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Heart failure outcomes among reduced and preserved ejection fraction patients on sodium-glucose cotransporter-2 inhibitors with different dosing patterns of diuretics: a systematic review and meta-analysis

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Abstract

The current review was conducted to provide information on the best dosing strategy of background loop diuretics with sodium-glucose cotransporter-2 inhibitors (SGLT2i) for heart failure and safety outcomes among reduced and preserved ejection fraction patients with comorbid conditions. The search was conducted in four databases. Study eligibility was evaluated independently, and a total of four randomized controlled trials were included in this review. Data extraction was performed using the Cochrane-modified extraction template. Statistical analyses and risk of bias assessment were conducted with RevMan version 5.4.1, while the certainty of evidence was appraised using the GRADEpro tool. The primary composite outcomes and hospitalization or urgent heart failure (HF) with SGLT2i and placebo were consistent across all the doses of loop diuretics. The primary composite outcome when loop diuretics were dosed at <40 mg and >40 mg [hazard ratio (HR): 0.77 and HR: 0.81] and showed high significance (p=0.0002), similar for hospitalization and urgent HF (HR: 0.73 and HR: 0.81) with (p=0.0007 and p=0.002). However, when the loop diuretics were dosed at 40 mg, they showed highly significant (p<0.01) efficacies for all cardiovascular outcomes, such as primary composite outcome (HR: 0.76), hospitalization or urgent HF (HR: 0.68), and mortality due to any cause (HR: 0.81), and marginally significant efficacy (p=0.05) for cardiovascular death (HR: 0.86). Compared to the SGLT2i and placebo groups, patients receiving SGLT2i with 40 mg of loop diuretics and placebo were less likely to experience volume depletion, with the odds ratio of 1.56 (p<0.05). The adverse renal effects and discontinuation of the drug were the same across all the doses of loop diuretics. We conclude that SGLT2i plus dosing of loop diuretics at 40 mg with placebo among heart failure patients demonstrated superior cardiovascular and safety outcomes.

Key words: ejection fraction, heart failure, loop diuretics, outcomes, safety and efficacy, SGLT2i.

Introduction

Heart failure (HF) affects 1 to 3 per cent of population worldwide [1]. Heart failure is commonly divided into two categories: reduced ejection fraction (HFrEF), where the left ventricular ejection fraction is less than 40%, and preserved ejection fraction (HFpEF), where it exceeds 50% [2]. Mortality rate among HFrEF (32%) has been higher than the HFpEF (22%) [3]. About 51% and 27% of HFrEF and HFpEF patients were reported to be associated with one or more co-morbid conditions directly linked with the nature of therapy and clinical outcomes [4]. Patients with multiple comorbidities faced a greater risk of mortality, with the 1-year mortality rate rising from 13% in those without comorbidities to 26% in those with five or more [5]. Additionally, about 12% of hospitalized diabetic patients experience HF [6].

The evidence-based approach to managing HF consists of aldosterone antagonists, beta-blockers, diuretics and angiotensin-converting enzyme (ACE) inhibitors as front-line drugs. Loop diuretics are the initial diuretic of choice used for decades to treat patients with HF. Recently, these diuretics have been used in conjunction with Sodium-glucose cotransporter-2 inhibitors (SGLT2i) to manage HF [7-9]. Among HF patients, fluid retention is a life-threatening adverse effect that has been frequently linked with most of the other oral anti-diabetic medications (OHAs). However, a ray of hope exists in managing HF patients as a new generation of OHA and SGLT2i overcomes adverse effects like fluid retention, which is experienced with other OHAs. Thus, starting in 2022, SGLT2i has become a popular treatment choice among clinicians [7-9]. Although loop diuretics are essential to mitigate congestion among HF patients, their prolonged use, especially at high doses, has been associated with neurohormonal activation, renal dysfunction, and electrolyte abnormalities [10]. Loop diuretics are combined with SGLT2i in patients with HF, and the latter augments the pharmacological action of loop diuretics by synergistically removing water and sodium from the body via urine along with its anti-diabetic action [11].

This strategy has remarkably reduced the dosing pattern of loop diuretics, thereby minimizing associated adverse effects. Further, Guidelines supported by the *American Heart Association (AHA)* and the *European Society of Cardiology (ESC)* state that combining SGLT2i with loop diuretics minimizes mortality and hospitalization among HFrEF and HFpEF patients [12]. Similarly, a systematic analysis by Padda *et al.,* 2023 found that SGLT2i improved symptoms and enhanced quality of life among HFpEF patients [7]. One of the most outstanding and significant issues in combining SGLT2i with loop diuretics is identifying the best loop diuretic dose. A study by Butler et al., 2023 discovered that lowering the dose of loop diuretic drugs from 80 mg to 40 mg daily for individuals with HF and diabetes receiving dapagliflozin resulted in better outcomes, including lower hospitalization rates and higher quality of life [13]. The

study conducted by Dhingra NK et al. (2024), in patients receiving empagliflozin 10 mg, those on furosemide-equivalent doses exceeding 80 mg demonstrated a reduced risk of hospitalization for heart failure compared with individuals on doses above 40 mg [14]. In certain studies, the diuretic dose remains unchanged. Additional information on loop diuretic dosing is complex and difficult to obtain among HF patients when used with SGLT2i. Discovering the best dosing strategy of loop diuretics in combination with SGLT2i is essential for better clinical outcomes and minimizing adverse effects while maintaining optimal fluid volume status. Therefore, this systematic review and meta-analysis (SR/MA) aim to present more accurate information on Heart failure and safety outcomes when SGLT2i is used with background diuretic therapy at different doses, along with Placebo, among HFrEF and HFpEF patients with co-morbid conditions when compared with SGLT2i and Placebo.

Methods

This review followed the PRISMA 2020 guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and the recommendations outlined in the Cochrane Handbook for Systematic Reviews of Interventions [15,16]. The protocol was prospectively registered in PROSPERO, the International Prospective Register of Systematic Reviews (registration ID: CRD42024581902) [17]. Ethical approval was not applicable since this study-level meta-analysis did not involve human subjects.

Criteria for selection of studies

The studies considered in SR/MA were all incorporated, following the criteria of PICOS (Patient, Intervention, Control, Outcomes, and Study design). Quasi-Randomized and Randomized controlled studies were considered. Only studies published in English were accounted for, while review articles, abstracts, observational studies, and case reports/series were excluded. The studies that did not mention the details of the outcome of interest and the required data were also excluded.

Eligibility criteria for selection of the type of population

The choice of population for this SR/MA was HF patients (HFrEF 40% and HEpEF 40%) with co-morbidity, aged above 18 years, NT-proBNP level more than 300pg/ml, and belonging to NYHA class II-IV who were treated with SGLT2i medications for at least three months, accompanied by background treatment with loop diuretics, at various doses (<40 mg, 40 mg and >40 mg of daily dose). However, the HF patients with eGFR < 3030ml/min/1.73m^2, type 1 DM and systolic BP <95 mm Hg were excluded from this review.

