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Effect of SGLT-2 inhibitors on acute kidney injury in patients with heart failure: a systematic review and meta-analysis

Xianghong Wang^{1†}, Meihong He^{2†}, Donghua Jin³, Chuanchuan Sun⁴ and Hongyun Lu^{1*}

Abstract

Background Sodium glucose cotransporter-2 (SGLT-2) inhibitors are known to reduce hospitalization and cardiovascular mortality in various heart failure (HF) populations, potentially through enhanced excretion of water and sodium. However, there are concerns regarding the risk of acute kidney injury (AKI) associated with their use. This meta-analysis aimed to unravel the effects of SGLT-2 inhibitors on risk of AKI in a variety of patients with HF.

Methods This study conducted a comprehensive literature search using PubMed, EMBASE, Cochrane Library, and clinicaltrials.gov for studies published up to January 1, 2024. Data were analyzed using both random-effects or fixed-effects models to estimate the overall relative risk (RR) with a 95% confidence interval (CI).

Results Our analysis included 25,172 patients with HF from 16 randomized controlled trials. Treatment with SGLT-2 inhibitors led to a 28% reduction in the risk of AKI progression compared to placebo (RR 0.72, 95% CI 0.61–0.85, $p < 0.0001$), without an increased risk of hypotension (RR 1.21, 95% CI 0.87–1.70, $p = 0.26$) and hypovolemia (RR 2.26, 95% CI: 0.70–7.33, $p = 0.17$). Notably, SGLT-2 inhibitors significantly decreased AKI in specific subgroups, including patients with HF with reduced ejection fraction (RR 0.59, 95% CI 0.43–0.80, $p = 0.0007$), those treated with empagliflozin (RR 0.70, 95% CI 0.57–0.88, $p = 0.002$) or dapagliflozin (RR 0.74, 95% CI 0.57–0.98, $p = 0.04$), in studies with a follow-up of at least 1 year (RR 0.67, 95% CI 0.55–0.82, $p = 0.0001$), and in patients aged 65 years or older (RR 0.72, 95% CI 0.61–0.85, $p < 0.0001$).

Conclusion Use of SGLT-2 inhibitors did not increase the incidence of AKI regardless of the ejection fraction environment (chronic and acute), type of SGLT-2 inhibitors, or patient age.

Keywords SGLT-2 inhibitors, Heart failure, Acute kidney injury, Hypotension, Hypovolemia, Meta-analysis

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Introduction

Despite significant advances in the treatment of heart failure (HF), its incidence and mortality rates remain high [1]. Sodium-glucose cotransporter 2 (SGLT-2) inhibitors have been demonstrated to reduce both hospitalization rates [2] and cardiovascular mortality [3] in patients with HF with reduced ejection fraction (HFrEF), irrespective of their type 2 diabetes mellitus (T2DM) status. Recent studies have also explored the efficacy of SGLT-2 inhibitors in patients with HF with preserved ejection fraction (HFpEF) [4, 5] and acute HF (AHF) [6, 7] demonstrating a reduction in hospitalization rates in these patients.

SGLT-2 inhibitors were originally developed as anti-diabetic agents in patients with T2DM, and they act by inhibiting the reabsorption of sodium and glucose in the proximal tubules of the kidney. In recent years, the cardioprotective effect of SGLT-2 inhibitors has been increasingly recognized: consistent cardiovascular benefits have been observed in studies on HFrEF treatment, suggesting that its therapeutic mechanism of action is not related to hypoglycemic effects, but may be related to water and sodium excretion [8]. However, the same mechanism raises concerns about potentially lowering blood pressure and renal perfusion, which could lead to acute kidney injury (AKI) [9]. Recent large-scale randomized controlled trials (RCTs) have assessed the incidence of AKI in patients with HF treated with SGLT-2 inhibitors [10–12]. However, uncertainties persist concerning the renal safety of these drugs, particularly across different SGLT-2 inhibitors, varied ejection fractions, and older patient populations.

This systematic review and meta-analysis assesses the relative risk of AKI in patients with HF treated with SGLT-2 inhibitors in RCTs. Additionally, factors such as hypotension and hypovolemia were taken into account to determine whether the risk associated with SGLT-2 inhibitors was consistent across various SGLT-2 inhibitors drugs, different ejection fraction groups, and age. The outcome of this analysis will assist clinicians in deciding whether to prescribe SGLT-2 inhibitors for patients with HF, thereby addressing a significant clinical concern.

Methods

The methodologies employed in this study rigorously comply with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [13]. This systematic review protocol is registered in the PROSPERO database under registration number CRD42024508011.

Data sources and search strategy

The search encompassed four principal medical databases—PubMed, Embase, Cochrane Library, and

ClinicalTrials.gov—spanning records from their inception through January 1, 2024. This study imposed no limitations on the date or language of publication. The specific search strings utilized are detailed in Additional file 1: Table S1–S4. Additionally, the reference lists of included studies and related meta-analysis were examined to uncover additional qualifying studies. Duplicate articles were excluded using EndNoteX9.2 software. Two researchers, XHW and MHH, independently screened the titles and abstracts using pre-established inclusion and exclusion criteria to pinpoint pertinent studies, followed by a full-text examination to establish relevance. Any differences in opinion were resolved by consulting a third researcher, CCS, to achieve consensus.

Outcomes

The primary endpoint was defined as the incidence rate of AKI. Secondary endpoints included the incidence rates of hypotension and hypovolemia. In existing literature, these conditions are categorized as serious adverse events. These rates were collated from the ClinicalTrials.gov registry and published studies.

Study selection

Inclusion criteria for the studies *in our analysis* were as follows: (1) RCTs; (2) participants diagnosed with HF, irrespective of ejection fraction (EF) or whether the condition was chronic or acute; (3) interventions involving SGLT-2 inhibitors and a placebo; (4) outcomes that included the incidence rates of AKI, hypotension, or hypovolemia. *The exclusion criteria* were (1) duplicate publications, conference abstracts, case reports, review articles, and animal studies; (2) other drug interventions besides SGLT-2 inhibitors; (3) RCTs with incomplete or unreported results.

Data extraction and quality assessment

Two researchers, XHW and MHH, performed the data extraction. They sourced the study data from the published manuscripts or the results listed on ClinicalTrials.gov. The extracted data included the following: (1) the RCT name, authors, ClinicalTrials.gov unique identifier, year of publication, and sample size; (2) participant baseline characteristics such as age and gender; (3) baseline health conditions and comorbidities, including the incidence of T2DM and prediabetes, average left ventricular ejection fraction, and the use of medications for HF; (4) details of the treatment including the regimen, dosage, and duration; (5) the duration of follow-up; (6) the primary outcomes measured; (7) reported serious adverse events, specifically the number of participants who experienced AKI, hypotension, and hypovolemia from the start to the conclusion of the study.

