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ORIGINAL PAPER

Cardiovascular and renal effects of SGLT2 inhibitor initiation in acute heart failure: a meta-analysis of randomized controlled trials

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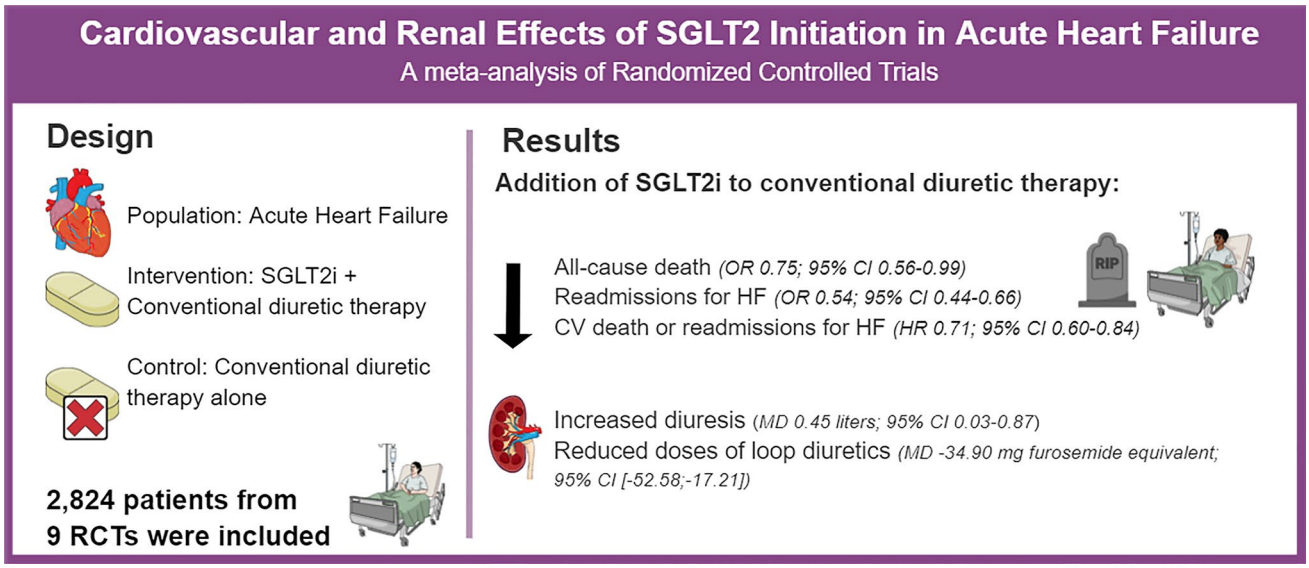
Abstract

Background We sought to compare cardiovascular outcomes, renal function, and diuresis in patients receiving standard diuretic therapy for acute heart failure (AHF) with or without the addition of SGLT2i.

Methods and results Systematic search of three electronic databases identified nine eligible randomized controlled trials involving 2,824 patients. The addition of SGLT2i to conventional therapy for AHF reduced all-cause death (odds ratio [OR] 0.75; 95% CI 0.56–0.99; $p=0.049$), readmissions for heart failure (HF) (OR 0.54; 95% CI 0.44–0.66; $p<0.001$), and the composite of cardiovascular death and readmissions for HF (hazard ratio 0.71; 95% CI 0.60–0.84; $p<0.001$). Furthermore, SGLT2i increased mean daily urinary output in liters (mean difference [MD] 0.45; 95% CI 0.03–0.87; $p=0.035$) and decreased mean daily doses of loop diuretics in mg of furosemide equivalent (MD -34.90; 95% CI [−52.58, −17.21]; $p<0.001$) without increasing the incidence worsening renal function (OR 0.75; 95% CI 0.43–1.29; $p=0.290$).

Conclusion SGLT2i addition to conventional diuretic therapy reduced all-cause death, readmissions for HF, and the composite of cardiovascular death or readmissions for HF. Moreover, SGLT2i was associated with a higher volume of diuresis with a lower dose of loop diuretics.

Graphical abstract



Keywords Acute heart failure · Sodium-glucose cotransporter-2 (SGLT2) inhibitors · Renal function · Diuresis

Extended author information available on the last page of the article

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Abbreviations

AHF	Acute heart failure
ADHF	Acute decompensated heart failure
CI	Confidence interval
CKD	Chronic kidney disease
CV	Cardiovascular
HF	Heart failure
HR	Hazard ratios
MD	Mean difference
OR	Odds ratio
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
RCT	Randomized controlled trial
RoB2	Cochrane tool for assessing risk of bias in randomized trials
SGLT2i	Sodium-glucose cotransporter 2 inhibitors

Introduction

Acute heart failure (AHF) is the leading cause of unplanned hospitalization in those over 65 years and is characterized by new-onset or worsening symptoms of heart failure (HF) [1, 2]. Most patients with AHF are admitted with evidence of fluid overload and are generally treated with escalating doses of intravenous loop diuretics to improve symptoms and reduce morbidity [3, 4]. However, this diuretic regimen is limited by worsening renal function and many patients do not obtain adequate decongestion during the hospital stay for AHF [5–7]. In fact, current treatment for AHF has not changed significantly in decades. Unsurprisingly, post-discharge outcomes have remained poor with 30-day readmission and 1-year mortality rates being as high as 20–30% [8–14]. Therefore, there is an unmet need for new therapeutic strategies in this population.

