RESEARCH PAPER

Clinical Trial Evidence on SGLT2 Inhibitors for Hospitalization and Mortality in Heart Failure: A Systematic Review and Meta-analysis of Randomized Controlled Trials

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Abstract:

Introduction: Heart failure remains a major contributor to morbidity, mortality, and healthcare utilization worldwide. In recent years, several large randomized controlled trials have evaluated sodium–glucose cotransporter-2 (SGLT2) inhibitors across the spectrum of left ventricular ejection fraction. Integration of cumulative trial-level evidence is necessary to clarify the magnitude and consistency of therapeutic benefit. The objective of this study was to synthesize randomized controlled trial data assessing the effect of SGLT2 inhibitors on hospitalization for heart failure, cardiovascular mortality, and all-cause mortality.

Materials and Methods: A systematic review and meta-analysis of phase III, placebo-controlled randomized trials was conducted in accordance with PRISMA 2020 guidelines. PubMed/MEDLINE, Embase, and Cochrane Central were searched for eligible studies published between 2018 and 2025. Hazard ratios (HRs) with 95% confidence intervals (CIs) were pooled using a random-effects model with the generic inverse variance method. Risk of bias was assessed using the Cochrane RoB 2 tool, and certainty of evidence was evaluated using the GRADE framework.

Results: Four multicenter randomized trials including over 20,000 participants were analyzed. SGLT2 inhibitors significantly reduced hospitalization for heart failure (HR 0.72; 95% CI 0.67–0.78; $I^2 = 0\%$) and cardiovascular mortality (HR 0.88; 95% CI 0.80–0.96; $I^2 = 0\%$). A modest reduction in all-cause mortality was observed (HR 0.93; 95% CI 0.86–1.00; $I^2 = 4\%$). Treatment effects were consistent across trials.

Conclusion: This meta-analysis demonstrates consistent reductions in heart failure hospitalization and cardiovascular mortality with SGLT2 inhibitors, supporting their role as evidence-based pharmacotherapy in heart failure management.

Keywords: Heart failure, Sodium-glucose transporter 2 inhibitors, Hospitalization, Cardiovascular mortality, Randomized controlled trials, Meta-analysis

Key Messages: This quantitative synthesis of large event-driven randomized trials confirms consistent reductions in heart failure hospitalization and cardiovascular mortality with SGLT2 inhibitors across phenotypes, highlighting the reproducibility and methodological robustness of treatment effects across independent clinical trial programs.

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INTRODUCTION

Heart failure (HF) remains a major cardiovascular disorder associated with substantial morbidity, mortality, and healthcare utilization worldwide.[1] In India, the prevalence of HF continues to increase due to rising rates of ischemic heart disease, hypertension, diabetes mellitus, and population aging.[2] Recurrent hospitalizations for decompensated heart failure are common and are associated with adverse clinical outcomes, impaired quality of life, and increased economic burden. Reduction in hospitalization and mortality therefore represents a central objective of contemporary heart failure management.

Heart failure is broadly classified into heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF). While

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advances in pharmacological therapy have substantially improved outcomes in HFrEF, therapeutic options for HFpEF have historically been limited, and event rates remain high across the ejection fraction spectrum.[3] Contemporary international guidelines from the European Society of Cardiology (ESC) and the American College of Cardiology/American Heart Association (ACC/AHA) recommend sodium–glucose cotransporter-2 (SGLT2) inhibitors as foundational therapy in patients with heart failure, irrespective of diabetes status and across ejection fraction categories.[3,4]

Originally developed as glucose-lowering agents for type 2 diabetes mellitus, SGLT2 inhibitors have demonstrated cardiovascular benefits beyond glycemic control. Large randomized controlled trials, including DAPA-HF and EMPEROR-Reduced in patients with HFrEF, and EMPEROR-Preserved and DELIVER in patients with mildly reduced or preserved ejection fraction, have evaluated their role in heart failure management.[5–8] These trials consistently demonstrated reductions in hospitalization for heart failure, with variable effects on cardiovascular and all-cause mortality. Collectively, these findings have led to incorporation of SGLT2 inhibitors into guideline-directed medical therapy.