The Cochrane Collaboration's risk of bias tool was employed to evaluate the methodological quality of the included studies [14]. Two researchers independently assessed the risk of bias at the levels of study, intervention, and outcome for each included study. Additionally, the GRADE method was utilized to determine the evidence quality of the summary results [15]. The domains assessed encompass bias risk, inconsistency, indirectness, imprecision, and risk of publication bias. The evidence quality was categorized into four grades: high, moderate, low, and very low. Any disagreement was resolved by consensus among the authors or by consulting a third author, CCS.

Statistical analyses

Data analysis was conducted using RevMan 5.3 (The Cochrane Collaboration, Oxford, England) and Stata 12.0 (StataCorp, Texas, USA) software. The results were presented as relative risk (RR) and 95% confidence intervals (CI), with the placebo serving as the reference for assessing the association between SGLT-2 inhibitors and clinical outcome measures. The significance of the overall results and RRs was determined using the Mantel-Haenszel method and the Z-test. Heterogeneity was assessed using the I^2 statistic, considering an I^2 value over 50% or a corresponding p-value less than 0.05 to indicate significant heterogeneity among studies, prompting the

utilization of a random-effects model for meta-analysis. Conversely, when $I^2 \leq 50\%$, $p \geq 0.05$, a fixed-effects model was employed. Funnel plots and Egger's test were used to assess potential publication bias. To further assess the robustness of results, subgroup analyses exploring the influence of variables such as the type of SGLT-2 inhibitors, HF classification, follow-up duration, and patient age were conducted. Furthermore, sensitivity analyses were conducted to assess the influence of individual studies on the aggregate effect size. Given that all randomized controlled trials incorporated in the analysis administered an identical dosage of SGLT-2 inhibitors, additional dose-related subgroup analyses were deemed unnecessary. A p-value of <0.05 was considered statistically significant.

Results

Search results and baseline characteristics

The process of literature retrieval is illustrated in Fig. 1. A total of 1782 articles or studies were identified as potentially relevant publications. After screening and excluding duplicated studies, 993 articles remained. These articles were screened based on the inclusion and exclusion criteria. Ultimately, 16 RCTs were included in our analysis [2, 3, 5, 7, 9, 16–25]. The total number of patients was 25,172, with 12,581 patients receiving SGLT-2 inhibitors and 12,591 patients receiving placebo. The follow-up

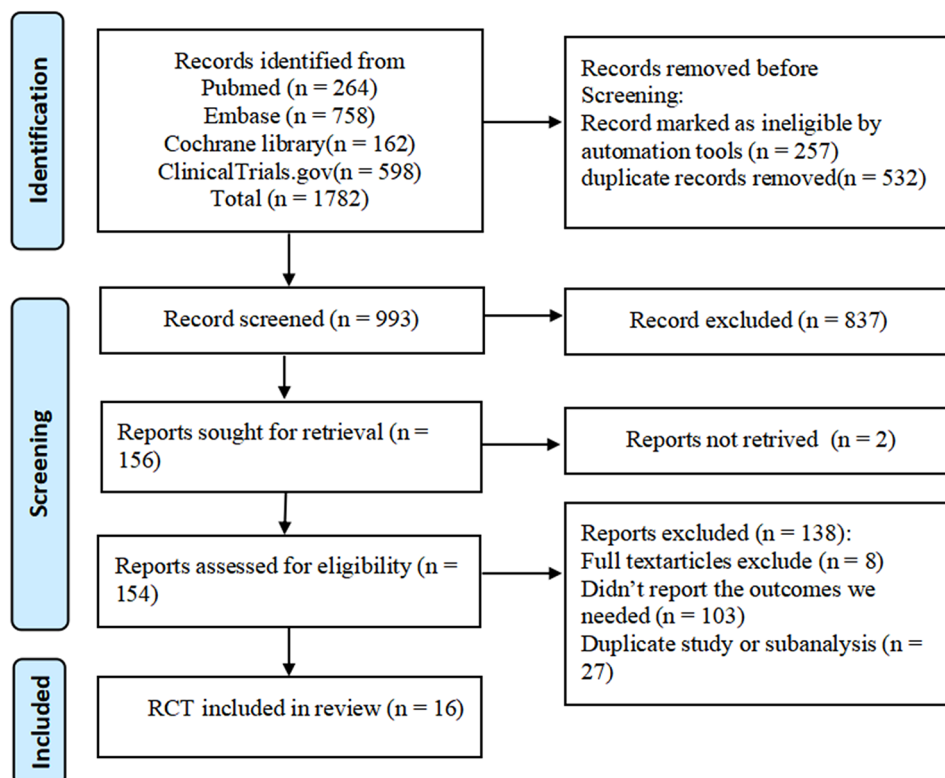


Fig. 1 Flow diagram of study selection process

period ranged from 60 to 1410 days, and the publication years ranged from 2020 to 2023. All studies compared the use of SGLT-2 inhibitors with placebo, eight trials used empagliflozin [2, 5, 9, 19, 20, 22, 23, 25], six used dapagliflozin [3, 16–18, 21], one used canagliflozin [24], and one used sotagliflozin [7]. Six trials included patients with HFrEF ($EF \leq 40\%$) [2, 3, 9, 18, 20], five trials included patients with HFpEF ($EF \geq 40\%$ or 45%) [5, 16, 17, 19, 21], three trials included patients with AHF [7, 22, 23], and two trials included patients with any type of HF, irrespective of baseline ejection fraction [24, 25]. Most studies required patients to receive standard HF treatment. The key clinical characteristics of the included studies are presented in Table 1 and Additional file 1: Table S5.

Risk of bias assessment

The risk of bias assessment for all included trials is summarized in Additional file: Figure S1. The majority of RCTs demonstrated adequate random sequence generation and allocation concealment, indicating a generally low risk of bias.

Primary outcome

The impact of SGLT-2 inhibitors on AKI in patients with HF

A meta-analysis of these 16 RCTs was conducted to assess the incidence of AKI in patients with HF. Among the 12,581 patients treated with SGLT-2 inhibitors, 228 AKI events were observed. However, in the placebo group consisting of 12,591 participants, 319 AKI events were observed. The meta-analysis demonstrates that SGLT-2 inhibitors significantly reduce the risk of AKI in patients with HF compared to placebo (RR 0.72, 95% CI 0.61–0.85, $p < 0.0001$) as shown in Fig. 2. Additionally, no significant heterogeneity was observed among the trials ($p = 0.83$; $I^2 = 0\%$). The funnel plot showed no notable asymmetry (Fig. 3), the Egger's test did not indicate significant publication bias ($p = 0.85$). Furthermore, sensitivity analysis conducted by sequentially excluding each study, showed that individual studies did not change the overall outcome, thus confirming the robustness of the results (Additional file 1: Figure S2).

