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SYSTEMATIC REVIEW

Dapagliflozin in Heart Failure: A Comprehensive Meta-analysis on Functional Capacity, Symptoms, and Safety Outcomes

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Abstract

Objective To evaluate the comparative effects of dapagliflozin versus placebo in patients with heart failure (HF), focusing on functional capacity, symptoms, and safety outcomes.

Background Despite advancements in heart failure (HF) therapy, HF is still a significant cause of recurrent hospitalization and death worldwide. Dapagliflozin has demonstrated potential in lowering hospitalizations and mortality associated with heart failure; however, its impact on functional capacity, particularly the 6-min walk distance (6MWD), and the comprehensive assessment of safety outcomes in diverse HF populations, including those with preserved or reduced ejection fraction (HFpEF and HFrEF, respectively), requires further investigation.

Methods PubMed, Web of Science, Cochrane Library, and Scopus databases were comprehensively searched to identify randomized controlled trials (RCTs) investigating the efficacy of dapagliflozin in comparison with control interventions for heart failure. The primary outcome was a change in the 6MWD, KCCQ score, and safety measures included hospitalization, all-cause mortality, and adverse events.

Results In our meta-analysis of ten studies involving 12,695 patients with heart failure, dapagliflozin showed significantly improved Kansas City Cardiomyopathy Questionnaire (KCCQ) scores [risk ratio (RR) of 2.75, 95% confidence interval (CI) (1.95–3.569), $p < 0.00001$] and no significant differences in 6-min walk distance [6MWD; RR of 3.59, 95% CI (− 1.44 to 8.63), $p = 0.16$]. Dapagliflozin demonstrated a notable reduction in hospitalization for heart failure [RR of 0.76, 95% CI (0.68–0.84), $p < 0.00001$], significant overall reduction on the effect of any cause mortality [RR of 0.90, 95% CI (0.83–0.99), $p = 0.03$). There was, however, no significant effect on adverse events [RR of 0.96, 95% CI (0.98–1.03), $p = 0.39$).

Conclusions Our meta-analysis of ten trials concluded that dapagliflozin significantly improved KCCQ scores in both HFrEF and HFpEF. The improvement in 6MWD was not statistically significant but trended toward dapagliflozin. Dapagliflozin also showed a mortality benefit in patients with reduced ejection fraction; however, in patients with preserved ejection fraction, the result was not statistically significant. There was also a statistically significant reduction in heart failure hospitalizations across all classes.

1 Introduction

Despite the implementation of established therapies, heart failure (HF) remains a primary cause of recurring hospital admissions and mortality worldwide [1]. The possibility of developing HF and its consequences, including mortality, increases in the presence of type 2 diabetes mellitus (T2DM) [2, 3].

SGLT-2 inhibitors have been demonstrated to lower the likelihood of heart failure-related hospitalization in patients with T2DM [4–7].

SGLT2 inhibitors have been identified in two large trials that included ambulatory patients with heart failure with reduced ejection fraction (HFrEF) to have been effective in reducing hospitalizations for worsening heart failure (and other episodes of heart failure exacerbation), as well as the risk of death from cardiovascular events [8, 9].

Two more trials have revealed a parallel benefit associated with SGLT2 inhibitors in patients suffering from heart failure with preserved ejection fraction (HFpEF). The combined analysis of these four trials consistently demonstrates favorable outcomes across the whole range of ejection fractions [10–13]. The results of these studies led to the integration

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Key Points

Dapagliflozin improved the functional capacity in patients with heart failure across all classes, with improvement in KCCQ scores in these patients.

Dapagliflozin showed a trend toward improving 6MWD; however, the results were not statistically significant.

Dapagliflozin showed a reduction in mortality in patients with HFrEF.

Dapagliflozin significantly reduced hospitalizations in all classes of patients with heart failure.

of SGLT-2 inhibitors as recommended medications for heart failure by the ACC/AHA/HFSA throughout the spectrum [14].

Improving symptoms and functional capacity are additional objectives in therapeutic interventions for heart failure, which are considered necessary by both patients and regulatory agencies [15, 16]. Symptom improvement has been observed in patients with HFrEF and HFpEF treated with SGLT2 inhibitors, as measured by the patient-reported Kansas City Cardiomyopathy Questionnaire (KCCQ). However, the persistent beneficial effects on objective markers of physical function have not been commonly recognized [8–11, 17–20].

Regarding physical activity, particularly the 6-min walk distance (6MWD), different studies reported diverse outcomes. The EMPERIAL-Reduced, EMPERIAL-Preserved found no benefit of empagliflozin with regards to improvement in symptoms as assessed by the 6MWD and KCCQ scores. [18]. In contrast, the PRESERVED-HF trial demonstrated a significant increase in 6MWD and improvement in KCCQ scores with dapagliflozin over the same period in patients with HFpEF [19]. Furthermore, 6MWD increase was not reproduced in the smaller HFrEF trial, DEFINE-HF [17].

These findings highlight conflicting results in 6 MWD and KCCQ. A recent large randomized controlled trial (RCT) on the effect of dapagliflozin with regards to symptoms in heart failure casts a new spotlight on this. In addressing a notable gap in the existing research and emphasizing the need to reconcile conflicting findings related to the impact of SGLT2 inhibitors on 6MWD and KCCQ scores, it is appropriate to have an updated systematic review. This systematic review and meta-analysis aimed to assess the comparative effects of dapagliflozin versus placebo in patients with heart failure, with a primary focus on functional capacity and physical activity including 6MWD and KCCQ score. Additionally, we will examine the safety outcomes, including all-cause mortality and HF hospitalization.

2 Methods

2.1 Eligibility Criteria

This meta-analysis included all randomized clinical trials that met our PICO criteria: population participants (P): individuals with heart failure, including those with either preserved or reduced ejection fraction; intervention (I): dapagliflozin plus standard therapy; comparator (C): standard therapy; outcomes (O): change in 6MWD, KCCQ score, any-cause mortality, hospitalization for heart failure, and adverse events.

2.2 Information Sources and Search Strategy

The PubMed, Scopus, Web of Science, and Cochrane Library databases were searched until January 2024. The primary search terms were as follows (Dapagliflozin OR "Farxiga" OR "BMS512148" OR "BMS-512148") AND ("Heart failure" OR "Cardiac Failure" OR "Heart Decompensation" OR "Systolic heart failure" OR "Diastolic heart failure" OR "Myocardial Failure" OR "Heart Insufficiency" OR HFrEF or "Heart failure with reduced ejection fraction" OR HFpEF OR "heart failure with preserved ejection fraction").

2.3 Selection Process:

Duplicates were eliminated using the EndNote software (Clarivate Analytics, PA). The obtained references were evaluated using two screening steps: the first involved a relevance assessment of the titles and abstracts and the second involved a full-text article screening of the selected abstracts to establish final eligibility for quantitative analysis. Two reviewers (B.A. and S.I.) independently performed title and abstract screening. Conflicts were resolved through a third author (W.A.). The selection procedure was conducted using Rayyan website, an online software that helps to expedite the initial screening of abstracts and titles and synthesize multiple RCTs [22].

2.4 Data Extraction

A predesigned extraction sheet was used to collect the following data: baseline characteristics [age, gender status (male), body mass index, and medical comorbidities such as hypertension and diabetes mellitus]; summary characteristics (study design, country, number of participants in each group, inclusion criteria, and duration of follow-up); outcome data (change in 6MDW, KCCQ score, any cause mortality, hospitalization for heart failure, any adverse events)

2.5 Risk of *Bias* and Quality Assessment

The revised Cochrane risk-of-bias tool for RCTs (ROB2) was used to evaluate the risk of bias in the included clinical trials was used [23]. This evaluation consistently assessed the randomization process, concealment of the allocation sequence, deviations from the intended interventions, utilization of appropriate analysis to estimate the effect of assignment to the intervention, measurement of the outcome, selection of the reported results, and overall risk of bias. Assessment of the methodological quality of the studies was classified as low risk, some concerns, or high risk of bias.

2.6 Statistical Analysis

RevMan v5.3 was used to conduct the statistical analysis [24]. The risk ratio (RR) was used to synthesize dichotomous outcomes, and the mean difference (MD) with 95% confidence interval (CI) was used to pool continuous outcomes. Chi-square and I^2 tests were both used in the assessment of heterogeneity. The I^2 test measured the degree of heterogeneity, while the chi-square test was used to determine whether heterogeneity existed. The Cochrane Handbook's (chapter nine) [25] interpretation of the I^2 is as follows: heterogeneity is not significant for percentages 0–40, moderate for percentages 30–60, significant for percentages 50–90, and significant for percentages 75–100. For the Chi-square test to identify significant heterogeneity, the alpha level must be less than 0.1. Leave-one-out sensitivity analysis was used to resolve heterogeneity by methodically removing each study from the pooled analysis.

3 Results

3.1 Literature Search Results

Our literature search resulted in 1201 records After removing duplicates using EndNote (Clarivate Analytics, Philadelphia, PA), we refined the dataset to 1047 records for further screening. Following a thorough full-text screening, we identified ten randomized controlled trials (RCTs) that matched the inclusion criteria for our meta-analysis, as shown in (Fig. 1). This meta-analysis was reported in compliance with the Preferred Reporting Items for Systematic Reviews and Meta- Analysis (PRISMA) statement [26].

3.2 Characteristics of the Included Studies

In our comprehensive meta-analysis, we incorporated ten studies [8, 11, 17, 19, 21, 25, 27–31], encompassing a sizable population of 12,695 individuals presenting with heart failure. This study included patients with both reduced ejection fraction (HFrEF) and preserved ejection fraction (HFpEF), all of whom received dapagliflozin in comparison with a control group receiving either placebo or standard therapy. The dapagliflozin group comprised a large number of participants ($n = 6350$), whereas the control group consisted of 6345 participants. Two studies [8, 31] initially focused on patients with chronic kidney disease (CKD) or type 2 diabetes but were incorporated based on their preplanned analysis of outcomes concerning the presence of heart failure at baseline. The primary outcomes were changes in 6-min walk distance (6MWD) and Kansas City Cardiomyopathy Questionnaire (KCCQ) scores. The secondary outcomes were all-cause mortality, hospitalization for heart failure, and adverse events. A summary of the included studies and the baseline characteristics of the participants are provided in Table 1 and Table 2, respectively.