Despite robust evidence from individual trials, differences in study populations, endpoint definitions, and ejection fraction criteria necessitate integrated quantitative synthesis to define the magnitude and consistency of benefit more precisely. A pooled evaluation of hospitalization and mortality outcomes across randomized trials may provide a clearer estimate of treatment effect and heterogeneity, thereby strengthening the evidence base for clinical decision-making.

In view of the expanding role of SGLT2 inhibitors in heart failure management, this systematic review and meta-analysis was undertaken to evaluate the effect of SGLT2 inhibitors compared with placebo on hospitalization for heart failure, cardiovascular mortality, and all-cause mortality across the spectrum of heart failure phenotypes.

MATERIALS AND METHODS

Study design and reporting standards

This systematic review and meta-analysis was undertaken to quantitatively evaluate the effect of sodium–glucose cotransporter-2 (SGLT2) inhibitors on hospitalization and mortality outcomes in patients with heart failure. The review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement to ensure methodological transparency and completeness of reporting.[9] The study protocol was prospectively registered with the Open Science Framework (OSF) registries prior to formal data extraction in order to minimize the risk of selective outcome reporting. As this study involved secondary analysis of published randomized controlled trials, institutional ethical approval and informed consent were not required.

Eligibility criteria

Eligibility criteria were defined a priori. Randomized controlled trials enrolling adults (≥18 years) with clinically diagnosed heart failure were considered eligible if they compared an SGLT2 inhibitor with placebo and reported hazard ratios with corresponding 95% confidence intervals for hospitalization for heart failure, cardiovascular mortality, and all-cause mortality. Trials including populations with heart failure with reduced ejection fraction (HFrEF) as well as heart failure with preserved ejection fraction (HFpEF) were included to allow assessment across the spectrum of disease.

Studies were included if they were peer-reviewed, placebo-controlled randomized controlled trials published in English between January 2018 and December 2025. Observational studies, registry-based analyses, non-randomized trials, post hoc subgroup analyses without independent reporting of relevant outcomes, conference abstracts without full publication, and duplicate reports from the same study population were excluded. Where multiple publications from a single trial were identified, the primary publication containing the most comprehensive outcome data was selected.

Search strategy

A systematic literature search was performed in PubMed/MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials to identify eligible studies published between January 2018 and December 2025. The search period was selected to capture contemporary large-scale cardiovascular outcome trials evaluating SGLT2 inhibitors in heart failure populations.

Medical Subject Headings (MeSH) and free-text terms were combined using Boolean operators. The search strategy included the terms: (“SGLT2 inhibitors” OR “dapagliflozin” OR “empagliflozin”) AND (“heart failure” OR “HFrEF” OR “HFpEF”) AND (“hospitalization” OR “cardiovascular mortality” OR “all-cause mortality”) AND (“randomized controlled trial”). Filters were applied to include peer-reviewed articles published in English. Reference lists of major heart failure guidelines and landmark randomized trials were manually screened to ensure completeness of eligible studies.

Study selection

Two reviewers independently screened titles and abstracts to assess eligibility. Full-text articles of potentially relevant studies were subsequently evaluated against predefined inclusion and exclusion criteria. Trials enrolling adult patients with clinically diagnosed heart failure and comparing an SGLT2 inhibitor with placebo were included if they reported hazard ratios with corresponding 95% confidence

intervals for hospitalization for heart failure, cardiovascular mortality, or all-cause mortality.

Disagreements between reviewers were resolved through discussion and consensus. Where consensus could not be reached, a third independent reviewer adjudicated the decision. The overall study selection process followed PRISMA recommendations.[9]

Data extraction

Data extraction was performed independently by two investigators using a standardized data collection form developed in Microsoft Excel 365 (Microsoft Corporation, Redmond, WA, USA). Extracted variables included study name, year of publication, sample size, baseline patient characteristics, heart failure phenotype (HFrEF or HFpEF), intervention details, duration of follow-up, and reported hazard ratios with 95% confidence intervals for relevant outcomes.