Subgroup analyses

Subgroup analyses were performed based on different types of HF, categorized mainly into HFrEF, HFpEF, AHF, and overall HF. Among patients with HFrEF, those treated with SGLT-2 inhibitors exhibited a significantly reduced risk of AKI (RR 0.59, 95% CI 0.43–0.80, $p = 0.0007$, $I^2 = 0\%$). However, RCTs for patients with HFpEF (RR 0.82, 95% CI 0.66–1.02, $p = 0.07$, $I^2 = 0\%$), AHF (RR 0.64, 95% CI 0.38–1.08, $p = 0.09$, $I^2 = 0\%$), and overall HF (RR 0.43, 95% CI 0.06–2.82, $p = 0.38$, $I^2 = 0\%$) did not show increased risk of AKI with the use of SGLT-2 inhibitors as shown in Fig. 4A and Table S7.

Subgroup analysis was performed based on the type of SGLT-2 inhibitors, which revealed that the use of empagliflozin (RR 0.70, 95% CI 0.57–0.88, $p = 0.002$, $I^2 = 0\%$) and dapagliflozin (RR 0.74, 95% CI 0.57–0.98, $p = 0.04$, $I^2 = 24\%$) significantly reduced the risk of AKI. However, sotagliflozin (RR 0.69, 95% CI 0.32–1.48, $p = 0.35$) and canagliflozin (RR 0.34, 95% CI 0.01–8.39, $p = 0.51$, $I^2 = 0\%$) did not exhibit increased risk of AKI with the use of SGLT-2 inhibitors (Fig. 4B and Table S7).

Additionally, among the analyzed RCTs, 4 had a follow-up period exceeding one year, whereas the remaining 12 had a follow-up period of less than one year. Subgroup analysis based on follow-up time revealed that for HF patients, the risk of AKI remained significantly decreased when the follow-up duration was more than one year (RR 0.67, 95% CI 0.55–0.82, $p = 0.0001$, $I^2 = 0\%$). However, no significant differences were observed in trials with a follow-up period of less than 1 year (RR 0.83, 95% CI 0.62–1.11, $p = 0.20$, $I^2 = 0\%$; Fig. 4C and Table S7).

Further subgroup analysis was conducted based on age. The risk of AKI was significantly reduced in patients aged ≥ 65 years (RR 0.72, 95% CI 0.61–0.85, $p = 0.0001$, $I^2 = 0\%$). In contrast, no significant increase in AKI risk was observed in patients under 65 years of age (RR 0.61, 95% CI 0.08–4.62, $p = 0.63$, $I^2 = 0\%$; Fig. 4D and Table S7).

Secondary outcomes

Effect of SGLT-2 inhibitors on hypotension rate in patients with HF

The data on hypotension were reported in 12 RCTs [2, 3, 5, 7, 16–18, 21, 23–25], involving a total of 24,171 HF patients. Among these patients, 131 reported hypotension events, with 72 patients in the SGLT-2 inhibitors group and 59 patients in the placebo group. The analysis showed no significant difference in the occurrence of hypotension between the SGLT-2 inhibitors group and placebo group (RR 1.21, 95% CI 0.87–1.70, $p = 0.26$; Fig. 5). Additionally, no heterogeneity was observed among the studies ($p = 0.61$; $I^2 = 0\%$). The funnel plot was visually basically symmetrical (Fig. 6) and Egger's test did not reveal significant publication bias ($p = 0.80$). Furthermore, sensitivity analysis that sequentially excluded each study showed that individual studies did not change the overall findings (Additional file 1: Figure S3), confirming the robustness of the results.

Further subgroup analyses were also performed based on the type of SGLT-2 inhibitor, HF type, age, and follow-up time. Consistent findings were shown across all subgroup analyses, and there was no increase in the incidence of hypotension in patients with HF irrespective of SGLT-2 inhibitors type, HF type, age, or follow-up time (Fig. 7 and Additional file 1: Table S8).

Table 1 Characteristics of included RCTs

Study	Year	Drug	Condition	Follow-up	Parti- cips pants (N)	Women (%) (Treatment/Control)	Age, mean (SD), y	LVEF, mean (SD), % (Treatment/Control)	Primary outcomes
DETERMINE-reduced	2021	dapagliflozin 10 mg	HFrEF	16 weeks	313	28.8%/23.3%	67.8 ± 10.41	NA	Change From Baseline in KCCQ-TSS, KCCQ-PLS and 6MWD
DETERMINE-preserved	2021	dapagliflozin 10 mg	HFpEF	16 weeks	502	36%/37.1%	71.8 ± 9.4	NA	Change From Baseline in KCCQ-TSS, KCCQ-PLS and 6MWD
PRESERVED-HF	2022	dapagliflozin 10 mg	HFpEF	12 weeks	324	56.8%/56.8%	70(63 to77)	60(55,65)/60(54,65)	Effect of Dapagliflozin, as Compared With Placebo, on Heart Failure Related Health Status Using the KCCQ-CS
DEFINE-HF	2022	dapagliflozin 10 mg	HFrEF	12 weeks	263	27.5%/25.8%	61.3 ± 11.5	27.2 ± 8.0/25.7 ± 8.2	Mean NT-proBNP, proportion of patients with > 5 point increase on the KCCQ score
EMPERIAL-Reduced	2020	empagliflozin 10 mg	HFrEF	12 weeks	311	22.4%/28.8%	69.0 ± 10.2	NA	Exercise Capacity as Measured by the 6MWT Distance
EMPERIAL-preserved	2020	empagliflozin 10 mg	HFpEF	12 weeks	315	44.6%/41.8%	73.5 ± 8.8	NA	Exercise Capacity as Measured by the 6MWT Distance
EMPEROR-Reduced	2021	empagliflozin 10 mg	HFrEF	16 months	3726	23.5%/24.4%	66.8 ± 11.0	27.7 ± 6.0/27.2 ± 6.1	Cardiovascular death or HFrEF
EMPEROR-Preserved	2022	empagliflozin 10 mg	HFpEF	1410 days	5964	44.7%/44.6%	71.9 ± 9.4	54.3 ± 8.8/54.3 ± 8.8	Cardiovascular death or HFrEF
DAPA-HF	2020	dapagliflozin 10 mg	HFrEF	28.3 months	4736	23.8%/23.0%	66.3 ± 10.9	31.2 ± 6.7/30.9 ± 6.9	Worsening of HF or death from cardiovascular causes
SUGAR-DM-HF	2020	empagliflozin 10 mg	HFrEF	36 weeks	105	34.6%/18.9%	68.7 ± 11.1	32.1 ± 10.3/32.9 ± 9.3	Left ventricular end-systolic volume and global longitudinal strain
DELIVER	2023	dapagliflozin 10 mg	HFpEF	42.2 months	6253	43.6%/44.2%	71.7 ± 9.6	54.0 ± 8.6/54.3 ± 8.9	An unplanned hospitalization for HF or an urgent visit for HF, or cardiovascular death
SOLOIST-WHF	2022	sotagliflozin 200 mg	AHF	21.9 months	1216	32.6%/34.9%	68.9 ± 9.1	NA	Cardiovascular death or HFrEF
EMPA-RESPONSE	2020	empagliflozin 10 mg	AHF	60 days	79	40%/25.6%	76 (68 to 83)	NA	Dyspnea, diuretic, response length of stay and plasma NTproBNP
CHIEF-HF	2023	canagliflozin 100 mg	HF	12 weeks	455	46.9%/42.9%	63.4 ± 13.32	NA	Change in Pulmonary Artery Diastolic Pressure
EMBRACE-HF	2021	empagliflozin 10 mg	HF	12 weeks	65	36.4%/37.5%	66.2 ± 12.9	46.7 ± 14.9/40.7 ± 17.2	Change From Baseline in KCCQ-TSS
EMPULSE	2022	empagliflozin 10 mg	AHF	127 days	524	35.1%/32.5%	68.5 ± 13.2	NA	Percentage of Pairwise Comparisons With Wins of Clinical Benefit, a Composite of Death, Number of HFrEFs, Time to the First HFrEF and ≥ 5-point Difference in CFB in KCCQ-TSS

