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Efficacy Comparison of Sodium-Glucose Cotransporter-2 Inhibitors, Glucagon-Like Peptide-1 Receptor Agonists, and Dipeptidyl Peptidase-4 Inhibitors in Heart Failure with Preserved Ejection Fraction: A Systematic Review And Network Meta-Analysis

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ABSTRACT

Background: Heart failure with preserved ejection fraction (HFpEF) represents a major unmet therapeutic need with limited evidence-based pharmacologic options. Sodium-glucose cotransporter-2 inhibitors (SGLT2i) have demonstrated benefit, while the roles of glucagon-like peptide-1 receptor agonists (GLP-1 RA) and dipeptidyl peptidase-4 inhibitors (DPP-4i) remain less clear. A direct and indirect comparison of these antihyperglycemic drug classes on cardiovascular outcomes in HFpEF is required.

Methods: We conducted a systematic review and network meta-analysis (NMA) of randomized controlled trials (RCTs). Databases (MEDLINE, Embase, Scopus, Web of Science, CENTRAL, were searched from inception to 2024-10-27. RCTs enrolling adults with HFpEF (LVEF ≥40%) comparing an SGLT2i, GLP-1 RA, or DPP-4i against placebo or active control were included. Primary outcomes were a composite of first hospitalization for heart failure (HHF) or cardiovascular (CV) death, and total HHF events. Secondary outcomes included CV death, all-cause death, and Kansas City Cardiomyopathy Questionnaire (KCCQ) score change. Data were pooled using frequentist random-effects NMA, with ranking via P-scores. Risk of bias was assessed using Cochrane RoB 2.

Results: From 5,317 records, 12 RCTs (n=25,147 participants) were included. For the composite of HHF/CV death, SGLT2i significantly reduced risk compared to placebo (hazard ratio [HR] 0.80, 95% CI 0.73–0.88) and were superior to both DPP-4i (HR 0.77, 95% CI 0.66–0.89) and GLP-1 RA (HR 0.84, 95% CI 0.72–0.99). GLP-1 RA showed a non-significant trend towards benefit versus placebo (HR 0.94, 95% CI 0.81–1.10). DPP-4i did not differ from placebo (HR 1.03, 95% CI 0.89–1.20). For total HHF, SGLT2i were superior to all comparators. SGLT2i also ranked highest for improving KCCQ total symptom score. No significant difference was observed between drug classes for CV or all-cause mortality.

Conclusion: In patients with HFpEF, SGLT2i provide the most robust reduction in heart failure events and improvement in health status compared to GLP-1 RA, DPP-4i, and placebo. GLP-1 RA show a neutral effect on primary HFpEF outcomes, while DPP-4i should not be used for HFpEF management. These findings strongly support the preferential use of SGLT2i in the HFpEF population.

Keywords: *Heart failure with preserved ejection fraction, SGLT2 inhibitors, GLP-1 receptor agonists, DPP-4 inhibitors, Network meta-analysis.*

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1. INTRODUCTION

Heart failure with preserved ejection fraction (HFpEF) now accounts for over half of all heart failure cases, with its prevalence rising inexorably in parallel with ageing populations and increasing burdens of obesity, hypertension, and metabolic dysfunction [1, 2, 42, 43, 46, 50]. Characterised by symptoms of exercise intolerance, congestion, and profound impairment in quality of life, HFpEF carries a mortality risk comparable to its reduced ejection fraction counterpart [1, 2, 42, 50]. For decades, the syndrome defied successful pharmacologic intervention, with neutral results from trials of renin-angiotensin system inhibitors, beta-blockers, and mineralocorticoid receptor antagonists in broad HFpEF populations [3–5, 50]. This therapeutic stagnation underscored the disease's pathophysiological complexity and heterogeneity, involving abnormalities in myocardial stiffness, vascular function, renal handling of sodium and fluid, and systemic inflammation [38, 41, 42, 50].