For quantitative synthesis, hazard ratios were logarithmically transformed, and corresponding standard errors were calculated using established statistical methods to permit pooling with inverse variance techniques. Any discrepancies in extracted data were verified against source publications and resolved by consensus.

Risk of bias assessment

Methodological quality of included trials was evaluated using the revised Cochrane Risk of Bias tool for randomized trials (RoB 2).[10] Domains assessed included the randomization process, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, completeness of outcome data, and selective reporting. Each study was categorized as having low, unclear, or high risk of bias across domains.

Outcomes

The primary outcome was hospitalization for heart failure. This outcome was selected due to its clinical relevance and its substantial contribution to morbidity and healthcare utilization in heart failure populations. Secondary outcomes included cardiovascular mortality and all-cause mortality.

Statistical analysis

Hazard ratios (HRs) with 95% confidence intervals (CIs) were used as summary measures of effect. Pooled estimates were calculated using the generic inverse variance method under a random-effects model to account for potential clinical variability across trials.

Statistical heterogeneity was assessed using the I^2 statistic, with values below 25% considered low, 25–50% moderate, and above 50% substantial heterogeneity.[11] A two-sided P value <0.05 was considered statistically significant. All analyses were performed using Review Manager (RevMan) version 5.4.1.

Predefined subgroup analyses were conducted according to heart failure phenotype (HFrEF versus HFpEF) to evaluate consistency of treatment effects across ejection fraction categories.

A leave-one-out sensitivity analysis was not performed due to negligible statistical heterogeneity (I^2 ranging from 0–4%) and consistent direction of effect across included trials. Given the limited number of studies and low heterogeneity, additional sensitivity analyses were unlikely to materially influence pooled estimates.

Formal assessment of publication bias using funnel plots or statistical testing (e.g., Egger's regression) was not undertaken. Methodological guidance suggests that funnel plot interpretation is unreliable when fewer than ten studies are included.[11] As only four randomized trials met eligibility criteria, such assessment would not provide meaningful inference.

Certainty of evidence assessment

The certainty of evidence for each outcome was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[12] Domains assessed included risk of bias, inconsistency, indirectness, imprecision, and potential publication bias.

Ethical considerations

This study was based exclusively on analysis of previously published randomized controlled trials and did not involve direct patient recruitment or access to individual-level data. Therefore, institutional ethical approval and informed consent were not required.

RESULTS

Study selection and sample characteristics

The systematic search identified 1,243 records across electronic databases. After removal of duplicates, 1,087 unique records were screened based on titles and abstracts. Of these, 1,072 were excluded for not meeting predefined eligibility criteria. Fifteen full-text articles were assessed for detailed evaluation. Eleven studies were excluded due to observational design, post-hoc subgroup analyses without independent outcome reporting, or duplication of trial populations. Ultimately, four randomized controlled trials met inclusion criteria and were included in the quantitative synthesis. The study selection process is summarized in Figure 1.