Notes: Values are shown as absolute numbers (percentages), mean ± SD, and median (IQR). HFpEF; heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; AHF, acute heart failure; HF, heart failure; NA, not applicable

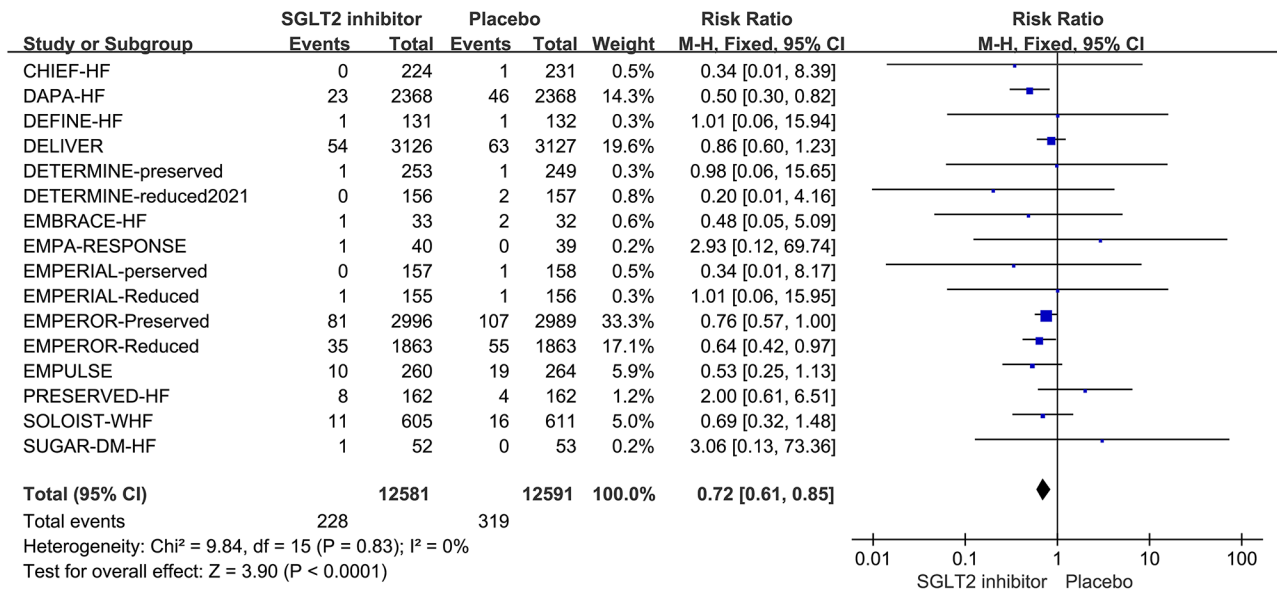


Fig. 2 Forest plot comparing the incidence of AKI between SGLT-2 inhibitors and placebo

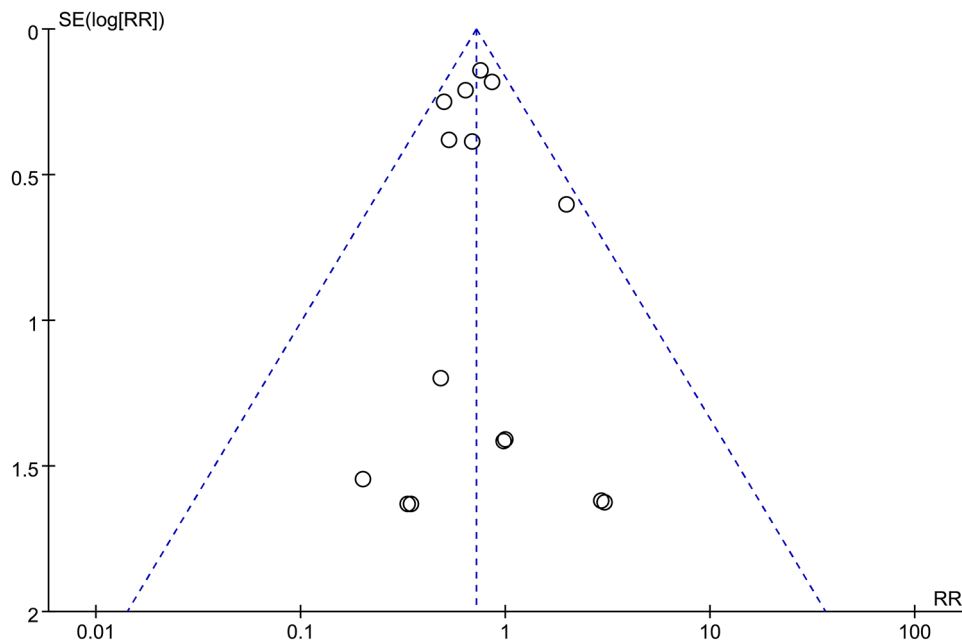


Fig. 3 Funnel plot of meta-analysis for the incidence of AKI

Effect of SGLT-2 inhibitors on hypovolemia rate in patients with HF

Only four RCTs reported data on hypovolemia [17, 18, 21, 23]. Among these studies, 3,679 patients were treated with SGLT-2 inhibitors and 3,685 patients with a placebo. No significant heterogeneity was observed between the studies ($p=0.53$; $I^2=0\%$) (Fig. 8). The analysis showed no significant difference in the occurrence of hypovolemia between the SGLT-2 inhibitors and placebo groups (RR=2.26, 95% CI: 0.70–7.33, $p=0.17$), as shown in Fig. 8. The results indicate that compared to placebo,

SGLT-2 inhibitors does not increase the risk of hypovolemia events in HF patients. Sensitivity analysis yielded consistent results (Additional file 1: Figure S4). Due to the inclusion of fewer than 10 studies, publication bias was not further assessed using funnel plot methods and the Egger’s test.