Type of interventions

Intervention Group: SGLT2 inhibitors with a background loop diuretic and Placebo in the following combination.

1. SGLT2i + < 40 mg Loop diuretics + Placebo
2. SGLT2i+ 40mg Loop diuretics + Placebo
3. SGLT2i+ >40mg Loop diuretics + Placebo

The study by Jackson et al. and Chatur et al. used Dapagliflozin 10 mg as the SGLT2i [12,18]. Butler et al. and Dhingra NK et al. conducted the study using Empagliflozin 10 mg [13,14]. The study by Jackson et al. used Furosemide 40 mg as the loop diuretic [12]. In contrast, Butler et al., Dhingra et al., and Chatur et al. used Torsemide 20 mg and Bumetanide 1mg, administering doses equivalent to Furosemide 40 mg as the loop diuretic in their studies [13,14,18]. According to Jackson et al., bumetanide 1 mg, torsemide 20 mg, azosemide 60 mg, and etacrynic acid 100 mg were considered equivalent to 40 mg intravenous or 80 mg oral furosemide [12]. In all four included trials, patients receiving different diuretics were stratified into subgroups based on furosemide-equivalent doses: <40 mg, 40 mg, and >40 mg. For this review, we adhered strictly to the subgroup classifications provided in the original studies, without applying any additional stratification or modifying the existing categories. Hence, the subgroup analysis for assessing heterogeneity among the different drugs was entirely based on the authors' original groupings.

Control Group: SGLT2i and Placebo.

Measures of outcomes

Primary outcomes: The primary outcomes accounted for in the review are Primary composite outcomes, hospitalization, cardiovascular death, urgent heart failure visits and deaths from other causes in patients prescribed with SGLT2i plus placebo and with background loop diuretics at doses of below 40 mg, 40 mg, and more than 40 mg. Each combination was compared with SGLT2i and Placebo without background loop diuretics.

Secondary outcomes: Secondary outcomes included adverse events such as drug discontinuation due to side effects, volume depletion, and renal complications.

Electronic search

The search was undertaken in and Cochrane Library Scopus, Web of Science, and PubMed, for the studies published between 2014 and July 2024. We used keywords and Medical Subject Heading (MeSH) terms for PubMed to create a basic search strategy and adjusted it for other

search engines. The main search algorithm used was: (SGLT2-inhibitors) AND (Loop diuretics) AND (Diabetes Mellitus) AND (Ejection Fraction) AND (Cardiac failure). Additionally, relevant articles' reference lists were screened to find other eligible reports. All articles were retrieved and imported from Rayyan in 'CSV' format for screening and review.

Selection process

We imported all the records from various databases into Rayyan and removed duplicates. (AS and MSM) two authors screened the titles and abstracts independently for all the articles to determine their eligibility. Any irrelevant reports were excluded, and we retrieved the full text of the eligible articles. Any differences in opinion regarding study selection were settled through consensus among the authors. During the screening of studies, the respective authors were blinded.

Data extraction

An adapted Cochrane data extraction form was used for data collection. Two authors (AS, MSM) independently extracted relevant data such as, study site, study design, Study ID, methods, study duration, medications used in each group, and participants' details, including co-morbid conditions and outcomes. The data collected for the outcome were dichotomous variables when the details of events were mentioned, and subsequently, Hazard Ratio (HR) and 95% confidence interval (CI) were also collected. RBS reviewed and resolved any discrepancies with the data collection.

Evaluation of quality of studies

Two independent authors (AS, SPK) assessed the risk of bias (ROB) using RevMan software version 5.4.1. With adequate judgment and clarification, the biases were categorised as "low," "high," or "unclear risk", and a ROB graph was created. All discrepancies were addressed and resolved by mutual agreement among the authors. Funnel plots were created to examine potential publication bias.

Level of evidence certainty

Outcomes were evaluated based on the magnitude of relative risk and absolute effect across the three groups. The findings were evaluated using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) framework, with the certainty of evidence categorized on a scale ranging from low to high.

Statistical analysis

The analysis used Review Manager software v5.4.1 (Cochrane Collaboration, Copenhagen, Denmark) to generate pooled estimates in forest plots. When the outcomes were available as dichotomous variables from the included studies, it was represented as odds ratios (OR) with 95% CI; for studies where the results were available in the form of the Hazard ratio and 95% CI, the pooled estimate of HR with 95% CI was calculated using the RevMan calculator with generic inverse variance method. The analysis incorporated hazard ratios (HRs) with 95% confidence intervals (CIs) from individual studies to calculate the log hazard ratio, standard error, and study-specific weights, which were subsequently displayed graphically. Heterogeneity was assessed using Cochrane's Q test (p-values), the Higgins I^2 statistic, and visual inspection. Inter-study variability was expressed as a percentage with corresponding p-values. Both fixed- and random-effects models were applied: the fixed-effects model was used when heterogeneity (I^2) was below 50%, whereas for substantial heterogeneity (I^2 between 50–90%), we applied the random-effects model. In cases of considerable heterogeneity, sensitivity analyses were conducted.

Results

Selection of the studies

In total, 462 records were detected via systematic search, of which 446 were screened for eligibility after removing duplicates. Based on the PICO approach, 420 records were excluded from the review. The rest of the 26 studies were set for retrieval and assessed for eligibility. Among the 26 studies, 22 numbers were excluded as wrong outcome (n=16), wrong study design (n=2), and ongoing trials (n=4). As a result, 3 RCTs and 1 Post hoc analysis were eligible for the review (Figure 1).

Jackson AM et al. (2020) had participants from China, Japan, Taiwan, Vietnam, India, the United States of America (USA), Denmark, Australia, Sweden, Argentina and Poland [12]. Dhingra NK et al. (2024) conducted studies in Europe, Latin America, North America, Asia, India, and Australia [14]. Chatur S et al. (2023) included sites in Asia, Latin America, Europe, and Saudi Arabia [18]. Butler J et al. (2023) conducted studies in centres based in Europe, America, Caribbean countries, and some regions of Asia, including India and Australia. All the studies were multicentric; their details are summarized in Table 1 [13].

All the included studies aim to identify the optimal dose of loop diuretics when combined with SGLT2i among heart failure patients with co-morbidities. Two studies evaluated the outcome measures among patients with HFrEF < 40%, and the other two evaluated the outcome measures for patients with HFpEF >40%.