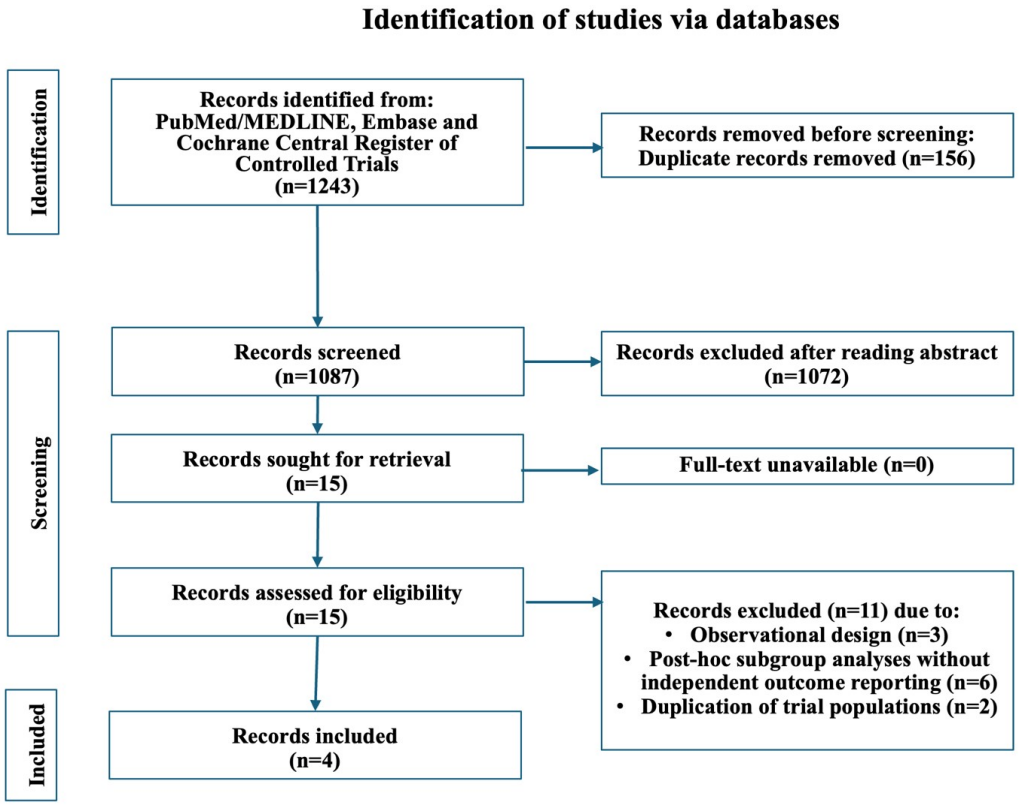

Figure 1: PRISMA flow diagram showing study selection process.

Study characteristics

The four included trials comprised a total study population exceeding 20,000 participants with chronic heart failure. Two trials enrolled patients with heart failure with reduced ejection fraction (HFrEF), while two included patients with mildly reduced or preserved ejection fraction (HFpEF).[5–8] All were multicenter, double-blind, placebo-controlled phase III randomized controlled trials, with follow-up durations ranging from approximately 18 to 28 months.

Baseline characteristics were broadly comparable across trials with respect to age, sex distribution, background guideline-directed medical therapy, and prevalence of comorbid conditions. All trials reported hazard ratios with 95% confidence intervals for hospitalization for heart failure, cardiovascular mortality, and all-cause mortality. Study characteristics are summarized in Table 1.

Table 1: Characteristics of included randomized controlled trials evaluating SGLT2 inhibitors in heart failure

Study	Year	Study design	Population	Sample Size (n)	LVEF criteria	Intervention	Comparator	Median Follow-up	Primary Outcome
DAPA-HF[5]	2019	Double-blind RCT	HFrEF	4,744	≤40%	Dapagliflozin 10 mg once daily	Placebo	18.2 months	Worsening HF or CV death
EMPEROR-Reduced[6]	2020	Double-blind RCT	HFrEF	3,730	≤40%	Empagliflozin 10 mg once daily	Placebo	16 months	CV death or HF hospitalization
EMPEROR-Preserved[7]	2021	Double-blind RCT	HFpEF	5,988	>40%	Empagliflozin 10 mg once daily	Placebo	26.2 months	CV death or HF hospitalization

DELIVER[8]	2022	Double-blind RCT	HFmrEF/HFpEF	6,263	>40%	Dapagliflozin 10 mg once daily	Placebo	27.6 months	Worsening HF or CV death

Abbreviations: HF = heart failure; HFrEF = heart failure with reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFmrEF = heart failure with mildly reduced ejection fraction; LVEF = left ventricular ejection fraction; CV = cardiovascular; RCT = randomized controlled trial

Hospitalization for heart failure

All four trials reported hospitalization for heart failure as a primary or key secondary endpoint.[5–8] Pooled analysis demonstrated that SGLT2 inhibitors significantly reduced the risk of hospitalization compared with placebo (hazard ratio [HR] 0.72; 95% confidence interval [CI] 0.67–0.78; P < 0.00001). Statistical heterogeneity was negligible (I^2 = 0%).