Furthermore, additional subgroup analyses were performed based on the type of SGLT-2 inhibitors, type of HF, age, and duration of follow-up. These analyses consistently showed no increased risk of hypovolemia across

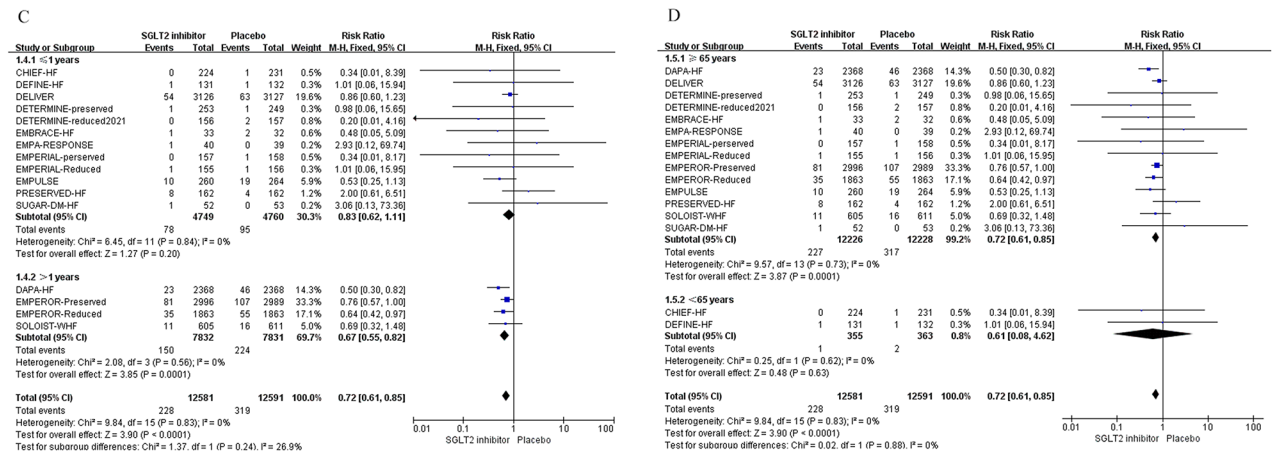
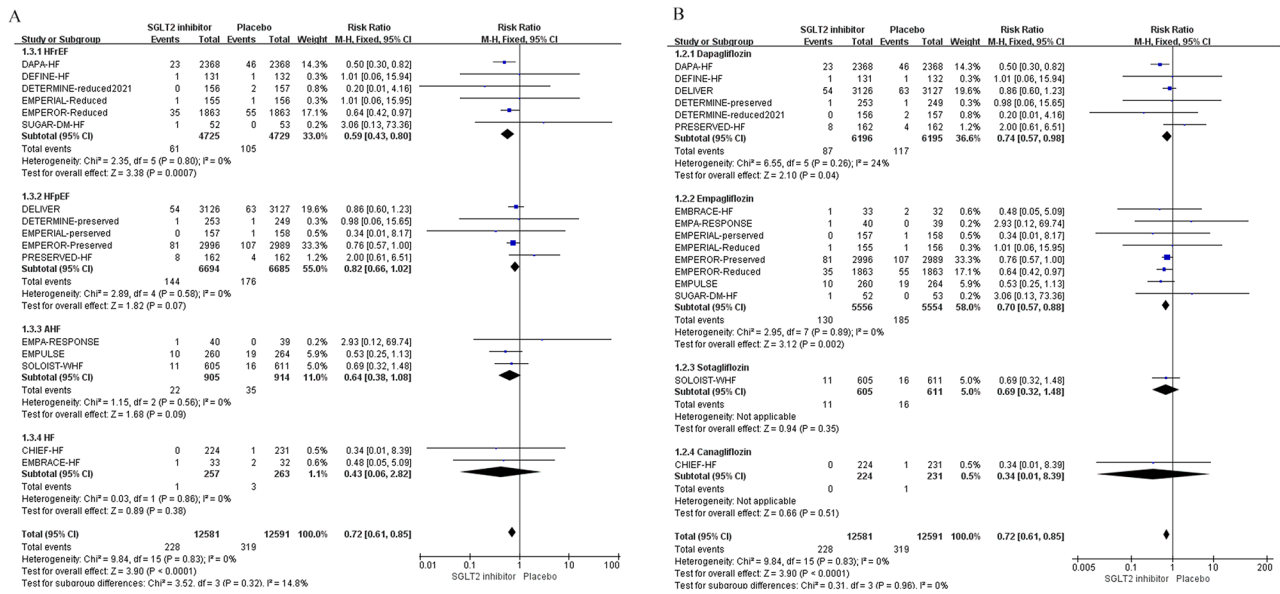


Fig. 4 Subgroup analysis of effects of SGLT-2 inhibitors on AKI. (A) Subgroup analysis based on type of heart failure. (B) Subgroup analysis based on the type of SGLT-2 inhibitors. (C) Subgroup analysis based on follow-up duration. (D) Subgroup analysis based on patient ages

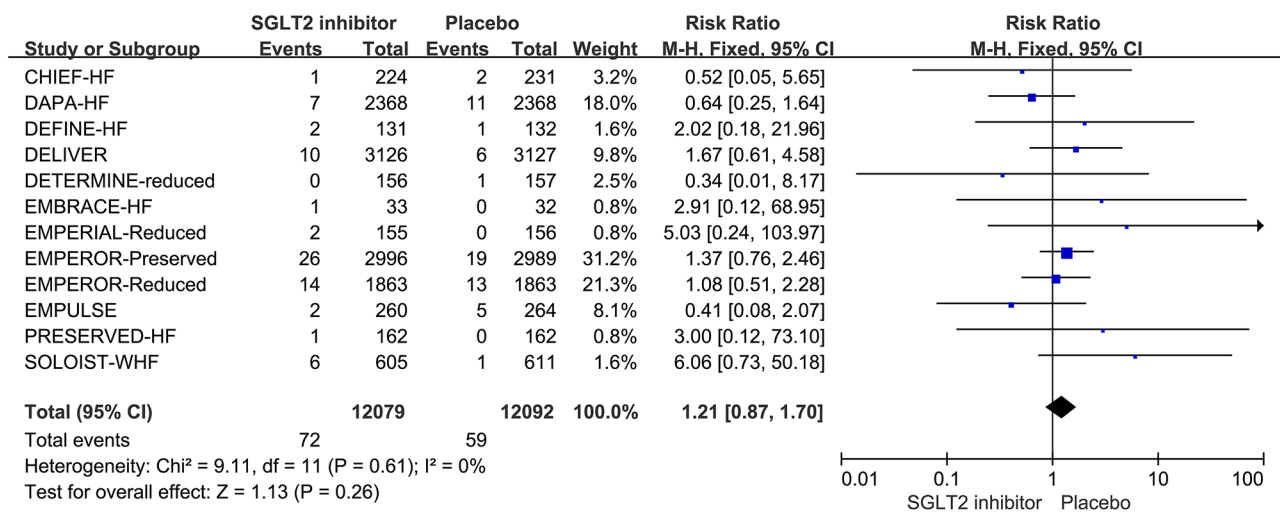


Fig. 5 Forest plot comparing the incidence of hypotension between SGLT-2 inhibitors and the placebo