Risk of bias

The risk of bias analysis reveals that Butler et al., 2023 have a predominantly low risk of bias across most criteria, thus showing the most reliable methodology [13]. Chatur S et al., 2023 show unclear risks in multiple areas, particularly for randomization, concealed allocation, and Outcome assessor blinding, making it more susceptible to bias [18]. Similarly, Jackson AM et al., 2020 demonstrate unclear risks in blinding participants and selective reporting, though it has low risks in other areas [12]. Meanwhile, Dhingra NK et al., 2024 show consistently low risks across all categories except blinding of participants and outcome assessment [14]. The details are mentioned in Figure 2 and *Supplementary Table 1*, respectively.

Outcome measures

Primary composite outcome

A total of 5578 participants received SGLT2i + <40 mg loop diuretics + Placebo, and 3080 received SGLT2i and Placebo. 2042 patients had HFrEF < 40% and 3536 had HFpEF > 40%. Patients who received SGLT2i with loop diuretics at doses < 40 mg and placebo were at lower risk of experiencing the primary composite outcome than those who received SGLT2i with placebo, in both HFrEF patients with an ejection fraction < 40% (HR: 0.75; 95% CI: 0.59, 0.95; p = 0.02) and HFpEF patients with an ejection fraction > 40% (HR: 0.78; 95% CI: 0.65, 0.94; p = 0.007). A substantial difference was observed between the groups. The pooled estimate had similar results (HR: 0.77;95% CI: 0.67, 0.88; p=0.0002). The heterogeneity among the population of HFrEF was substantially less (χ^2=1.17; I^2=15%; p=0.28), and no heterogeneity was detected in a population enrolled in the study with HFpEF (χ^2=0.11; I^2=0%; p=0.007). The details are depicted in Figure 3(a).

6450 participants received SGLT2i + 40 mg loop diuretics + placebo, and 3080 received SGLT2i and placebo. Among the participants, 2776 had HFrEF <40%, and 3674 had HFpEF >40%. The participants who were treated with SGLT2i+ 40mg loop diuretics and placebo, among HFrEF and HFpEF groups, were less likely to experience primary composite outcomes compared to another group (HR: 0.70; 95% CI: 0.59,0.83; p < 0.0001 for HFrEF; HR: 0.81; 95% CI: 0.70, 0.95; p = 0.007 for HFpEF). Pooled estimates had similar results (HR: 0.76; 95% CI: 0.68, 0.86; p= 0.00001). No heterogeneity was detected, with a population enrolled in the study with HFrEF (χ^2=0.76; I^2=0%; p=0.38) and HFpEF (χ^2=0.01; I^2=0%; p=0.94). The details are depicted in Figure 3 (b).

A total of 4473 participants received SGLT2i + >40 mg loop diuretics + Placebo, and 3080 received SGLT2i and Placebo. Among the participants, 2236 had HFrEF <40% and 2237

experienced HFpEF > 40%. The participants who took SGLT2i plus loop diuretic >40 mg with placebo were less likely to experience primary composite outcome (HR:0.82; 95% CI: 0.70, 0.96; p= 0.01 and HR:0.81; 95% CI: 0.69, 0.94; p= 0.007). A substantial difference was noted between the groups. Pooled estimate also had similar results (HR:0.81; 95% CI: 0.73,0.91; p= 0.0002). No heterogeneity was detected (χ^2=0.87; I^2=0%; p=0.01) and (χ^2=0.29; I^2=0%; p=0.59). The details are depicted in Figure 3(c).

Hospitalization or urgent HF visit

A total of 5578 participants received SGLT2i + <40 mg loop diuretics + Placebo, and 3080 received SGLT2i and Placebo. 2042 participants had HFrEF < 40% and 3536 had HFpEF > 40%. The participants who received SGLT2i with loop < 40 mg and placebo were at lower risk of experiencing emergency heart failure visits and hospitalization (HR: 0.65; 95% CI: 0.45, 0.94; p= 0.02 and HR: 0.79; 95% CI: 0.63, 0.99; p= 0.04). A substantial difference was observed between both groups. Pooled estimate had similar results (HR: 0.73; 95% CI: 0.61, 0.88; p= 0.0007). The heterogeneity was moderate with HFrEF <40% (χ^2=1.59; I^2=37%; p=0.21), and no heterogeneity was detected among the study population experiencing HFpEF (χ^2=0.36; I^2=0%; p=0.55). The details are depicted in Figure 3(d).

Overall, 6450 participants received SGLT2i + 40 mg loop diuretics + placebo, and 3080 received SGLT2i and placebo. Among the participants, 2776 patients had HFrEF <40%, and 3674 had HFpEF >40%. The participants treated with SGLT2i+ 40mg loop diuretics and placebo, in both the HFrEF and HFpEF groups, significantly reduced the hospitalization or emergency heart failure visits (HR: 0.60; 95% CI: 0.48, 0.75; $p < 0.0001$ and HR: 0.74; 95% CI: 0.61,0.91; $p = 0.004$). The pooled estimate had similar results (HR: 0.68; 95% CI: 0.58, 0.79; p= 0.00001) with significant differences between the groups. Very low heterogeneity was seen among included studies, with HFrEF (χ^2=1.01; I^2=1%; p=0.31) and no heterogeneity with HFpEF (χ^2=0.15; I^2=0%; p=0.70). The details are in Figure 3 (e).

Overall, 4473 participants received SGLT2i + >40 mg loop diuretics + Placebo, and 3080 received SGLT2i and Placebo. Among the participants, 2236 patients had HFrEF <40% and 2237 had HFpEF > 40% with T2DM. The participants receiving SGLT2i with loop diuretic >40 mg and placebo did show any significant difference between the groups when the patients had HFpEF < 40%, while lesser incidence of hospitalization with HF with a significant difference was seen among the patients with and HFpEF > 40%, respectively (HR: 0.84; 95% CI: 0.69, 1.03; p= 0.09) and (HR: 0.78; 95% CI: 0.64, 0.94; p= 0.01). The pooled estimate showed a lower incidence of hospitalization (HR: 0.81; 95% CI: 0.70, 0.93; p 0.0002) with significant

differences between groups. No heterogeneity was detected ($\chi 2$=0.71; I^2=0%; p=0.40), (χ^2=0.09; I^2=0%; p=0.76). The details are depicted in Figure 3 (f).

Cardiovascular death

A total of 5578 participants received SGLT2i + <40 mg loop diuretics + Placebo, and 3080 received SGLT2i and Placebo. 2042 patients had HFrEF < 40% and 3536 had HFpEF > 40% with T2DM. The patients who received SGLT2i with loop < 40 mg and placebo among HFrEF and HFpEF, do not support a statistically significant difference between the groups (HR:0.86; 95% CI: 0.64, 1.16; p 0.33 and HR: 0.88; 95% CI: 0.67, 1.16; p 0.38). The pooled estimate also had similar results (HR: 0.87; 95% CI: 0.71, 1.07; p= 0.19). No heterogeneity was detected (χ^2=0.01; I^2=0%; p=0.91) and HFpEF (χ^2=0.23; I^2=0%; p=0.63). The details are depicted in Figure 4 (g).