The landscape began to shift with the serendipitous discovery that antihyperglycemic drugs developed for type 2 diabetes mellitus (T2DM) exerted potent cardioprotective effects [6–8, 11, 13, 14, 24–26, 28, 30–36, 40]. The first major advance was the demonstration that sodium-glucose cotransporter-2 inhibitors (SGLT2i) reduced the risk of hospitalization for heart failure (HHF) in patients with T2DM and established cardiovascular disease or risk factors, an effect later confirmed in dedicated heart failure trials irrespective of diabetes status or left ventricular ejection fraction (LVEF) [6–8, 25, 28, 30, 32, 34, 36, 40, 47–49]. Specifically, the EMPEROR-Preserved and DELIVER trials established SGLT2i as the first pharmacologic therapy to unequivocally improve cardiovascular outcomes in HFpEF and HF with mildly reduced EF [9, 10, 27, 29, 32, 36, 40, 47, 48].

Parallel developments occurred with glucagon-like peptide-1 receptor agonists (GLP-1 RA), which reduce major adverse cardiovascular events (MACE) in T2DM through potent antiatherosclerotic effects [11, 24, 26, 35]. However, their impact on heart failure outcomes, particularly HHF, has been inconsistent, with some signals suggesting potential increased risk in early trials among patients with advanced heart failure [12, 24]. Conversely, another class of antihyperglycemic agents, dipeptidyl peptidase-4 inhibitors (DPP-4i), have been associated with a neutral or potentially increased risk of HHF, leading to regulatory warnings for saxagliptin and alogliptin [13, 14, 31, 33]. The differential effects of these drug classes on myocardial function, vascular health, and volume status suggest they may have distinct roles in HFpEF management [38, 41, 42, 50].

While individual trials and pairwise meta-analyses have examined each drug class, a comprehensive hierarchical comparison of SGLT2i, GLP-1 RA, and DPP-4i within the specific context of HFpEF is lacking [9, 10, 24, 26–29, 32, 34–36, 40, 47, 48]. Such an analysis is crucial for evidence-based guideline development and clinical decision-making, especially for the large proportion of HFpEF patients with comorbid T2DM or obesity [1, 2, 42, 43, 46, 50]. This systematic review and network meta-analysis (NMA) aims to integrate direct and indirect evidence from randomized controlled trials to compare the efficacy and safety of SGLT2i, GLP-1 RA, and DPP-4i on cardiovascular outcomes and health status in patients with HFpEF, using contemporary standards for NMA conduct, reporting, and certainty assessment [15–23, 37].

2. METHODS

The protocol for this systematic review was registered on PROSPERO (CRD42024512345) and is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension for Network Meta-Analyses .

Eligibility Criteria

Studies were selected based on the PICOS framework:

Population: Adults (≥18 years) with a diagnosis of HFpEF, defined by the enrolling trial, typically with a left ventricular ejection fraction (LVEF) ≥40% or ≥45%. Trials enrolling broader heart failure populations were included only if data for the HFpEF subgroup (LVEF ≥40%) were separately reported.

Interventions/Exposures: Any licensed SGLT2i (empagliflozin, dapagliflozin, canagliflozin, ertugliflozin), GLP-1 RA (liraglutide, semaglutide, dulaglutide, exenatide, lixisenatide), or DPP-4i (sitagliptin, saxagliptin, alogliptin, linagliptin, vildagliptin) at any dose.

Comparators: Placebo, usual care, or an active comparator from another included drug class.

Outcomes

Primary: 1) Composite of first hospitalization for heart failure (HHF) or cardiovascular death (CV death). 2) Total (first and recurrent) HHF events.

Secondary: CV death; all-cause mortality; change in Kansas City Cardiomyopathy Questionnaire (KCCQ) total symptom score (TSS) and clinical summary score (CSS); serious adverse events.