3.3 Risk of *Bias* Assessment

According to the Cochrane RoB2, nine randomized clinical trials had an overall some concern risk of bias and two studies had a low risk of bias, as shown in the risk of bias graph (Fig. 2)

3.4 Primary Outcome:

3.4.1 Changes in 6-min walk distance (6MWD)

The overall analysis did not show a significant difference in changes in 6-min walk distance (6MWD) between the dapagliflozin and control groups [RR of 3.59, 95% confidence interval (CI) (− 1.44 to 8.63), $p = 0.16$). Pooled analysis demonstrated homogeneity ($I^2 = 37\%$, $p = 0.17$). Regarding subgroup analysis, no significant difference in changes in 6MWD was observed between the dapagliflozin and control groups for patients with HFpEF and HFrEF [RR = 0.87, 95% CI (− 5.68 to 7.42), $p = 0.79$] and [RR of 7.52, 95% CI (− 0.35 to 15.39), $p = 0.06$, respectively] (Fig. 3).

3.4.2 Changes in Kansas City Cardiomyopathy Questionnaire (KCCQ) Scores

The overall analysis demonstrated a statistically significant improvement in (KCCQ) scores for patients receiving dapagliflozin compared with the control group [RR of 2.75, 95% CI (1.95–3.56), $p < 0.00001$]. Pooled analysis demonstrated homogeneity ($I^2 = 0\%$, $p = 0.81$). In the subgroup analysis, the improvement in the KCCQ score was noticed in both heart failure groups. In the HFpEF group, the improvement in KCCQ score was associated with a RR of 1.76, 95% CI

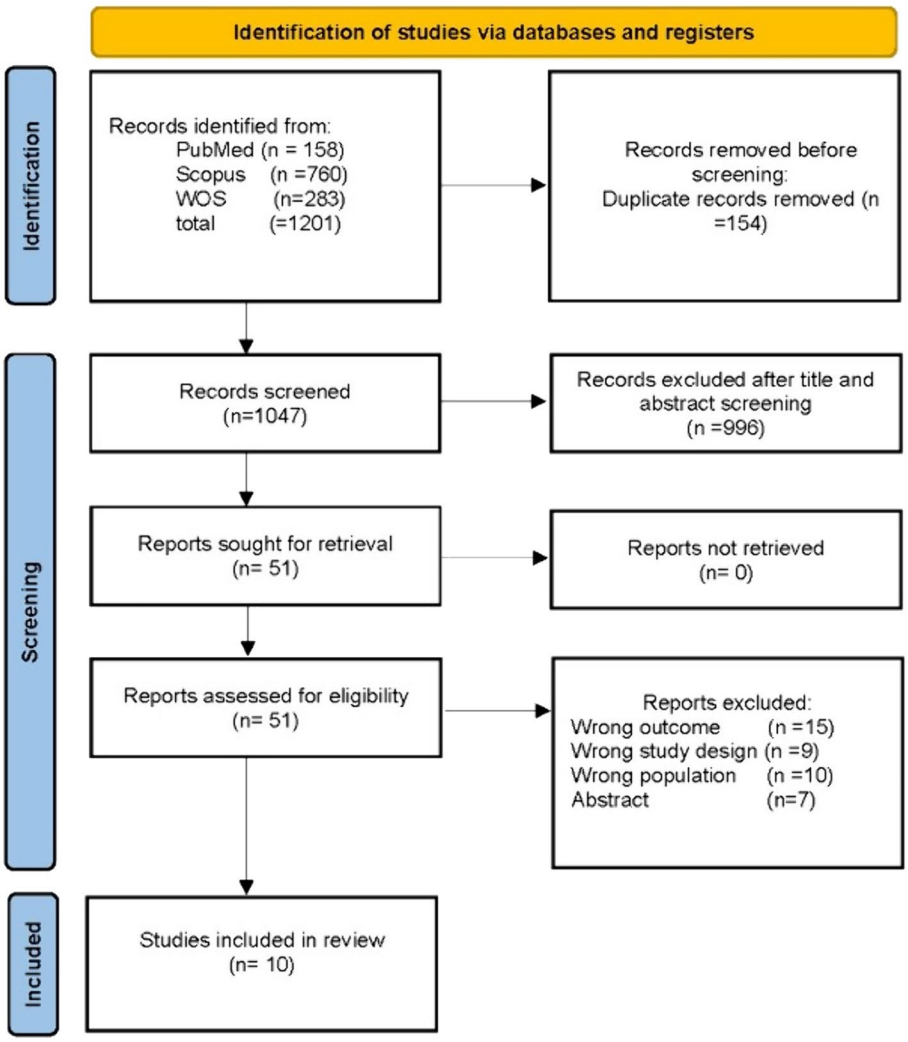

Fig. 1 PRISMA flow diagram of the study selection process. PRISMA-Preferred Reporting Items for Systematic Review and Meta-Analysis

(0.18–3.33), $p = 0.03$, while in the HFrEF group when compared with placebo, RR of 3.10, 95% CI (2.17–4.04), $p < 0.00001$ (Fig. 4).

3.5 Secondary Outcome

3.5.1 Hospitalization for HF

The analysis revealed a significant reduction in the risk of hospitalization for heart failure in patients receiving dapagliflozin compared with that in the control group [RR = 0.76, 95% CI (0.68–0.84), $p < 0.00001$). Pooled analysis demonstrated homogeneity ($I^2 = 0\%$, $p = 0.86$) (Fig. 5).

3.5.2 Any Cause of Mortality

The overall analysis also revealed a statistically significant difference in the all-cause mortality between dapagliflozin and control groups [RR = 0.90, 95% CI (0.83–0.99), $p = 0.03$). Pooled analysis demonstrated homogeneity ($I^2 = 0\%$, $p = 0.87$). In the subgroup analysis, the reduction in all-cause mortality was also observed in the HFrEF group. In the HFrEF subgroup, when compared with placebo, RR of 0.84, 95% CI (0.72–0.97), $p = 0.02$. This mortality benefit was not seen in the HFpEF group, when compared with placebo [RR = 0.94, 95% CI (0.84–1.06), $p = 0.31$) (Fig. 6).

3.5.3 Any Adverse Events

The overall analysis demonstrated no statistically significant reduction in the risk of adverse events in patients receiving dapagliflozin compared with the control group [RR of 0.98, 95% CI (0.93–1.03), $p = 0.39$]. Pooled analysis demonstrated homogeneity ($I^2 = 6.9\%$, $p = 0.30$). The subgroup analysis did not reveal a significant difference between the two groups for patients with HFrEF and HFpEF ([RR = 1.03, 95% CI (0.92–1.16), $p = 0.61$] and [RR = 0.96, 95% CI (0.91–1.02), $p = 0.17$], respectively) (Fig. 7).

Table 1 Summary of the included studies

Study ID	Year	Setting	Follow-up period	Exclusion criteria	Inclusion criteria	Main findings
Ibrahim 2020	2020	Single center	From admission till discharge	(1) Other causes of fluid overload different than HF (2) Marked hyponatremia; sodium level below 125 mmol/L (3) Unstable patients; acute coronary syndrome, cardiogenic shock (4) Patients requiring positive inotropic agents, or renal dialysis, pregnant or breast-feeding, advanced hepatic disease, advanced kidney disease with glomerular filtration rate (GFR) < 45 mL/min/1.73 m^2 and patients with diabetic ketoacidosis	(1) Age more than 18 years (2) Type 2 diabetic patients with history of chronic HF and had indication for admission to cardiac care unit (decompensated HF) (3) The patients were included as they had at least one symptom (respiratory discomfort or orthopnea) and one clinical sign (peripheral edema, engorged jugular vein, or pulmonary congestion) (4) The patients were already on furosemide for at least 1 month before admission plus other conventional anti-failure treatment, had left ventricular ejection fraction (LVEF) ≤ 40% and there was no prespecified inclusion criterion with respect to HF etiology	There was a statistically significant difference between the two groups regarding the change in body weight and body mass index with no significant change in kidney functions
McMurray 2019	2019	Multicenter	Recruitment period of 18 months and an average follow-up period of approximately 24 months, (median of 18.2 months)	(1) Recent treatment with or unacceptable side effects associated with an SGLT2 inhibitor (2) Type 1 diabetes mellitus (3) Symptoms of hypotension or a systolic blood pressure of less than 95 mmHg 4) Estimated glomerular filtration rate (eGFR) below 30 mL per minute per 1.73 m^2 of body-surface area (or rapidly declining renal function)	(1) Age of at least 18 years (2) An ejection fraction of 40% or less (3) New York Heart Association (NYHA) class II, III, or IV symptoms (4) Patients were required to have a plasma level of N-terminal pro-B-type natriuretic peptide (NT-proBNP) of at least 600 pg/mL (or ≥ 400 pg/mL if they had been hospitalized for heart failure within the previous 12 months) (5) Patients with atrial fibrillation or atrial flutter on baseline electrocardiography were required to have an NT-proBNP level of at least 900 pg/mL, regardless of their history of hospitalization for heart failure	Dapagliflozin reduced the risk of worsening heart failure or cardiovascular death. The risk reduction was consistent regardless of the presence or absence of diabetes. Adverse events related to volume depletion, renal dysfunction, and hypoglycemia were similar between treatment groups

Table 1 (continued)