In recent years, sodium-glucose cotransporter 2 inhibitors (SGLT2i) have been proved to be effective in the treatment of HF for reducing cardiovascular mortality and hospitalizations, regardless of diabetes or ejection fraction status [4, 15–17]. SGLT2i also reduce the composite outcome of cardiovascular death or deterioration of renal function in patients with chronic kidney disease (CKD) [18]. However, less is known about the safety and efficacy of adding SGLT2i to conventional diuretic therapy in patients admitted with AHF.

A prior meta-analysis examining this issue found a reduction in rehospitalizations for HF in patients treated with SGLT2i. However, there was no significant decrease in mortality with SGLT2i, which may have been related to limited power [19]. Therefore, we aimed to perform an updated systematic review and meta-analysis of randomized controlled trials (RCTs) comparing conventional diuretic therapy with or without concomitant SGLT2i for cardiovascular and renal endpoints in patients with AHF.

Methods

This systematic review with meta-analysis was registered in the international prospective register of systematic reviews (PROSPERO) under protocol CRD42022351714. This study was designed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline [20].

Study eligibility

We included studies that met the following eligibility criteria: (1) peer-reviewed RCTs; (2) comparing conventional diuretic therapy with or without SGLT2i; (3) initiated on hospitalization or within 30 days of hospitalization for AHF; (4) regardless of diabetes or ejection fraction status; and (5) reporting at least one of the clinical outcomes of interest. We excluded studies with (1) patients already taking SGLT2i at the time of admission with AHF; (2) no outcomes of interest; and (3) an overlapping patient population with a larger trial. There were no restrictions concerning the date or language of publication.

Search strategy and data extraction

MEDLINE, Cochrane, and Embase databases were systematically searched on August 27, 2022. The search strategy was as follows: ("acute heart failure" OR "decompensated heart failure" OR "worsening heart failure") AND (SGLT2 OR ?gliflozin OR empagliflozin OR canagliflozin OR sotagliflozin OR dapagliflozin OR ertugliflozin). We extracted data for (1) all-cause death; (2) readmission for HF defined as rehospitalization or urgent visits for HF; (3) cardiovascular death; (4) the composite endpoint of cardiovascular (CV) death or readmissions for HF; (5) incidence of worsening renal function (WRF); (6) daily urinary output; and (7) daily need of loop diuretic. Incidences of urinary tract infections, ketoacidosis, hypotension, hypoglycemia, and amputations were also accessed for safety evaluation. Endpoint definitions of WRF and readmissions for HF for each included study are shown in Supplementary Table 11 in the Appendix. All identified articles were systematically assessed using the inclusion and exclusion criteria. Article selection and data extraction were undertaken independently by at least two reviewers (between P.C., T.V., and C.D.). Disagreements were resolved by consensus.

Quality assessment

The cochrane tool for assessing risk of bias in randomized trials (RoB 2) was utilized for quality assessment of randomized studies [21]. The risk of bias evaluation was performed independently by two authors (P.C., T.V.) with disagreements resolved by consensus. Publication bias was assessed with funnel-plot analysis and Egger's test of the all-cause death endpoint to evaluate the symmetric distribution of trials with similar weights.

Sensitivity analysis

We performed a prespecified sensitivity analysis for all-cause death and HF readmissions including only studies with SGLT2i initiation in-hospital setting. In addition, we performed a metaregression analysis for all-cause death to assess for any interaction with the following characteristics: prevalence of diabetes mellitus and the proportion of patients admitted with new-onset HF (de novo HF). We also performed sensitivity analyses restricted to (1) studies with placebo control; (2) a follow-up period of 1 to 12 months; and (3) time-to-event statistical analyses reported as hazard ratios. Concerning the heterogeneous definitions of WRF across studies, we performed leave-one-out sensitivity analyses to ensure the results were not dependent on a single study. We also evaluated the Baujat plot to identify studies that had high contributions to the heterogeneity. Finally, we performed a subgroup analysis of studies with the same definitions of WRF.

Data analysis

Treatment effects for binary endpoints were compared using pooled odds ratios (OR) or hazard ratios (HR) with 95% confidence intervals, whereas continuous endpoints were compared using mean difference (MD) with 95% confidence intervals. We adopted the Mantel–Haenszel test in all binary endpoints and the inverse-variance for continuous endpoints. Heterogeneity was examined with Cochran's Q test, I^2 statistics, and Tau-square using the restricted maximum-likelihood estimator. Heterogeneity was reported as low ($I^2 = 0$–25%), moderate ($I^2 = 26$–50%), or high ($I^2 > 50\%$). The fixed-effects model was used for outcomes with low heterogeneity ($I^2 < 25\%$) and the random-effects model for studies with moderate to high heterogeneity ($I^2 > 25\%$). All statistical analyses were performed using R statistical software, version 4.2.1 (R Foundation for Statistical Computing).

Results

Study selection and baseline characteristics

Our systematic search yielded 596 potential articles, as detailed in Fig. 1. After removing duplicate records and studies with an exclusion criterion based on title/abstract review, 37 remained and were thoroughly reviewed for inclusion and exclusion criteria. Ultimately, 9 RCTs were included, with a total of 2,824 patients, of whom 1,411 patients were assigned to SGLT2i plus conventional diuretic therapy and 1,413 patients were assigned to conventional diuretic therapy alone. Study characteristics are present in Table 1, with additional information in the Supplementary Tables 2 and 3.

