Comparative Effectiveness of SGLT2 Inhibitors and GLP-1 Receptor Agonists in Heart Failure: A Systematic Review

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Citation : Putri EA, Putri AW, Andreago, Welliangan AS, Guantoro V, Mardiah H. Comparative Effectiveness of SGLT2 Inhibitors and GLP-1 Receptor Agonists in Heart Failure: A Systematic Review. Medicinus. 2025 June; 14(3):238-249.
Keywords: Cardiovascular outcomes; Glucagon-like peptide-1 receptor agonists; Heart failure; SGLT2 inhibitors
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Online First : June 2025

Abstract

Background: Heart failure (HF) affects over 64 million individuals globally and is associated with high morbidity and mortality, particularly in patients with type 2 diabetes mellitus (T2DM). Sodium-glucose co-transporter 2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are emerging therapies with reported cardiovascular benefits. However, their comparative efficacy in HF-specific outcomes remains unclear. This systematic review aimed to assess and compare the safety and efficacy of SGLT2 inhibitors and GLP-1 RAs in patients with HF.

Methods: We systematically searched PubMed, EMBASE, and Scopus up to 1 May 2025 for randomized controlled trials (RCTs) evaluating SGLT2 inhibitors or GLP-1 RAs in adults with HF. Primary outcomes included all-cause and cardiovascular mortality; secondary outcomes included HF hospitalization and major adverse cardiovascular events (MACE). Risk of bias was assessed using the Cochrane RoB 2 tool and certainty of evidence with the GRADE approach.

Result: Fourteen RCTs comprising 30,867 patients (52.2% female; 63.2% with T2DM) were included. SGLT2 inhibitors significantly reduced cardiovascular mortality (RR: 0.85, 95% CI: 0.78–0.93, $p < 0.001$, $I^2 = 14\%$), all-cause mortality (RR: 0.88, 95% CI: 0.81–0.95, $p = 0.002$, $I^2 = 21\%$), and HF hospitalizations (RR: 0.72, 95% CI: 0.67–0.77, $p < 0.001$, $I^2 = 0\%$). GLP-1 RAs did not demonstrate significant effects on these outcomes. Overall risk of bias was low to moderate; GRADE certainty ranged from moderate to high.

Conclusions: SGLT2 inhibitors provide consistent reductions in mortality and hospitalization in HF patients across glycemic statuses. GLP-1 RAs showed limited benefit in HF-specific outcomes, supporting the preferential use of SGLT2 inhibitors in HF treatment strategies.

Introduction

Heart failure (HF) is a progressive clinical syndrome that affects an estimated 64 million individuals worldwide, posing a substantial burden on global healthcare systems.[1] In the United States, over 6.7 million adults are living with HF, and projections indicate a 46% increase in prevalence by 2030, underscoring the need for effective, scalable therapeutic strategies. HF is associated with high rates

of hospitalization and mortality, with a 5-year survival rate of approximately 50%, making it a leading cause of death and a major contributor to healthcare expenditures.[2] HF is two to four times higher than in non-diabetic populations, due to shared pathophysiological mechanisms including endothelial dysfunction, systemic inflammation, and atherothrombosis.[3] These comorbidities contribute to a complex clinical phenotype that often requires multifaceted treatment approaches.

In this context, sodium-glucose co-transporter 2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have emerged as antidiabetic therapies with notable cardiovascular benefits. Beyond glycemic control, SGLT2 inhibitors have demonstrated consistent reductions in HF hospitalization and cardiovascular mortality in both diabetic and non-diabetic patients.[3] Randomized controlled trials (RCTs) such as DAPA-HF, EMPEROR-Reduced, and EMPEROR-Preserved have shown relative risk reductions of 30–35% in HF hospitalizations and significant improvements in mortality and symptom burden.[4–6] These benefits have led to their incorporation into HF management guidelines across the spectrum of ejection fraction, irrespective of glycemic status. In contrast, GLP-1 RAs have primarily demonstrated efficacy in reducing major adverse cardiovascular events (MACE), including myocardial infarction and stroke, as evidenced in trials such as LEADER, SUSTAIN-6, and PIONEER-6.[7–9] However, their impact on HF-specific outcomes has been inconsistent, with neutral or potentially adverse effects observed in some studies involving HFrEF patients.