Study ID	Year	Setting	Follow-up period	Exclusion criteria	Inclusion criteria	Main findings
McMurray 2021	2021	Multicenter	The median follow-up period was 2.4 years (25th, 75th percentile range 2.0–2.7 years)	(1) Documented diagnosis of type 1 diabetes, polycystic kidney disease, lupus nephritis, or antineutrophil cytoplasmic antibody-associated vasculitis (2) Participants who had received immunotherapy for primary or secondary kidney disease within 6 months before enrollment	(1) Provision of signed informed consent prior to any study specific procedures (2) Female or male aged ≥ 18 years at the time of consent (3) eGFR ≥ 25 and ≤ 75 mL/min/1.73m^2 (CKD-EPI formula) at visit 1 (4) UACR ≥ 200 and ≤ 5000 mg/g at visit 1 (5) Stable and for the patient maximum tolerated labelled daily dose, treatment with ACE-I or ARB for at least 4 weeks before visit 1, if not medically contraindicated	Dapagliflozin reduced the risk of kidney failure and cardiovascular death/HF hospitalization The relative risk reduction was 50–60% in both subgroups (with and without HF) The absolute risk reduction was around 5% in each subgroup The rate of decline in eGFR over time was not steeper in patients with HF Longer-term follow-up is needed to assess the impact of HF on future risk of end-stage kidney disease
McMurray 2023	2023	Multicenter	16 weeks	(1) Systolic blood pressure < 95 mmHg (2) Estimated glomerular filtration rate (eGFR) < 25 mL/min/1.73 m^2 (3) Type 1 diabetes or other conditions likely to prevent participation in the trial or greatly limit life expectancy (4) Any condition precluding exercise testing was also an exclusion criterion [e.g., intermittent claudication, bradyarrhythmia or uncontrolled tachyarrhythmia, musculoskeletal disease, pulmonary disease, severe obesity (body mass index ≥ 50.0 kg/m^2)].	(1) Men and women 18 years of age (or 40 years of age with HFpEF) (2) Diagnosis of HF for 2 months (3) New York Heart Association functional class II through IV HF (4) Left ventricular ejection fraction (LVEF) ≥ 40 for DETERMINE-Reduced (5) LVEF ≥ 40 and evidence of structural heart disease for DETERMINE-Preserved (6) NT-proBNP level ≥ 400 pg/mL for DETERMINE-Reduced (7) NT-proBNP level ≥ 250 pg/mL for DETERMINE-Preserve	Dapagliflozin improved the total symptom score (TSS) in patients with HF with reduced ejection fraction Dapagliflozin did not improve the physical limitation scale (PLS) or 6-min walk distance (6MWD) in patients with HF with reduced ejection fraction Dapagliflozin did not improve the TSS, PLS, or 6MWD in patients with HF with preserved ejection fraction In a post hoc analysis including all patients, dapagliflozin had a beneficial effect on TSS and PLS but not 6MWD

Table 1 (continued)

Study ID	Year	Setting	Follow-up period	Exclusion criteria	Inclusion criteria	Main findings
Nassif 2019	2019	Multi-center	12 weeks	(1) Recent hospitalization for decompensated heart failure within 30 days (2) Estimated glomerular filtration rate (eGFR) less than 30 mL/min/1.73m^2 (3) History of type 1 diabetes mellitus	(1) Adult ambulatory patients with or without T2D (2) Established HF for at least 16 weeks (3) LVEF ≥ 40 (4) NYHA class II–III HF	Dapagliflozin may improve disease-specific health status in heart failure patients The benefits of dapagliflozin may extend to patients with or without type 2 diabetes mellitus
Nassif 2021	2021	Multi-center	12 weeks	(1) Recent hospitalization (within 7 days) for decompensated HF (2) eGFR < 20 mL/min/1.73m^2 at the screening visit (3) Type 1 diabetes or previous history of DKA	(1) Adult ambulatory patients with or without T2D (2) Clinical diagnosis of HFpEF (3) LVEF ≥ 45% and NYHA classII–IV symptoms were screened for participation (4) Patients additionally had to have elevated natriuretic peptides (NTproBNP ≥ 225 or BNP ≥ 75pg/mL; if AF, NTproBNP ≥ 375 pg/mL or BNP ≥ 100 pg/mL) (5) Requirement for diuretic therapy (loop, thiazide or potassium-sparing diuretics) and either HF hospitalization or urgent HF visit with intravenous diuretic treatment in the past 12 months (6) Documented elevated filling pressures on right or left heart catheterization; or echocardiographic evidence of structural heart abnormalities	Dapagliflozin significantly improved symptoms, physical limitations, and exercise function in patients with HFpEF The treatment benefits were large, clinically meaningful, and consistent across all subgroups The health status benefits of dapagliflozin were consistent in diverse patient populations The study population had a diverse demographic, including women and African American participants Dapagliflozin showed consistent benefits regardless of the presence of type 2 diabetes

Table 1 (continued)

Study ID	Year	Setting	Follow-up period	Exclusion criteria	Inclusion criteria	Main findings
Palau 2022	2022	Multi-center	3 months	(1) Inability to perform a valid baseline cardiopulmonary exercise test (CPET) (2) HF due to restrictive cardiomyopathy, active myocarditis, constrictive pericarditis, hypertrophic (obstructive) cardiomyopathy, or uncorrected severe primary cardiac valve disease (3) Myocardial infarction, unstable angina, stroke, or transient ischemic attack within 12 weeks prior to enrollment (4) Patients receiving therapy with an SGLT2i within 8 weeks prior to enrollment or previous intolerance of an SGLT2i (5) Type 1 diabetes (6) Coronary revascularization or cardiac valve repair/replacement within 12 weeks prior to enrollment or planned to undergo any of these operations after randomization (7) Implantation of a cardiac resynchronization therapy (CRT) device within 12 weeks prior to enrollment or intent to implant a CRT device (8) Previous cardiac transplantation or implantation of a ventricular assist device or implantation expected after randomization (9) Symptomatic bradycardia or second or third-degree heart block without a pacemaker (10) Renal dysfunction or prior admission for acute renal failure in the last 4 weeks (11) Pregnant or lactating women (12) Woman of childbearing age, unless they are using highly effective contraceptive methods (13) Patients with severe hepatic impairment (Child–Pugh class C)	(1) Adult patients > 18 years old with stable symptomatic HF in NYHA class II–III during the last 2 months (2) LVEF ≤ 40% documented in the last 3 months by echocardiography or cardiac magnetic resonance (3) N-terminal probrain natriuretic peptide (NT-proBNP) ≥ 600 pg/mL (4) Estimated glomerular filtration rate (eGFR) ≥ 30 mL/min/1.73 m^2 (modification of Diet in renal disease formula) at enrollment (5) Optimal and stable background standard of care for HFrEF	Dapagliflozin significantly improved symptoms, physical limitations, and exercise function in patients with HFpEF The treatment benefits were large, clinically meaningful, and consistent across all subgroups Dapagliflozin showed consistent benefits regardless of the presence of type 2 diabetes
Singh 2020	2020	Single center	1 year	N/A	(1) Participants had a diagnosis of T2DM and history of symptomatic HF with a previously documented reduction in EF using echocardiography (2) They were on stable therapy for at least 3 months before recruitment, with a maximum loop diuretic dose of 80 mg/day (3) Baseline estimated glomerular filtration rate (eGFR) of ≥ 45 mL/min/1.73 m^2	Dapagliflozin had no effect on left ventricular remodeling in patients with heart failure and type 2 diabetes mellitus Dapagliflozin reduced diastolic blood pressure and loop diuretic requirements Dapagliflozin increased hemoglobin, hematocrit, and ketone bodies The effects of dapagliflozin on heart failure outcomes may be due to mechanisms other than left ventricular remodeling

Table 1 (continued)

Study ID	Year	Setting	Follow-up period	Exclusion criteria	Inclusion criteria	Main findings
Solomon 2022	2022	Multi-center	median of 2.3 years	(1) Receiving therapy with an SGLT2 inhibitor within 4 weeks prior to randomization or previous intolerance to an SGLT2 inhibitor (2) Type 1 diabetes mellitus (3) eGFR < 25 mL/min/1.73 m^2 (CKD-EPI formula) at visit 1 (4) Systolic blood pressure < 95 mmHg on two consecutive measurements at 5 min intervals, at visit 1 or at visit 2 (5) Systolic blood pressure ≥ 160 mmHg if not on treatment with greater than or equal to three blood pressure lowering medications or ≥ 180 mmHg irrespective of treatments, on two consecutive measurements at 5 min intervals at visit 1 or at visit 2 (6) Myocardial infarction, unstable angina, coronary revascularization (percutaneous coronary intervention or coronary artery bypass grafting), ablation of atrial flutter/fibrillation, valve repair/replacement within 12 weeks prior to enrollment. Before enrollment, these patients must have their qualifying echocardiography and/or cardiac magnetic resonance examination at least 12 weeks after the event (7) Planned coronary revascularization, ablation of atrial flutter/fibrillation and valve repair/replacement (8) Stroke or transient ischemic attack within 12 weeks prior to enrollment (9) Probable alternative or concomitant diagnoses, which, in the opinion of the investigator, could account for the patient's heart failure symptoms and signs (e.g., anemia, hypothyroidism) (10) Body mass index > 50 kg/m^2 (11) Primary pulmonary hypertension, chronic pulmonary embolism, severe pulmonary disease including COPD (i.e., requiring home oxygen, chronic nebulizer therapy or chronic oral steroid therapy, or hospitalization for exacerbation of COPD requiring ventilatory assistance within 12 months prior to enrollment) (12) Previous cardiac transplantation, or complex congenital heart disease. Planned cardiac resynchronization therapy (13) Heart failure due to any of the following: known infiltrative cardiomyopathy (e.g., amyloid, sarcoid, lymphoma, endomyocardial fibrosis), active myocarditis, constrictive pericarditis, cardiac tamponade, known genetic hypertrophic cardiomyopathy or obstructive hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy/dysplasia, or uncorrected primary valvular disease (14) A life expectancy of less than 2 years due to any noncardiovascular condition, based on investigator's clinical judgement (15) Inability of the patient, in the opinion of the investigator, to understand and/or comply with study medications, procedures and/or follow-up or any conditions that, in the opinion of the investigator, may render the patient unable to complete the study (16) Active malignancy requiring treatment (with the exception of basal cell or squamous cell carcinomas of the skin) (17) Acute or chronic liver disease with severe impairment of liver function (e.g., ascites, esophageal varices, coagulopathy)	(1) Ability to give written informed consent (2) Men and women age ≥ 40 years (3) Documented diagnosis of symptomatic heart failure (NYHA class II–IV) at enrollment, and a medical history of typical symptoms/signs of heart failure ≥ 6 weeks before enrollment with at least intermittent need for diuretic treatment (requiring recurrent intermittent dosing) (4) LVEF > 40% and evidence of structural heart disease (i.e., left ventricular hypertrophy or left atrial enlargement) documented by the most recent echocardiogram, and/or cardiac magnetic resonance within the last 12 months prior to enrollment. For patients with prior acute cardiac events or procedures that may reduce LVEF, e.g., as defined in exclusion criterion, qualifying cardiac imaging assessment at least 12 weeks following the procedure/event is required. Structural heart disease will be defined as: (a) LA enlargement with at least one of the following: LA width (diameter) ≥ 3.8 cm or LA length ≥ 5.0 cm, or LA area ≥ 20 cm, or LA volume ≥ 55 mL or LA volume index ≥ 29 mL/m (b) Left ventricular hypertrophy with septal thickness or posterior wall thickness ≥ 1.1 cm (5) NT-proBNP ≥ 300 pg/mL at visit 1 for patients without ongoing atrial fibrillation/flutter. If ongoing atrial fibrillation/flutter at visit 1, NT-proBNP must be ≥ 600 pg/mL	Dapagliflozin reduced the combined risk of worsening heart failure or cardiovascular death among patients with heart failure and a mildly reduced or preserved ejection fraction