Cardiovascular endpoints

Starting SGLT2i during hospitalization for AHF or shortly after hospital discharge reduced the rate of all-cause deaths (OR 0.75; 95% CI 0.56–0.99; $p = 0.049$; $I^2 = 0\%$; Fig. 2A),

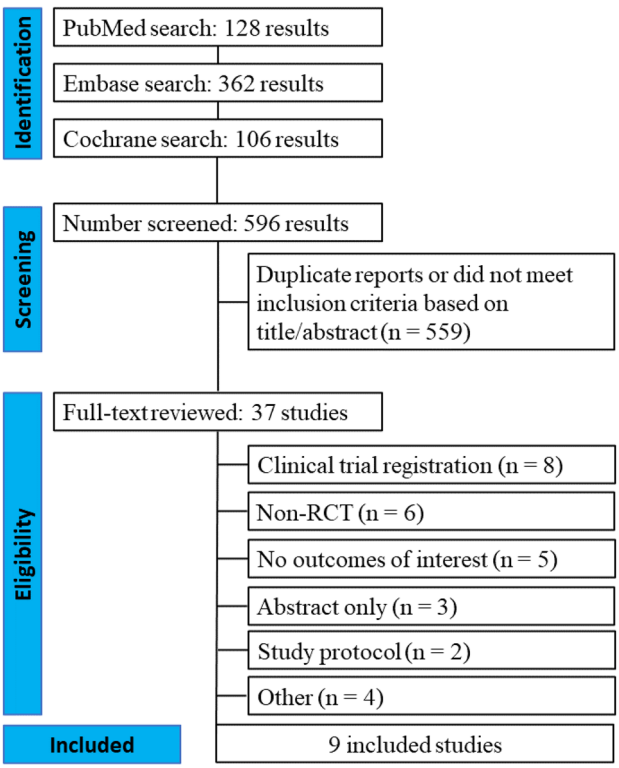

Fig. 1 PRISMA flow diagram of study screening and selection. PRISMA flow diagram of study screening and selection. The search strategy in Embase, MEDLINE, and Cochrane yielded 596 studies, of which 37 were fully reviewed for inclusion and exclusion criteria. Nine studies were included in the meta-analysis

