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Review Article

Redefining treatment paradigms: Early use of dapagliflozin and empagliflozin in acute heart failure – a systematic review and meta-analysis of randomized controlled trials

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Abstract

Sodium-glucose co-transporter 2 inhibitors (SGLT2i) have proven to significantly reduce mortality and rehospitalization in heart failure with reduced ejection fraction (HFrEF). Supported by the 2023 European Society of Cardiology (ESC) guidelines and the safety, tolerability, and efficacy of rapid optimization of heart failure (STRONG-HF) trial, SGLT2i offer improved outcomes with a favorable safety profile, emphasizing their pivotal role in HFrEF management. The aim of this study was to evaluate early initiation with dapagliflozin and empagliflozin, focusing on their efficacy and safety in acute heart failure (AHF). Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, we searched seven databases for randomized controlled trials on SGLT2i in AHF (2019–2024). Outcomes included all-cause mortality, heart failure (HF)-related events, all-cause rehospitalization, length of hospital stay, diuretic response, serum electrolytes, and adverse events (AEs). The Cochrane Risk of Bias 2 tool was used. Data were analyzed using a random-effects model and presented as standardized mean differences and risk ratios with 95% confidence intervals. A subgroup analysis was conducted based on intervention. Nine studies encompassing 1,417 patients with a generally low risk of bias were included. Initiating SGLT2i within five days of admission significantly reduced in-hospital all-cause mortality risk by 42% and in-hospital worsening HF during rehospitalization by 39%. SGLT2i also significantly reduced serious AEs risk by 27%. No significant differences were found in other outcomes, including specific AEs (acute kidney injury, hepatic injury, symptomatic hypotension, hypoglycemia, urinary tract infections, and diabetic ketoacidosis). The analysis showed homogeneity, with no significant differences between SGLT2i. The study highlights that initiating SGLT2i within five days of admission significantly reduces all-cause mortality and worsening HF during rehospitalization, with a better safety profile than placebo.

Keywords: Sodium-glucose co-transporter 2 inhibitors, acute heart failure, dapagliflozin, empagliflozin, randomized controlled trials

Introduction

Acute heart failure (AHF) poses a significant and growing global health challenge, particularly among individuals aged 65 and older, leading to over one million hospital admissions annually in

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the United States alone [1]. The incidence of AHF increases with age, peaking between 70 and 73 years, where the management becomes increasingly complex due to the interplay of multiple chronic conditions and geriatric syndromes [2,3]. Despite advancements in medical care, AHF continues to contribute substantially to morbidity and mortality, highlighting an urgent need for more effective therapeutic strategies.

Traditionally, AHF management has focused on symptomatic relief and hemodynamic stabilization, offering limited options to alter the disease trajectory [4,5]. However, the therapeutic landscape is transforming with the introduction of sodium-glucose co-transporter 2 inhibitors (SGLT2i), specifically dapagliflozin and empagliflozin. Initially developed for glycemic control in type 2 diabetes mellitus (T2DM), these agents have demonstrated significant cardiovascular benefits that extend beyond glucose lowering [6,7]. Recent landmark trials have unveiled the potential of SGLT2i in reducing mortality, hospitalization rates, and symptom burden in heart failure (HF) patients, irrespective of their diabetic status [7]. A study reported that early initiation of SGLT2i post-AHF hospitalization significantly lowers the risk of all-cause mortality and HF events within the first nine months after discharge [6]. Similarly, another study found that starting SGLT2i during hospitalization for acute decompensated heart failure (ADHF) improves post-discharge outcomes. Monzo *et al.* [8] further confirmed the broad clinical applicability of these agents, demonstrating benefits across various ejection fractions and care settings. Despite these promising findings, critical questions remain regarding the optimal timing for initiating SGLT2i in AHF and the full extent of their therapeutic benefits. Early intervention with dapagliflozin and empagliflozin can enhance patient outcomes and redefine treatment paradigms in AHF management.

The aim of this study was to evaluate the early initiation of SGLT2i (dapagliflozin and empagliflozin) in AHF comprehensively. By synthesizing data from multiple studies, this study sought to address critical clinical questions about the timing of initiation, impact on patient outcomes, and potential adverse events (AEs). Through rigorous analysis, this study might offer clear evidence to support clinical decision-making and potentially reshape current treatment guidelines, emphasizing the importance of early intervention with dapagliflozin and empagliflozin in AHF management.

Methods

This systematic review and meta-analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guideline and was registered with the International Prospective Register of Systematic Reviews (PROSPERO); registration number CRD42024585838 [9].

Database and literature search

A comprehensive literature search was conducted on July 22, 2024, across multiple electronic databases: PubMed, ProQuest, SAGE Journals, EBSCOhost, Wiley Online Library, Google Scholar, and the Cochrane Library. The search strategy employed a combination of relevant keywords and medical subject headings (MeSH) terms, including “sodium-glucose transporter 2 inhibitors,” “dapagliflozin,” “empagliflozin,” “acute heart failure,” and “acute decompensated heart failure”. Boolean operators (AND/OR) were used to refine the search results. Filters were applied to include studies published in English between 2019 and 2024. Additionally, reference lists of pertinent reviews were manually screened to identify any additional relevant studies. Duplicates were removed using EndNote X9 (Clarivate Plc., London, England) duplicate removal function.

Eligibility criteria

Randomized controlled trials (RCTs) focusing on adult patients (≥18 years old) with AHF who received dapagliflozin or empagliflozin within the first five days of hospitalization were included. We excluded studies that employed other SGLT2i or non-pharmacological interventions, were not original RCTs (e.g., observational studies, case reports, or reviews), enrolled pediatric populations, or did not involve patients with AHF, initiated dapagliflozin or empagliflozin

treatment later than five days post-admission, failed to report our prespecified outcomes, or were not published in English.

Study selection and data extraction

Three investigators (SSI, ERY, and GT) independently screened the titles and abstracts of retrieved studies for eligibility. Full-text articles were obtained for studies that met the inclusion criteria or when eligibility was uncertain from the abstract. Any discrepancies during the screening process were resolved through discussion with senior authors (AEPS, IP, and VB). Data were extracted using a standardized form and included study characteristics (year of publication, study design, sample size), participant demographics, and clinically relevant outcomes such as all-cause mortality, HF-related events (e.g., worsening HF, rehospitalization), AEs, and other pertinent clinical endpoints.

Risk of bias assessment

The risk of bias for each included study was independently evaluated by three investigators (SSI, ERY, and GT) using the Cochrane Risk of Bias 2 (RoB 2) tool [10]. This instrument assesses five domains: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in the measurement of outcomes, and bias in the selection of reported results. Each domain has a low risk of bias, some concerns, or a high risk of bias. A study was considered low risk if all domains were judged to be low risk. If it had at least one domain with some concerns and none at high risk, it was judged as having some concerns. If any domain was rated high risk or if there were multiple domains with some concerns that reduced confidence in the outcome, the study was considered high risk. Only studies classified as low risk or some concerns were included in the analysis. Any discrepancies were resolved through discussion with the senior investigators (AEPS, IP, and VB).