Pharmacologically, the divergence in therapeutic profiles between these drug classes is attributable to their distinct mechanisms of action. SGLT2 inhibitors exert multiple HF-relevant effects, including osmotic diuresis, reduction in preload and afterload, attenuation of myocardial fibrosis, improvement in ventricular remodeling, and favorable alterations in myocardial energetics and renal hemodynamics.[10] These mechanisms act synergistically to modify disease trajectory in both HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF).[10] In contrast, GLP-1 RAs primarily exert metabolic effects—enhancing insulin secretion, reducing glucagon levels, promoting weight loss, and exerting anti-inflammatory and anti-atherosclerotic actions.[11] While these properties confer benefit in atherosclerotic cardiovascular disease (ASCVD), their limited influence on volume status and myocardial stress may explain the lack of consistent benefit in HF endpoints. Notably, some GLP-1 RAs have been associated with increased heart rate, a potential concern in HFrEF management.[11]

Despite the growing evidence base for each drug class individually, direct comparisons of their effectiveness in HF remain limited. Both classes are now commonly co-prescribed or considered as alternative options in patients with T2DM and cardiovascular disease, raising critical questions about therapeutic prioritization, sequencing, and HF phenotype-specific efficacy. Understanding the comparative clinical effectiveness of SGLT2 inhibitors versus GLP-1 RAs in HF is essential to inform individualized treatment strategies, guide multidisciplinary care decisions, and optimize long-term outcomes. This systematic review aims to comprehensively evaluate and compare the impact of SGLT2 inhibitors and GLP-1 receptor agonists on patients HF.

Material And Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.[12] A comprehensive literature search was performed in PubMed, EMBASE, and Scopus databases to identify relevant studies published up to 1 May 2025. The search strategy was designed to capture randomized controlled trials (RCTs) evaluating the effects of SGLT2 inhibitors or GLP-1 receptor agonists in patients with heart failure, regardless of ejection fraction status or presence of type 2 diabetes mellitus. The search combined terms and Medical Subject Headings (MeSH) related to heart failure, SGLT2 inhibitors (e.g., empagliflozin, dapagliflozin), GLP-1 receptor agonists (e.g., liraglutide, semaglutide), and randomized controlled trials. No language or publication date restrictions were applied. Reference lists of included studies and relevant reviews were manually screened for additional eligible trials.

Eligible studies were randomized controlled trials (RCTs) involving adult participants (≥18 years) with a clinical diagnosis of heart failure, irrespective of ejection fraction or diabetes status. Trials were included if they evaluated any sodium-glucose co-transporter 2 (SGLT2) inhibitor or glucagon-like peptide-1 receptor agonist (GLP-1 RA), compared against placebo, standard care, or each other. Studies were required to report on safety outcomes as the primary endpoint, including all-cause mortality and cardiovascular death. Secondary outcomes of interest included efficacy endpoints, such as heart failure hospitalization rate and major adverse cardiac events (MACE). Only full-text articles published in peer-reviewed journals were considered. Studies were excluded if they were observational, non-randomized, lacked HF-specific data, or did not report relevant safety or efficacy outcomes.

All retrieved articles were imported into reference management software, and

duplicates were removed. Titles and abstracts were screened, followed by full-text review, conducted independently by three authors. Relevant data—including study design, population characteristics, interventions, comparators, outcomes, and follow-up duration—were extracted using a standardized form. Disagreements at any stage were resolved through discussion and consensus among the authors.

Risk of bias for each included trial was independently assessed by three reviewers using the Cochrane Risk of Bias 2 (RoB 2) tool. This tool evaluates bias across five domains: the randomization process, deviations from intended interventions, missing outcome data, measurement of outcomes, and selection of reported results. Each domain and the overall judgment were rated as low risk, some concerns, or high risk. Conflicts were resolved through group discussion.

The certainty of evidence for each outcome was graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. The evidence was rated as high, moderate, low, or very low, considering risk of bias, inconsistency, indirectness, imprecision, and publication bias.