6450 participants received SGLT2i + 40 mg loop diuretics + placebo, and 3080 received SGLT2i and placebo. Among the participants, 2776 patients experienced HFrEF <40% and 3674 had HFpEF >40%. The participants receiving SGLT2i+ 40mg loop diuretics and placebo, in both the HFrEF and HFpEF groups, have no decrease in the difference in incidence of cardiovascular death among both groups (HR: 0.82; 95% CI: 0.65, 1.04; p = 0.10 and HR: 0.89; 95% CI: 0.72, 1.10; *p* = 0.27). The pooled estimate also had similar results (HR: 0.86; 95% CI: 0.73, 1.00; p= 0.05). No heterogeneity was detected ($\chi 2$=0.26; I2=0%; p=0.61) and (χ^2=0.46; I^2=0%; p=0.50). The details are depicted in Figure 4 (h).

A total of 4473 participants received SGLT2i + >40 mg loop diuretics + Placebo, and 3080 received SGLT2i and Placebo. Among the participants, 2236 patients had HFrEF <40% and 2237 had HFpEF >40%. These groups did not differ significantly (HR: 0.93; 95% CI: 0.75, 1.15; p= 0.49), (HR: 0.90; 95% CI: 0.70, 1.15; p= 0.41). The pooled estimate had similar results (HR: 0.92; 95% CI: 0.78, 1.08; p= 0.29) No heterogeneity was detected (χ^2=0.09; I^2=0%; p=0.77) and (χ^2=0.19; I^2=0%; p=0.66). The details are depicted in Figure 4(i).

Death resulting from any cause

A total of 5578 participants received SGLT2i + <40 mg loop diuretics + Placebo, and 3080 received SGLT2i and Placebo. 2042 patients had HFrEF < 40% and 3536 had HFpEF > 40% with T2DM. These groups did not differ significantly, causing death from any other causes (HR: 0.83; 95% CI: 0.63, 1.09; p = 0.18, HR: 1.04; 95% CI: 0.86, 1.25; p = 0.72). Pooled estimates also had similar results (HR: 0.96; 95% CI: 0.82, 1.13; p= 0.64). No heterogeneity was detected

(χ^2=0.12; I^2=0%; p=0.73) and (χ^2=0.00; I^2=0%; p=0.96). The details are depicted in Figure 4 (j).

6450 participants received SGLT2i + 40 mg loop diuretics + placebo, and 3080 received SGLT2i and placebo. Among the participants, 2776 experienced HFrEF <40%, and 3674 had HFpEF >40%. For the participants who were receiving SGLT2i+ 40mg loop diuretics and placebo, in both the HFrEF and HFpEF groups, the deaths due to other causes significantly reduced (HR: 0.78; 95% CI: 0.63, 0.97; p < 0.03 and HR: 0.83; 95% CI: 0.71, 0.97; *p* = 0.02). Pooled estimates also had similar results (HR: 0.81; 95% CI: 0.72, 0.93; p= 0.002). No heterogeneity was detected (χ^2=0.01; I^2=0%; p=0.91) and (χ^2=0.77; I^2=0%; p=0.38). The details are depicted in Figure 4 (k).

A total of 4473 participants received SGLT2i + >40 mg loop diuretics + Placebo, and 3080 received SGLT2i and Placebo. Among the participants, 2236 patients had HFrEF <40% and 2237 had HFpEF >40% with T2DM. For the patients who received SGLT2i with loop diuretic >40 mg in both the groups of HFrEF and HFpEF, the hazard ratio was (HR: 0.92; 95% CI: 0.76, 1.12*; p < 0.42),* (HR: 1.06; 95% CI: 0.89, 1.27*; p < 0.50*) indicating a no-significant in mortality rate reduction due to other causes. Pooled estimates had similar results (HR: 1.00; 95% CI: 0.88, 1.13; p= 0.74). No heterogeneity was detected (χ^2=0.03; I^2=0%; p=0.87) and (χ^2=0.13; I^2=0%; p=0.71). The details are depicted in Figure 4 (l).

Adverse drug reactions

The analysis included three studies to assess the extent to which participants did not continue the drugs as they experienced adverse events and renal adverse events. Two studies assessed volume depletion. The participants receiving SGLT2i + Placebo were more likely to experience AEs and discontinue the drug (OR:1.21; 95% CI: 0.84, 1.74; p=0.31), but no notable difference was seen between the groups, and there was substantial heterogeneity (χ2=4.51; I2=56%; p=0.10). Similarly, the participants receiving SGLT2i + Placebo are more likely to experience the condition of volume depletion (OR:1.08; 95% CI: 0.72, 1.63; p=0.72), and patients on SGLT2i + Placebo with loop diuretics less than 40 mg are less likely to experience renal adverse effects (OR:0.86; 95% CI: 0.59, 1.25; p=0.43) without any notable significant difference between the groups. No heterogenicity was detected (χ^2=0.05; I^2=0%; p= 0.83) and (χ^2=0.17; I^2=0%; p=0.92). The details are depicted in *Supplementary Figure 1*.

The participants receiving SGLT2i+Placebo are likely to have AEs and discontinue the drug (OR:1.08; 95% CI: 0.75, 1.55; p=0.68), but the results lack statistical difference with substantial heterogeneity (χ2=3.96; I2=49%; p=0.14). Similarly, the patients who received SGLT2i + Placebo experienced the condition of volume depletion (OR: 1.56; 95% CI: 1.05,

2.31; p=0.03), whereas the participants on SGLT2i+ loop diuretics 40 mg + Placebo were at lower risk of experiencing renal adverse effects (OR: 0.93; 95% CI: 0.68, 1.27; p=0.63). No heterogeneity was detected for both the outcomes (χ2=0.67; I2=0%; p=0.41) and (χ^2=0.99; I^2=0%; p=0.61). The details are depicted in *Supplementary Figure 2*.

The patients who received SGLT2i + loop diuretics >40 mg + Placebo were less likely to experience AEs and discontinue the drug (OR: 0.97; 95% CI: 0.55, 1.69; p=0.91), but the findings lack statistical significance. The included study had substantial heterogeneity (χ^2=8.31; I^2=76%; p= 0.02). Similarly, the patients who received SGLT2i + Placebo slightly experienced the condition of volume depletion (OR:1.22; 95% CI: 0.48, 3.06; p=0.68) and the heterogeneity was very evident (χ^2=3.66; I^2=73%; p= 0.06), whereas those who were on SGLT2i+ loop diuretics >40 mg + Placebo did not much experienced renal adverse effects (OR:0.78; 95% CI: 0.59, 1.02; p=0.07), no heterogenicity was detected (χ^2=0.69; I^2=0%; p=0.71). The details are depicted in *Supplementary Figure 3*.