Table 1 (continued)

Study ID	Year	Setting	Follow-up period	Exclusion criteria	Inclusion criteria	Main findings
				(18) Women of child-bearing potential (i.e., those who are not chemically or surgically sterilized or postmenopausal) not willing to use a medically accepted method of contraception considered reliable in the judgement of the investigator or who have a positive pregnancy test at randomization or who are breast feeding (19) Involvement in the planning and/or conduct of the study (applies to both AstraZeneca personnel and/or personnel at the study site) (20) Previous randomization in the present study (21) Participation in another clinical study with an investigational product or device during the last month prior to enrollment	(6) Patients may be ambulatory, or hospitalized; patients must be off intravenous heart failure therapy (including diuretics) for at least 12 h prior to enrollment and 24 h prior to randomization	
Borlaug 2023	2023	Single center	24 weeks	(1) Type 1 diabetes or type 2 diabetes with poor control (HbA1c ≥ 10%) (2) Primary cardiomyopathy or pericardial disease, significant left-sided valvular heart disease, dyspnea primarily related to lung disease or ischemic heart disease, and severe anemia, liver, or kidney disease (estimated glomerular filtration rate < 30)	(1) 18 years of age or older (2) Symptoms of exertional dyspnea (New York Heart Association class II–III) and left ventricular ejection fraction ≥ 50% (3) Patients were required to display elevated PCWP during exercise (≥ 25 mmHg) at the baseline invasive exercise test after consent	Treatment with dapagliflozin reduces pulmonary capillary wedge pressure (PCWP) at rest and during exercise in patients with HFpEF Dapagliflozin decreases exertional right atrial pressures and pulmonary artery pressures Dapagliflozin leads to reductions in body weight and plasma volume Dapagliflozin has no effect on rest or exercise cardiac output, Ca-vO2, or peak VO2 Dapagliflozin reduces arterial lactate during 20 W exercise

Table 2 Characteristics of the study populations

(a)

Study ID	Group	Number	Age, years	Male, *n* (%)	Race	Body mass index (kg/m^2)	HT, *n* (%)
Amiguet 2023	DAP	45	69.8 (62.4–74)	35 (77.8)	N/A	27.3 ± 4.4	33 (73.3)
	PLA	42	67.5 (60.1–74.3)	31 (73.8)		28.3 ± 4.3	34 (81)
Ibrahim 2020	DAP	50	62.02 ± 8.8	28 (56%)	N/A	27.78 ± 2.3	N/A
	PLA	50	60.64 ± 9.9	26 (52%)		28.23 ± 3.3	N/A
McMurray 2019	DAP	2373	66.2 ± 11.0	1809 (76.2%)	White, Black, Asian, other	28.2 ± 6.0	N/A
	PLA	2371	66.5 ± 10.8	1826 (77%)		28.1 ± 5.9	N/A
McMurray 2021	No heart failure	3,836	61.4 (12.3)	2580 (67.3%)	White, Black or African American, Asian, other	29.2 ± 6	3,658 (95.4%)
	Heart failure	468	65.3 (12.1)	299 (63.9%)		31.7 ± 6.8	463 (98.9%)
McMurray 2023	DETERMINE-Reduced	DAP 156	69 (62, 76)	111 (71.2)	White, Black, other	28 (24, 34)	N/A
		PLA 157	69 (60, 76)	122 (77.7)		29 (24, 33)	N/A
	DETERMINE-Preserved	DAP 253	73 (67, 78)	162 (64.0)		29 (25, 34)	N/A
		PLA 251	73 (73, 79)	158 (62.9)		28 (25, 33)	N/A
Nassif 2019	DAP	131	62.2 ± 11.0	95 (72.5%)	White, African American	30.7 (27.3, 35.9)	N/A
	PLA	132	60.4 ± 12.0	98 (74.2%)		30.6 (27.6, 36.4	N/A
Nassif 2021	DAP	162	69 (64, 77)	70 (43.2%)	White, African American	35.1 (30.4, 41.8)	N/A
	PLA	162	71 (63, 78)	70 (43.2%)		34.6 (29.7, 40.4)	N/A
Palau 2022	DAP	45	69.8 (62.4–74.0)	35 (77.8)	N/A	27.3 ± 4.4	33 (73.3)
Borlaug 2023	DAP	21	67 (9)	7 (33%)	N/A	35.0 (7.2)	14 (67)
	PLA	17	67 (9)	6 (35)		34.5 (5.7)	10 (59)

(b)

Study ID	Group	DM, *n* (%)	AF, *n* (%)	HR (bpm)	SBP (mm Hg)	LVEF (%)	History of IHD, *n* (%)	eGFR (ml/min/1.73 m^2)
Amiguet 2023	DAP	16 (35.6)	26 (57.8)	70 (60–80)	120 (110–124)	35.4 (30.2–37.7)	27 (60)	64.1 ± 20.7
	PLA	13 (28.9)	23 (54.8)	71 (63–83)	117.5 (110–130)	35.4 (30–37.9)	21 (50)	68.8 ± 23
Ibrahim 2020	DAP	N/A	N/A	N/A	110.74 ± 12.51	Mean + SD: 32.54 ± 2.99		N/A
	PLA	N/A	N/A	N/A	27.78 ± 2.3	Mean + SD: 32.23 ± 2.49		N/A
McMurray 2019	DAP	993 (41.8)	916 (38.6)	71.5 ± 11.6	122.0 ± 16.3	Mean + SD: 31.2 ± 6.7	1316 (55.5)	66.0 ± 19.6
	PLA	990 (41.8)	902 (38.0)	71.5 ± 11.8	121.6 ± 16.3	Mean + SD: 30.9 ± 6.9	1358 (57.3)	65.5 ± 19.3
McMurray 2021	No Heart Failure	2,545 (66.3%)	138 (3.6%)	73.1 ± 11.7	136.9 ± 17.6	N/A	N/A	≥ 60 mL/min/1.73 m^2 = 403 (10.5) 45–59 mL/min/1.73 m2 = 1187 (30.9) 30-44 mL/min/1.73 m^2 = 1694 (44.2) < 30 mL/min/1.73 m^2=552 (14.4)

Table 2 (continued)

(b)

Study ID	Group	DM, *n* (%)		AF, *n* (%)	HR (bpm)	SBP (mm Hg)	LVEF (%)	History of IHD, *n* (%)	eGFR (ml/min/1.73 m^2)
	Heart Failure	361 (77.1%)		89 (19.0%)	71.3 ± 9.7	138.9 ± 15.9	N/A	N/A	≥ 60 mL/min/1.73 m^2=51 (10.9) 45–59 mL/min/1.73 m^2 = 141 (30.1) 30–44 mL/min/1.73 m^2 = 204 (43.6) < 30 mL/min/1.73 m^2 = 72 (15.4)
McMurray 2023	DETERMINE-Reduced	DAP	72 (46.2)	55 (35.3)	N/A	114 (104, 132)	30 (24, 35)	N/A	60 (47, 74.6)
		PLA	73 (46.5)	62 (39.5)	N/A	115 (106, 126)	29 (23, 35)	N/A	62 (50, 79)
	DETERMINE-Preserved	DAP	109 (43.1)	137 (54.2)	N/A	128 (116, 137)	50.0 (45, 59)	N/A	57 (44, 72)
		PLA	111 (44.2	125 (49.8)	N/A	128 (116, 140)	53 (45, 60)	N/A	58 (46, 72)
Nassif 2019	DAP	81 (61.8%)		57 (43.5%)	72.2 ± 12.4	122.3 ± 20.1	27.2 ± 8.0%	70 (53.4%)	66.9 ± 21.1
	PLA	85 (64.4%)		49 (37.1%)	71.8 ± 11.3	124.8 ± 21.6	25.7 ± 8.2%	69 (52.3%)	71.2 ± 23.1
Nassif 2021	DAP	90 (55.6%)		82 (50.6%)	70 (61, 77)	134 (120, 152)	60 (55, 65)	32 (19.8%)	56 (42, 69)
	PLA	91 (56.2%)		89 (54.9%)	68 (62, 75)	132 (118, 148)	60 (54, 65)	31 (19.1%)	54 (41, 69)
Palau 2022	DAP	16 (35.6)		26 (57.8)	70 (60–80)	120 (110–124)	N/A	27 (60.0)	64.1 ± 20.7
	PLA	13 (28.9)		23 (51.1)	71 (63–83)	118 (110–130)		22 (48.9)	69.4 ± 23
Singh 2020	DAP	28 (100%)		N/A	N/A	N/A	N/A	N/A	72
	PLA	28 (100%)							
Solomon 2022	DAP	1401 (44.7)		227/1327 (AF at enrollment)	N/A	≤ 128 mm Hg = 280/1568 > 128 mm Hg = 232/1563	54.0 ± 8.6	N/A	61 ± 19
	PLA	1405 (44.9)		271/1317 (AF at enrollment)		≤ 128 mm Hg = 300/1590 > 128 mm Hg = 310/1542	54.3 ± 8.9		61 ± 19
Wiviott 2019	DAP	8582 (100%)		N/A	N/A	135.1±15.3	N/A	2824 (32.9)	85.4 ± 15.8
	PLA	8578 (100%)				134.8±15.5		2834 (33.0)	85.1 ± 16.0
Borlaug 2023	DAP	6 (29)		8 (38)	N/A	N/A	61 (6)	4 (19)	71 (17)
	PLA	1 (6)		6 (35)			63 (6)	5 (29)	73 (16)