All statistical analyses were performed using RStudio (version 2024.03.1+402). For dichotomous outcomes, risk ratios (RRs) with 95% confidence intervals (CIs) were calculated. Meta-analyses were conducted using a random-effects model, regardless of heterogeneity, to accommodate clinical and methodological variability across studies. Between-study heterogeneity was quantified using Tau^2, calculated via the DerSimonian and Laird method, and Wald-type methods were used to derive confidence intervals. Statistical significance was set at $p < 0.05$. Subgroup analyses were restricted to comparisons of SGLT2 inhibitors versus placebo and GLP-1 receptor agonists versus placebo. Forest plots were generated to visually present effect estimates for each outcome. To assess potential publication bias, funnel plots were constructed for each pooled outcome. Additionally, Egger's regression test and Begg's rank correlation test were performed to statistically evaluate small-study effects. Results from these tests were interpreted in conjunction with visual asymmetry of the funnel plots.

Result

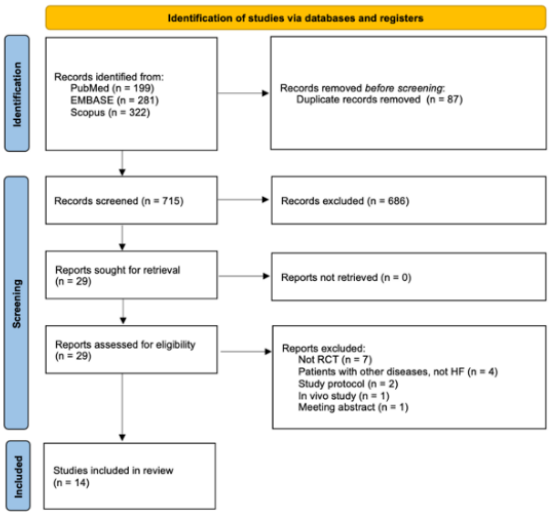


Figure 1. PRISMA flow diagram.

A total of 802 records were initially identified through database searches, including 199 from PubMed, 281 from EMBASE, and 322 from Scopus. After removing 87 duplicates, 715 records remained for screening. Of these, 686 were excluded based on titles and abstracts, leaving 29 full-text reports assessed for eligibility. No reports were excluded due to retrieval issues. Among the 29 full-text articles reviewed, 15 were excluded for the following reasons: not being randomized controlled trials (n = 7), involving patients with conditions other than heart failure (n = 4), being study protocols (n = 2), in vivo studies (n = 1), or meeting abstracts (n = 1). Ultimately, 14 studies met the inclusion criteria and were included in the final systematic review.[4–9,13–21]

Among these, SGLT-2 inhibitor studies included DAPA-HF, DELIVER, EMPEROR-Reduced, EMPEROR-Preserved, and SOLOIST-WHF, with follow-up durations ranging from 9 to 28 months. These studies enrolled patients with heart failure characterized by varying left ventricular ejection fractions and NYHA classes II–IV, including: DAPA-HF (II = 3203, III–IV = 1541), DELIVER (II = 4713, III–IV = 1549), EMPEROR-Reduced (II = 2800, III–IV = 930), and EMPEROR-Preserved (II = 4883, III–IV = 1101), while SOLOIST-WHF did not report NYHA classification. GLP-1 agonist studies included FIGHT, LIVE, Lepore 2016, LEADER, EXSCEL, HARMONY, SUSTAIN-6, PIONEER-6, and ELIXA, involving patients with a history of heart failure or reduced ejection fraction. Reported NYHA class distributions were: FIGHT (II = 87, III = 189, IV = 15), LIVE (I = 71, II = 129, III = 33), LEADER (I = 348, II = 1091, III = 214, IV = 14), and EXSCEL (I = 738, II = 1333, III = 303, IV = 13), while other GLP-1 studies did not provide NYHA data. Interventions used included liraglutide, albiglutide, exenatide, semaglutide, and lixisenatide, with follow-up durations ranging from 3 months to 3.8 years. Across all studies, the total cohort included 30,867 participants, with 19,525 having diabetes mellitus as a comorbidity and 16,118 being female.

In patients with heart failure, from our meta-analysis, the overall effect estimate for major adverse cardiac events following treatment with GLP-1 agonists or SGLT-2 inhibitors was a risk ratio (RR) of 0.94 (95% CI: 0.91 to 0.97; p = 0.0008; I^2 = 0%) (Figure 2). For all-cause mortality, the RR was 0.94 (95% CI: 0.89 to 1.00; p = 0.05; I^2 = 0%) (Figure 3). For cardiovascular death, the RR was 0.89 (95% CI: 0.83 to 0.97; p = 0.005; I^2 = 0%) (Figure 4). The hospitalization rate due to heart failure showed an RR of 0.86 (95% CI: 0.76 to 0.97; p = 0.02; I^2 = 69%) (Figure 5).