Subgroup analysis according to heart failure phenotype showed consistent benefit across ejection fraction categories. In patients with HFrEF, the pooled HR was 0.69 (95% CI 0.62–0.78), while in HFpEF populations the pooled HR was 0.74 (95% CI 0.67–0.83). No significant heterogeneity was observed within subgroups.

These findings correspond to an approximate 28% relative reduction in the risk of heart failure hospitalization with SGLT2 inhibitor therapy across the spectrum of ejection fraction. The forest plot is presented in Figure 2.

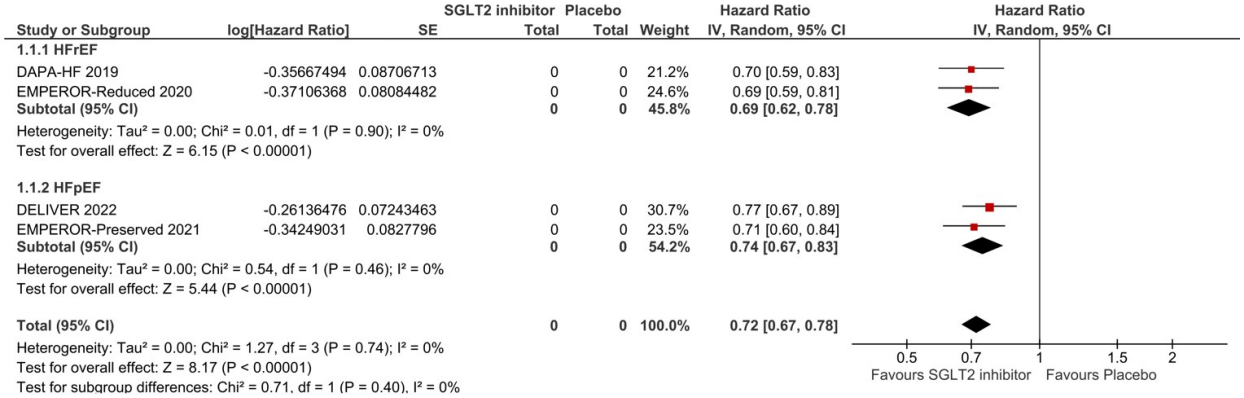

Figure 2: Forest plot showing pooled hazard ratio for hospitalization for heart failure comparing SGLT2 inhibitors with placebo.

Cardiovascular mortality

Cardiovascular mortality data were available from all four trials.[5–8] The pooled estimate demonstrated a statistically significant reduction in cardiovascular mortality with SGLT2 inhibitors compared with placebo (HR 0.88; 95% CI 0.80–0.96; P = 0.005), with no observed heterogeneity (I^2 = 0%).

In subgroup analysis, patients with HFrEF showed a significant reduction in cardiovascular mortality (HR 0.86; 95% CI 0.76–0.98), whereas the effect in HFpEF populations did not reach conventional statistical significance (HR 0.89; 95% CI 0.79–1.01). The direction of effect remained consistent across phenotypes. The corresponding forest plot is shown in Figure 3.