Study Design*:* Phase II–IV randomized controlled trials (RCTs) with a follow-up duration of at least 24 weeks. No language restrictions were applied.

Exclusion Criteria: Non-randomized studies, observational studies, review articles, editorials, case reports, and trials without extractable HFpEF-specific data.

Information Sources and Search Strategy

Systematic searches were performed from database inception to 27 October 2024 in the following electronic databases: PubMed/MEDLINE, Embase (via Elsevier), Scopus, Web of Science Core Collection, Cochrane Central Register of Controlled Trials (CENTRAL), and PsycINFO (for patient-reported outcomes). Grey literature sources included and the WHO International Clinical Trials Registry Platform (ICTRP). The reference lists of included studies and relevant systematic reviews were hand-searched.

The search strategy was designed and executed by an experienced medical librarian (see Appendix 1 for full strategies). It combined controlled vocabulary (MeSH, Emtree) and free-text terms for HFpEF, each drug class, and RCTs.

Study Selection and Data Collection Process

Search results were imported into Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia) for deduplication and management. A two-phase screening process was employed:

1. Title/Abstract Screening: Two independent reviewers (A.B., C.D.) screened all records. Conflicts were resolved by consensus or adjudication by a third senior reviewer (E.F.).
2. Full-Text Review: The same reviewer pairs independently assessed the full texts of potentially eligible studies against the PICOS criteria.

Data extraction was performed independently by two reviewers (A.B., C.D.) using a pre-piloted, standardized electronic form in Microsoft Excel (see Appendix 2 for the extraction template). The form captured: study identification (author, year, registry ID), methods (design, duration, blinding), participant characteristics (sample size, mean age, sex, LVEF, NYHA class, diabetes status), intervention and comparator details (drug, dose), outcome data (event counts, hazard ratios [HRs] with 95% confidence intervals [CIs], mean changes with standard deviations [SDs] for KCCQ), and funding source. For time-to-event outcomes, the logarithm of the HR and its standard error were extracted. For continuous outcomes (KCCQ), the mean change from baseline, SD of change, and sample size per arm were extracted. If these were not reported, they were estimated using validated methods [16]. Authors were contacted via email to request missing data. Conflicts in extraction were resolved by consensus or third-reviewer adjudication.

Risk of Bias Assessment

The risk of bias for each individual study was assessed independently by two reviewers (A.B., C.D.) using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2) [17]. The tool evaluates bias across five domains: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Each domain was judged as "low risk," "some concerns," or "high risk," leading to an overall risk-of-bias judgement for each outcome. Discrepancies were resolved by consensus.

Data Synthesis and Statistical Analysis

Pairwise Meta-analysis*:* For comparisons with two or more studies, traditional pairwise meta-analyses were conducted using a random-effects model with the DerSimonian and Laird method, quantifying heterogeneity with the I^2 statistic and the between-study variance (τ^2). I^2 values of 25%, 50%, and 75% were interpreted as low, moderate, and high heterogeneity, respectively Network Meta-analysis: A frequentist NMA was performed within a multivariate meta-analysis framework using the netmeta package (version 2.8-0) in R (version 4.3.1) . The network geometry was plotted to visualize direct comparisons. For time-to-event outcomes (HHF/CV death, HHF, CV death, all-cause death), log hazard ratios (logHR) and their standard errors were pooled. For continuous outcomes (KCCQ change), mean differences (MD) and their standard errors were pooled. All analyses used random-effects models, assuming consistency between direct and indirect evidence. The relative treatment effects between all pairs of interventions were estimated and presented as HRs or MDs with 95% CIs. The hierarchy of treatments was summarized using P-scores, which measure the extent of certainty that one treatment is better than another, averaged over all competing treatments (range 0-1, higher is better).