Data synthesis and statistical analysis

Statistical analyses were performed using review manager (RevMan) version 5.4 (Cochrane Collaboration, Copenhagen, Denmark). For dichotomous outcomes, a pooled risk ratio (RR) with 95% confidence interval (CI) was calculated using the Mantel-Haenszel method. For continuous outcomes, pooled standardized mean difference (SMD) with 95% CIs were calculated using the inverse variance method. A random-effects model was employed to account for potential heterogeneity among studies. Statistical significance was set at $p<0.05$. Heterogeneity was assessed using the I^2 statistic, with values above 50% or a Chi-squared $p<0.10$ indicating substantial heterogeneity. In cases of significant heterogeneity, subgroup analyses were conducted to explore potential sources.

Sensitivity analysis and quality of evidence

Sensitivity analyses were conducted by removing studies classified as high risk of bias, defined as having at least one domain rated high risk or multiple domains rated as some concerns according to the RoB 2 tool, to evaluate the stability of the pooled results. The certainty of evidence for each outcome was assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework (high, moderate, low, or very low), briefly considering factors such as risk of bias, inconsistency, indirectness, imprecision, and publication bias [11].

Results

Study selection

A total of 473 records were identified through database searches, and one additional record was found via manual hand-searching, yielding 474 records for initial consideration. After the removal of 79 duplicates, 395 titles and abstracts were screened. Of these, 371 studies were excluded for being irrelevant to the research question. The full texts of the remaining 24 articles were assessed for eligibility. Fifteen studies were excluded at this stage: ten for evaluating different outcomes, four for containing irrelevant data, and one for different group intervention. Ultimately, nine RCTs met the inclusion criteria and were included in the final analysis. The study selection process is outlined in the PRISMA flow diagram (**Figure 1**).

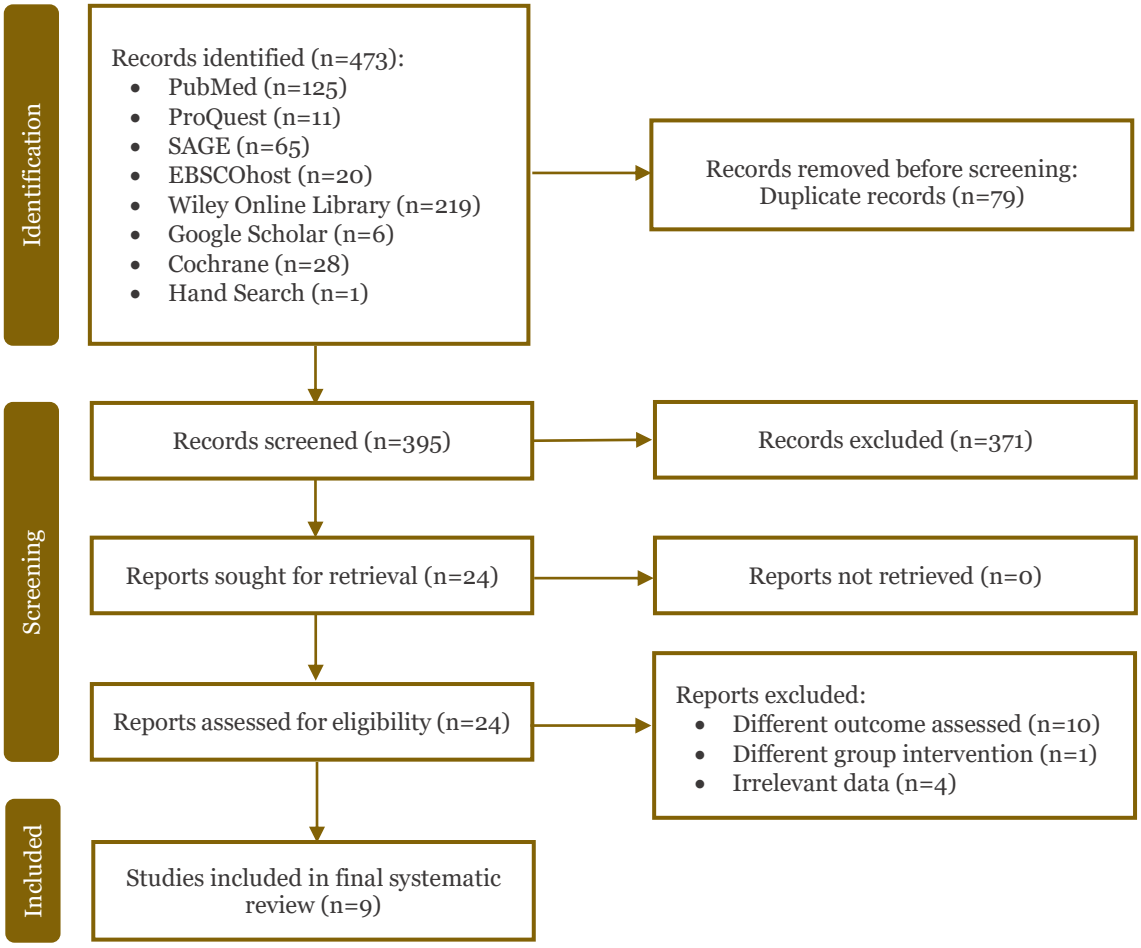

Figure 1. PRISMA flow diagram depicting study selection.

Risk of bias assessment

The risk of bias for each included study was evaluated using the Cochrane RoB 2 tool (**Figure 2**). Overall, four studies were rated as having some concerns regarding the risk of bias across the five assessed domains. Ibrahim *et al.* [12] exhibited concerns due to unclear blinding of participants and allocation concealment in Domains 1 and 2. Charaya *et al.* [13,14] raised concerns due to the lack of blinding of participants and personnel in Domain 2. Similarly, Cox *et al.* [15] was assessed with concerns in Domain 2 because neither participants nor personnel were blinded to treatment assignments.

The nine included studies were all RCTs published between 2020 and 2024 (**Table 1**). The total sample size comprised 1,417 patients with AHF. Of these, 28.44% received early dapagliflozin, 21.52% received early empagliflozin, and the remaining patients received a placebo. Among the patients, 70.94% had ADHF, while 29.06% were presented with de novo HF. Approximately 49.36% of the patients had comorbid diabetes. Detailed baseline characteristics, including patient demographics and clinical features, are presented in **Table 1**.

Effects of early initiation of dapagliflozin and empagliflozin on in-hospital all-cause mortality among AHF patients

The pooled analysis from all included studies assessing in-hospital all-cause mortality demonstrated that early initiation of dapagliflozin and empagliflozin significantly reduced the risk compared to placebo (RR: 0.58; 95%CI: 0.36–0.91; p=0.02) (**Figure 3**). The analysis showed no significant heterogeneity (I^2=0%), indicating consistent results across studies. According to the GRADE approach (**Table 2**), the quality of evidence for this outcome was classified as high.