Table 1. Demographic characteristics of included studies.

Study ID	Patients details	Age, years	Female, n	LVEF	NYHA, n	Intervention details	Follow up duration
SGLT-2 Inhibitor							
DAPA-HF, (n = 4744) ⊕⊕⊕	LVEF ≤40%; elevated NT-proBNP; NYHA functional class II–IV	66.3 ± 10.9	3635	31.1%	II = 3203 III – IV = 1541	Dapagliflozin	18 months
DELIVER, (n = 6263) ⊕⊕⊕⊕	LVEF >40% and evidence of structural heart disease; elevated NT-proBNP; NYHA functional class II–IV; ambulatory or hospitalised patients	71.7 ± 9.6	3516	54.2%	II = 4713 III – IV = 1549	Dapagliflozin	28 months
EMPEROR-Reduced (n = 3730), ⊕⊕⊕⊕	LVEF ≤40%; elevated NT-proBNP; NYHA functional class II–IV	66.5 ± 11.2	2837	27.2%	II = 2800 III – IV = 930	Empagliflozin	16 months
EMPEROR-Preserved (n = 5988), ⊕⊕⊕⊕	LVEF >40%; evidence of structural heart disease or history of heart failure hospitalisation within 12 months; elevated NT-proBNP; NYHA functional class II–IV	71 ± 9.6	3312	54.3%	II = 4883 III – IV = 1101	Empagliflozin	26 months
SOLOIST-WHF (n = 1222),⊕⊕⊕⊕	Type 2 diabetes; admitted to the hospital, or urgent heart failure visit for worsening heart failure; previous treatment with loop diuretic for >30 days; previous diagnosis of heart failure (>3 months); elevated BNP or NT-proBNP; randomised when haemodynamically stable, before hospital discharge or within 3 days of discharge	70 (64–76)	810	35%	NA	Sotagliflozin	9 months
GLP1 agonist							
FIGHT, (n = 300), ⊕⊕⊕	Advanced HFrEF (≤40%)	61	64	25%	II = 87; III = 189; IV = 15	Liraglutide	6 months
LIVE, (n = 241), ⊕⊕⊕⊕	Chronic HFrEF (LVEF ≤ 45%)	65	26	34.5%	I = 71; II = 129; III = 33	Liraglutide	24 months
Lepore 2016, (n = 82), ⊕⊕⊕⊕	Chronic HFrEF (<40%)	56	21	<40%	NA	Albiglutide	3 months
LEADER, (n = 1667) ⊕⊕⊕	History of HF (NYHA class I–III)	64	684	31.5%	I = 348; II = 1091; III = 214 IV = 14	Liraglutide	3.8 years
EXSCEL, (n = 2389) ⊕⊕⊕⊕	History of congestive HF	64	849	NA	I = 758; II = 1333; III = 303; IV = 13	Exenatide	3.2 years
HARMONY, (n = 1922) ⊕⊕⊕⊕	History of congestive HF	NA	NA	NA	NA	Albiglutide	≥ 1.5 years
SUSTAIN-6, (n = 573) ⊕⊕⊕⊕	Prior HF (NYHA class II or III)	64	246	NA	NA	Semaglutide	2.1 years
PIONEER-6, (n = 388) ⊕⊕⊕⊕	Prior HF (NYHA class II or III)	65	118	NA	NA	Semaglutide	1.3 years
ELIXA, (n = 1358) ⊕⊕⊕⊕	Prior HF	NA	NA	NA	NA	Lixisenatide	25 months

The pooled effect estimate for OS demonstrated a HR of 0.81 (95% CI: 0.65 to 1.00; p = 0.05; I^2 = 0%) across five studies (Figure 3). For progression-free survival (PFS), the combined HR was 0.80 (95% CI: 0.62 to 1.05; p = 0.07; I^2 = 0%) based on three studies (Figure 4). The analysis of grade ≥ 3 adverse events showed a RR of 0.31 (95% CI: 0.02 to 6.09; p = 0.23; I^2 = 90%), also from three studies (Figure 5).