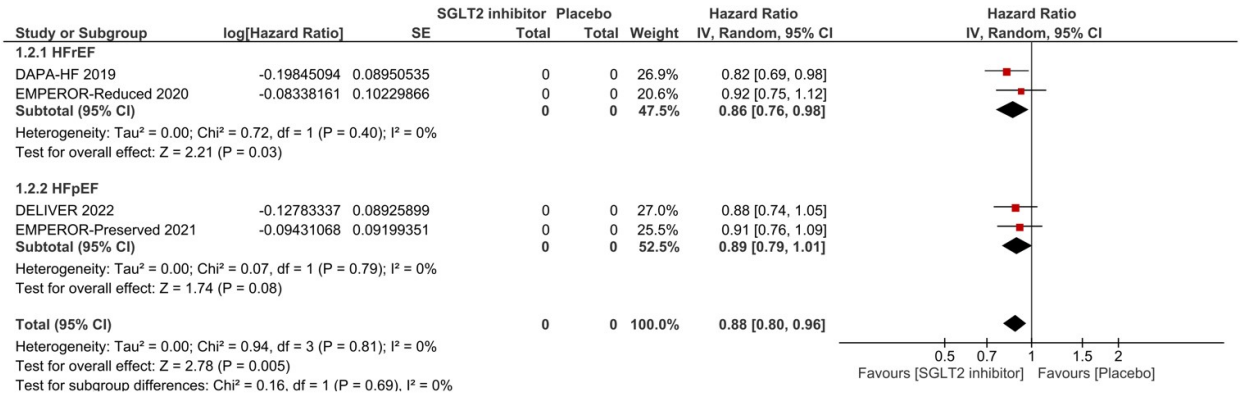

Figure 3: Forest plot showing pooled hazard ratio for cardiovascular mortality.

All-cause mortality

All-cause mortality was reported in each included trial.[5–8] Pooled analysis demonstrated a modest reduction that approached statistical significance (HR 0.93; 95% CI 0.86–1.00; P = 0.05), with low statistical heterogeneity (I^2 = 4%). In subgroup analysis, a statistically significant reduction was observed among patients with HFrEF (HR 0.87; 95% CI 0.77–0.98), whereas no significant reduction was observed in HFpEF populations (HR 0.97; 95% CI 0.88–1.06). The forest plot for all-cause mortality is presented in Figure 4.

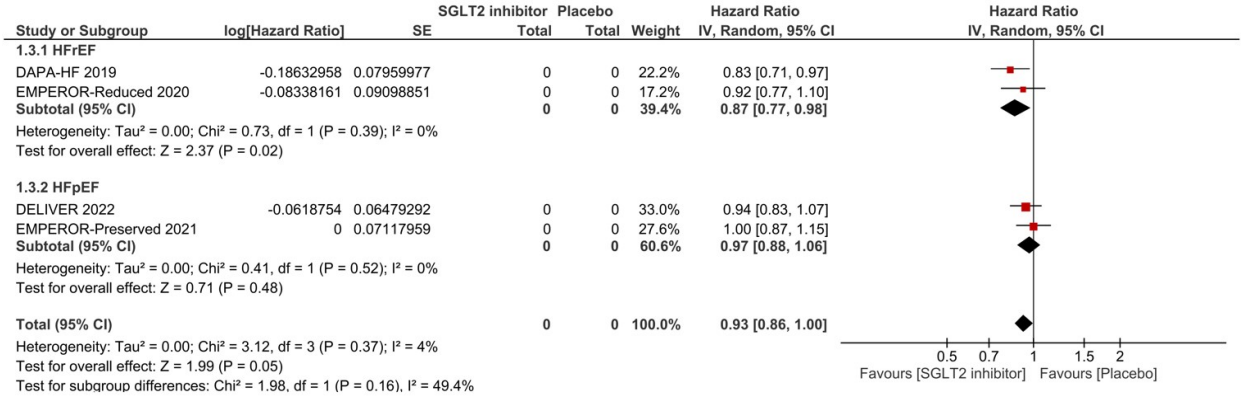

Figure 4: Forest plot showing pooled hazard ratio for all-cause mortality.

Risk of bias assessment

Assessment using the Cochrane Risk of Bias tool (RoB 2) indicated low risk of bias across all included trials. Random sequence generation, allocation concealment, blinding of participants and outcome assessors, and completeness of outcome data were adequately addressed in each study. No evidence of selective reporting was identified. A graphical summary of risk of bias assessment is presented in Figure 5.