Table 2 (continued)

(c)

Study ID	Group	NT-proBNP (pg/mL)	NYHA class II	NYHA class III	NYHA class IV	DAP regimen	Medical treatment	Time frame
Amiguet 2023	DAP	1085 (889–1688)	41 (91.1)	N/A	N/A	N/A	Loop diuretics ARNI MRA ACEI/ARB/ARNI	3 months after initiation of treatment.
	PLA	1839 (924–2416)	37 (88.1)	N/A	N/A			
Ibrahim 2020	DAP	N/A	N/A	N/A	N/A	DAP 10 mg QD	Diuretics (Furosemide), Anti-HF treatment (ACEi/ARB, B-blocker, MRA, ivrabradine), Insulin	From admission till discharge
	PLA	N/A	N/A	N/A	N/A			
McMurray 2019	DAP	1428 (857–2655)	1606 (67.7)	747 (31.5)	20 (0.8)	DAP 10 mg QD	Diuretic ACEI ARB ARNI Digitalis MRA Beta-blocker Insulin GLP-1 RA DPP-4 inhibitor Sulfonylurea Biguanide	A median of 18.2 months
	PLA	1446 (857–2641)	1597 (67.4)	751 (31.7)	23 (1.0)			
McMurray 2021	No HF	N/A	N/A	N/A	N/A	DAP 10 mg QD	Beta-blocker Diuretic MRA ACEI/ARB/other RAS blocker Digitalis glycoside Hydralazine CCB Antiplatelet Statin Other lipid-lowering therapy Insulin GLP-1 RA DPP-4 inhibitor Sulfonylurea Biguanide	A median of 2.4 years
	HF	N/A	N/A	N/A	N/A			

Table 2 (continued)

(c)

Study ID	Group	NT-proBNP (pg/mL)		NYHA class II	NYHA class III	NYHA class IV	DAP regimen	Medical treatment	Time frame
McMurray 2023	DETERMINE-Reduced	DAP	1426 (715, 2561)	130 (83.3)	25 (16.0)	1 (0.6)	DAP 10 mg QD	ACEI ARB ARNI ACEI/ARB ACEI/ARB/ARNI Beta-blockers MRA Diuretic	16 weeks
		PLA	1224 (650, 1921)	125 (79.6)	32 (20.4)	0			
	DETERMINE-Preserved	DAP	850 (462, 1607)	205 (81.0)	48 (19.0)	0			
		PLA	716 (397, 1457)	216 (86.4	34 (13.6)	0			
Nassif 2019	DAP	1136 (668, 2465)		91 (69.5%)	40 (30.5%)	N/A	DAP 10 mg QD in addition to guideline directed standard of care therapy	ACEI/ARB ARNI Beta-blockers Hydralazine Long-acting nitrates MRA Loop diuretics Digoxin Lipid-lowering agents Anticoagulant agent Insulin GLP-1 RA DPP-4 inhibitor Sulfonylurea Metformin	12 weeks
	PLA	1136 (545, 2049)		82 (62.1%)	50 (37.9%)	N/A			
Nassif 2021	DAP	641 (373, 1210)		96 (59.3%)	65 (40.1%)		DAP 10 mg QD	ACEI/ARB ARNI Beta-blockers MRA Loop diuretic Lipid-lowering agents Anticoagulant agents	12 weeks
	PLA	710 (329, 1449)		90 (55.6%)	72 (44.4%)				
Palau 2022	DAP	1085 (889–2100)		NYHA class II/IV = 39 (86.7)			DAP 10 mg QD	Loop diuretic ACEI/ARB/ARNI ARNI MRA Beta-blockers	3 months
	PLA	1620 (889–2328)		NYHA class II/IV = 41 (91.1)					
Singh 2020	DAP PLA	N/A		87.5% were in NYHA class I or II	N/A	N/A	DAP 10 mg QD on top of usual therapy	N/A	1 year
Solomon 2022	DAP	≤ 1011 pg/mL = 173/1555 > 1011 pg/mL = 339/1576		2314 (73.9)	807 (25.8)	10 (0.3)	DAP 10 mg QD on top of usual therapy	N/A	A median of 2.3 years
	PLA	≤ 1011 pg/mL = 208/1578 > 1011 pg/mL = 402/1553		2399 (76.6)	724 (23.1)	8 (0.3)			

Table 2 (continued)

(c)

Study ID	Group	NT-proBNP (pg/mL)	NYHA class II	NYHA class III	NYHA class IV	DAP regimen	Medical treatment	Time frame
Wiviott 2019	DAP PLA	N/A	N/A	N/A	N/A	DAP 10 mg QD	Insulin GLP-1 RA DPP-4 inhibitor Sulfonylurea Metformin Antiplatelet agents ACEI/ARB Beta-blocker Statin or ezetimibe Diuretics	Patients were followed for a median of 4.2 years
Borlaug 2023	DAP PLA	235 (102, 394) 118 (76, 226)	7 (33) 5 (29)	14 (67) 12 (71)	N/A	DAP 10 mg QD	ACEI/ARB/ARNI Beta-blockers MRA Diuretic	24 weeks

HT hypertension, *AF* atrial fibrillation, *DAP* dapagliflozin, *DM* diabetes mellitus, *eGFR* estimated glomerular filtration rate, *HR* heart rate, *IHD* ischemic heart disease, *LVEF* left ventricular ejection fraction, *N/A* not available, *PLA* placebo, *SBP* systolic blood pressure, *ACEI* angiotensin converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *ARNI* angiotensin receptor neprilysin inhibitor (sacubitril-valsartan), *CCB* calcium channel blocker, *DAP* dapagliflozin, *DPP* dipeptidyl peptidase, *GLP-1 RA* glucagon-like peptide 1 receptor agonist, *HF* heart failure, *HR* heart rate, *IHD* ischemic heart disease, *LVEF* left ventricular ejection fraction, *MRA* mineralocorticoid receptor antagonist, *N/A* not available, *NT-proBNP* N-terminal pro-brain natriuretic peptide, *NYHA* New York Heart Association, *PLA* placebo, *QD* once daily

4 Discussion

4.1 Summary of Main Results

This meta-analysis aims to assess the effect of dapagliflozin on functional capacity in patients with heart failure, considering both reduced and preserved ejection fractions. The findings suggest dapagliflozin was associated with a notable improvement in KCCQ scores across all heart failure classes. With regards to 6MWD, though not statistically significant in either subgroup, there was a trend toward the dapagliflozin group. The mortality benefit of dapagliflozin was only seen in the heart failure with reduced EF subclass. The was no statistically significant reduction in adverse events in either subgroup. Consistency prevailed in the results across all the studies included, and there was statistical homogeneity in the analysis of various outcomes.

4.2 Justification of Results

4.2.1 Importance of Using Dapagliflozin for Patients with Heart Failure and Related Adverse Events

The effect of dapagliflozin in individuals with heart failure with and without diabetes has been widely acknowledged.

By targeting SGLT-2 receptors in the kidney, dapagliflozin induces osmotic diuresis of glucose, along with natriuresis and water loss. This process contributes to a decreased preload on the heart in patients with heart failure [32]. An additional potential mechanism is the impact of dapagliflozin on afterload through its interaction with the endothelium, which primarily leads to a decrease in vascular resistance, ultimately lowering

Fig. 2 Cochrane risk of bias assessment

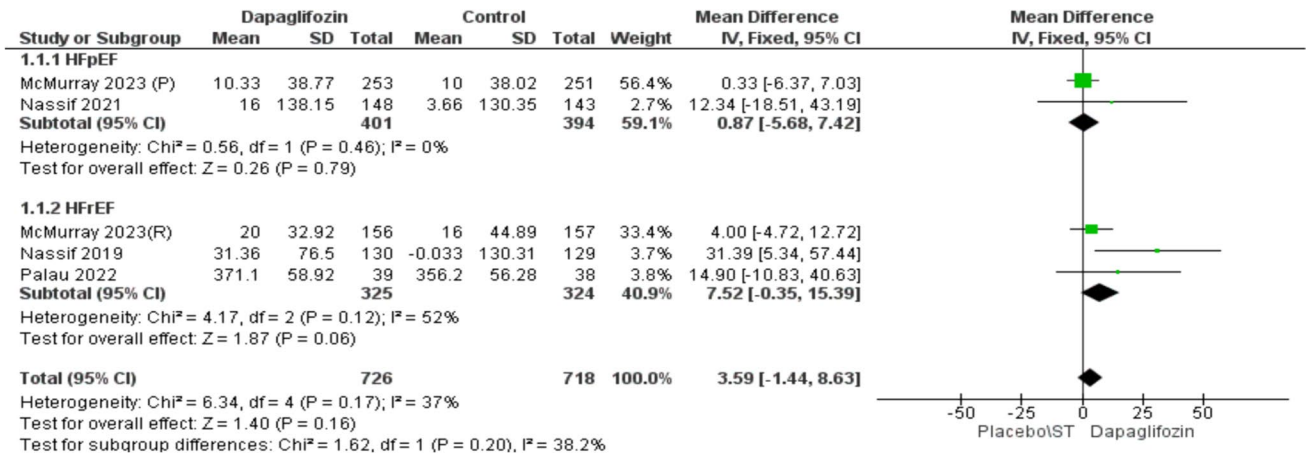

Fig. 3 Change in 6MWD

afterload [33]. The optimization of myocardial substrate utilization, which leads to an increase in cardiac output, is facilitated by SGLT2 inhibitors. This is achieved through the reduction of cardiac carbohydrate uptake and augmentation in the uptake of β-hydroxybutyrate and ketone bodies [34]. In addition to its anti-inflammatory effects, this drug class also plays a role in preventing myocardial fibrosis [35]. In clinical applications, dapagliflozin is associated with various adverse effects such as mycotic infections in the genital tract and urinary tract infections [36]. Other side effects associated with dapagliflozin include hypotension, hypoglycemia, and reduction in serum uric acid levels [37]. An association between SGLT2 inhibitors and diabetic ketoacidosis (DKA) was noted in the DAPA-HF trial, where every case of DKA occurred exclusively in patients with T2DM. The incidence of DKA was reported to be 0.1% with dapagliflozin and 0% with placebo [38].

