patient. Fourth, CIs in several results were exceptionally wide (eg, comparisons between ertugliflozin and canagliflozin or empagliflozin and canagliflozin for orthostatic hypotension). These results should be interpreted with caution because the effect estimates were presumably sensitive to individual events due to the small number of outcomes, potentially causing the unstable estimation and wide CIs. Given these uncertainties in the estimation, it is essential for providers to judge the relevance and significance of the comparisons in each outcome depending on the clinical context. Fifth, due to the nature of network meta-analysis, multiple comparisons have been done, which might have caused type I errors.[59] Additionally, although we demonstrated the efficacy of SGLT2 inhibitors in patients without diabetes, these data were not available across the SGLT2 inhibitors. Because the approved doses of SGLT2 inhibitors for specific indications (eg, HF or glycemic control for patients with diabetes) vary, and the benefit of empagliflozin and dapagliflozin seemed promising regardless of diabetic status, the effects of different doses and other agents in patients without diabetes should be investigated.

CONCLUSIONS

In this systematic review and network meta-analysis of large RCTs, the differences in reducing cardiovascular and kidney outcomes, as well as safety profiles, across SGLT2 inhibitors were not consistently significant, although empagliflozin might benefit patients without CKD. Our findings may assist clinicians in tailoring the optimal SGLT2 inhibitors to each patient's individual clinical scenario; however, further well-designed studies are warranted to clarify these findings.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S32
Figures S1–S11
References 4, 60–67

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