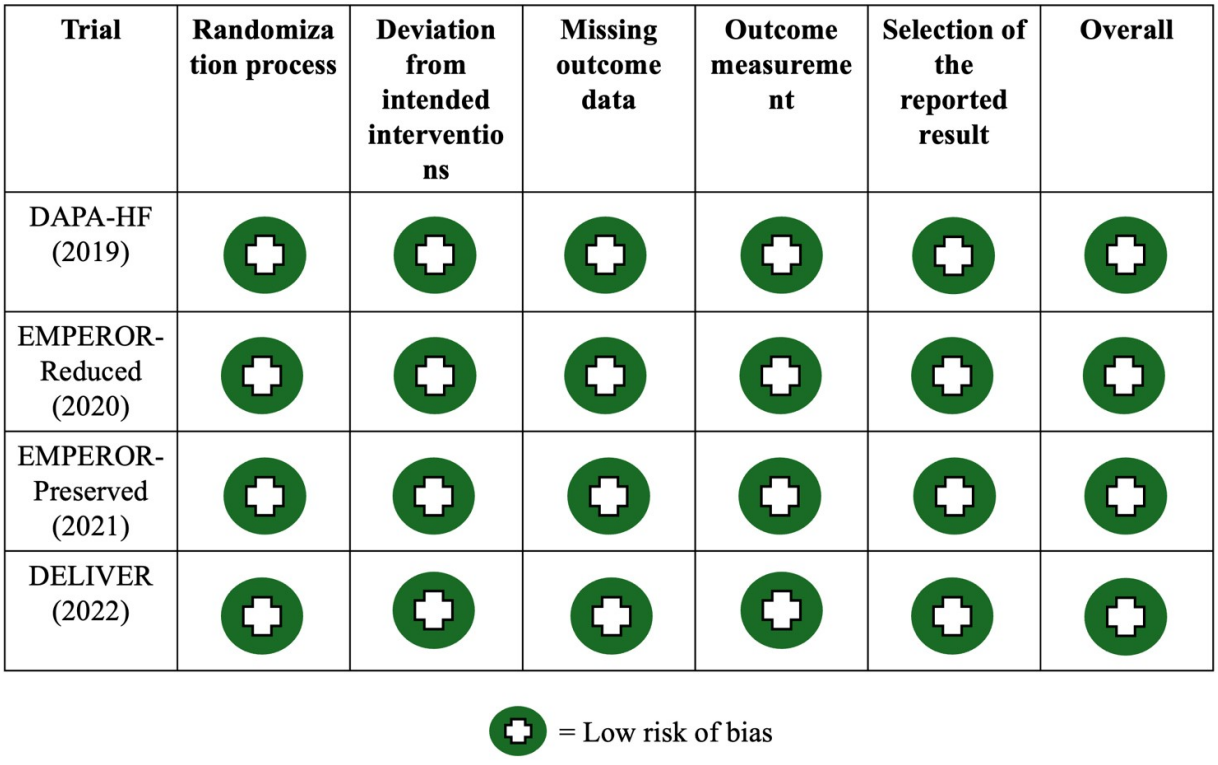

Figure 5: Summary of risk of bias assessment using the Cochrane RoB 2 tool.

Certainty of evidence (GRADE assessment)

Using the GRADE framework, certainty of evidence was rated as high for hospitalization for heart failure and cardiovascular mortality outcomes, reflecting inclusion of large, randomized trials with low risk of bias and negligible heterogeneity. For all-cause

mortality, certainty was rated as moderate to high owing to borderline precision of effect estimates.

DISCUSSION

In this systematic review and meta-analysis of four contemporary randomized controlled trials, SGLT2 inhibitors were associated with a significant reduction in hospitalization for heart failure across both reduced and preserved ejection fraction phenotypes.[5–8] A reduction in cardiovascular mortality was also observed, whereas the effect on all-cause mortality was modest and predominantly driven by trials enrolling patients with reduced ejection fraction.[5–8] The absence of meaningful statistical heterogeneity across pooled outcomes indicates consistency of treatment effects across diverse study populations and clinical settings.[11]

Heart failure continues to represent a substantial clinical and economic burden worldwide.[1] In India, increasing prevalence, delayed presentation, and resource constraints contribute to high rates of recurrent hospitalization.[2] Interventions that reduce hospital admissions therefore have significant implications for long-term disease management and healthcare sustainability.