4.2.2 Understanding the Variations in 6MWD in Patients with Heart Failure using Dapagliflozin

Contrary to the recognized benefits of dapagliflozin in various aspects of heart failure such as mortality, hospitalization, and adverse events, our analysis did not reveal a significant difference in 6MWD between the dapagliflozin and control groups.

For many years, the 6MWD has been used as a standard to evaluate capacity for function in heart failure (HF). Nevertheless, using this measure to evaluate the implications of SGLT2 inhibitors resulted in interesting results.

The uncertainty of established successful medicines, such as sacubitril/valsartan, and the failure to correlate 6MWD improvements with survival benefits represents a comparative issue. This pattern remains in the HFpEF studies (DETERMINE-Preserved and EMPERIAL-Preserved) emphasizing 6MWD's limitations of [18, 21, 39]. In contrast, the PRESERVED-HF trial demonstrated a significant increase in the 6MWD with dapagliflozin [19]. However, this improvement is contrasted by lower baseline limitations in the KCCQ and 6MWD compared with the DETERMINE and EMPERIAL trials [18, 21], highlighting the potential influence of baseline characteristics on responsiveness to SGLT2 inhibitors.

4.2.3 Improvement of Kansas City Cardiomyopathy Questionnaire (KCCQ) Score

Our meta-analysis revealed that dapagliflozin was associated with an improvement in the KCCQ score compared with the control group. Additionally, a subgroup analysis based on HF type of heart failure was conducted.

In the HFrEF subgroup, self-reported symptoms, as assessed by the KCCQ total symptom score (TSS), showed a median improvement in the DETERMINE-Reduced Trials [21]. This improvement aligns with findings from other trials, including DAPA-HF and smaller trials [17]. Collective evidence suggests that dapagliflozin leads to improvement in patient-reported symptoms, which persist for at least 12 months and beyond. There was an improvement in KCCQ physical limitation score (PLS) in the DEFINE-HF and DAPA-HF trials. This score assesses limitations in routine activities such as dressing, showering, walking, and housework [8, 17]. Although KCCQ-PLS has not been consistently demonstrated, in comparison with KCCQ-TSS, the cumulative data suggest a modest enhancement of KCCQ-PLS by SGLT2 inhibitors in individuals with (HFrEF).

In the HFpEF subgroup, no significant effect on KCCQ-TSS was observed in DETERMINE-Preserved, aligning with DELIVER and PRESERVED-HF. This is similar to the finding seen with empagliflozin in the EMPEROR-Preserved, and EMPERIAL-Preserved [10,11,18,19,21,]. The KCCQ-PLS score indicated no significant difference between the two groups in DETERMINE-Preserved [21], consistent with the findings in EMPEROR-Preserved [10].