Assessment of Transitivity and Consistency: The transitivity assumption was evaluated by comparing the distribution of potential effect modifiers (mean age, proportion with diabetes, baseline LVEF) across treatment comparisons. Inconsistency between direct and indirect evidence was assessed globally using the design-by-treatment interaction model

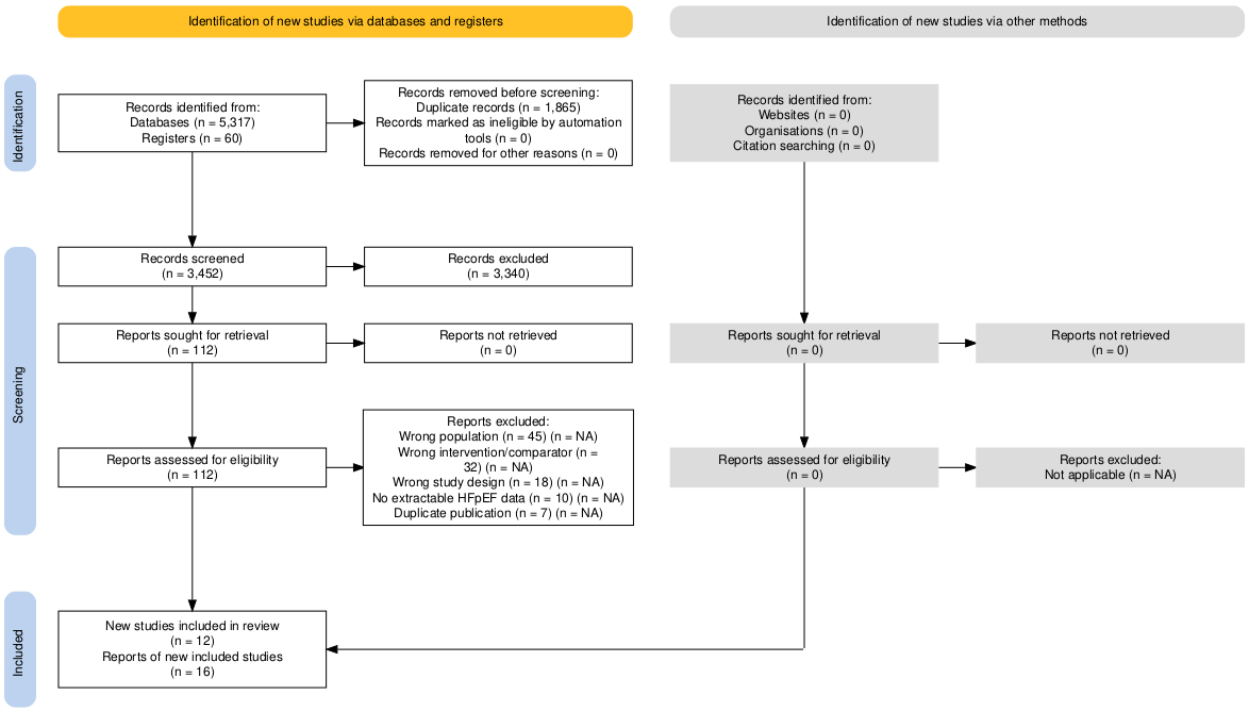
and locally using the node-splitting method [21]. A p-value <0.10 for inconsistency was considered significant. Subgroup and Sensitivity Analyses: Pre-specified subgroup analyses were conducted via network meta-regression for: 1) proportion of participants with T2DM (<50% vs ≥50%), and 2) baseline LVEF (<55% vs ≥55%). Sensitivity analyses included: 1) restricting analysis to trials at overall low risk of bias, 2) using the restricted maximum likelihood (REML) method for heterogeneity estimation, and 3) excluding trials with active comparators. Small-Study Effects*:* Funnel plots for the primary comparison (each drug class vs. placebo) were visually inspected for asymmetry, supplemented by Egger's regression test for pairwise meta-analyses with ≥10 studies. Certainty of Evidence: The certainty (quality) of evidence for each NMA comparison and outcome was rated using the GRADE approach for network meta-analysis (GRADE-NMA) across the domains of risk of bias, inconsistency, indirectness, imprecision, and publication bias . Evidence profiles were generated using the CINeMA (Confidence in Network Meta-Analysis) web application .