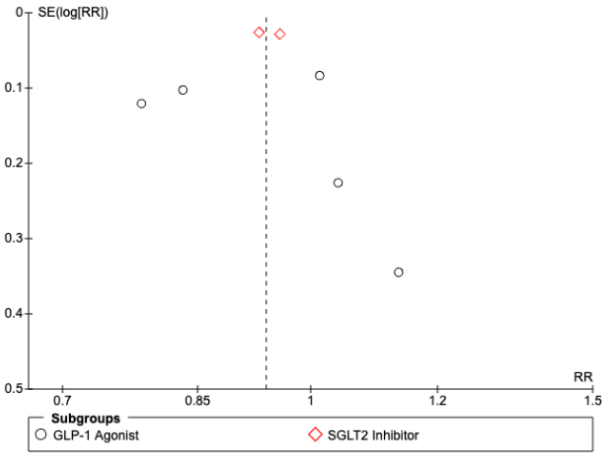
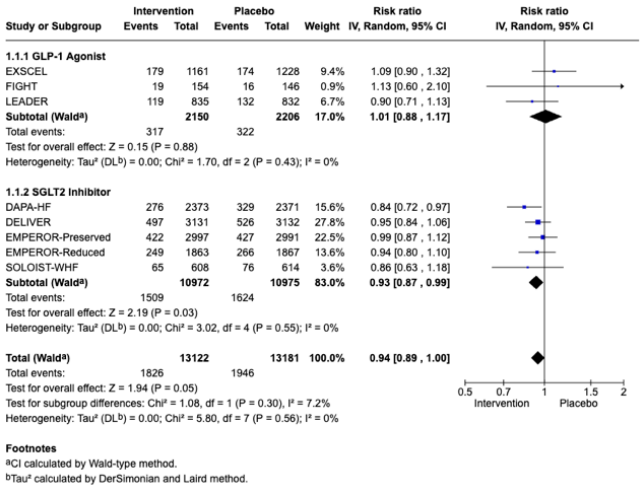
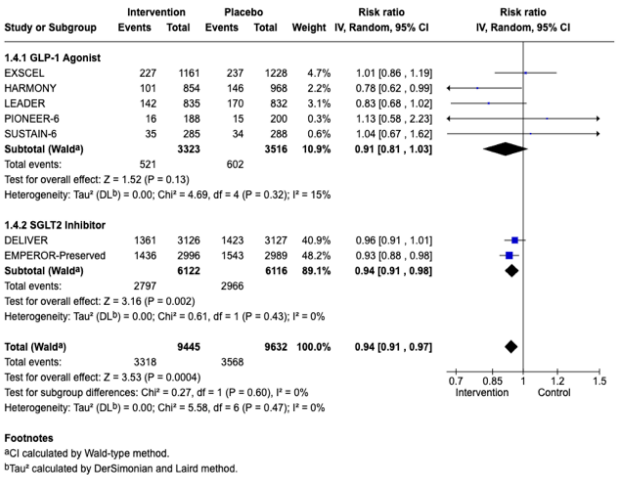


Figure 2. Meta-analysis for major adverse cardiac events following GLP-1 agonists or SGLT-2 inhibitors in patients with HF.





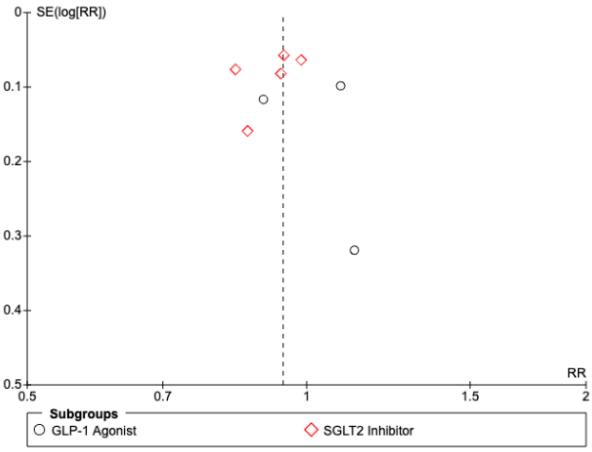
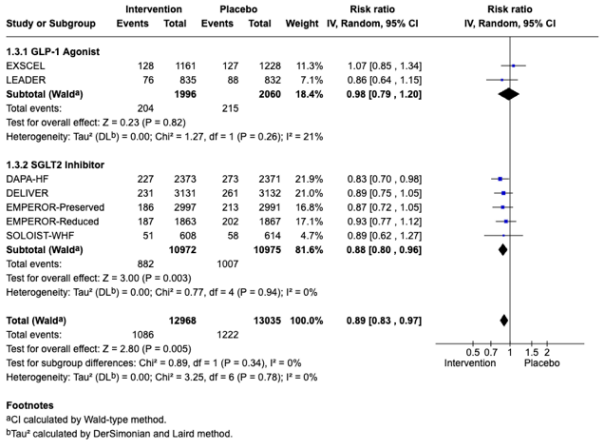