Risk of publication bias

No publication bias was found for outcome measures, as all the funnel plots are symmetrical. The details are mentioned in *Supplementary Figures 4-18*.

Outcomes of the GRADE approach assessment

The GRADE pro method was applied to evaluate the certainty of evidence. For all assessed outcomes, the evidence was rated as high. A summary of the findings is provided in *Supplementary Table 2*.

Discussion

HF is a complex clinical condition, often contributing to the greater rate of morbidity and mortality across the globe. The burden is often attributed to higher healthcare expenditure, frequent hospitalization and diminished quality of life [19]. In managing HF, the guidelines recommend combining SGLT2i with loop diuretics significantly reduces hospitalization rates and mortality [2]. However, a dilemma exists in the dosing strategy of loop diuretics when combined with SGLT2i. Hence, this review was focused on gathering additional information on the Heart failure outcomes and safety aspects when SGLT2i is used with background diuretic therapy at different doses.

Loop diuretics are the primary therapy for relieving congestion and fluid overload in HF patients, as they enhance sodium and water elimination, thereby improving symptoms and lowering hospitalization rates. Nonetheless, their utility is constrained by complications such

as resistance to diuretic action, electrolyte disturbances, and impaired renal function [20-22]. In contrast, SGLT2i exert natriuretic and osmotic diuretic effects while simultaneously offering cardioprotective benefits, including mitigation of hypoxic injury, preservation of mitochondrial function, reduction of oxidative stress, and improved myocardial energy metabolism [23,24]. The combination of SGLT2i with loop diuretics is particularly advantageous, as it addresses both intravascular and interstitial congestion, mitigates diuretic resistance, and allows for a reduction in loop diuretic dosage requirements among patients with HF [25,26]. Another advantage of this combination is the possibility of reducing loop diuretic dose and further discontinuing loop diuretics. It was substantiated by the finding of Alsalem et al., as there was a 54.8% reduction in the dosage of loop diuretics and 12.9% of drug discontinuation among the participants who received SGLT2i and loop diuretics in combination when compared to those who received diuretics alone group [27].

The dosing of loop diuretics, combined with SGLT2i, remains uncertain. The higher dose of diuretics is considered a risk marker for the severity of HF, and it also causes adverse outcomes. Kapelios et al. found that usage of a high dose of loop diuretics (Median dose of 80mg) was linked to higher overall death and hospitalization rates, which is potentially associated with stimulation of the sympathetic nervous system and the renin–angiotensin–aldosterone system, leading to depletion of the blood volume with worsening the condition of HF patients. In addition, the electrolyte imbalance could contribute to arrhythmias and produce dismal outcomes among HF patients [28]. Dosing less than 40mg of loop diuretics can significantly impact clinical outcomes. Low doses of loop diuretics may provide suboptimal diuresis, potentially leading to unresolved fluid overload and exacerbation of heart failure symptoms. Alshibani et al. reported that inadequate diuretic therapy at the time of discharge was associated with increased hospital readmissions among patients with acute decompensated heart failure [29]. These findings were consistent with our meta-analysis of four articles that measured the safety and therapeutic effectiveness of the combination of SGLT2i with background loop diuretics at different doses. The pooled analysis revealed that SGLT2i when prescribed with loop diuretics equivalent to 40 mg, showed better efficacy and safety outcomes than the background loop diuretic dosed below or above 40 mg.

Although this meta-analysis is the first to appraise the optimal dose of background loop diuretics prescribed with SGLT2i, it has the benefits of including multicentric RCTs conducted across wide regions, representing real-world data from populations with T2DM and other heart-related co-morbid conditions, with low publication bias and heterogeneity. Evidence of the included studies is high for all the outcomes measured in this review. The limitation of this review is that some of the criteria for risk of bias had an unclear risk, and the safety data were

not available in the Dhingra NK et al. study [14]. Most of the data included in the meta-analysis are from the post-hoc analysis, and these results are best viewed as exploratory and should be interpreted with caution due to limited statistical power. Nevertheless, this review offers practical guidance to clinicians on diuretic dose adjustments in patients initiating SGLT2i therapy, addressing the currently unclear interaction between diuretic dosing and SGLT2i outcomes, which will further provide insights into the extent of benefit and harm when using these medications.

Conclusions

The results of certain cardiovascular outcomes concerning primary composite outcomes and hospitalization or urgent HF with SGLT2i and placebo were consistent across all the doses of loop diuretics. However, when the loop diuretics were dosed at 40mg with SGLT2i and placebo, they showed efficacies for all cardiovascular outcomes. The patients who received an SGLT2i with 40 mg loop diuretics and placebo were less prone to experience volume depletion than those on SGLT2i and placebo. The renal adverse effects and discontinuation of the drug were the same across all the doses of loop diuretics. Thus, SGLT2 inhibitors and a 40 mg dose of background loop diuretics showed better efficacy and safety outcomes when compared with when the background loop diuretic is dosed at below or above 40 mg.

List of abbreviations

SGLT2i	Sodium-Glucose Cotransporter 2 Inhibitor
EF	Ejection Fraction
HF	Heart Failure
HR	Hazards Ratio
HFrEF	Heart Failure with reduced Ejection Fraction
HFpEF	Heart Failure with preserved Ejection Fraction
ACEi	Angiotensin-converting enzyme inhibitors
OHA	Oral Hypoglycaemic Agent
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
SR/MA	Systemic Review/ Meta-Analysis
NYHA	New York Heart Association
DM	Diabetes Mellitus
CI	Confidence Interval
ROB	Risk of Bias
OR	Odds Ratio
RCT	Randomized Control Trial
T2DM	Type 2 Diabetes Mellitus

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Online supplementary material:

Supplementary Figure 1. The forest plot illustrates the adjusted hazard ratios for discontinuation of the drug due to adverse events, volume depletion, and renal adverse events among patients with heart failure with reduced ejection fraction and heart failure with preserved ejection fraction, stratified by treatment with sodium-glucose co-transporter 2 inhibitor (SGLT2i), placebo, and SGLT2i plus loop diuretics at doses below 40 mg.

Supplementary Figure 2. The forest plot illustrates the adjusted hazard ratios for discontinuation of the drug due to adverse events, volume depletion, and renal adverse events among patients with heart failure with reduced ejection fraction and heart failure with preserved ejection fraction, stratified by treatment with sodium-glucose co-transporter 2 inhibitor (SGLT2i), placebo, and SGLT2i plus loop diuretics at doses equal to 40 mg.