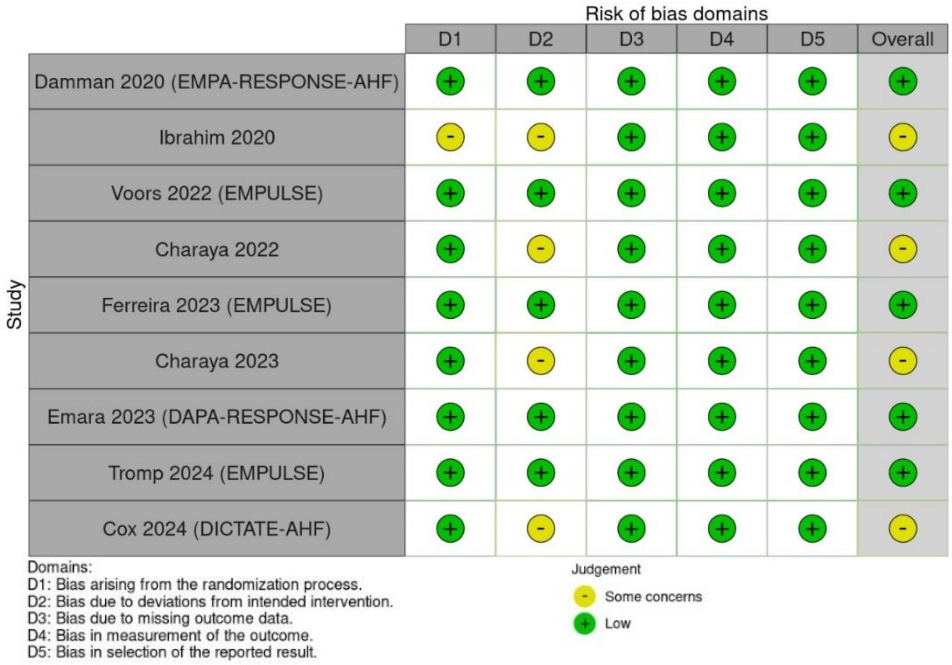

Figure 2. Risk of bias assessment using the Cochrane Risk of Bias 2 tool (RoB 2).

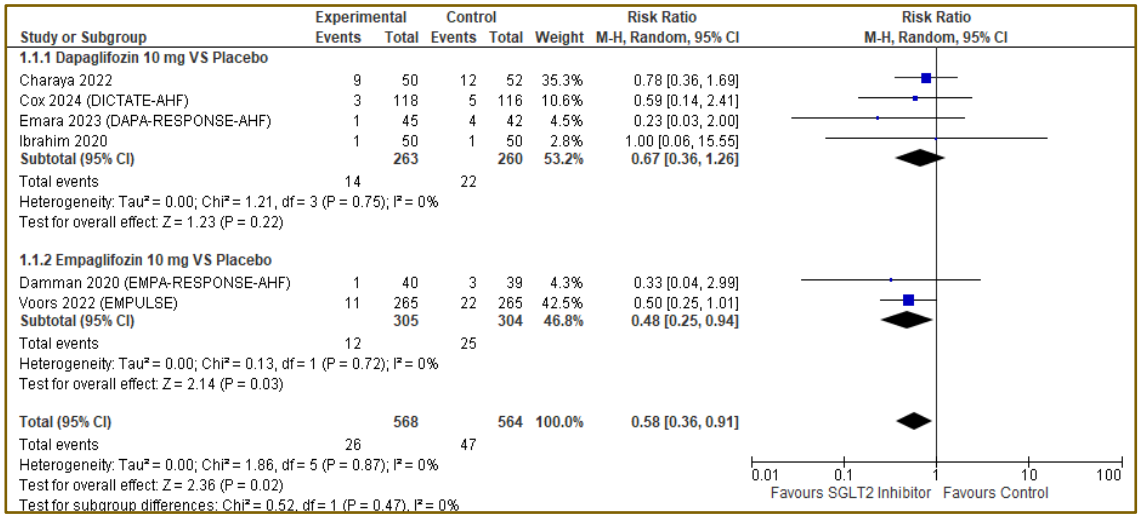

Figure 3. Forest plot showing the effects of early initiation of dapagliflozin and empagliflozin on in-hospital all-cause mortality among acute heart failure (AHF) patients.

Effects of early initiation of dapagliflozin and empagliflozin on in-hospital worsening heart failure among AHF patients

Early treatment with dapagliflozin and empagliflozin significantly decreased the risk of in-hospital worsening HF events compared to placebo (RR: 0.61; 95%CI: 0.43–0.86; p=0.005) (**Figure 4**). No significant heterogeneity was observed (I^2=0%), suggesting reliable and consistent findings among the included studies. The GRADE assessment rated the evidence for this outcome as high quality.

Table 1. Baseline characteristics of the included studies

Study	Year	Groups	n	Age (mean±SD, years)	Male (%)	History of heart failure (%)	Diabetes (%)	Initiation of treatment	Duration of hospital stay (days)	Follow-up (days)
Damman *et al.* [16]	2020	Empagliflozin 10 mg	40	78.20±7.60	60.00	42.0	38.0	24h post-admission, *quaque die* (QD) or once a day	30	60
		Placebo	39	72.20±16.90	74.00	44.0	28.0			
Ibrahim *et al.* [12]	2020	Dapagliflozin 10 mg	50	62.02±8.80	56.00	100.0	100.0	Timing not specified, QD	4.64±1.01	Length of follow-up was not mentioned
		Placebo	50	60.64±9.90	52.00	100.0	100.0		4.92±1.52	
Voors *et al.* [17]; Ferreira *et al.* [18]; Tromp *et al.* [19]	2022; 2023; 2024	Empagliflozin 10 mg	265	70.20±11.90	67.50	66.8	46.8	24 hours-5 days post-admission, QD	90	90
		Placebo	265	68.90±14.10	64.90	67.2	43.8			
Charaya *et al.* [13]	2022	Dapagliflozin 10 mg	50	72.60±12.20	58.00	66.0	30.0	24 hours post-admission, QD	6	30
		Placebo	52	74.20±11.30	52.00	62.0	30.0			
Charaya *et al.* [14]	2023	Dapagliflozin 10 mg	140	72.00±12.00	56.00	66.0	31.0	First 24 hours, QD	30	30
		Placebo	145	75.00±13.00	50.00	65.6	38.0			
Emara *et al.* [20]	2023	Dapagliflozin 10 mg	45	61.10±11.80	77.80	73.3	35.6	First 24 hours, QD	30	60
		Placebo	42	63.90±10.00	64.30	66.7	52.4			
Cox *et al.* [15]	2024	Dapagliflozin 10 mg	118	64.60±3.70	66.00	86.0	71.0	First 24 hours, QD	30	30
		Placebo	116	78.20±7.50	56.00	87.0	71.0			
Summary[¶]			1,417	70.23±12.47	61.04	70.9	51.1		4.78±1.29	50