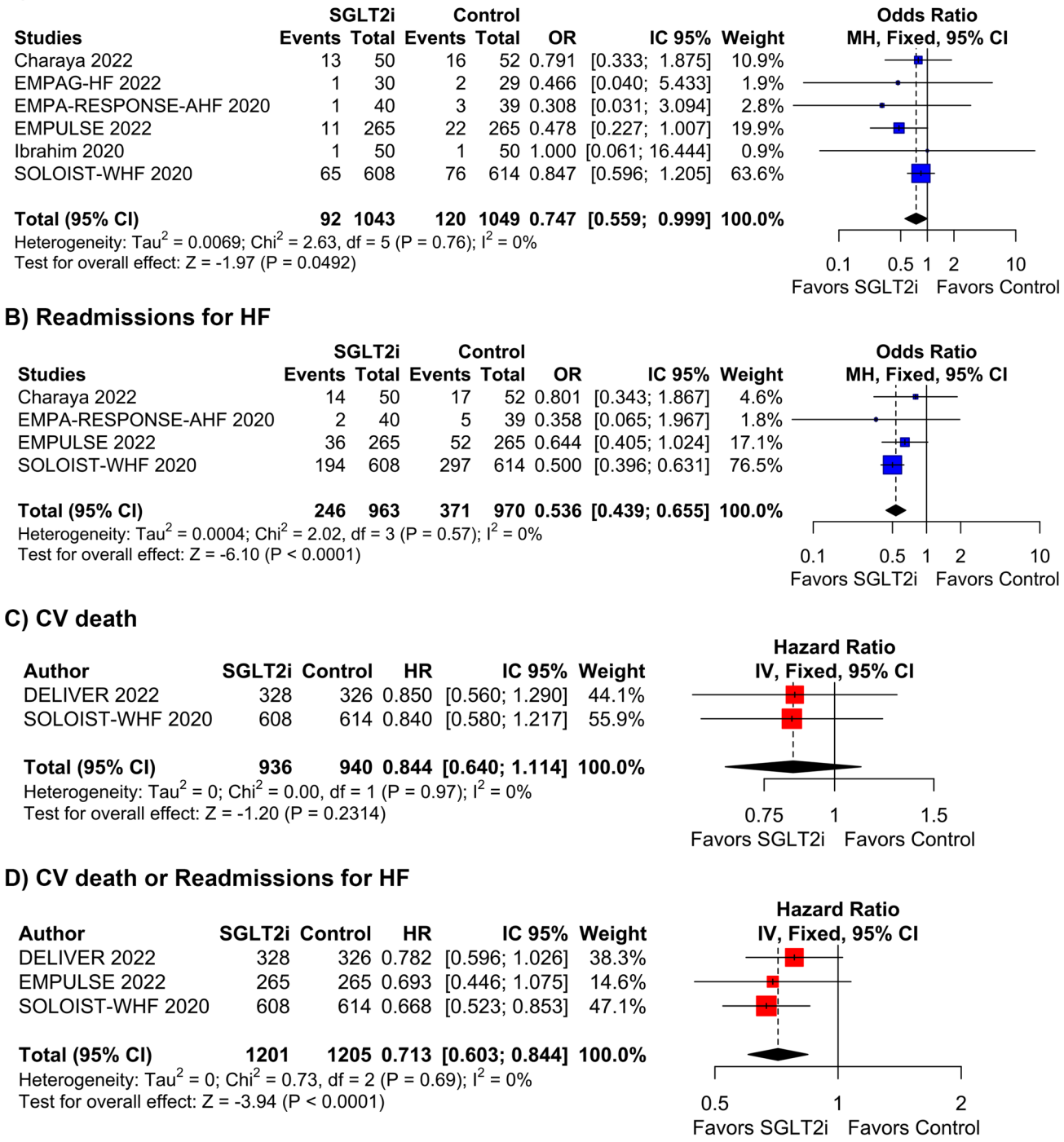

Fig. 2 Forrest plot of cardiovascular endpoints with or without SGLT2i in AHF

readmissions for HF (OR 0.54; 95% CI 0.44–0.66; $p < 0.001$; $I^2 = 0\%$; Fig. 2B), and the composite of CV death or readmissions for HF (HR 0.71; 95% CI 0.60–0.84; $p < 0.001$; $I^2 = 0\%$; Fig. 2D). There was no difference in CV deaths (HR 0.84; 95% CI 0.64–1.11; $p = 0.231$; $I^2 = 0\%$; Fig. 2C) between groups. SOLOIST-WHF had the highest weight for these endpoints, and 51.2% of its population was assigned to SGLT2i treatment only after hospital discharge. All other studies for these endpoints had SGLT2i initiated in the hospital. Thus, we performed a sensitivity analysis withdrawing SOLOIST-WHF from the pooled analysis to address the effects of SGLT2i initiation before hospital discharge. In this

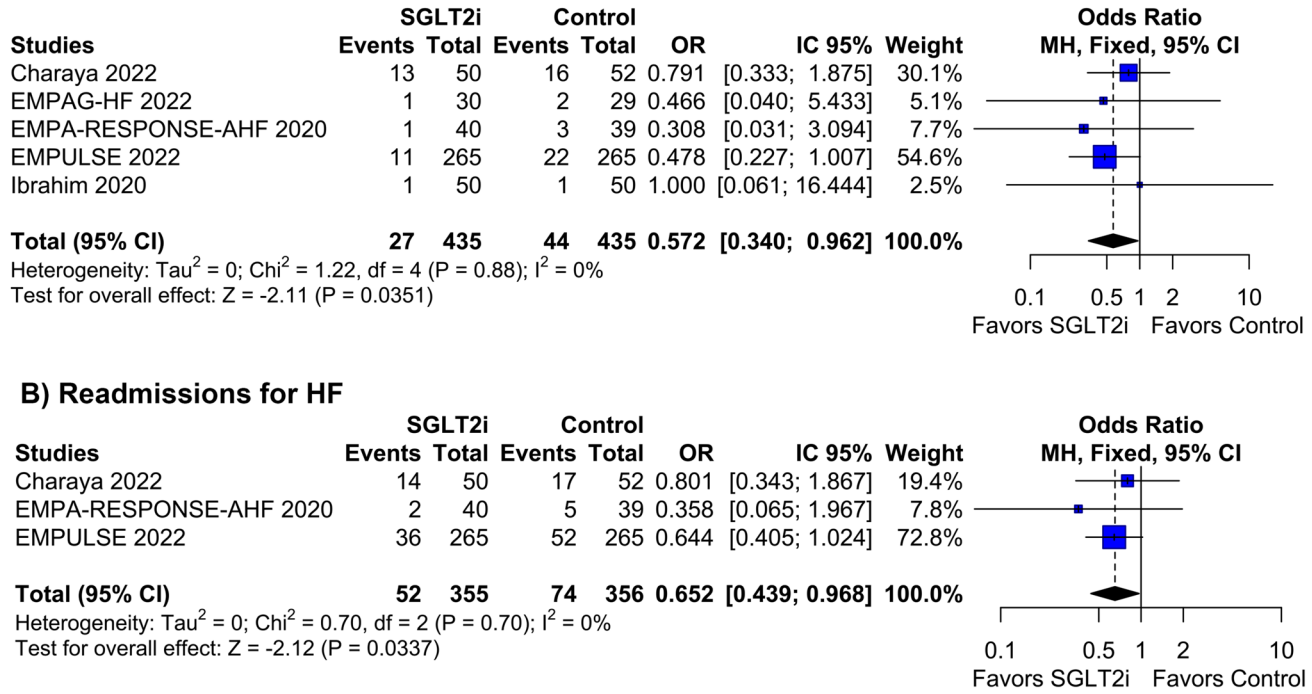

Fig. 3 Subgroup analysis of studies with in-hospital treatment initiation with or without SGLT2i

analysis, similar results were found in all-cause deaths (OR 0.57; 95% CI 0.34–0.96; $p=0.035$; $I^2=0\%$; Fig. 3A) and readmissions for HF (OR 0.65; 95% CI 0.44–0.97; $p=0.034$; $I^2=0\%$; Fig. 3B).

Prespecified metaregressions were performed showing no significant interaction between all-cause death and covariants of (1) diabetes mellitus prevalence and (2) the proportion of patients admitted with new-onset HF (de novo HF). These results are available in Figs. S1–S2 in the supplementary appendix.

In the sensitivity analysis, the beneficial effect of SGLT2i was preserved after restricting follow-up periods to 1–12 months. All-cause deaths (OR 0.75; 95% CI 0.56–0.99; $p=0.048$; $I^2=0\%$), readmissions for HF (OR 0.54; 95% CI 0.44–0.66; $p<0.001$; $I^2=0\%$), and the composite of CV death and readmission for HF (HR 0.67; 95% CI 0.54–0.83; $p<0.001$; $I^2=0\%$) were significantly lower with SGLT2i relative to control. Due to insufficient data, the analysis of CV death in this setting was not performed. These results are available in Fig. S3 in the supplementary appendix.