Supplementary Figure 3. The forest plot illustrates the adjusted hazard ratios for discontinuation of the drug due to adverse events, volume depletion, and renal adverse events among patients with heart failure with reduced ejection fraction and heart failure with preserved ejection fraction, stratified by treatment with sodium-glucose co-transporter 2 inhibitor (SGLT2i), placebo, and SGLT2i plus loop diuretics at doses above 40 mg.

Supplementary Figure 4. A funnel plot comparing the primary composite outcome in patients with heart failure with reduced ejection fraction and heart failure with preserved ejection fraction, those treated with sodium-glucose co-transporter 2 inhibitor (SGLT2i) and placebo *vs.* SGLT2i, placebo, and loop diuretics at doses below 40 mg.

Supplementary Figure 5. A funnel plot comparing the primary composite outcome in patients with heart failure with reduced ejection fraction and heart failure with preserved ejection fraction, those treated with sodium-glucose co-transporter 2 inhibitor (SGLT2i) and placebo *vs.* SGLT2i, placebo, and loop diuretics at doses equal to 40 mg.

Supplementary Figure 6. A funnel plot comparing the primary composite outcome in patients with heart failure with reduced ejection fraction and heart failure with preserved ejection fraction, those treated with sodium-glucose co-transporter 2 inhibitor (SGLT2i) and placebo *vs.* SGLT2i, placebo, and loop diuretics at doses above 40 mg.

Supplementary Figure 7. A funnel plot comparing the hospitalization or urgent HF visit in patients with heart failure with reduced ejection fraction and heart failure with preserved ejection fraction, those treated with sodium-glucose co-transporter 2 inhibitor (SGLT2i) and placebo *vs.* SGLT2i, placebo, and loop diuretics at doses below 40 mg.

Supplementary Figure 8. A funnel plot comparing the hospitalization or urgent HF visit in patients with heart failure with reduced ejection fraction and heart failure with preserved ejection fraction, those treated with sodium-glucose co-transporter 2 inhibitor (SGLT2i) and placebo *vs.* LT2i, placebo, and loop diuretics at doses equal to 40 mg.

Supplementary Figure 9. A funnel plot comparing the hospitalization or urgent HF visit in patients with heart failure with reduced ejection fraction and heart failure with preserved ejection fraction, those treated with sodium-glucose co-transporter 2 inhibitor (SGLT2i) and placebo *vs.* SGLT2i, placebo, and loop diuretics at doses above 40 mg.

Supplementary Figure 10. A funnel plot comparing the cardiovascular death in patients with heart failure with reduced ejection fraction and heart failure with preserved ejection fraction, those treated with sodium-glucose co-transporter 2 inhibitor (SGLT2i) and placebo *vs.* SGLT2i, placebo, and loop diuretics at doses below 40 mg.

Supplementary Figure 11. A funnel plot comparing the cardiovascular death in patients with heart failure with reduced ejection fraction and heart failure with preserved ejection fraction, those treated with sodium-glucose co-transporter 2 inhibitor (SGLT2i) and placebo *vs.* SGLT2i, placebo, and loop diuretics at doses equal to 40 mg.

Supplementary Figure 12. A funnel plot comparing the cardiovascular death in patients with heart failure with reduced ejection fraction and heart failure with preserved ejection fraction, those treated with sodium-glucose co-transporter 2 inhibitor (SGLT2i) and placebo *vs.* SGLT2i, placebo, and loop diuretics at doses above 40 mg.

Supplementary Figure 13. A funnel plot comparing the death resulting from any cause in patients with heart failure with reduced ejection fraction and heart failure with preserved ejection fraction, those treated with sodium-glucose co-transporter 2 inhibitor (SGLT2i) and placebo *vs.* SGLT2i, placebo, and loop diuretics at doses below 40 mg.

Supplementary Figure 14. A funnel plot comparing the death resulting from any cause in patients with heart failure with reduced ejection fraction and heart failure with preserved ejection fraction, those treated with sodium-glucose co-transporter 2 inhibitor (SGLT2i) and placebo *vs.* SGLT2i, placebo, and loop diuretics at doses equal to 40 mg.

Supplementary Figure 15. A funnel plot comparing the death resulting from any cause in patients with heart failure with reduced ejection fraction and heart failure with preserved

ejection fraction, those treated with sodium-glucose co-transporter 2 inhibitor (SGLT2i) and placebo *vs.* SGLT2i, placebo, and loop diuretics at doses above 40 mg.

Supplementary Figure 16. A funnel plot comparing the discontinuation due to adverse event, volume depletion, renal adverse event in patients with heart failure with reduced ejection fraction and heart failure with preserved ejection fraction, those treated with sodium-glucose co-transporter 2 inhibitor (SGLT2i) and placebo *vs.* SGLT2i, placebo, and loop diuretics at doses below 40 mg.

Supplementary Figure 17. A funnel plot comparing the discontinuation due to adverse event, volume depletion, renal adverse event in patients with heart failure with reduced ejection fraction and heart failure with preserved ejection fraction, those treated with sodium-glucose co-transporter 2 inhibitor (SGLT2i) and placebo *vs.* SGLT2i, placebo, and loop diuretics at doses equal to 40 mg.

Supplementary Figure 18. A funnel plot comparing the discontinuation due to adverse event, volume depletion, renal adverse event in patients with heart failure with reduced ejection fraction and heart failure with preserved ejection fraction, those treated with sodium-glucose co-transporter 2 inhibitor (SGLT2i) and placebo *vs.* SGLT2i, placebo, and loop diuretics at doses above 40 mg.

Supplementary Table 1. Details of risk of bias.

Supplementary Table 2. Illustrating the summary findings.