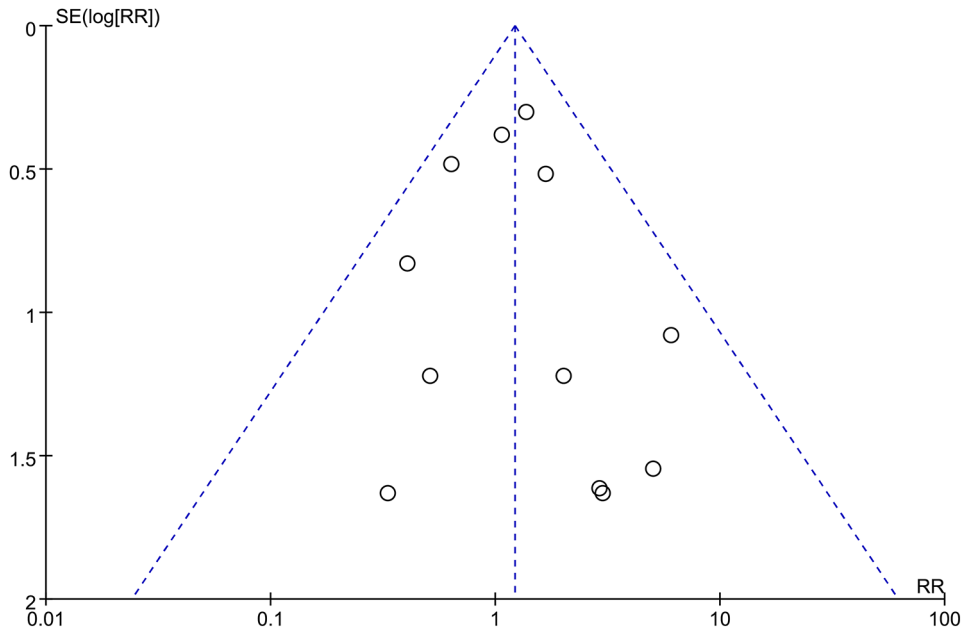


Fig. 6 Funnel plot of meta-analysis for hypotension

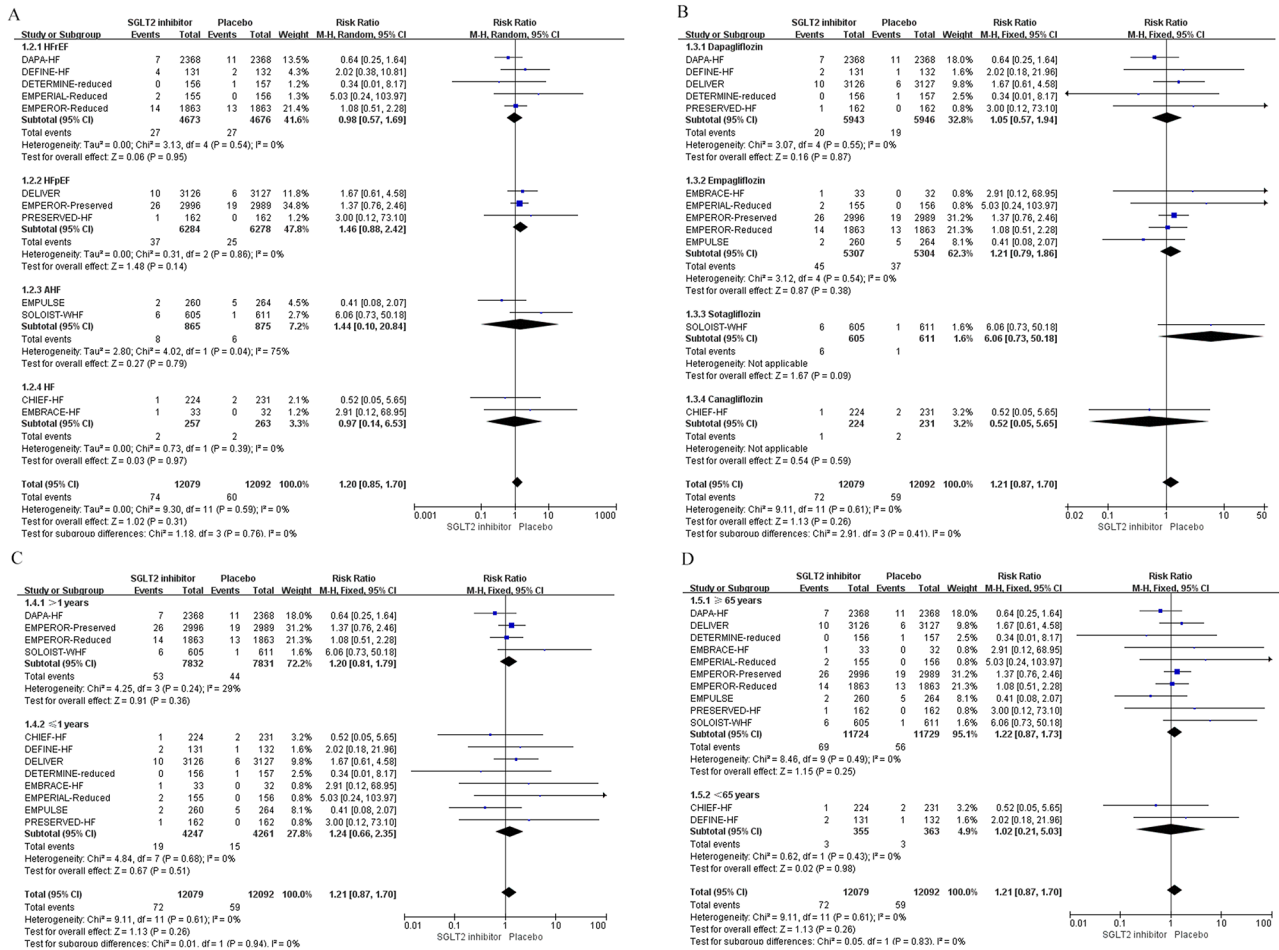


Fig. 7 Subgroup analysis of effects of SGLT-2 inhibitors on hypotension. (A) Subgroup analysis based on type of heart failure. (B) Subgroup analysis based on the type of SGLT-2 inhibitors. (C) Subgroup analysis based on follow-up duration. (D) Subgroup analysis based on patient age

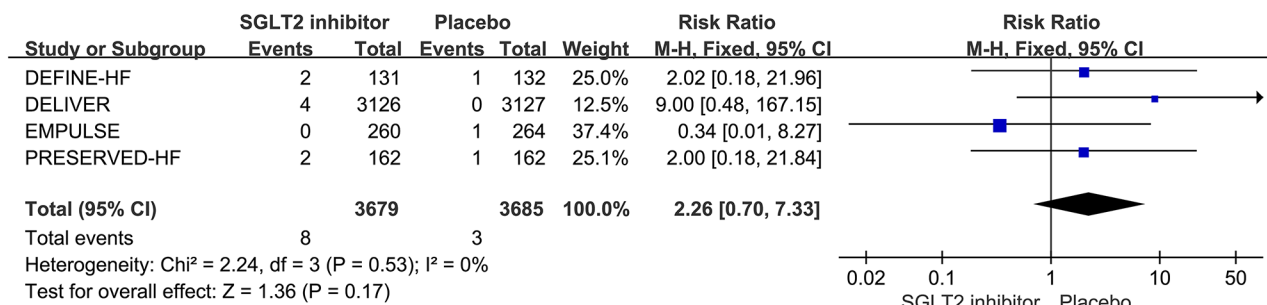


Fig. 8 Forest plot comparing the incidence of hypovolemia between SGLT-2 inhibitors and the placebo

all subgroups, regardless of these factors (Fig. 9 and Additional file 1:Table S9).