Additionally, a time-to-event sensitivity analysis calculating HR found similar results to the pooled analysis. CV deaths and the composite of CV death or readmission for HF had already been calculated as HR for the effect estimate because only these data were available for such outcomes. The sensitivity analysis for readmissions for HF (HR 0.69; 95% CI 0.56–0.84; $p<0.001$; $I^2=0\%$) also demonstrated a benefit in favor of SGLT2 inhibitors. There was no difference between the groups regarding all-cause deaths (HR 0.89; 95% CI 0.71–1.12; $p=0.317$; $I^2=0\%$) in the time-to-event analysis, albeit this was likely due to reduced power, as only two studies reported this outcome. These results are available in Fig. S4 in the Supplementary Appendix.

We also performed a subgroup analysis restricted to placebo-controlled studies. Results were similar to those found in the overall pooled analysis of all studies. Readmissions for HF (OR 0.52; 95% CI 0.43–0.64; $p<0.001$; $I^2=0\%$) and the composite of CV death or readmissions for HF (HR 0.71; 95% CI 0.60–0.84; $p<0.001$; $I^2=0\%$) were reduced with SGTL2 inhibitors. There was no difference in the occurrence of CV deaths (0.84; 95% CI 0.64–1.11; $p=0.231$; $I^2=0\%$) between groups. There was also a trend toward reduced all-cause deaths with SGLT2 inhibitor use relative to placebo (OR 0.74; 95% CI 0.54–1.01; $p=0.056$; $I^2=0\%$), though power was also reduced (4 studies). These results are available in Fig. S5 in the supplementary Appendix.

Renal function assessment

There was no difference in the occurrence of WRF between patients treated with or without SGLT2i (OR 0.75; 95% CI 0.43–1.29; $p=0.290$; $I^2=48\%$; Fig. 4B). The definition of WRF in each study is reported in Table S1 of the Supplementary Appendix. Due to high heterogeneity, we performed

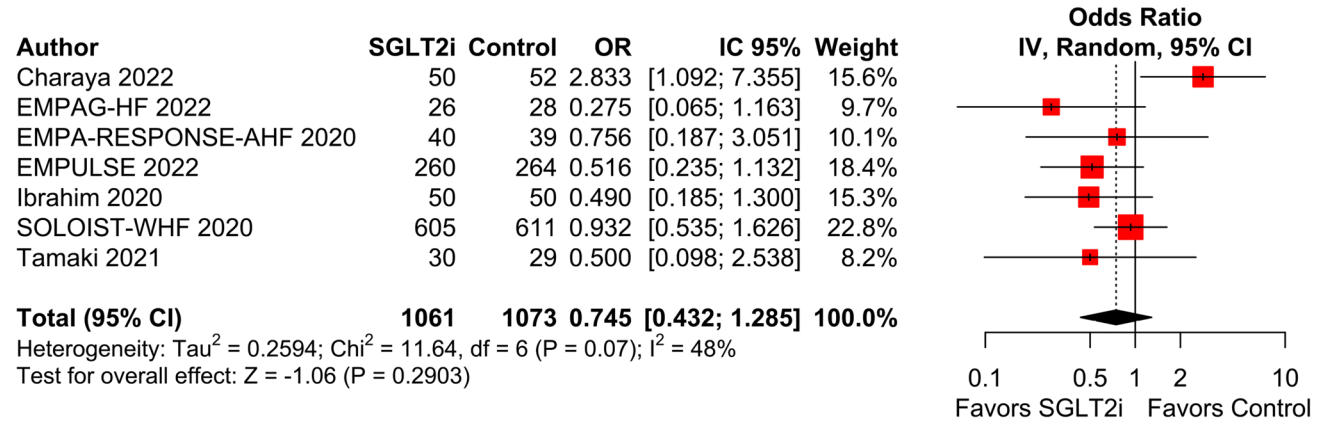

Fig. 4 The incidence of worsening renal function was similar with or without SGLT2i in AHF

a leave-one-out sensitivity analysis by iteratively removing one study at a time to ensure the results were not dependent on a single study. The removal of each study from the pooled analysis did not affect the WRF endpoint, except for the study from Charaya et al. [22]. The withdrawal of this study reduced the frequency of WRF in the SGLT2i group compared with the control group and eliminated the heterogeneity in the endpoint (OR 0.64; 95% CI 0.43–0.95; $p=0.029$; $I^2=0\%$; Fig. S6 in the Supplementary Appendix). The Baujat plot also confirmed the heterogeneity in this endpoint was predominantly from Charaya et al. (Fig. S7 in the Supplementary Appendix).

We also performed a sensitivity analysis joining only studies with the same definition of WRF (an increase ≥ 0.3 mg/dL of serum creatinine level). This analysis found a reduced frequency of WRF in the SGLT2i group compared with the control group (OR 0.43; 95% CI 0.21–0.88; $p=0.021$; $I^2=0\%$; Fig. S8 in the Supplementary Appendix). Moreover, a subgroup analysis including only placebo-controlled trials showed similar results in the frequency of WRF (OR 0.70; 95% CI 0.47–1.06; $p=0.094$; $I^2=7\%$; Fig. S9 in the Supplementary Appendix).

Diuresis parameters

SGLT2i therapy improved diuresis parameters. The mean daily doses of loop diuretics in mg of furosemide equivalent was lower with SGLT2i (MD −34.90; 95% CI [−52.58, −17.21]; $p<0.001$; $I^2=77\%$; Fig. 5A) compared with control group, whereas the mean daily urinary output, in liters, significantly increased (MD 0.45; 95% CI 0.03–0.87; $p=0.035$; $I^2=35\%$; Fig. 5B).