[¶]Accounting for only the available data and excluding duplicates

Table 2. Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework

Outcome	Certainty assessment							Summary of findings				
	Participants (studies) follow-up	Risk of bias	IC	ID	IM	Publication bias	Overall certainty of evidence	Study event rates (%)			Anticipated absolute effects	
								With control	With early dapagliflozin and empagliflozin	Relative effect (95%CI)	Risk with control	Risk difference with early dapagliflozin and empagliflozin
All-cause mortality (follow-up: range 5 days to 90 days)	1132 (6 RCTs) [12,13,15-17,20]	Not serious	Not serious	Not serious	Not serious	None	⊕⊕⊕⊕ High	47/564 (8.3%)	26/568 (4.6%)	RR 0.58 (0.36–0.91)	47/564 (8.3%)	4 fewer per 100 (from 5 fewer to 1 fewer)
In-hospital worsening heart failure	1032 (5 RCTs) [13,15-17,20]	Not serious	Not serious	Not serious	Not serious	None	⊕⊕⊕⊕ High	78/514 (15.2%)	47/518 (9.1%)	RR 0.61 (0.43–0.86)	78/514 (15.2%)	6 fewer per 100 (from 9 fewer to 2 fewer)
Heart failure-related rehospitalization (follow-up: range 30 days to 60 days)	843 (3 RCTs) [15-17]	Not serious	Not serious	Not serious	Serious	None	⊕⊕⊕◯ Moderate[a]	25/420 (6.0%)	22/423 (5.2%)	RR 0.88 (0.50–1.55)	25/420 (6.0%)	1 fewer per 100 (from 3 fewer to 3 more)
30-days all-cause rehospitalization	866 (3 RCTs) [13,15,18]	Not serious	Not serious	Not serious	Serious[a]	None	⊕⊕⊕◯ Moderate[a]	114/433 (26.3%)	93/433 (21.5%)	RR 0.82 (0.64–1.04)	114/433 (26.3%)	5 fewer per 100 (from 9 fewer to 1 more)
Length of hospital stay	368 (4 RCTs) [12,13,16,20]	Not serious	Not serious	Not serious	Serious[a]	None	⊕⊕⊕◯ Moderate[a]	183	185	-	-	SMD 0.03 lower (0.28 lower to 0.23 higher)
Change in weight/ 40 mg IV furosemide or diuretic response in Kg/40mg furosemide	313 (2 RCTs) [15,16]	Not serious	Not serious	Not serious	Serious[a]	None	⊕⊕⊕◯ Moderate[a]	155	158	-	155	SMD 0.05 (0.27 lower to 0.17 higher)

Outcome	Certainty assessment							Summary of findings				
	Participants (studies) follow-up	Risk of bias	IC	ID	IM	Publication bias	Overall certainty of evidence	Study event rates (%)			Anticipated absolute effects	
								With control	With early dapagliflozin and empagliflozin	Relative effect (95%CI)	Risk with control	Risk difference with early dapagliflozin and empagliflozin
Sodium serum	385 (2 RCTs) [12,14]	Not serious	Serious[b]	Not serious	Serious[a]	None	⊕⊕◯◯ Low[a,b]	195	190	-	195	SMD 0.08 higher (0.3 lower to 0.46 higher)
Adverse events	764 (2 RCTs) [15,17]	Not serious	Not serious	Not serious	Serious[a]	None	⊕⊕⊕◯ Moderate[a]	261/381 (68.5%)	241/383 (62.9%)	RR 0.91 (0.82–1.00)	261/381 (68.5%)	6 fewer per 100 (from 12 fewer to 0 fewer)
Acute kidney injury	843 (3 RCTs) [15,16]	Not serious	Not serious	Not serious	Serious[a]	None	⊕⊕⊕◯ Moderate[a]	20/420 (4.8%)	15/423 (3.5%)	RR 1.20 (0.27–5.25)	20/420 (4.8%)	1 more per 100 (from 3 fewer to 20 more)
Symptomatic hypotension	945 (4 RCTs) [13,15,16,19]	Not serious	Not serious	Not serious	Serious[a]	None	⊕⊕⊕◯ Moderate[a]	36/472 (7.6%)	32/473 (6.8%)	RR 0.89 (0.57–1.41)	36/472 (7.6%)	1 fewer per 100 (from 3 fewer to 3 more)
Hypoglycemia	930 (4 RCTs) [15-17,20]	Not serious	Not serious	Not serious	Serious[a]	None	⊕⊕⊕◯ Moderate[a]	14/462 (3.0%)	13/468 (2.8%)	RR 0.91 (0.44–1.89)	14/462 (3.0%)	0 fewer per 100 (from 2 fewer to 3 more)
Urinary tract infection	1032 (5 RCTs) [13,15-17,20]	Not serious	Not serious	Not serious	Serious[a]	None	⊕⊕⊕◯ Moderate[a]	19/514 (3.7%)	11/518 (2.1%)	RR 0.61 (0.30–1.22)	19/514 (3.7%)	1 fewer per 100 (from 3 fewer to 1 more)
Serious adverse events	696 (3 RCTs) [16,17,20]	Not serious	Not serious	Not serious	Not serious	None	⊕⊕⊕⊕ High	126/346 (36.4%)	92/350 (26.3%)	RR 0.73 (0.59–0.90)	126/346 (36.4%)	10 fewer per 100 (from 15 fewer to 4 fewer)

CI: confidence interval; IC: inconsistency; ID: indirectness; IM: imprecision; RR: risk ratio; SMD: standardised mean difference
[a]Downgraded by one level due to wide confidence intervals
[b]Downgraded by one level due to substantial heterogeneity, which was not resolved by sensitivity analysis

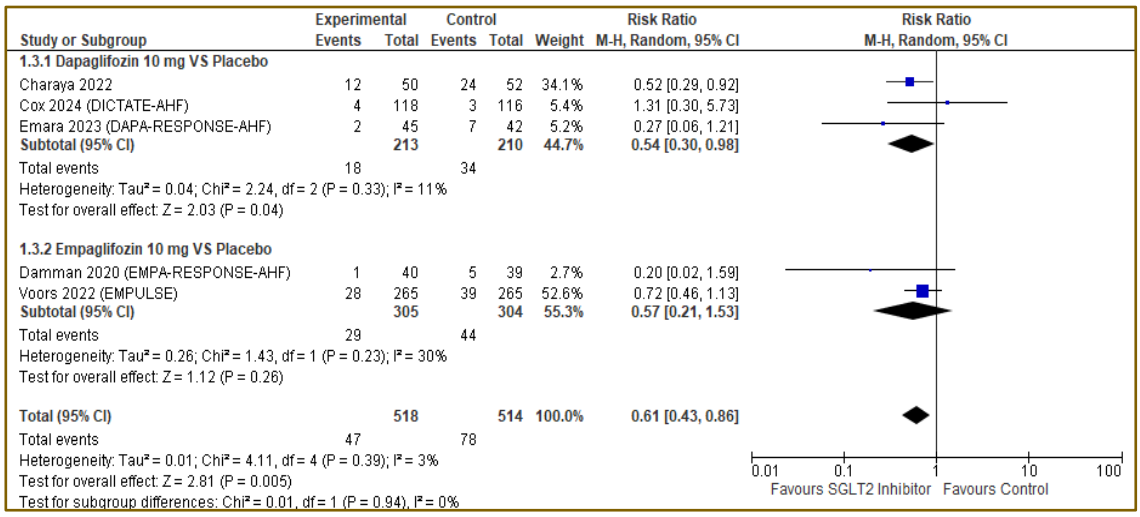

Figure 4. Forest plot showing the effects of early initiation of dapagliflozin and empagliflozin on in-hospital worsening heart failure among acute heart failure (AHF) patients.