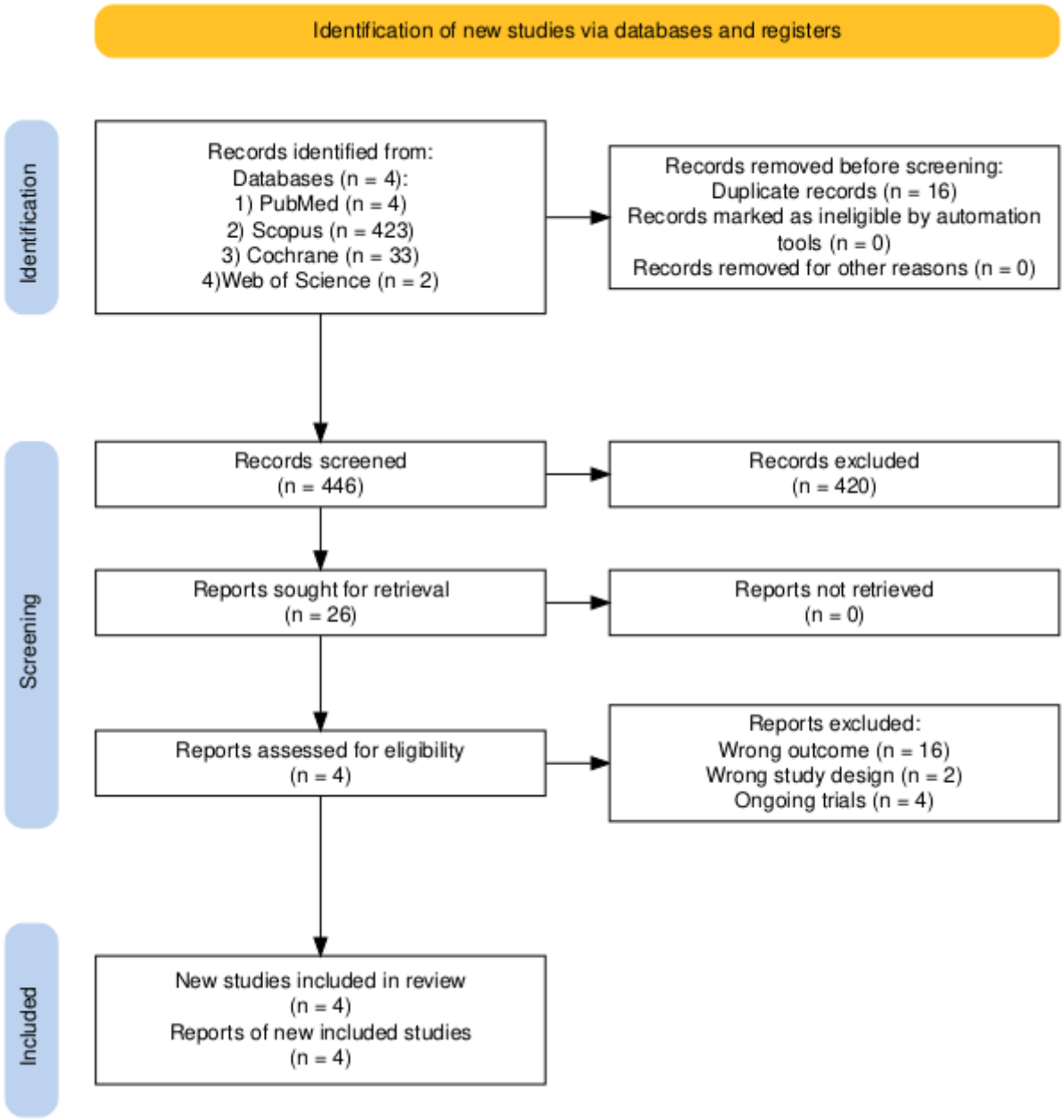

Figure 1. The flow diagram of the included studies in the review.

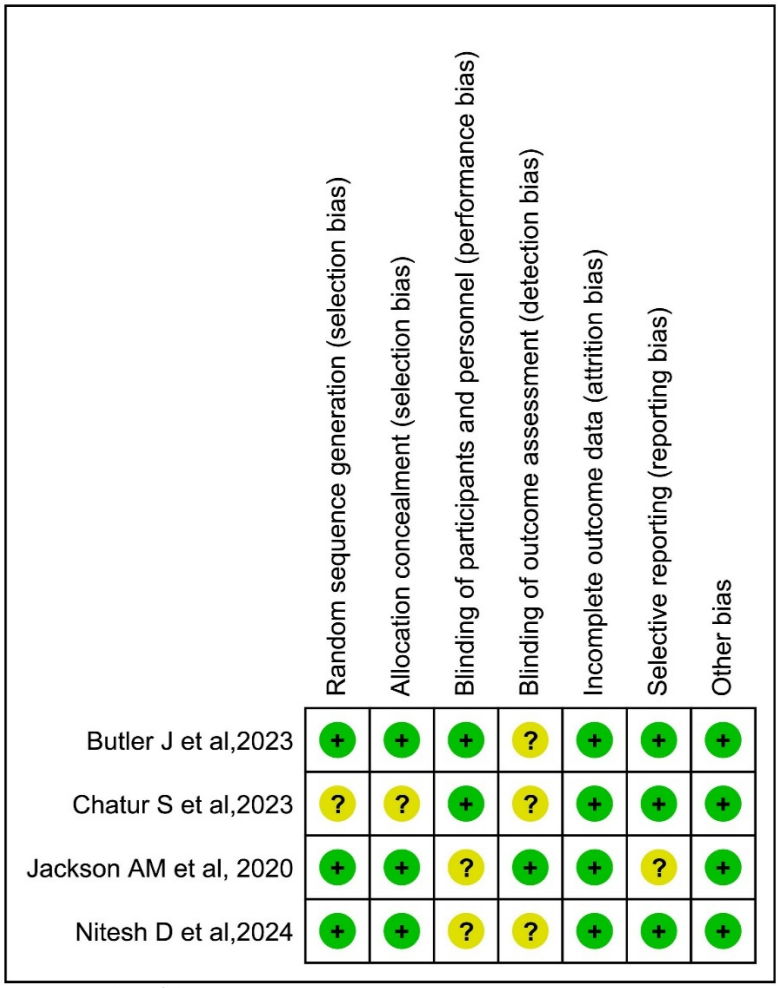

Figure 2. Risk of bias.

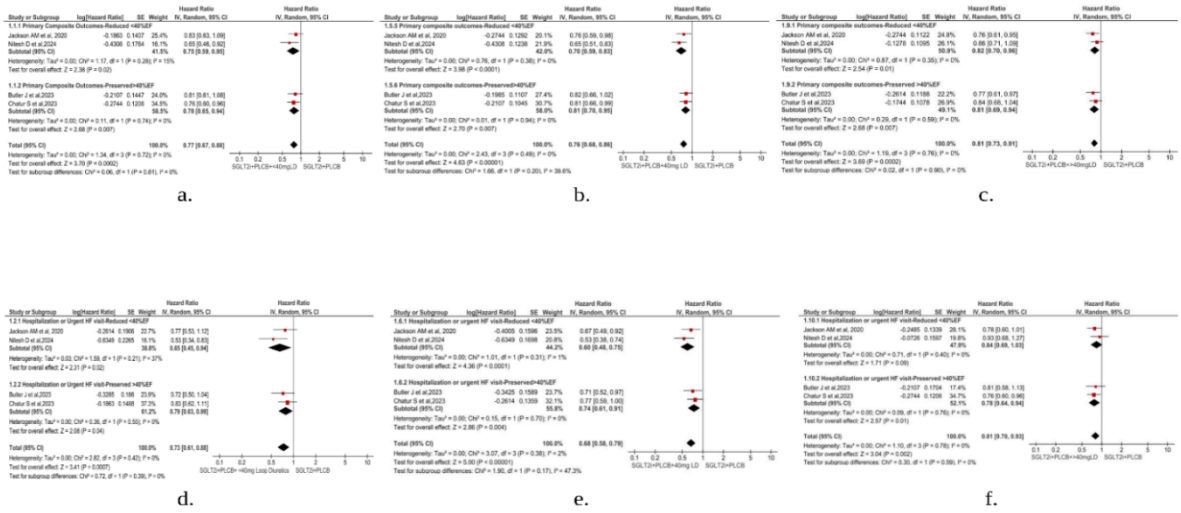

Figure 3. Forest Plot illustrates the adjusted hazard ratios for comparisons of primary composite outcome (a, b, c) and HF hospitalizations/urgent visits (d, e, f) in patients with HFrEF and HFpEF: SGLT2 inhibitors plus placebo vs. combination with <40mg, 40mg and >40mg loop diuretics. SGLT2i, sodium-glucose co-transporter 2 inhibitor; PLCB, Placebo; LD, Loop Diuretics; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction.