Safety outcomes

There was no difference between groups in the incidence of urinary tract infection (OR 0.99; 95% CI 0.70–1.42; $p=0.969$; $I^2=22\%$), hypotension (OR 1.16; 95% CI 0.73–1.84; $p=0.526$; $I^2=0\%$), ketoacidosis (OR 0.67; 95% CI 0.19–2.36; $p=0.528$; $I^2=0\%$), amputations (OR 2.35; 95% CI 0.61–9.10; $p=0.217$; $I^2=0\%$). In contrast, the incidence of hypoglycemia was higher in the SGLT2i group (OR 4.27; 95% CI 1.07–17.02; $p=0.039$; $I^2=0\%$). These results are plotted in Figure S10 of the supplementary appendix.

Quality assessment

The risk of Bias 2 (RoB 2) tool was used for quality assessment [21]. No studies were considered at high risk of bias as described in figure S11 in the supplementary appendix. On funnel plot analysis, studies occupied symmetrical distribution according to weight and converged toward the pooled effect as the weight increased. Egger's test also indicates no evidence of publication bias ($p=0.26$; Fig. S12 in the Supplementary Appendix).

Discussion

In this systematic review and meta-analysis of 9 RCTs including 2824 patients, the addition of SGLT2i to conventional therapy was compared to conventional diuretic therapy alone in patients admitted with AHF. The main findings from the pooled analysis were: (1) SGLT2i reduced all-cause death, readmissions for HF, and the composite of CV death or readmissions for HF compared with conventional diuretic therapy alone; (2) SGLT2i was associated with lower daily doses of loop diuretics and higher mean daily urinary output in liters as compared with conventional diuretic therapy alone without SGLT2i; and (3) the incidence of WRF was not significantly different with versus without the addition of SGLT2i to conventional diuretic therapy.

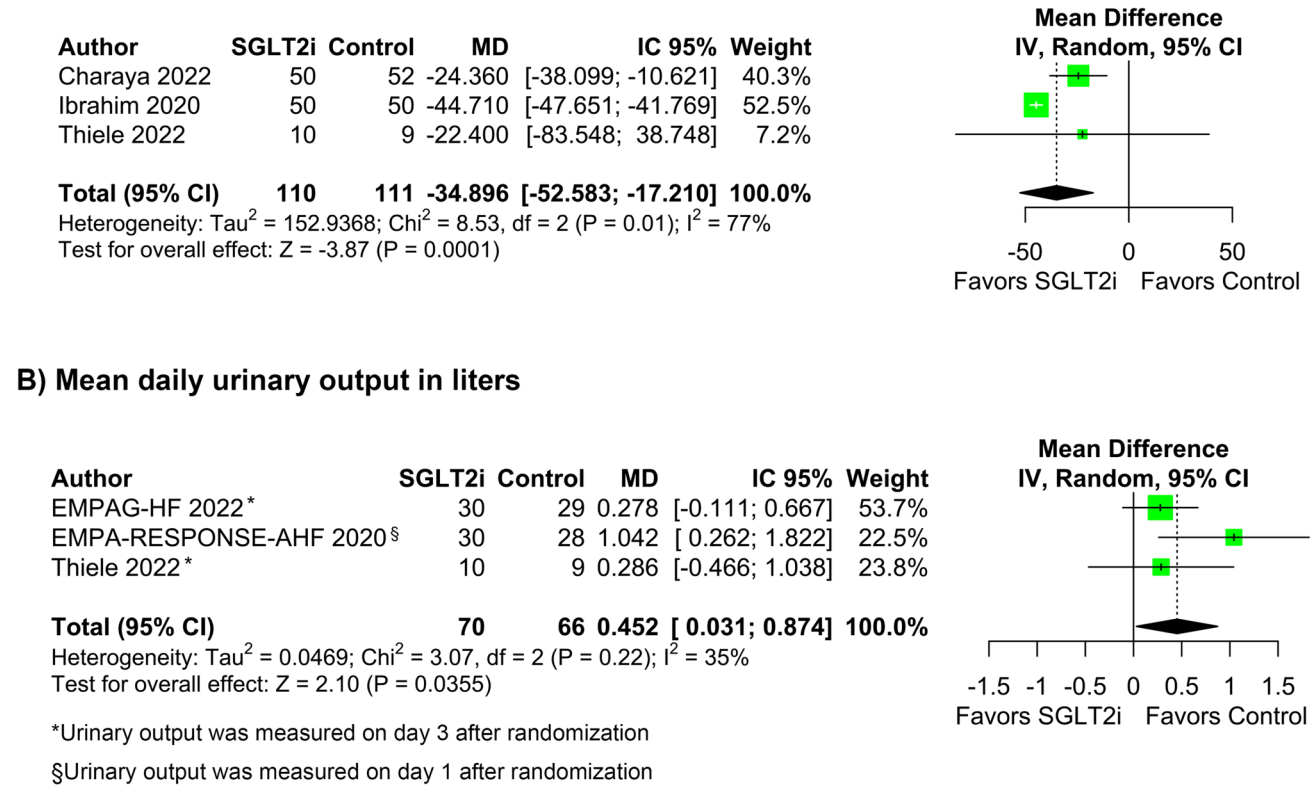

Fig. 5 The mean daily dose of loop diuretics in milligrams furosemide equivalent was significantly lower with SGLT2i therapy in AHF (**A**). Daily urinary output in liters was significantly higher with SGLT2i added to conventional diuretic therapy compared with diuretic therapy alone (**B**)

It is well established that loop diuretics are the first-line therapy for volume overload in patients with AHF aiming to produce natriuresis and a negative fluid balance. However, the resulting volume depletion triggers sodium retention due to activation of the renin–angiotensin–aldosterone system and sympathetic nervous system, especially in tubular sites not targeted by loop diuretics [1, 32]. Therefore, one strategy to overcome diuretic resistance is the combination of two different classes of diuretics.