Effects of early initiation of dapagliflozin and empagliflozin on heart failure-related rehospitalization across in-hospital among AHF patients

Early treatment with dapagliflozin and empagliflozin did not significantly decrease the risk of rehospitalization across in-hospital at the longest follow-up (**Figure 5**). The analysis showed no significant heterogeneity (I^2=0%), suggesting consistent and reliable results across the included studies. The GRADE assessment rated the certainty of the evidence as moderate.

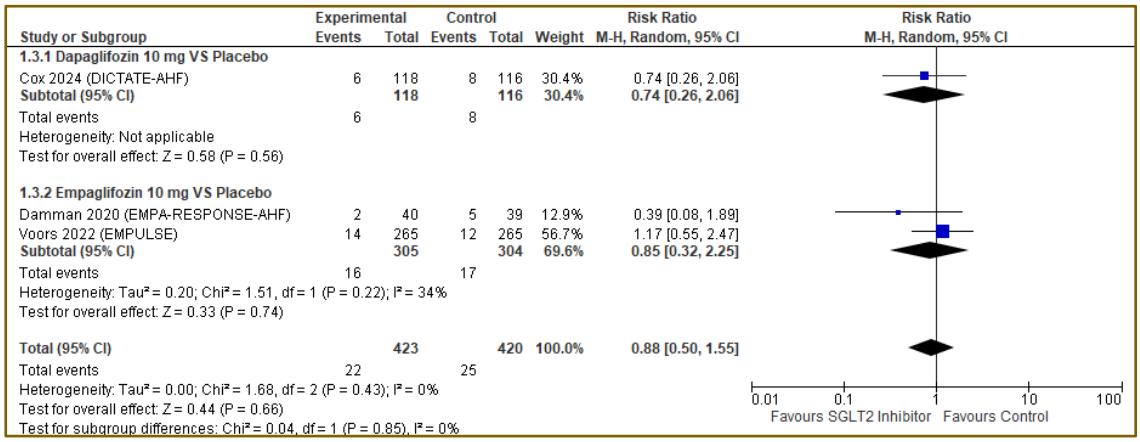

Figure 5. Forest plot showing the effects of early initiation of dapagliflozin and empagliflozin on heart failure-related rehospitalization across in-hospital, at the longest follow-up among acute heart failure (AHF) patients.

Effects of early initiation of dapagliflozin and empagliflozin on 30-day all-cause rehospitalization among AHF patients

Early treatment with dapagliflozin and empagliflozin also did not significantly affect the risk of 30-day all-cause rehospitalization. The analysis showed no significant heterogeneity (I^2=0%) in **Figure 6**, suggesting consistent and reliable results across the included studies. The GRADE assessment rated the certainty of the evidence as moderate.

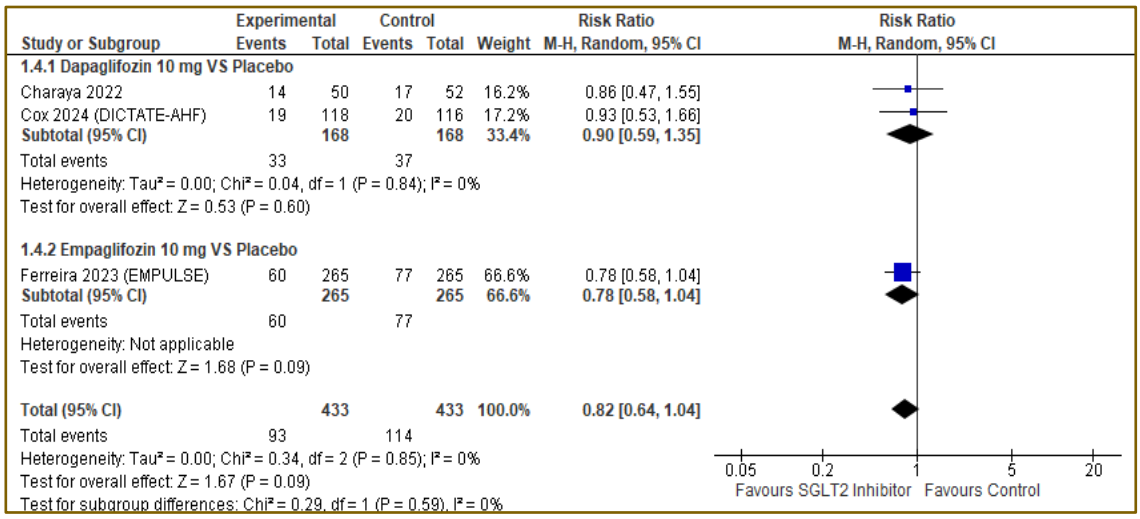

Figure 6. Forest plot showing the effects of early initiation of dapagliflozin and empagliflozin on 30-day all-cause rehospitalization among acute heart failure (AHF) patients.

Effects of early initiation of dapagliflozin and empagliflozin on length of hospital stay, diuretic response, and serum sodium levels at discharge among AHF patients

Both dapagliflozin and empagliflozin did not significantly affect the length of hospital stay (SMD: -0.03; 95%CI: -0.28–0.23; p=0.09; I^2=36%) with moderate degree of certainty (**Figure 7**), diuretic response (SMD: -0.05; 95%CI: -0.27–0.17; p=0.65; I^2=0%) with moderate degree of certainty (**Figure 8**), and serum sodium levels at discharge (SMD: 0.08; 95%CI: -0.30–0.46; p=0.67; I^2=64%) with significant heterogeneity and a low degree of certainty based on GRADE approach (**Figure 9**). There were no significant differences in subgroup analysis for any outcome.

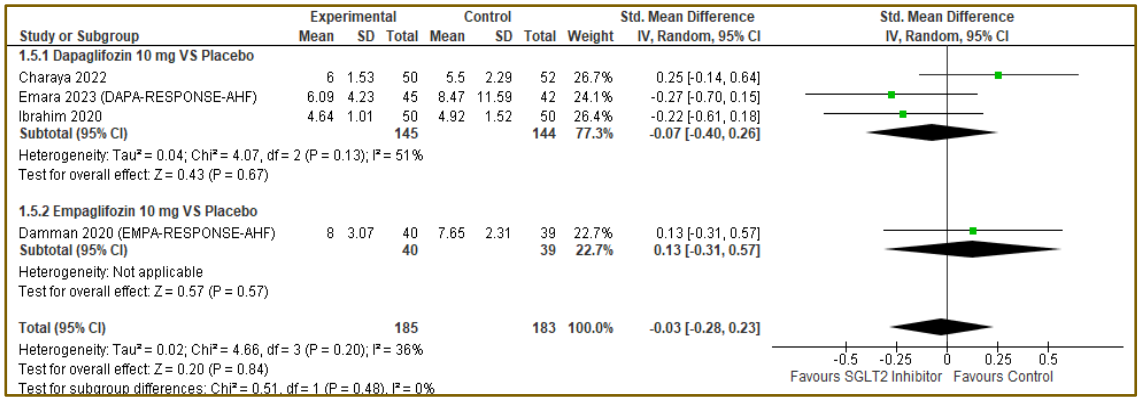

Figure 7. Forest plot showing the effects of early initiation of dapagliflozin and empagliflozin on length of hospital stay among acute heart failure (AHF) patients.