GRADE investigates the quality of evidence results

For the primary outcome, AKI, and the secondary outcome, hypovolemia, the quality of evidence is rated as “high”. However, for the secondary composite outcome, including hypotension, the quality of evidence is rated as “moderate” due to issues of imprecision (Additional file 1:Table S10A-C).

Discussion

The results of this systematic review and meta-analysis indicate that SGLT-2 inhibitors compared with placebo, significantly reduce the risk of AKI in patients with HFrEF and do not increase the risk of AKI in HFrEF and AHF. Subgroup analysis revealed that the use of empagliflozin and dapagliflozin significantly decreased the risk of AKI in patients with HF. Additionally, treatment with SGLT-2 inhibitors with a follow-up exceeding one year is also significantly associated with a reduced risk of AKI. It is noteworthy that increasing age in patients with HF receiving SGLT-2 inhibitors did not lead to an increase in the incidence rate of AKI. Furthermore, SGLT-2 inhibitors did not increase the risk of hypotension or hypovolemia events in patients with HF.

To the best of our knowledge, this is the most extensive and comprehensive meta-analysis to date on the effect of SGLT-2 inhibitors on the risk of AKI among patients with HF, incorporating twice the number of AKI events compared with the findings in previous meta-analyses [26]. These findings provide further evidence supporting the safety of SGLT-2 inhibitors in patients with HF, thereby suggesting that SGLT-2 inhibitors may be a valuable therapeutic option to prevent the risk of AKI.

AKI is a common event in HF patients, and influencing factors include hemodynamic status, and a low cardiac output or congestive status. As expected, the incidence of AKI increased in patients with eGFR < 60 mL/min/1.73 m², and the greater the decrease in eGFR, the higher the incidence and severity of AKI. In previous meta-analyses, the relationship between SGLT-2 inhibitors and AKI

has been discussed, and the results indicate that SGLT-2 inhibition not only reduces the progression of chronic kidney disease and the probability of AKI occurring during hospitalization or non-hospitalization treatment, but also has a preventive effect on AKI [27]. In other studies, it was found that SGLT-2 inhibitors can reduce the risk of kidney disease progression in non-diabetes patients by 37% and the risk of AKI by 23% [28]. The underlying mechanism involved may be related to reducing water and sodium excretion and reducing renal perfusion. Due to the low renal function reserve generated by HF, or the increased risk of renal function deterioration due to age and comorbidities, there are concerns that the use of SGLT-2 inhibitors in HF patients may lead to AKI. Our study further showed that regardless of the ejection fraction of HF patients, the use of SGLT-2 inhibitors did not increase the occurrence of AKI.

Accumulating evidence increasingly substantiates the beneficial effects of SGLT-2 inhibitors in preventing progressive renal injury. Our research findings align with the SOLOIST-WHF [29] and EMPULSE [30] trials conducted in patients with deteriorating HF, which investigated the protective effect of SGLT-2 inhibitors in patients with HF exacerbation and the significant reduction in the risk of hospitalization due to HF and renal disease progression. In addition, our findings confirmed that regardless of the ejection fraction and whether the setting was chronic and acute. Clinicians can be confident in initiating SGLT-2 inhibitors therapy, as it does not augment the incidence of AKI. Although SGLT-2 inhibitors usage in HF can preserve the estimated glomerular filtration rate (eGFR) over time [8], our study goes further by demonstrating a reduction in AKI risk. A randomized study has indicated that early initiation of SGLT-2 inhibitors in patients with HFrEF, regardless of diabetes or early chronic kidney disease presence, is safe and well tolerated, with no adverse effects on renal function [9]. A recent meta-analysis on AHF supports our findings, showing no increased risk of AKI or hypotension with SGLT-2 inhibitors, which aligns with our results [31].

It is noteworthy that only empagliflozin and dapagliflozin were significantly associated with a decreased