SGLT2i may be ideal to combine with loop diuretics in patients with AHF. These agents reduce glucose and sodium reabsorption in the proximal tubule. Considering that a large amount of sodium is reabsorbed in the proximal tubule, SGLT2i probably helps to overcome diuretic resistance by increasing natriuresis. Therefore, a higher urinary output is found in the SGLT2i group, in addition to lower requirements of loop diuretics, likely due to the natriuretic effect of SGLT2i [33, 34]. Indeed, higher urinary sodium concentration has been associated with better in-hospital and post-discharge outcomes in patients with AHF [35–38]. Recent studies in patients with AHF have shown greater urinary sodium excretion and lower natriuretic peptides in the SGLT2i-treated individuals [26, 30, 39, 40]. In addition, increased glucosuria promotes osmotic diuresis, which may be a pivotal mechanism responsible for increased diuresis with SGLT2i, as observed in the EMPA-RESPONSE-AHF trial [25, 41]. SGLT2i are also more effective in eliminating fluid from interstitial space rather than intravascular space by excreting more electrolyte-free water. [34]

Once tubular content of glucose and sodium are high with SGLT2i use, there is a decrease in the tubuloglomerular feedback, which, in turn, lowers the glomerular capillary pressure, the renal transport work, and oxygen consumption. This mechanism may explain the acute reduction in eGFR observed after initiation of SGLT2i and the long-term preservation of eGFR observed in patients with CKD, for example [33]. In patients with AHF, individual studies found a mild reduction in eGFR with the initiation of SGLT2i. Our study showed that this initial reduction in eGFR is transient, as the incidence of WRF was not significantly different with versus without the addition of SGLT2i to conventional diuretic therapy. These data corroborate findings of diuretic therapy in AHF, wherein the acute decline in eGFR is not

Table 1 Baseline characteristics of included studies

	Charaya et al. 2022 [22]	DELIVER 2022 [23]	EMPA-RESPONSE-AHF 2021 [24, 25]	EMPAG-HF 2022 [26]	EMPULSE 2022 [27]	Ibrahim et al. 2020 [28]	SOLOIST-WHF 2020 [29]	Tamaki et al.[a] 2021 [30]	Thiele et al.[a] 2022 [31]
Patients (*n*) SGLT2i/control	50/52	328/326	40/39	30/29	265/265	50/50	608/614	30/29	10/9
Age (Years) SGLT2i/control	72.6 ± 12.2/74.2 ± 11.3	71.9 ± 9.1/71.9 ± 9.2	79 (73–83)/73 (61–83)	72.9 ± 11.2/76.5 ± 8.3	71 (62–78)/70 (59–78)	62.02 ± 8.8/60.64 ± 9.9/	69 (63–76)/70 (64–76)	80 (77–83)/82 (75–84)	71.8 ± 13.4/72.3 ± 9.9
% Male SGLT2i/control	58/52	50.6/52.8	60/74	63.3/58.6	67.5/64.9	56/52	67.4/65.1	60/62	60/33.3
%De novo HF SGLT2i/control	34/38	0/0	48/46	60/48	33.2/32.8	0/0	0/0	NA	NA
%DM2 SGLT2i/control	30/30	50.9/46.6	38/28	43.3/34.5	46.8/43.8	100/100	100/100	100/100	40/11
%Hypertension SGLT2i/control	92/92	NA	68/56	90/86.2	77.4/83.4	56/62	NA	97/93	NA
NTproBNP baseline levels	5333 (2029–9902)/4381 (2313–11,514)	1316 (766, 2377), 1256 (732, 2458)	4406 (2873–6979)/6168 (3180–10,489)	4726 ± 4516/4823 ± 4995	3299 (1843–6130)/3106 (1588–6013)	NA	1817 (855–3659)/1741 (843–3582)	2750 (1660–4710)/3950 (2200–8870)	3562 ± 2527/3996 ± 6293
LVEF SGLT2i/control	45.6 ± 15.7/44.4 ± 13.6	52.2 ± 7.9/52.8 ± 8.5	36 ± 17/37 ± 14	45 ± 16/44 ± 14	31.0 (23.0–45.0)/32.0 (22.5–49.0)	32.54 ± 2.99/32.23 ± 2.49	35 (28–47)/35 (28–45)	44 (32–61)/39 (32–51)	34 ± 11/38 ± 11
SBP at mm Hg	132.9 ± 17.9/130.1 ± 21.1	127.0 ± 15.2/127.4 ± 14.9	127 ± 22/121 ± 25	139 ± 25/132 ± 21	120 (109.0–135.0)/122 (110.0–138.0)	110.74 ± 12.51/113.08 ± 14.97	122 (111–135)/122 (112–133)	120 ± 18/115 ± 16	139 ± 23/126 ± 24
eGFR baseline SGLT2i/control	55.65 ± 18.17/52.7 ± 17.34	57.4 ± 19.0/58.0 ± 18.7	55 ± 18/55 ± 18	58.2 ± 19.3/62.2 ± 18.2	50.0 (36.0–65.0)/54.0 (39.0–70.0)	NA	49.2 (39.5–61.2)/50.5 (40.5–64.6)	40 (31–54)/35 (23–54)	60 ± 20/56 ± 16
SGLT2i drug	Dapagliflozin 10 mg per day	Dapagliflozin 10 mg per day	Empagliflozin 10 mg per day	Empagliflozin 25 mg per day	Empagliflozin 10 mg per day	Dapagliflozin 10 mg per day	Sotagliflozin 200-400 mg per day	Empagliflozin 10 mg per day	Empagliflozin 10 mg per day
Follow-up period	30 days	Median of 2.3 years	60 days	30 days	90 days	Length of hospital stay	Median of 9.2 months	7 days	30 days
Placebo-controlled	No	Yes	Yes	Yes	Yes	No	Yes	No	Yes