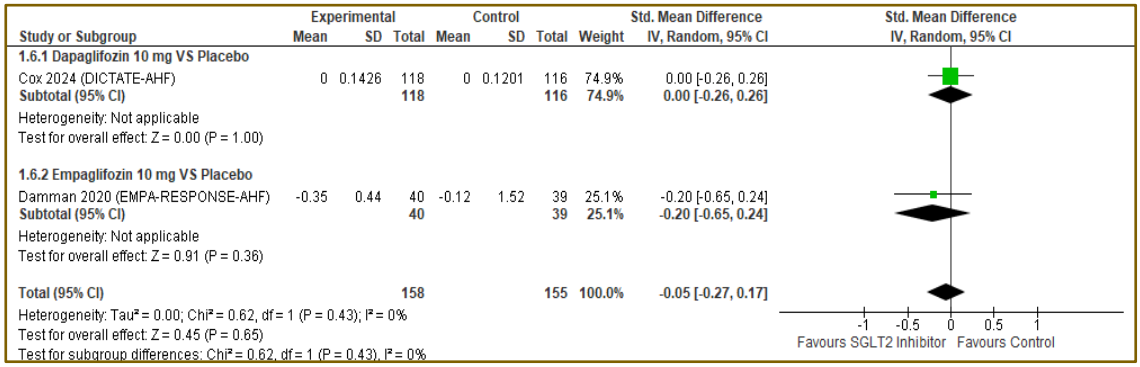

Figure 8. Forest plot showing the effects of early initiation of dapagliflozin and empagliflozin on diuretic response in acute heart failure (AHF) patients.

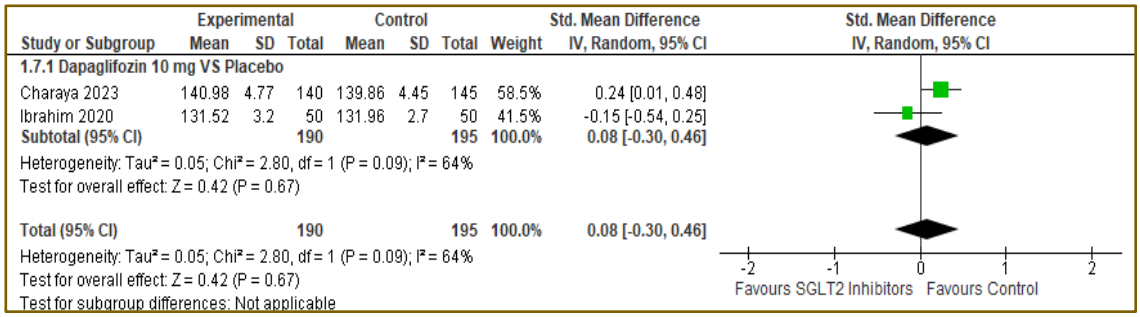

Figure 9. Forest plot showing the effects of early initiation of dapagliflozin and empagliflozin on discharge serum sodium levels among acute heart failure (AHF) patients.

Adverse events of dapagliflozin and empagliflozin in AHF patients

Analysis of AEs is reported in **Figure 10** until **Figure 15**. All analyses showed early dapagliflozin and empagliflozin did not significantly affect AEs (**Figure 10**), acute kidney injury (AKI) (**Figure 11**), symptomatic hypertension (**Figure 12**), hypoglycemia (**Figure 13**), and urinary tract infection (UTI) (**Figure 14**). However, empagliflozin showed a significant decrease in the risk of serious AEs compared to control (RR: 0.73; 95%CI: 0.59–0.90; p=0.004), with no significant heterogeneity (I^2=0%) (**Figure 15**). According to the GRADE approach, most AEs outcomes were classified as having a moderate degree of certainty, while serious AEs were classified as having high degree of certainty.

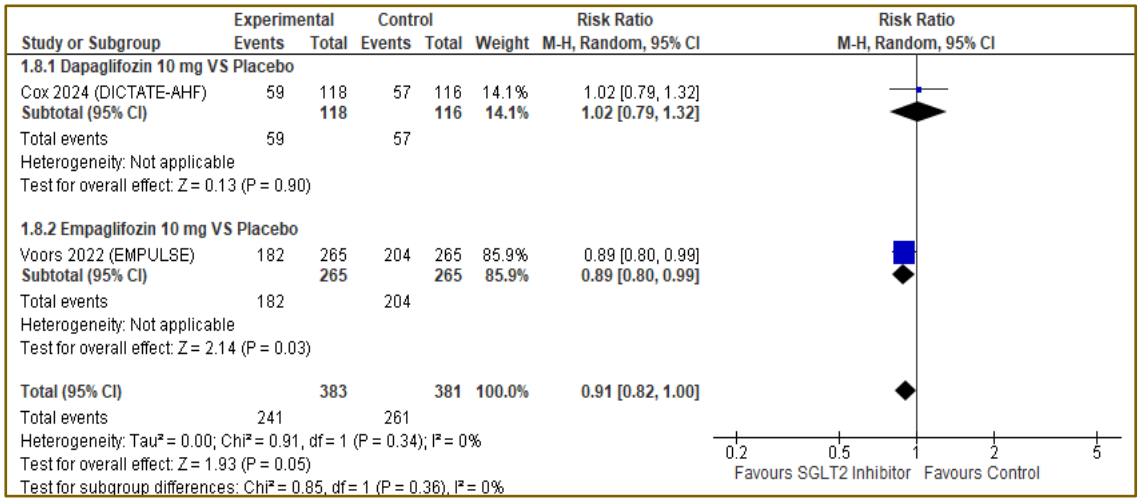

Figure 10. Forest plot showing the effects of early initiation of dapagliflozin and empagliflozin on adverse events among acute heart failure (AHF) patients.