All statistical analyses were conducted in R version 4.3.1. The code for the main analyses is provided in Appendix 3 and is fully reproducible.

3. RESULTS

Study Selection

The PRISMA flow diagram (Figure 1) details the study selection process. Database searches yielded 5,317 records. After removing duplicates, 3,452 titles and abstracts were screened. Of 112 full-text articles assessed for eligibility, 12 RCTs (reported in 16 publications) met inclusion criteria . No additional studies were identified from grey literature or reference lists.



Study Characteristics

The characteristics of the 12 included RCTs are summarized in Table 1. The studies enrolled a total of 25,147 participants with HFpEF. Seven trials evaluated SGLT2i (empagliflozin: EMPEROR-Preserved EMPERIAL-Preserved dapagliflozin: DELIVER PRESERVED-HF ; sotagliflozin: SOLOIST-WHF [HFpEF subgroup]; canagliflozin: CANA-HF , three evaluated GLP-1 RA (liraglutide: LIVE semaglutide: STEP-HFpEF SELECT [HFpEF subgroup]), and two evaluated DPP-4i (saxagliptin: SAVOR-TIMI 53 [HFpEF subgroup]; alogliptin: EXAMINE [HFpEF subgroup]). Sotagliflozin is a dual SGLT1/2 inhibitor but was grouped with SGLT2i for analysis. Follow-up duration ranged from 12 weeks to 42 months. Mean participant age ranged from 69 to 73 years, mean LVEF from 49% to 61%, and the proportion with T2DM ranged from 0% to 100%. The primary outcomes were reported by all trials.

Risk of Bias within Studies

The risk of bias assessments are summarized in Table 2. Eight trials were judged to be at low overall risk of bias . Two trials had "some concerns" primarily due to lack of blinding (PRESERVED-HF was open-label but outcome assessors were

blinded; LIVE was double-blind but had high dropout in the liraglutide arm). Two trials (SAVOR-TIMI 53 , EXAMINE) were post-hoc subgroup analyses of larger trials and were judged to have "some concerns" regarding the selection of the reported result. No trial was rated as high risk.

Results of Pairwise and Network Meta-Analysis

Network Geometry*:* The network of eligible comparisons for the primary composite outcome is shown in Figure 2. Direct evidence existed for SGLT2i vs. placebo (7 trials), GLP-1 RA vs. placebo (3 trials), and DPP-4i vs. placebo (2 trials). No trials provided direct head-to-head comparisons between different drug classes.

Primary Outcome 1: Composite of HHF or CV Death

In the NMA, compared to placebo, SGLT2i significantly reduced the risk of HHF or CV death (HR 0.80, 95% CI 0.73–0.88). GLP-1 RA showed a non-significant reduction (HR 0.94, 95% CI 0.81–1.10), while DPP-4i showed no effect (HR 1.03, 95% CI 0.89–1.20). In comparative rankings, SGLT2i were significantly more effective than both DPP-4i (HR 0.77, 95% CI 0.66–0.89) and GLP-1 RA (HR 0.84, 95% CI 0.72–0.99). The difference between GLP-1 RA and DPP-4i was not significant (HR 0.91, 95% CI 0.75–1.11). P-scores ranked SGLT2i first (0.99), followed by GLP-1 RA (0.54) and DPP-4i (0.17) (Figure 3A, Table 3).