Table 1 (continued)

	Charaya et al. 2022 [22]	DELIVER 2022 [23]	EMPA-RESPONSE-AHF 2021 [24, 25]	EMPAG-HF 2022 [26]	EMPULSE 2022 [27]	Ibrahim et al. 2020 [28]	SOLOIST-WHF 2020 [29]	Tamaki et al.[a] 2021 [30]	Thiele et al.[a] 2022 [31]
The time between hospital admission and randomization to SGLT2i	Until 24 h according to inclusion criteria	13.76% in-hospital, 22.48% 1 to 7 days after discharge, 63.76% 8 to 30 days after discharge	Until 24 h according to inclusion criteria	Until 12 h according to inclusion criteria	The median time from hospital admission to randomization was 3 days	SGLT2i was initiated during hospitalization without specifying a time	48.8% in hospital, 51.2% within a median of 2 days after discharge	Until 96 h according to inclusion criteria	The median time between hospital admission and randomization was 72 h

Values are mean ± SD or median (interquartile range)

DM2, Diabetes mellitus type 2; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal probrain natriuretic peptide; SBP, systolic blood pressure

[a]These studies were prematurely terminated due to the COVID-19 pandemic

associated with death or hospitalization for HF if there is concomitant evidence of decongestion [42, 43].

Observational studies comparing diuretic therapy with or without SGLT2i in patients with AHF have found a reduction in the composite endpoint of mortality and hospitalization for HF with SGLT2i, as well as in HF rehospitalization rates [40, 44]. In contrast, RCTs have shown conflicting results about the use of SGLT2i in this population. The recently published Dapagliflozin Evaluation to Improve the LIVEs of Patients with Preserved Ejection Fraction Heart Failure (DELIVER) trial found no evidence of benefit from dapagliflozin with regards to the primary endpoint of worsening HF or cardiovascular death in the patients enrolled during or following hospitalization [23]. The Effect of Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes Post Worsening Heart Failure (SOLOIST-WHF) trial, however, found a benefit in the same endpoint for patients who were recently hospitalized with worsening HF and were randomized to receive sotagliflozin as compared with placebo [29].

None of these studies, whether observational or randomized, showed a benefit in all-cause or cardiovascular mortality, as individual endpoints, for SGLT2i use in this scenario. To the best of our knowledge, this is the first meta-analysis to find a significant difference in all-cause mortality with SGLT2i in patients with AHF. Our meta-analysis expands on prior findings by also showing a significant reduction in the incidence of readmissions for HF, as well as the composite of CV death or readmission for HF in patients with AHF treated with SGLT2i compared with conventional diuretic therapy alone.

Our study has some limitations. First, there were slight differences between the RCTs included in terms of the patient population, control group (placebo and no treatment), and time of follow-up. However, the absence of heterogeneity in the pooled analysis of cardiovascular outcomes suggests that the studies are similar enough in terms of the relative efficacy of SGLT2i vs. control to be pooled in this meta-analysis. Moreover, we performed sensitivity analyses to address these issues, which largely showed similar findings to the pooled data. Second, our findings may not apply to all patients with AHF. In general, the selected trials excluded patients with AHF triggered by acute coronary syndrome, as well as those with end-stage renal disease and advanced liver failure. Third, a large proportion of the cohort was enrolled after discharge; however, our sensitivity analysis restricted to in-hospital initiation of SGLT2i found similar results for the endpoints of all-cause death and for HF hospitalization. Fourth, we included patients with acute-on-chronic HF, as well as de novo HF, which may have somewhat different prognosis [9]. Given the lack of individual data, it was not possible to perform analyses to stratify these two populations. However, we performed a metaregression

addressing the influence of de novo HF in all-cause death and found no statistical significance. Fifth, the outcomes of mean daily urinary output and mean daily dose of loop diuretics were based on small samples, as these outcomes were not reported in all studies, with broad confidence intervals and high heterogeneity. And, finally, the endpoint of WRF had elevated heterogeneity, identified as originating from Charaya et al. [22]. This study found a non-statistically significant increase in WRF with SGLT2i relative to no SGLT2i therapy. However, SGLT2i treatment was initiated within 24 h of admission and without necessarily achieving stable diuretic doses. Removal of this study from WRF analysis demonstrated a significant reduction in WRF with SGLT2i initiation for AHF.

Conclusions

In patients admitted with AHF, the addition of SGLT2i to conventional diuretic therapy was associated with lower all-cause death, readmissions for HF, and the composite of CV death or readmissions for HF. Moreover, SGLT2i increased the daily urinary output and reduced the mean daily doses of loop diuretics during hospitalization, without a significant increase in WRF. These findings suggest that SGLT2i should be considered in the treatment of patients with AHF.

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Declarations

Conflict of interest All authors report no relationships that could be construed as a conflict of interest. All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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