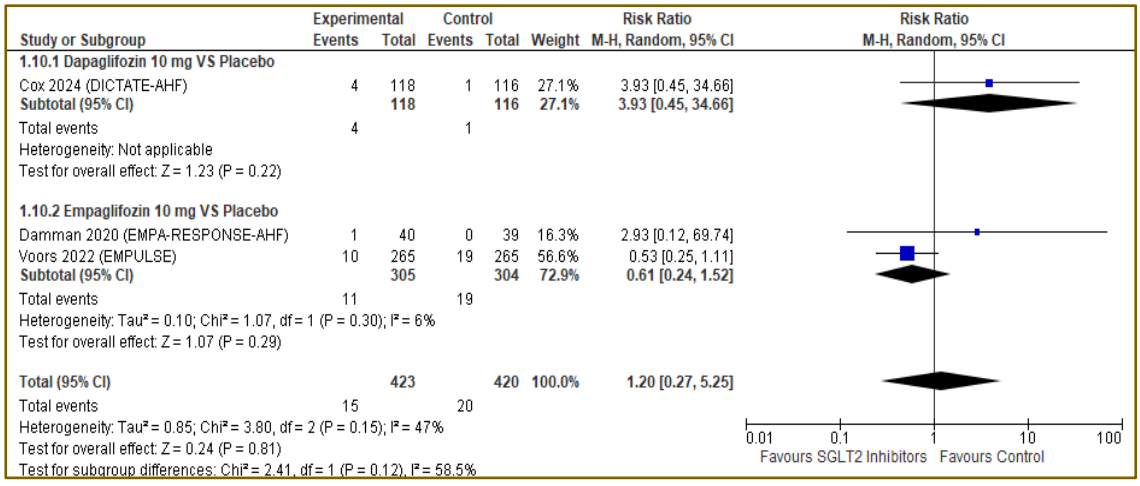

Figure 11. Forest plot showing the effects of early initiation of dapagliflozin and empagliflozin on acute kidney injury among acute heart failure (AHF) patients.

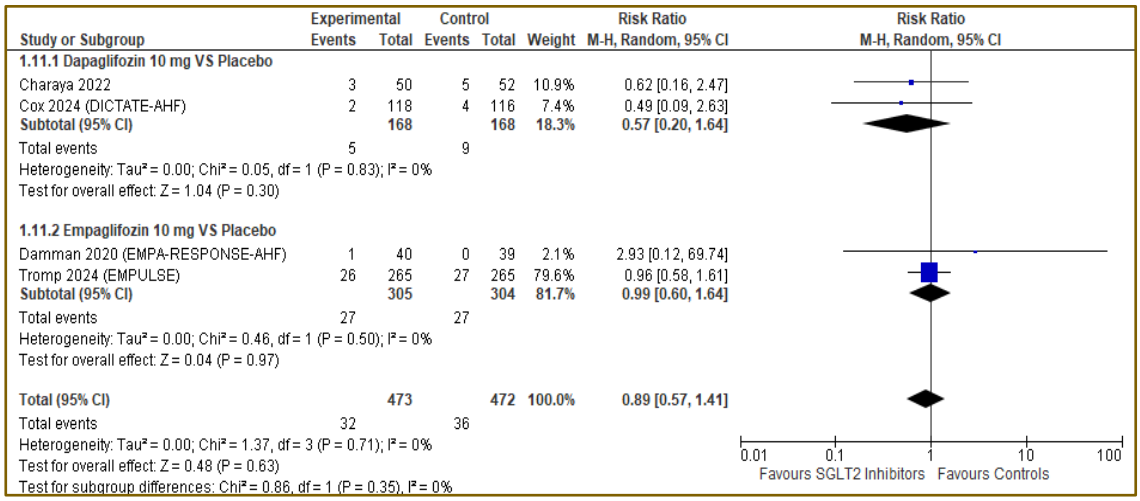

Figure 12. Forest plot showing the effects of early initiation of dapagliflozin and empagliflozin on symptomatic hypotension among acute heart failure (AHF) patients.

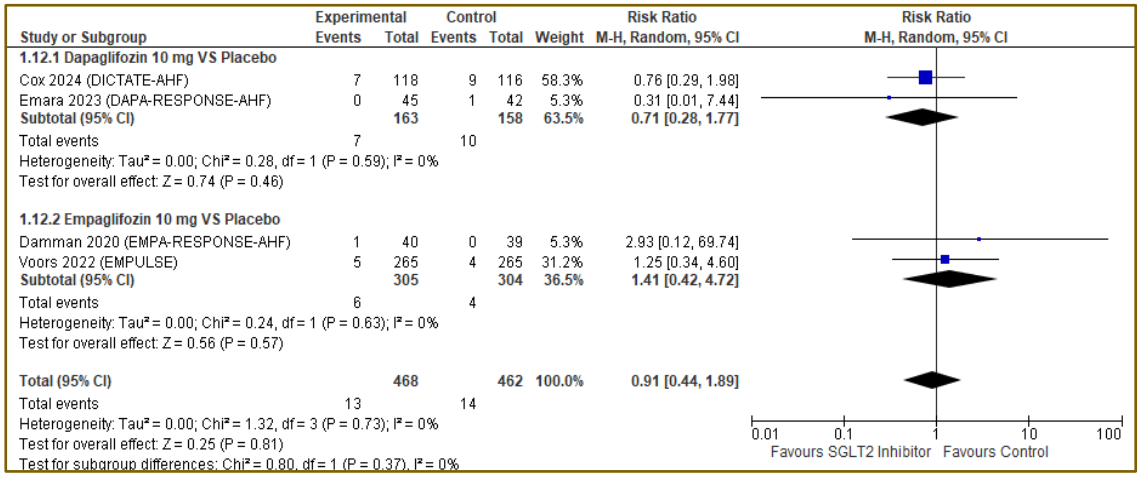

Figure 13. Forest plot showing the effects of early initiation of dapagliflozin and empagliflozin on hypoglycemia among acute heart failure (AHF) patients.

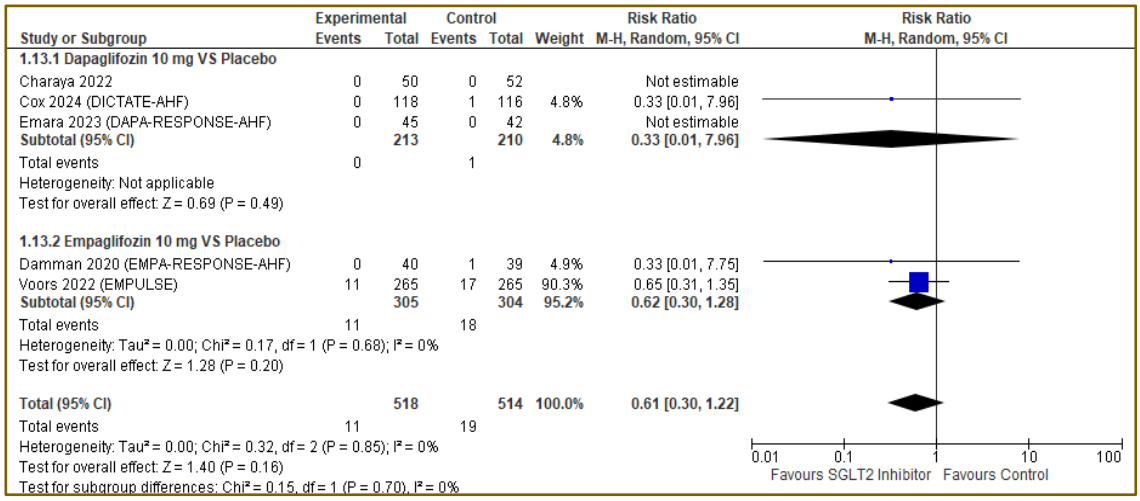

Figure 14. Forest plot showing the effects of early initiation of dapagliflozin and empagliflozin on urinary tract infection among acute heart failure (AHF) patients.