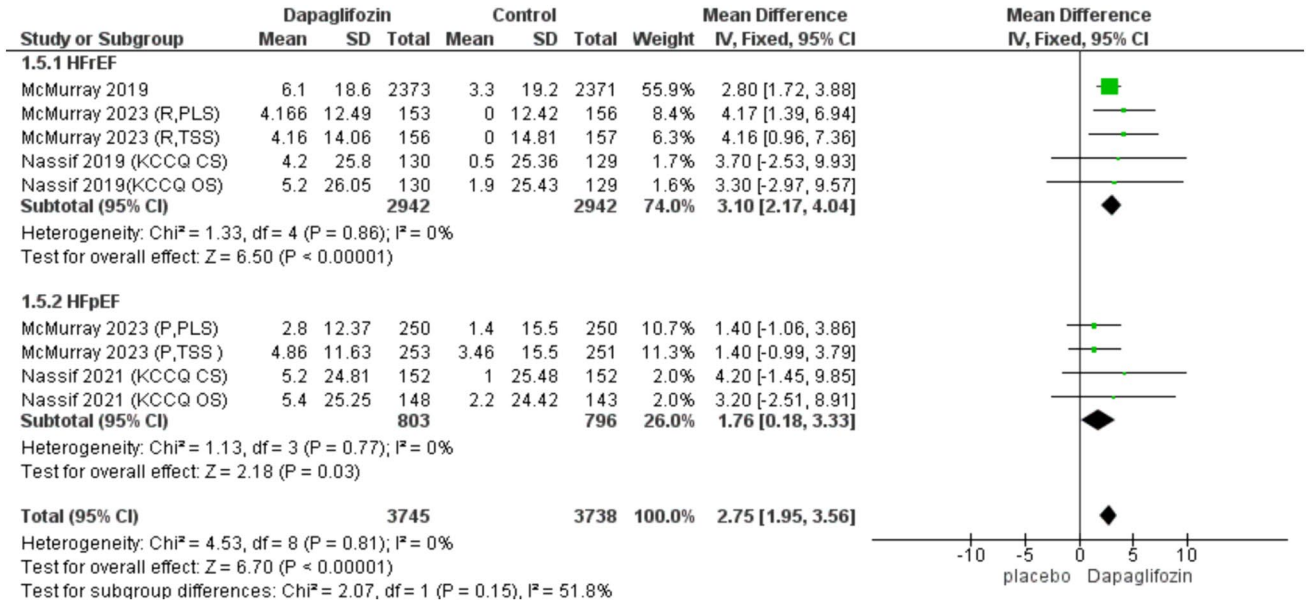

Fig. 4 Change in Kansas City Cardiomyopathy Questionnaire (KCCQ) score

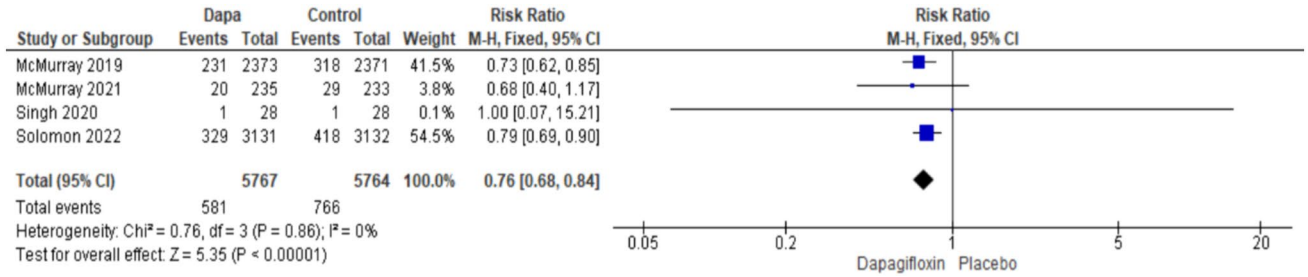

Fig. 5 Hospitalizations for heart failure

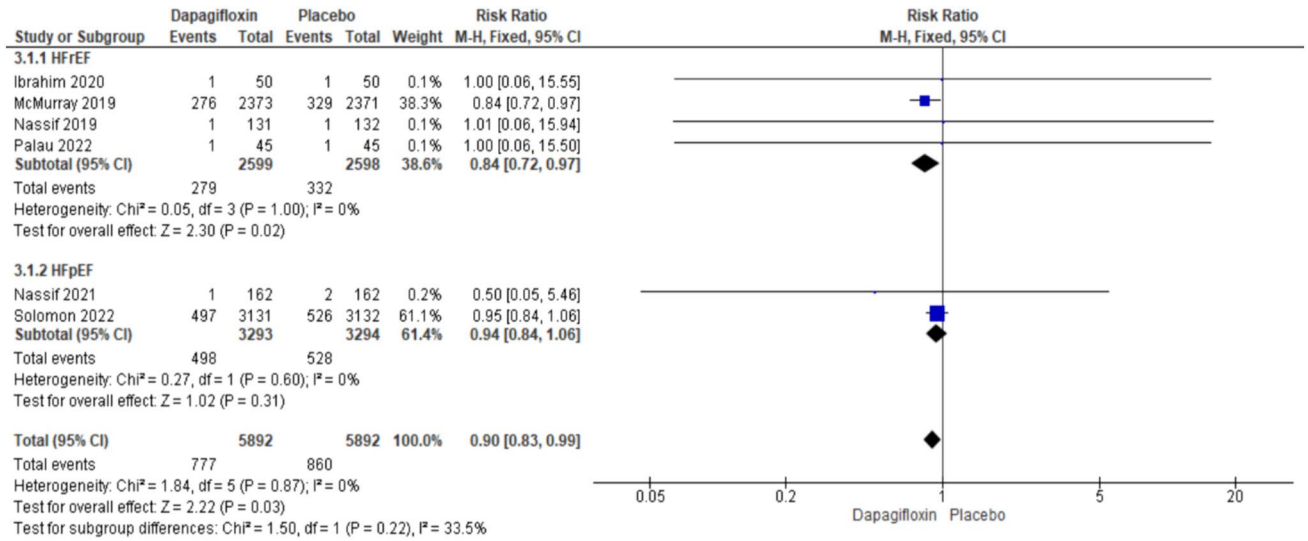

Fig. 6 Any cause mortality

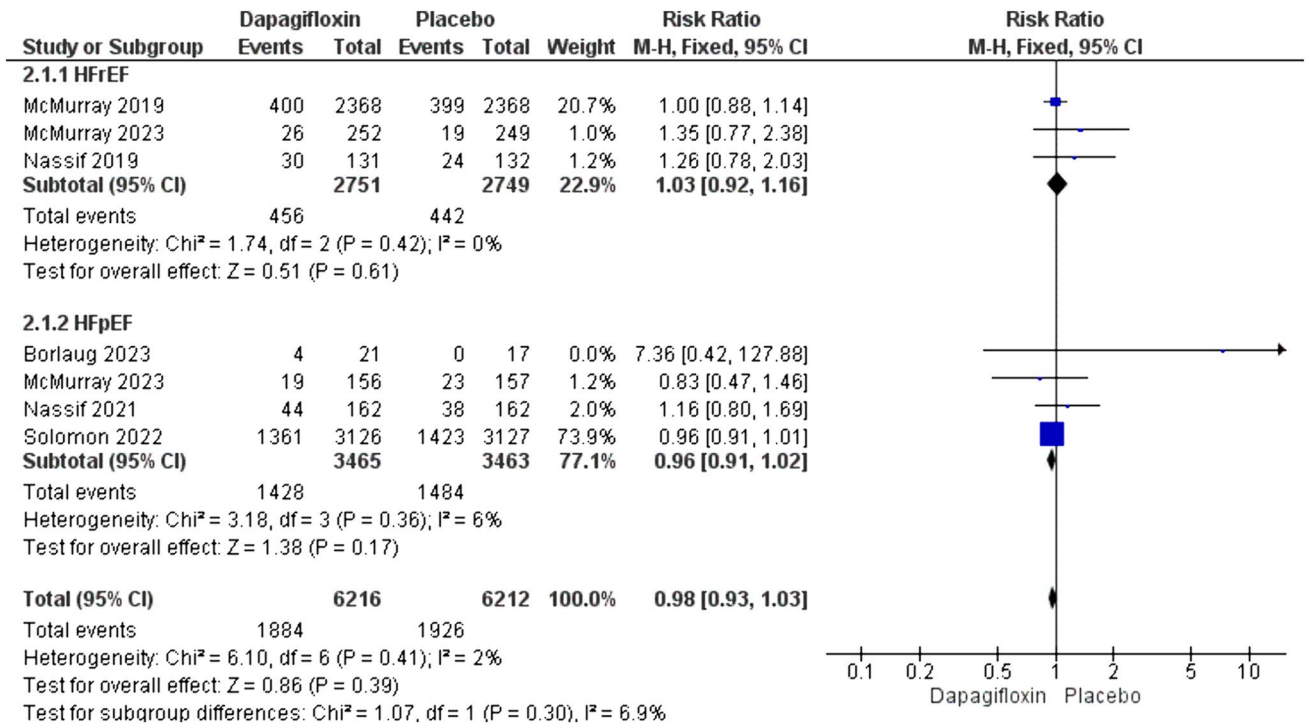

Fig. 7 Adverse event

However, this contrasts with the PRESERVED-HF [19] trial where dapagliflozin significantly improved the KCCQ-PLS score. This systematic review shows a trend toward improvement in KCCQ score in patients with HFpEF.

To sum up, these findings clearly suggested dapagliflozin was associated with improvement in KCCQ score in two heart failure types but with a pronounced effect in HFrEF. It remains uncertain whether these findings truly indicate a lesser impact of dapagliflozin on KCCQ scores in patients with HFpEF or if the study's power was constrained by the relatively small sample size.

4.2.4 Safety Outcomes of Dapagliflozin in Heart Failure

Regarding hospitalization for heart failure, the findings from our meta-analysis underscore the demonstrated impact of dapagliflozin on safety outcomes in patients with HF. The observed significant reduction in the risk of hospitalization for heart failure aligns with previous evidence [6, 8, 11] suggesting the efficacy of dapagliflozin in preventing HF-related events.

Regarding the any-cause mortality, a thorough assessment within the subgroup analysis showed a notable reduction in the risk of all-cause mortality in patients with HFrEF. Despite not obtaining a similar finding in the HFpEF group, our analysis found a statistically significant difference in overall any-cause mortality between the dapagliflozin and control groups. The favorable response of a specific subgroup to dapagliflozin indicated that the drug may be useful in reducing mortality risks in a well-defined population.

Regarding the risk for adverse events, there were no significant difference in adverse events between the patients with HFrEF and HFpEF according to the subgroup analyses and the overall comparison with placebo.

4.3 Agreement and Disagreement with Previous Studies

4.3.1 Agreement

Our comprehensive study and the most recent meta-analysis [40] revealed a consistently favorable impact of dapagliflozin. Specifically, both highlighted a noteworthy reduction in all-cause mortality, a significant decrease in the overall risk of adverse events, and a substantial reduction in hospitalization for heart failure among patients receiving dapagliflozin. This systematic review went a step further to illustrate important symptom benefits of dapagliflozin.

4.3.2 Disagreement

Our study comprehensively assessed the safety profile of dapagliflozin in patients with heart failure, examining not only its safety but also its effectiveness in enhancing both

the functional capacity of the heart and overall physical function.

In comparison to past meta-analyses [40], For the change in 6MWD, our study provides the most updated evidence regarding the effect of dapagliflozin on 6MWD, which previous meta-analysis did not provide. Moreover, while analyzing the differences in KCCQ scores, it is important to keep in mind that although both studies show improvement, there are variations concerning the degree of improvement shown in the HFpEF and HFrEF. Furthermore, it is essential to take into consideration the particular scales that are utilized for measurement, such as KCCQ-TSS and KCCQ-PLS. In our study, each of these measurements was covered in detail.

4.4 Strength Points and Limitations

Our meta-analysis has various advantages: the study provided a comprehensive assessment and thorough evaluation of dapagliflozin's impact on heart failure, considering both HFrEF and HFpEF, and explores various outcomes, including symptoms, functional capacity, hospitalizations, mortality, and adverse events. Symptoms and functional capacity of our patients gets overlooked and this meta-analysis suggest that despite the mortality benefits of dapagliflozin, there is also a symptom improvement as assessed by the KCCQ score. In addition, all clinical trials in which patients with heart failure were the initial study population or whose population randomization was predetermined based on whether or not heart failure was present at baseline were included.

Furthermore, the study conducted subgroup analyses based on heart failure type, providing valuable insights into the differential effects of dapagliflozin in patients with HFrEF and HFpEF.

This meta-analysis has various limitations, and certain included studies exhibited incomplete information concerning the baseline characteristics of patients. Some of the studies included in the analysis had limited sample sizes, particularly in the context of HFpEF, potentially limit the generalizability of findings for this specific subgroup. The fact that there is a statistical benefit in KCCQ scores in all classes of heart failure and that significance is not seen in the 6MWD does bring into question the importance of this metric in assessing patients with heart failure.

Moreover, the primary emphasis of the study was on outcomes over the short to medium term, indicating that investigations with prolonged follow-up periods would be valuable for understanding the sustained effects of dapagliflozin.

4.5 Implications for Clinical Practice

The study suggests that dapagliflozin is valuable addition to the management of heart failure, offering benefits in symptom improvement, reduced hospitalizations, and favorable safety profiles. Furthermore, the differential response observed between HFrEF and HFpEF suggest these benefits are better seen in the HFrEF subtype.

4.6 Recommendations for Future Researchers

To overcome the limitation of diversity in trial outcomes emphasizes the importance of considering patient characteristics and baseline limitations when evaluating the efficacy of a treatment. Larger trials can be carried out to especially focus on the benefit of dapagliflozin in the subtype of patients with preserved EF.

4.7 Conclusions

Our comprehensive meta-analysis, which included ten randomized controlled trials with patients treated with dapagliflozin and diagnosed with heart failure, concludes that dapagliflozin shows significant improvements in KCCQ scores, a notable decrease in hospitalizations, and any cause of mortality across all ranges of heart failure. Consistent benefits for both HFrEF and HFpEF are emphasized in the study. However, it is crucial to acknowledge that no significant difference was noted between the two groups in terms of changes in 6MWD.

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Declarations

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Conflict of Interest B.A., W.A., S.I., and P.B. declare that they have no potential conflicts of interest that might be relevant to the contents of this manuscript.

Ethics Approval Not applicable.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Data Availability The datasets generated during and /or analyzed during the current study are available from the corresponding author on reasonable request.

Code Availability Not applicable.

Author's Contributions B.A.: conceptualization, supervision, validation, writing, and reviewing. W.A.: writing, reviewing, and methodology. S.I.: analysis and investigation. P.B.: writing and reviewing.