Figure 3. Meta-analysis for all-cause mortality following GLP-1 agonists or SGLT-2 inhibitors in patients with HF.



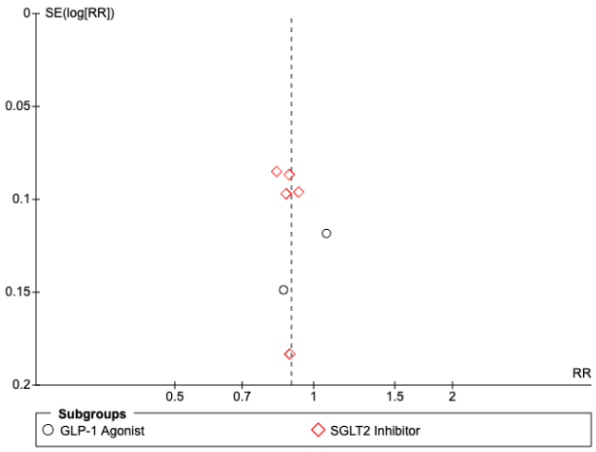
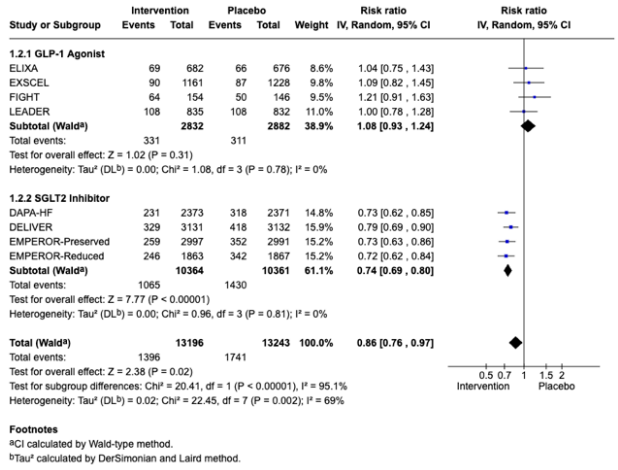


Figure 4. Meta-analysis for cardiovascular death following GLP-1 agonists or SGLT-2 inhibitors in patients with HF.



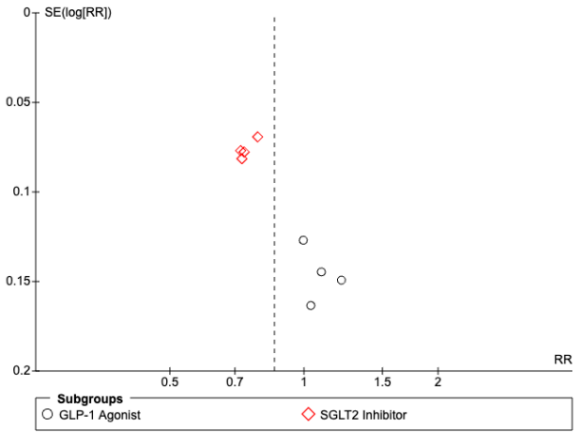


Figure 5. Meta-analysis for hospitalization rate due to HF following GLP-1 agonists or SGLT-2 inhibitors.

Risk of bias assessment (figure 6) across the included randomized controlled trials indicated a low to moderate risk of bias overall, with most studies having adequate randomization and outcome reporting. According to GRADE criteria, the certainty of evidence was rated as moderate to high for the major outcomes. This reflects consistency across studies, precise estimates, and direct applicability to the patient population with heart failure.