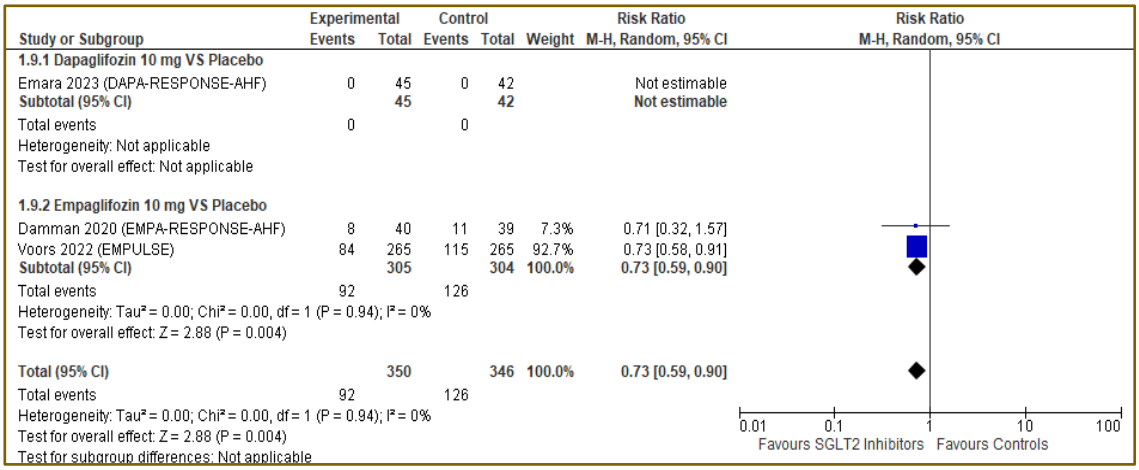

Figure 15. Forest plot showing the effects of early initiation of dapagliflozin and empagliflozin on serious adverse events among acute heart failure (AHF) patients.

Discussion

This systematic review and meta-analysis of nine RCTs involving 1,417 patients with AHF demonstrated that initiating SGLT2i—specifically dapagliflozin and empagliflozin—within five days of hospital admission significantly reduced in-hospital all-cause mortality by 42% and in-hospital worsening HF by 39%. Additionally, SGLT2i use was associated with a 27% reduction in serious AEs risk. No significant differences were observed in other outcomes, including specific AEs such as AKI, hepatic injury, symptomatic hypotension, hypoglycemia, UTIs, and diabetic ketoacidosis. The analysis showed homogeneity across studies, with no significant differences between the effects of dapagliflozin and empagliflozin.

Our findings on mortality align with previous studies [21,22], which reported that early initiation of SGLT2i can prevent significant deterioration in cardiac function. The hemodynamic stability provided by SGLT2i, resulting from their natriuretic effects, contributes to the prevention of functional decline in HF patients and reduces the need for intensified diuretic therapy. This benefit is particularly notable with prolonged treatment, highlighting the efficacy of SGLT2i in stabilizing patients with AHF.

The significant reduction in in-hospital worsening HF corroborates previous studies [22,23], which attributed these benefits to favorable changes in natriuretic peptide concentrations, leading to decreased left ventricular mass and attenuation of cardiac remodeling. These physiological effects may contribute to the improved clinical outcomes observed with early SGLT2i initiation in AHF patients.

Contrastingly, some studies reported differing results regarding rehospitalization and length of hospital stay. Other studies [24,25] supported the beneficial effects of early dapagliflozin on reducing rehospitalization risk, particularly in patients with acute de novo HF. However, another study indicated that SGLT2i reduces rehospitalization risk compared to non-SGLT2i treatments. Variations in study populations, definitions of HF subtypes, and trial designs may explain these discrepancies. Our findings did not significantly impact the length of hospital stay, differing from one previous study [25], which reported a shorter hospital stay with early dapagliflozin initiation.

The lack of significant influence of SGLT2i on diuretic response, measured by weight loss, contrasts with previous studies [26,27], which suggested that the benefits of SGLT2i may vary depending on body mass index (BMI). One previous study [27] observed a consistent weight loss effect with empagliflozin across all BMI categories. Discrepancies may result from variations in patient characteristics, BMI distributions, and the duration of follow-up in different studies.

Our findings that SGLT2i did not significantly affect discharged serum sodium levels are consistent with a previous study [28], which observed that early SGLT2i treatment leads to an initial reduction in sodium concentration due to osmotic and natriuretic diuresis. This is followed by compensatory mechanisms, such as increased vasopressin secretion and reduced free-water clearance, ultimately stabilizing serum sodium levels at discharge.

Regarding safety outcomes, we did not observe significant differences in the incidence of specific AEs, which aligns with previous studies [29,30], suggesting that early SGLT2i initiation is generally safe in AHF patients. However, the significant reduction in serious AEs with empagliflozin observed in our study corroborates findings reported in previous research [22]. Although we did not find a significant increase in AKI among patients treated with SGLT2i, some studies have reported transient changes in renal function parameters, indicating that further investigation is warranted to elucidate the long-term implications on renal function in AHF patients.

Our analysis did not show a significant increase in UTIs or hypoglycemia, which is consistent with previous studies [30,31]. The glycemic effects of empagliflozin were observed primarily in patients with T2DM, with minimal impact on those with normoglycemia or prediabetes, as reported in previous research [27] which aligns with the mechanism of SGLT2i targeting hyperglycemia.

This study has several limitations that should be considered. First, the included trials varied in their designs, patient populations, and outcome definitions, which may contribute to heterogeneity despite statistical homogeneity. Second, the relatively short follow-up periods may not capture long-term outcomes and AEs associated with SGLT2i use. Third, the majority of patients had comorbid T2DM, which may limit the generalizability of the findings to non-diabetic AHF populations. Additionally, the analysis did not fully account for the potential influences of concomitant medications and variations in standard HF therapies.

Conclusion

Early initiation of dapagliflozin and empagliflozin in patients with AHF offers significant benefits in reducing in-hospital mortality and worsening HF, without increasing the risk of AEs. These findings support their use as a potential therapeutic strategy in this population, particularly due to their safety profile and efficacy in preventing serious AEs. However, the lack of impact on rehospitalization, length of stay, and other secondary outcomes indicates that further research is warranted to evaluate these aspects comprehensively.

Ethics approval

Not required.

Acknowledgment

None.

Competing interests

All the authors declare that there are no conflicts of interest.

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Underlying data

Derived data supporting the findings of this study are available as part of the study. from the corresponding author on request.

Declaration of artificial intelligence use

We hereby confirm that no artificial intelligence (AI) tools or methodologies were utilized at any stage of this study, including during data collection, analysis, visualization, or manuscript preparation. All work presented in this study was conducted manually by the authors without the assistance of AI-based tools or systems.

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