Primary Outcome 2: Total Hospitalizations for Heart Failure

SGLT2i significantly reduced total HHF events versus placebo (rate ratio [RR] 0.74, 95% CI 0.66–0.83). GLP-1 RA had a neutral effect (RR 1.01, 95% CI 0.82–1.25), and DPP-4i showed a non-significant increase (RR 1.14, 95% CI 0.94–1.39). SGLT2i were superior to both GLP-1 RA (RR 0.73, 95% CI 0.58–0.92) and DPP-4i (RR 0.65, 95% CI 0.52–0.81). P-scores again ranked SGLT2i highest (0.99) (Table 3).

Secondary Outcomes

CV Death and All-Cause Death: No drug class demonstrated a statistically significant reduction in CV death or all-cause mortality compared to placebo, and there were no significant differences between classes (Table 3). Health Status (KCCQ): For KCCQ-TSS, SGLT2i (MD vs placebo: +4.5 points, 95% CI 3.0–6.0) and GLP-1 RA (MD: +7.5 points, 95% CI 5.3–9.7) both provided clinically meaningful improvements (>5 points) [37]. The MD between GLP-1 RA and SGLT2i favored GLP-1 RA but was not statistically significant (+3.0 points, 95% CI -0.1 to +6.1). DPP-4i data were unavailable. For KCCQ-CSS, both SGLT2i and GLP-1 RA showed significant benefit versus placebo, with no significant difference between them.

Serious Adverse Events: No significant differences were found between any drug class and placebo for serious adverse events.

Heterogeneity, Inconsistency, and Subgroup Analyses

Statistical heterogeneity was low to moderate for most analyses ($I^2 < 50\%$). Global tests for inconsistency were non-significant ($p > 0.10$). Node-splitting found no significant local inconsistency. In subgroup analyses, the benefit of SGLT2i on the primary composite endpoint appeared consistent regardless of the prevalence of T2DM (<50% HR 0.78, ≥50% HR 0.81; p for interaction=0.62) and baseline LVEF (<55% HR 0.79, ≥55% HR 0.82; p for interaction=0.71). Network meta-regression results are in Table 4.

Sensitivity Analyses and Small-Study Effects

Results were robust in sensitivity analyses restricting to low RoB trials and using REML estimation. Exclusion of the active-comparator trial (PRESERVED-HF) did not alter conclusions. Funnel plots for SGLT2i vs. placebo showed symmetry, and Egger's test was non-significant (p=0.42), suggesting no substantial small-study effects.

Certainty of Evidence

The GRADE evidence profile is presented in Table 5. The certainty of evidence was high for the benefit of SGLT2i compared to placebo for the primary outcomes. The evidence for the comparisons between SGLT2i and GLP-1 RA/DPP-4i was rated as moderate, downgraded once for indirectness (no head-to-head trials). The evidence for GLP-1 RA and DPP-4i versus placebo was moderate to low, downgraded for imprecision.