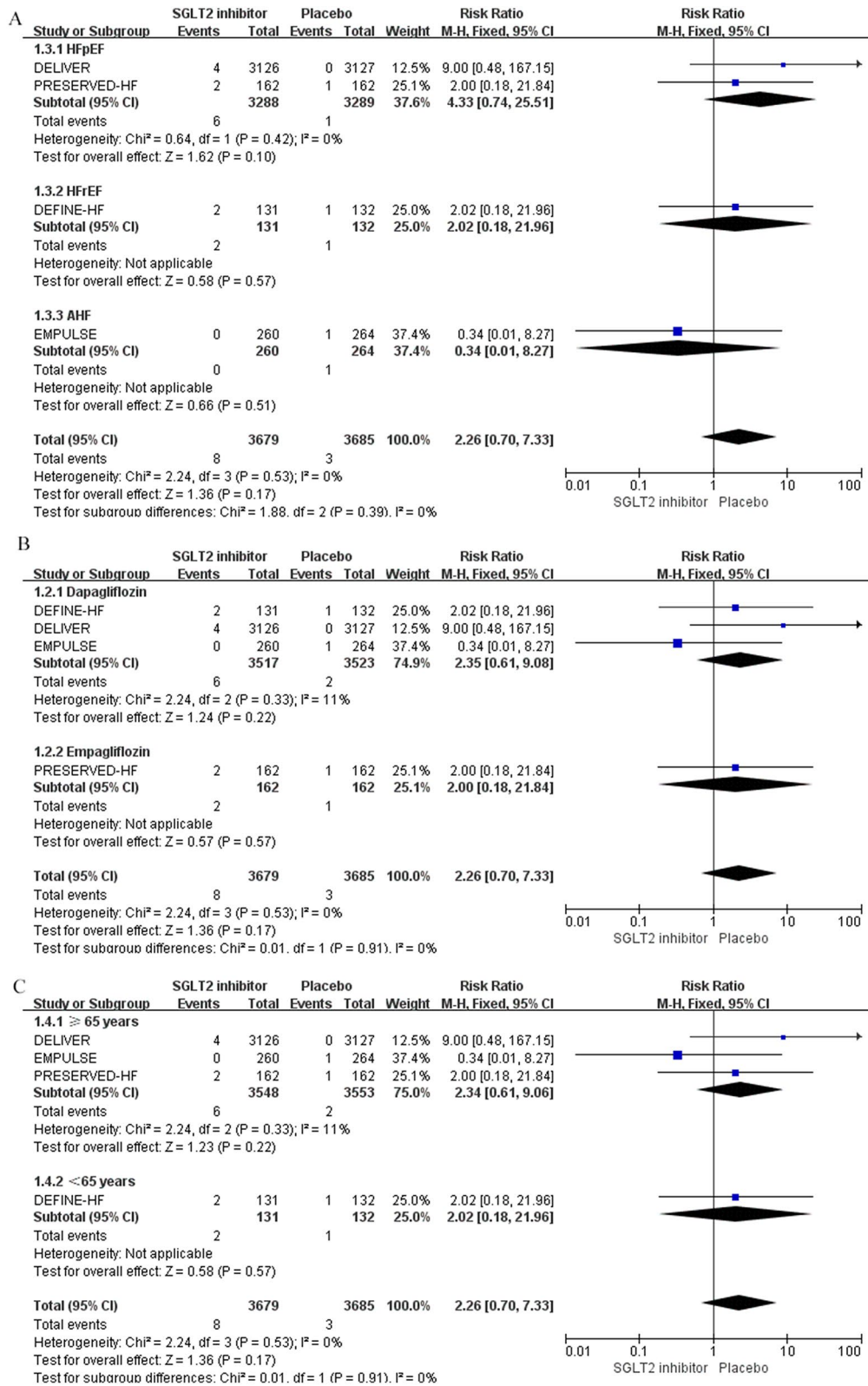


Fig. 9 Subgroup analysis of effects of SGLT-2 inhibitors on hypovolemia. **(A)** Subgroup analysis based on type of heart failure. **(B)** Subgroup analysis based on the type of SGLT-2 inhibitors. **(C)** Subgroup analysis based on patient age

risk of AKI events in HF patients compared to placebo. However, a limited number of studies was included involving the use of canagliflozin and sotagliflozin in HF patients in the included research, with only one study each for these two medications, the impact of these two SGLT-2 inhibitors, thus on the risk of AKI in such patients needs to be further determined. Recent large-scale clinical studies have shown that dapagliflozin provides long-term cardiovascular and renal protection benefits without increasing the risk of severe renal adverse events [32, 33]. Previous meta-analyses have demonstrated that empagliflozin and dapagliflozin significantly reduce the risk of composite renal endpoints in patients with HFrEF [34]. These findings are consistent with our research findings. In addition, our study has demonstrated that the use of SGLT-2 inhibitors in HFpEF and AHF populations is safe and does not increase the risk of serious renal adverse events. In addition, most RCTs in our study had more than 50% of patients who received treatment with renin-angiotensin system inhibitors (RASIs), and the proportion of patients receiving RASIs treatment was similar to the proportion in the SGLT-2 inhibitors group and the placebo group (Additional file 1: Table S5). SGLT-2 inhibitors can reduce the risk of AKI in HF patients regardless of whether they receive ACEI/ARB treatment at the same time, thereby indicating that the beneficial effect on the kidney is obvious.

Further analysis revealed that the use of SGLT-2 inhibitors has slightly different effects on AKI in patients with HF who belonged to different age groups, with a more significant reduction in the incidence of AKI observed in patients older than 65 years. Considering the challenges associated with polypharmacy and the increased mortality risk in older patients—coupled with their underutilization of guideline-recommended treatments—physicians may worry about the diminished efficacy and safety of SGLT-2 inhibitors treatment in this demographic [35, 36]. However, our findings suggest that SGLT-2 inhibitors do not lead to an increased risk of AKI with advancing age, affirming their safety and effectiveness for older patients with HF. Moreover, in the DELIVER trial, the efficacy of SGLT-2 inhibitors was not compromised by advancing age in patients with either HFrEF or HFpEF [10]. In contrast to younger patients, many older individuals with HFpEF exhibit smaller left ventricular size, higher estimated ejection fractions, and evident cardiac remodeling patterns, suggesting that therapeutic benefits of SGLT-2 inhibitors in HF are not reduced by increasing age.

Notably, clinicians often hesitate to prescribe SGLT-2 inhibitors to patients with lower baseline systolic blood pressure (SBP) due to fears of adverse hemodynamic effects. Our meta-analysis indicates that the use of

SGLT-2 inhibitors in HF patients is not associated with an increased risk of hypotension or hypovolemia compared to placebo. In previous studies, it was found that the reduction in SBP in patients with heart failure treated with SGLT-2 inhibitors therapy after initiation is clinically insignificant [37]. The DELIVER trial demonstrated that dapagliflozin had a minor effect on blood pressure and did not increase the risk of severe hypovolemia-related adverse events [33]. Although empagliflozin can lower SBP in patients with HF, its effect is slight in those with already low SBP [38], and it has beneficial effects on renal function that are independent of baseline SBP values [39].

The underlying mechanisms through which SGLT-2 inhibitors exert their benefits in patients with HF have not been fully elucidated. However, it appears that their effects are not directly related to glucose control, likely stem from direct cardioprotective and nephroprotective actions. These effects might involve modulation of sodium balance, enhancement of energy homeostasis, and alleviation of cellular stress, or they could be triggered by alterations in renal hemodynamics [8, 40]. Additionally, SGLT-2 inhibitors may also potentially improve renal function indirectly by reducing activation of the sympathetic nervous system, alleviating inflammation, and ameliorating oxidative stress [41]. They have also been suggested to boost erythropoietin production, inhibit peritubular inflammation and fibrosis—thereby safeguarding the renal tubules [42], and induce changes in the tubules that reduce their sensitivity to AKI [43]. Further research is needed to delineate the beneficial mechanisms of SGLT-2 inhibitors therapy in HF.

This study has several limitations that need to be considered. Firstly, no trial has identified the risk of AKI as a primary endpoint of a study, which may result in discrepancies between our conclusions and reality. Secondly, the drug sotagliflozin, used in the SOLOIST-WHF trial, inhibits both SGLT-2 and SGLT-1 receptors, which may affect the specificity of the results. Thirdly, SGLT-2 inhibitors are hypoglycemic agents mainly used in patients with type 2 diabetes and its associated kidney disease, and there is still no indication for the treatment of HF in some countries. Fourthly, trials were unable to stratify based on comorbidities since not all trials reported baseline prevalence of diabetes, chronic kidney disease, or coronary artery disease. Further research is needed to validate and extend these findings. Fifthly, there is a lack of clarity in the definition and measurement of endpoints potentially biasing our results. Lastly, none of the included studies reported staging of AKI, creating challenges in the analysis of the effect of SGLT-2 inhibitors on different severity levels of AKI. In the future, further validation can be achieved by designing large-scale

clinical studies with varying degrees of AKI as the primary outcome.

Conclusions

In summary, this meta-analysis indicates that the use of SGLT-2 inhibitors does not increase the occurrence of AKI and has no impact on hypotension and hypovolemia, regardless of the ejection fraction environment (chronic and acute), type of SGLT-2 inhibitors, or patient age. These results provide substantial evidence for the use of SGLT-2 inhibitors in patients with HF.

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

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XW and MH contributed to the literature database search, data collection, data extraction, data analysis, and writing of the manuscript. CS, and DJ performed data analysis of the results. HL reviewed and revised this article. All authors read and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

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