References

1. Metra M, Carubelli V, Ravera A, Stewart Coats AJ. Heart failure 2016: still more questions than answers. Int J Cardiol. 2016;227:766–77. https://doi.org/10.1016/j.ijcard.2016.10.060.
2. Mentz RJ, Kelly JP, von Lueder TG, Voors AA, Lam CS, Cowie MR, et al. Noncardiac comorbidities in heart failure with reduced versus preserved ejection fraction. J Am Coll Cardiol. 2014;64(21):2281–93. https://doi.org/10.1016/j.jacc.2014.08.036.
3. Kannel WB, Hjortland M, Castelli WP. Role of diabetes in congestive heart failure: the Framingham study. Am J Cardiol. 1974;34(1):29–34. https://doi.org/10.1016/0002-9149(74)90089-7.
4. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015;373(22):2117–28. https://doi.org/10.1056/NEJMoa1504720.
5. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med. 2017;377(7):644–57. https://doi.org/10.1056/NEJMoa1611925.
6. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2019;380(4):347–57. https://doi.org/10.1056/NEJMoa1812389.
7. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med. 2019;380(24):2295–306. https://doi.org/10.1056/NEJMoa1811744.
8. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, Ponikowski P, Sabatine MS, Anand IS, Bělohlávek J, DAPA-HF Trial Committees and Investigators, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med. 2019;381:1995–2008. https://doi.org/10.1056/NEJMoa1911303.
9. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, Januzzi J, Verma S, Tsutsui H, Brueckmann M, EMPEROR-Reduced Trial Investigators, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med. 2020;383:1413–24. https://doi.org/10.1056/NEJMoa2022190.
10. Anker SD, Butler J, Filippatos G, Shahzeb Khan M, Ferreira JP, Bocchi E, Böhm M, Brunner-La Rocca HP, Choi DJ, Chopra V, EMPEROR-Preserved Trial Committees and Investigators, et al. Baseline characteristics of patients with heart failure with preserved ejection fraction in the EMPEROR-Preserved trial. Eur J Heart Fail. 2020;22:2383–92. https://doi.org/10.1002/ejhf.2064.
11. Solomon SD, McMurray JJV, Claggett B, de Boer RA, DeMets D, Hernandez AF, Inzucchi SE, Kosiborod MN, Lam CSP, Martinez F, DELIVER Trial Committees and Investigators, et al. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. N Engl J Med. 2022;387:1089–98. https://doi.org/10.1056/NEJMoa2206286.
12. Jhund PS, Kondo T, Butt JH, Docherty KF, Claggett BL, Desai AS, Vaduganathan M, Gasparyan SB, Bengtsson O, Lindholm D, et al. Dapagliflozin across the range of ejection fraction in patients with heart failure: a patient-level, pooled meta-analysis of DAPA-HF and DELIVER. Nat Med. 2022;28:1956–64. https://doi.org/10.1038/s41591-022-01971-4.
13. Vaduganathan M, Docherty KF, Claggett BL, Jhund PS, de Boer RA, Hernandez AF, Inzucchi SE, Kosiborod MN, Lam CSP, Martinez F, et al. SGLT-2 inhibitors in patients with heart failure: a comprehensive metaanalysis of five randomised controlled trials. Lancet. 2022;400:757–67. https://doi.org/10.1016/S0140-6736(22)01429-5.
14. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, et al. 2022 ACC/AHA/HFSA Guideline for the Management of Heart Failure. J Cardiac Fail. 2022;28(5):e1–167. https://doi.org/10.1016/j.cardfail.2022.02.009.
15. Fiuzat M, Lowy N, Stockbridge N, Sbolli M, Latta F, Lindenfeld J, Lewis EF, Abraham WT, Teerlink J, Walsh M, et al. Endpoints in heart failure drug development: history and future. JACC Heart Fail. 2020;8:429–40. https://doi.org/10.1016/j.jchf.2019.12.011.
16. Zannad F, Garcia AA, Anker SD, Armstrong PW, Calvo G, Cleland JG, Cohn JN, Dickstein K, Domanski MJ, Ekman I, et al. Clinical outcome endpoints in heart failure trials: a European Society of Cardiology Heart Failure Association consensus document. Eur J Heart Fail. 2013;15:1082–94. https://doi.org/10.1093/eurjhf/hft095.
17. Nassif ME, Windsor SL, Tang F, Khariton Y, Husain M, Inzucchi SE, McGuire DK, Pitt B, Scirica BM, Austin B, et al. Dapagliflozin effects on biomarkers, symptoms, and functional status in patients with heart failure with reduced ejection fraction: the DEFINE-HF trial. Circulation. 2019;140:1463–76. https://doi.org/10.1161/1161/CIRCULATIONAHA.119.042929.
18. Abraham WT, Lindenfeld J, Ponikowski P, Agostoni P, Butler J, Desai AS, Filippatos G, Gniot J, Fu M, Gullestad L, et al. Effect of empagliflozin on exercise ability and symptoms in heart failure patients with reduced and preserved ejection fraction, with and without type 2 diabetes. Eur Heart J. 2021;42:700–10. https://doi.org/10.1093/eurheartj/ehaa943.
19. Nassif ME, Windsor SL, Borlaug BA, Kitzman DW, Shah SJ, Tang F, Khariton Y, Malik AO, Khumri T, Umpierrez G, et al. The SGLT2 inhibitor dapagliflozin in heart failure with preserved ejection fraction: a multicenter randomized trial. Nat Med. 2021;27:1954–60. https://doi.org/10.1038/s41591-021-01536-x.
20. Spertus JA, Birmingham MC, Nassif M, Damaraju CV, Abbate A, Butler J, Lanfear DE, Lingvay I, Kosiborod MN, Januzzi JL. The SGLT2 inhibitor canagliflozin in heart failure: the CHIEF-HF remote, patient-centered randomized trial. Nat Med. 2022;28:809–13. https://doi.org/10.1038/s41591-022-01703-8.
21. McMurray JJV, Docherty KF, de Boer RA, Hammarstedt A, Kitzman DW, Kosiborod MN, Maria Langkilde A, Reicher B, Senni M, Shah SJ, Wilderäng U, Verma S, Solomon SD. Effect of dapagliflozin versus placebo on symptoms and 6-minute walk distance in patients with heart failure: the DETERMINE Randomized Clinical Trials. Circulation. 2023. https://doi.org/10.1161/CIRCULATIONAHA.123.065061 **(Epub ahead of print. PMID: 38059368)**.
22. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. Syst Rev. 2016;5(1):210. https://doi.org/10.1186/s13643-016-0384-4.
23. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:4l4898. https://doi.org/10.1136/bmj.l4898.
24. Collaboration TCC. RevMan. Oxford, UK: The Cochrane Collaboration; 2014.
25. Chapter 9: Summarizing study characteristics and preparing for synthesis | Cochrane Training. Available at: https://training.cochrane.org/handbook/current/chapter-09. Accessed 25 Dec 2023.
26. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372: n71. https://doi.org/10.1136/bmj.n71.
27. Borlaug BA, Reddy YNV, Braun A, Sorimachi H, Omar M, Popovic D, Alogna A, Jensen MD, Carter R. Cardiac and

metabolic effects of dapagliflozin in heart failure with preserved ejection fraction: the CAMEO-DAPA Trial. Circulation. 2023;148(10):834–44. https://doi.org/10.1161/CIRCULATIONAHA.123.065134 **(Epub 2023 Aug 3. PMID: 37534453; PMCID: PMC10529848)**.

28. Ibrahim A, Ghaleb R, Mansour H, Hanafy A, Mahmoud NM, Abdelfatah Elsharef M, Kamal Salama M, Elsaughier SM, Abdel-Wahid L, Embarek Mohamed M, Ibrahim AK, Abdel-Galeel A. Safety and efficacy of adding dapagliflozin to furosemide in type 2 diabetic patients with decompensated heart failure and reduced ejection fraction. Front Cardiovasc Med. 2020;7(7):602251. https://doi.org/10.3389/fcvm.2020.602251 **(PMID:33426003;PMCID:PMC7793915)**.
29. Palau P, Amiguet M, Domínguez E, Sastre C, Mollar A, Seller J, Garcia Pinilla JM, Larumbe A, Valle A, Gómez Doblas JJ, de la Espriella R, Miñana G, Mezcua AR, Santas E, Bodí V, Sanchis J, Pascual-Figal D, Górriz JL, Baýes-Genís A, Núñez J, DAPA-VO2 Investigators (see Appendix). Short-term effects of dapagliflozin on maximal functional capacity in heart failure with reduced ejection fraction (DAPA-VO2): a randomized clinical trial. Eur J Heart Fail. 2022;24(10):1816–26. https://doi.org/10.1002/ejhf.2560 **(Epub 2022 Jun 6. PMID: 35604416)**.
30. Singh JSS, Mordi IR, Vickneson K, Fathi A, Donnan PT, Mohan M, Choy AMJ, Gandy S, George J, Khan F, Pearson ER, Houston JG, Struthers AD, Lang CC. Dapagliflozin versus placebo on left ventricular remodeling in patients with diabetes and heart failure: the REFORM trial. Diabetes Care. 2020;43(6):1356–9. https://doi.org/10.2337/dc19-2187 **(Epub 2020 Apr 3. PMID: 32245746; PMCID: PMC7245350)**.
31. McMurray JJV, Wheeler DC, Stefánsson BV, Jongs N, Postmus D, Correa-Rotter R, Chertow GM, Hou FF, Rossing P, Sjöström CD, Solomon SD, Toto RD, Langkilde AM, Heerspink HJL, DAPA-CKD Trial Committees and Investigators. Effects of dapagliflozin in patients with kidney disease, with and without heart failure. JACC Heart Fail. 2021;9(11):807–20. https://doi.org/10.1016/j.jchf.2021.06.017 **(Epub 2021 Aug 23. Erratum in: JACC Heart Fail. 2022 Jun;10(6):446-447. PMID: 34446370)**.
32. Pabel S, Hamdani N, Luedde M, Sossalla S. SGLT2 Inhibitors and Their Mode of Action in Heart Failure-Has the Mystery Been Unravelled? Curr Heart Fail Rep. 2021;18(5):315–28. https://doi.org/10.1007/s11897-021-00529-8.
33. Lee TM, Chang NC, Lin SZ. Dapagliflozin, a selective SGLT2 Inhibitor, attenuated cardiac fibrosis by regulating the macrophage polarization via STAT3 signaling in infarcted rat hearts. Free Radic Biol Med. 2017;104:298–310. https://doi.org/10.1016/j.freeradbiomed.2017.01.035.
34. Zhai M, Du X, Liu C, Xu H. The effects of dapagliflozin in patients with heart failure complicated with type 2 diabetes: a meta-analysis of placebo-controlled randomized trials. Front Clin Diabetes Healthc. 2021;2: 703937. https://doi.org/10.3389/fcdhc.2021.703937.
35. Anderson SL. Dapagliflozin efficacy and safety: a perspective review. Ther Adv Drug Saf. 2014;5(6):242–54. https://doi.org/10.1177/2042098614551938.
36. Anitha AP, Balasubramanian S, Ramalingam AG, Samuel Kennady SR, Ganamurali N, Dhanasekaran D, et al. An exploration of the experience of dapagliflozin in clinical practice. Future Sci OA. 2022;8(8):Fso816. https://doi.org/10.2144/fsoa-2022-0038.
37. Blair HA. Dapagliflozin: A review in symptomatic heart failure with reduced ejection fraction. Am J Cardiovasc Drugs. 2021;21(6):701–10. https://doi.org/10.1007/s40256-021-00503-8.
38. Heerspink HJL, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, et al. Dapagliflozin in patients with chronic kidney disease. N Engl J Med. 2020;383(15):1436–46. https://doi.org/10.1056/NEJMoa2024816.
39. Piepoli MF, Hussain RI, Comin-Colet J, Dosantos R, Ferber P, Jaarsma T, Edelmann F. OUTSTEP-HF: randomised controlled trial comparing shortterm effects of sacubitril/valsartan versus enalapril on daily physical activity in patients with chronic heart failure with reduced ejection fraction. Eur J Heart Fail. 2021;23:127–35. https://doi.org/10.1002/ejhf.2076.
40. Ali AE, Mazroua MS, ElSaban M, Najam N, Kothari AS, Mansoor T, Amal T, Lee J, Kashyap R. Effect of dapagliflozin in patients with heart failure: a systematic review and meta-analysis. Glob Heart. 2023;18(1):45. https://doi.org/10.5334/gh.1258.PMID:37636033;PMCID:PMC10453961.