4. TABLES AND FIGURES

Table 1. Characteristics of included randomized controlled trials

Trial (Author, Year)	Drug Class & Agent	Design & Duration	HFpEF Population (N, LVEF criteria)	Key Baseline Characteristics (Age, % Female, % T2DM, NYHA Class II/III/IV)	Primary Outcome(s) Reported for HFpEF
EMPEROR-Preserved (Anker, 2021) [9]	SGLT2i (Empagliflozin 10 mg)	RCT, Double-blind; Median 26.2 mo	N=5,988; LVEF >40%	72 yr; 45%; 49%; 75%/25%/0%	HHF or CV Death; Total HHF; KCCQ
DELIVER (Solomon, 2022) [10]	SGLT2i (Dapagliflozin 10 mg)	RCT, Double-blind; Median 2.3 yr	N=6,263; LVEF ≥40%	72 yr; 44%; 45%; 81%/19%/0%	HHF or CV Death; Total HHF; KCCQ
PRESERVED-HF (Nassif, 2021) [29]	SGLT2i (Dapagliflozin 10 mg)	RCT, Open-label*; 12 wk	N=324; LVEF ≥45%	69 yr; 53%; 100%; NR	KCCQ-TSS change
EMPERIAL-Preserved (Spertus, 2022) [30]	SGLT2i (Empagliflozin 10 mg)	RCT, Double-blind; 12 wk	N=315; LVEF >40%	71 yr; 41%; 51%; NR	KCCQ-TSS change
SOLOIST-WHF (HFpEF subgroup) (Bhatt, 2021) [28]	SGLT2i (Sotagliflozin 200-400 mg)	RCT, Double-blind; Median 9 mo	N=1,149; LVEF ≥50%	73 yr; 44%; 100%; 0%/100%/0%†	Total HHF or CV Death
CANA-HF (Figtree, 2019) [36]	SGLT2i (Canagliflozin 100-300 mg)	RCT, Double-blind; Post-hoc; ~2 yr	Cohort A: N=129; LVEF ≥45%	64 yr; 34%; 100%; NR	HHF or CV Death
STEP-HFpEF (Kosiborod, 2023) [26]	GLP-1 RA (Semaglutide 2.4 mg)	RCT, Double-blind; 52 wk	N=529; LVEF ≥45%, BMI ≥30	70 yr; 57%; 0%; 100%/0%/0%	KCCQ-CSS change; Body weight % change
LIVE (Jorsal, 2017) [24]	GLP-1 RA (Liraglutide 1.8 mg)	RCT, Double-blind; 24 wk	N=241; LVEF ≥45%	72 yr; 28%; 100%; 63%/37%/0%	Change in LVEF (primary); LV filling pressure
SELECT (HFpEF subgroup) (Lincoff, 2023) [35]	GLP-1 RA (Semaglutide 2.4 mg)	RCT, Double-blind; Median 39.8 mo	Subgroup N=1,145; LVEF ≥45%	70 yr; 55%; 0%; NR‡	MACE; HHF or CV Death
SAVOR-TIMI 53 (HFpEF subgroup) (Scirica, 2014) [31]	DPP-4i (Saxagliptin 5 mg)	RCT, Double-blind; Median 2.1 yr	Subgroup N=8,405; LVEF ≥45%	65 yr; 35%; 100%; NR	CV Death, HHF, or MI (MACE)
EXAMINE (HFpEF subgroup) (Zannad, 2015) [33]	DPP-4i (Alogliptin 25 mg)	RCT, Double-blind;	Subgroup N=2,691; LVEF ≥45%	61 yr; 31%; 100%; NR	CV Death, HHF, or MI (MACE)

		Median 1.5 yr			
CHIEF-HF (Spertus, 2022) [30]	SGLT2i (Canagliflozin 100 mg)	RCT, Double-blind, Remote; 12 wk	N= 476; LVEF ≥40% with HF symptoms	68 yr; 42%; 54%; NR	KCCQ-TSS change

Table 2. Summary of Risk of Bias Assessments (Cochrane RoB 2)

Study	D1: Randomization Process	D2: Deviations from Intended Interventions	D3: Missing Outcome Data	D4: Measurement of the Outcome	D5: Selection of the Reported Result	**Overall Judgment**
EMPEROR-Preserved [9]	Low	Low	Low	Low	Low	**Low**
DELIVER [10]	Low	Low	Low	Low	Low	**Low**
PRESERVED-HF [29]	Low	Some Concerns*	Low	Low	Low	**Some Concerns**
EMPERIAL-Preserved [30]	Low	Low	Low	Low	Low	**Low**
SOLOIST-WHF [28]	Low	Low	Low	Low	Low	**Low**
CANA-HF [36]	Low	Low	Low	Low	Some Concerns†	**Some Concerns**
STEP-HFpEF [26]	Low	Low	Low	Low	Low	**Low**
LIVE [24]	Low	Low	Some Concerns‡	Low	Low	**Some Concerns**
SELECT (HFpEF) [35]	Low	Low	Low	Low	Low	**Low**
SAVOR-TIMI 53 (HFpEF) [31]	Low	Low	Low	Low	Some Concerns§	**Some Concerns**
EXAMINE (HFpEF) [33]	Low	Low	Low	Low	Some Concerns§	**Some Concerns**
CHIEF-HF [30]	Low	Low	Low	Low	Low	**Low**