The reduction in hospitalization observed in the present analysis is concordant with findings from the pivotal DAPA-HF, EMPEROR-Reduced, EMPEROR-Preserved, and DELIVER trials.[5–8] These studies were conducted in patients receiving contemporary guideline-directed medical therapy, indicating that the benefit of SGLT2 inhibitors is additive to established treatments. Current European and American guidelines recommend SGLT2 inhibitors as foundational therapy for heart failure irrespective of diabetes status.[3,4] The consistency of effect across the ejection fraction spectrum is particularly notable given the historical lack of effective pharmacological options for HFpEF.[3] A large meta-analysis of cardiovascular outcome trials in patients with type 2 diabetes demonstrated significant reductions in heart failure hospitalization with SGLT2 inhibitors, suggesting a class effect beyond glycemic control.[13]

The observed reduction in cardiovascular mortality, although smaller in magnitude than the reduction in hospitalization, remains clinically relevant.[5–8] Proposed mechanisms underlying cardiovascular benefit include enhanced natriuresis, improved myocardial energetics, reduction in ventricular wall stress, and favorable effects on cardiac remodeling.[14,15] These pathophysiological effects may collectively contribute to reduced heart failure progression and cardiovascular death.

The differential impact on all-cause mortality between HFrEF and HFpEF populations parallels findings from individual trials.[7,8] The heterogeneous pathophysiology of HFpEF, including systemic inflammation, metabolic dysregulation, and microvascular dysfunction, may partly account for variability in mortality outcomes. Nevertheless, the consistent reduction in hospitalization across phenotypes reinforces the therapeutic relevance of SGLT2 inhibition.

Our findings are aligned with previously published collaborative analyses. A prespecified meta-analysis of major randomized trials demonstrated significant reductions in cardiovascular death and heart failure hospitalization with minimal heterogeneity.[16] Subsequent pooled analyses across a broader ejection fraction range similarly reported consistent reductions in heart failure events irrespective of baseline ventricular function.[17,18] The concordance of these independent analyses strengthens confidence in the reproducibility and generalizability of treatment effects.

From a primary care standpoint, the implications are particularly relevant. In many Indian settings, patients with heart failure are initially managed by family physicians or general practitioners, especially outside tertiary centers.[2] Early initiation of evidence-based therapies may reduce recurrent decompensation and prevent avoidable admissions. The once-daily dosing and favorable safety profile observed in large trials enhance feasibility in outpatient practice.[5–8] Integration of SGLT2 inhibitors into primary care algorithms, in accordance with contemporary guidelines, may improve longitudinal outcomes.[3,4]

The principal strengths of this meta-analysis include inclusion of large, placebo-controlled randomized trials with low risk of bias as assessed using the RoB 2 framework. Statistical heterogeneity across outcomes was negligible, enhancing reliability of pooled estimates. Certainty of evidence, evaluated using the GRADE approach, was high for hospitalization and cardiovascular mortality outcomes. As only four randomized trials fulfilled eligibility criteria, formal assessment of publication bias was not undertaken, consistent with methodological recommendations when fewer than ten studies are available.[9,11]

Certain limitations warrant consideration. The number of eligible trials was limited, although they represent the most robust contemporary evidence in this therapeutic area. Individual patient-level data were not available, precluding more granular subgroup analyses. Follow-up durations were restricted to approximately two to three years, and longer-term outcomes require further evaluation. As with all meta-analyses, pooled estimates are dependent upon predefined endpoint definitions within the original trials.

Overall, the integration of multiple high-quality randomized trials provides a comprehensive assessment of the effect of SGLT2 inhibitors on clinically meaningful outcomes in heart failure. The consistency of benefit across independent study programs reinforces the strength of the evidence base supporting this therapeutic class.

CONCLUSION

this systematic review and meta-analysis demonstrates that SGLT2 inhibitors significantly reduce hospitalization for heart failure across the spectrum of ejection fraction and confer a meaningful reduction in cardiovascular mortality. These findings reinforce

current guideline recommendations and support early integration of SGLT2 inhibitors into heart failure management, including within primary care settings where timely therapeutic optimization may prevent recurrent hospitalization and improve patient-centered outcomes.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest related to this manuscript.

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