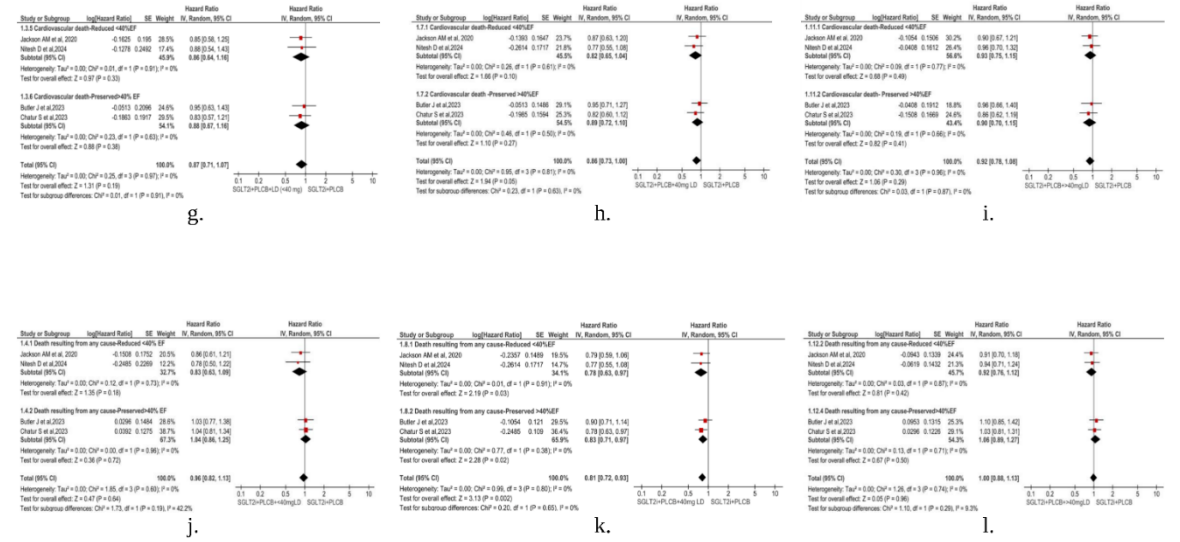

Figure 4. Forest plot illustrates the adjusted hazard ratios for comparisons of cardiovascular death (g, h, i) and all-cause mortality (j, k, l) in HFrEF and HFpEF: SGLT2 inhibitors plus placebo vs. combination with <40 mg, 40mg, >40mg loop diuretics. SGLT2i, sodium-glucose co-transporter 2 inhibitor; PLCB, Placebo; LD, Loop Diuretics; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction.

Table 1. Characteristics table of the included studies.

Author, Year	Study Centre	Study sample	Study design	Population	Intervention group	Control group	Co-morbidities	Outcomes of interest
Jackson et al. 2020 [12]	Multicentre	4616	Post hoc analysis of RCTs	HF with NYHA class II-IV, HFrEF < 40% with elevated NT pro-BNP level	1. SGLT2i +PLCB + < 40 mg LD (n=1311). 2. SGLT2i + PLCB+ 40mg LD (N=1365) 3. SGLT2i + PLCB+ >40mg LD (N=1204)	SGLT2i + PLCB (n=736)	T2DM, AF, HTN, Prior HFH	• Primary composite outcomes, • Hospitalization or urgent HF visit, • Cardiovascular death, • Death resulting from any cause, • Discontinuation due to adverse events, • Volume depletion, • Renal adverse event
Dhingra et al, 2024 [14]	Multicentre	3656	Post –Hoc analysis of RCTS	HF with NYHA class II-IV HFrEF < 40% with elevated NT pro-BNP level	1. SGLT2i +PLCB + < 40 mg LD (n=731) 2. SGLT2i + PLCB+ 40mg LD (N=1411) 3. SGLT2i + PLCB+ >40mg LD (N=1032)	SGLT2i + PLCB (n=482)	T2DM, AF, HTN, Prior HFH	• Primary composite outcomes, • Hospitalization or urgent HF visit, • Cardiovascular death, • Death resulting from any cause,
Chatur et al, 2023 [18]	Multicentre	6263	Post hoc analysis of RCTs	HF with NYHA class II-IV HFpEF >40% with elevated NT pro-BNP level	1. SGLT2i +PLCB + < 40 mg LD (n=1811) 2. SGLT2i + PLCB+ 40mg LD (N=1902) 3. SGLT2i + PLCB+ >40mg LD (N=1098)	SGLT2i +PLCB (n=683)	T2DM, AF, HTN, Prior HFH, stroke, MI	• Primary composite outcomes, • Hospitalization or urgent HF visit, • Cardiovascular death, • Death resulting from any cause, • Discontinuation due to adverse event, • Volume depletion, • Renal adverse event
Butler et al 2023 [13]	Multicentre	5815	Post hoc analysis of RCTs	HF with NYHA class II-IV HFpEF >40% with elevated NT pro-BNP level	1. SGLT2i +PLCB + < 40 mg LD (n=1725) 2. SGLT2i + PLCB+ 40mg LD (N=1772) 3. SGLT2i + PLCB+ >40mg LD (N=1139)	SGLT2i + PLCB (n=1179)	AF, HTN, CKD, T2DM, CAD	• Primary composite outcomes, • Hospitalization or urgent HF visit, • Cardiovascular death, • Death resulting from any cause, • Renal adverse event

RCT, randomized control study; T2DM, type 2 diabetes mellitus; HFrEF, heart failure with reduced ejection fraction; SGLT2i, sodium-glucose co transporter 2 inhibitor; HFpEF, heart failure with preserved ejection fraction; HTN, hypertension; CKD, chronic kidney disease; CAD, coronary artery disease; MI, myocardial infarction; NYHA class, New York Heart Association classification; NT- pro BNP level, N-terminal pro-B-type natriuretic peptide; PLCB, placebo; LD, loop diuretics; AF, atrial fibrillation; HFH, heart failure hospitalization; HF, heart failure.