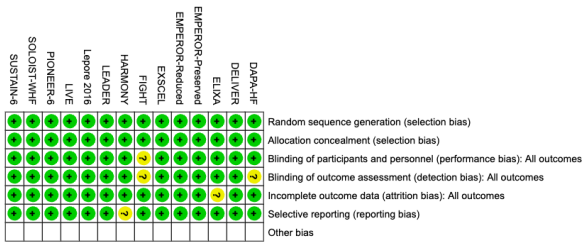


Figure 6. Risk of bias assessment using the Cochrane RoB version 2.

Discussion

This meta-analysis adds to the growing body of evidence supporting the use of SGLT-2 inhibitors in heart failure, showing consistent benefits across major cardiovascular outcomes. Previous trials such as DAPA-HF and EMPEROR-Reduced have already established SGLT-2 inhibitors as effective therapies in HFrEF. In DAPA-HF, dapagliflozin led to a 26% relative risk reduction in the composite of cardiovascular death or worsening heart failure (HR: 0.74; 95% CI: 0.65–0.85), while EMPEROR-Reduced demonstrated a 25% risk reduction in the same composite outcome with empagliflozin (HR: 0.75; 95% CI: 0.65–0.86). These benefits were observed regardless of diabetic status, indicating a mechanism of action beyond glycemic control.

The clinical utility of SGLT-2 inhibitors in heart failure is supported by their multifaceted pharmacological effects. By promoting glycosuria and natriuresis, they reduce intravascular volume and lower both preload and afterload.[22] This directly addresses the hemodynamic burden in heart failure. Additionally, SGLT-2 inhibitors have been associated with favorable myocardial remodeling, reduced fibrosis, and improved cardiac efficiency through shifts in substrate utilization toward ketone metabolism.[23,24] These effects are particularly relevant in patients with symptomatic heart failure, where volume management and metabolic efficiency play key roles in disease progression and quality of life.

While GLP-1 receptor agonists have proven cardiovascular benefits in patients with type 2 diabetes and established atherosclerotic cardiovascular disease—as seen in the LEADER trial (liraglutide reduced cardiovascular death by 22%, HR: 0.78; 95% CI: 0.66–0.93)—their role in heart failure remains uncertain.[7,8] Some trials have reported neutral or even adverse effects on heart failure outcomes. For instance, the FIGHT trial found no significant benefit of liraglutide on post-hospitalization outcomes in HFrEF patients and noted a trend toward increased heart rate.[17] These findings suggest that GLP-1 receptor agonists may not confer the same cardiac-specific advantages and should be used selectively, especially in patients with established heart failure.

In routine practice, the reduction in heart failure hospitalizations observed with SGLT-2 inhibitors is particularly impactful, given the high rates of readmission and associated morbidity.[25] Real-world data from registries and observational studies have echoed these trial findings, showing improvements in functional status, reductions in NT-proBNP levels, and fewer HF-related emergency visits.[26] Given these effects, SGLT-2 inhibitors are increasingly regarded not just as antidiabetic agents, but as integral components of comprehensive heart failure management strategies.

A potential limitation of this study lies in the heterogeneity of patient populations across the included trials, particularly in terms of heart failure subtype, background therapies, and comorbid conditions such as diabetes and chronic kidney disease, which may have influenced treatment responses and obscured subgroup-specific effects. Additionally, differences in study design, follow-up duration, and outcome definitions—especially regarding hospitalization for heart failure—introduce variability that may impact the pooled estimates. The inclusion of trials with varying baseline risk and inconsistent reporting of functional class limits the precision of clinical applicability. While efforts were made to assess methodological quality, some studies still carried a moderate risk of bias due to open-label designs or incomplete outcome data. Finally, although the GRADE assessment indicated moderate to high certainty for key outcomes, the reliance on trial-level data rather than individual patient data restricts more nuanced exploration of effect modifiers such as age, sex, or ejection fraction.

Conclusion

This meta-analysis reinforces the cardiovascular benefits of SGLT-2 inhibitors in patients with heart failure, demonstrating consistent reductions in hospitalization and cardiovascular mortality, regardless of diabetic status. The findings align with established clinical trial data and support the incorporation of SGLT-2 inhibitors into standard heart failure management. While GLP-1 receptor agonists have shown cardiovascular benefit in patients with diabetes and atherosclerotic disease, their role in heart failure remains less clear, warranting further investigation. Overall, these results emphasize the importance of tailoring pharmacologic therapy to individual patient profiles, with growing evidence supporting the cardioprotective effects of certain glucose-lowering agents beyond glycemic control.

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