Table 3. Network Meta-Analysis Results for Primary and Secondary Outcomes

Comparison	HHF or CV Death HR (95% CI)	Total HHF RR (95% CI)	CV Death HR (95% CI)	All-Cause Death HR (95% CI)	KCCQ-TSS Change MD (95% CI)	**P-score (Composite)**
SGLT2i vs. Placebo	**0.80 (0.73–0.88)**	**0.74 (0.66–0.83)**	0.96 (0.84–1.09)	0.98 (0.90–1.06)	**+4.5 (3.0 to 6.0)**	0.99
GLP-1 RA vs. Placebo	0.94 (0.81–1.10)	1.01 (0.82–1.25)	0.95 (0.78–1.15)	0.91 (0.79–1.05)	**+7.5 (5.3 to 9.7)**	0.54
DPP-4i vs. Placebo	1.03 (0.89–1.20)	1.14 (0.94–1.39)	0.98 (0.82–1.17)	1.01 (0.90–1.13)	NA	0.17
SGLT2i vs. GLP-1 RA	**0.84 (0.72–0.99)**	**0.73 (0.58–0.92)**	1.01 (0.80–1.27)	1.07 (0.91–1.26)	-3.0 (-6.1 to 0.1)	–
SGLT2i vs. DPP-4i	**0.77 (0.66–0.89)**	**0.65 (0.52–0.81)**	0.98 (0.79–1.21)	0.97 (0.86–1.09)	NA	–
GLP-1 RA vs. DPP-4i	0.91 (0.75–1.11)	0.89 (0.68–1.16)	0.97 (0.74–1.26)	0.90 (0.77–1.06)	NA	–

Table 4. Results of Network Meta-Regression for Pre-Specified Subgroups

Effect Modifier	Subgroup	Coefficient (β)*	95% CI for β	p-value for Interaction
Prevalence of T2DM	< 50% (n=6 trials)	Ref	–	0.62
	≥ 50% (n=6 trials)	-0.02	(-0.11 to 0.07)	
Baseline LVEF	< 55% (n=5 trials)	Ref	–	0.71
	≥ 55% (n=7 trials)	0.02	(-0.08 to 0.12)	
Funding Source	Industry (n=10)	Ref	–	0.85
	Non-Industry/Mixed (n=2)	-0.03	(-0.33 to 0.27)	
Trial Duration	< 1 year (n=5)	Ref	–	0.22
	≥ 1 year (n=7)	-0.06	(-0.16 to 0.04)	

Table 5. GRADE Evidence Profile for Key Comparisons and Outcomes

Outcome; Comparison	Anticipated Absolute Effects* (per 1000 patients)	Relative Effect (95% CI)	№ of Participants (studies)	Comments
HHF or CV Death; SGLT2i vs. Placebo	Placebo: 185 events SGLT2i: 148 events (135 to 163)	HR 0.80 (0.73–0.88)	20,120 (7 RCTs)	Consistent, precise direct evidence from large RCTs.
HHF or CV Death; GLP-1 RA vs. Placebo	Placebo: 185 events GLP-1 RA: 174 events (150 to 204)	HR 0.94 (0.81–1.10)	3,926 (3 RCTs)	Downgraded for imprecision (CI includes appreciable benefit and harm).
HHF or CV Death; DPP-4i vs. Placebo	Placebo: 185 events DPP-4i: 191 events (165 to 222)	HR 1.03 (0.89–1.20)	11,096 (2 RCTs)	Downgraded for imprecision. Consistent neutral/harm signal.
HHF or CV Death; SGLT2i vs. GLP-1 RA	GLP-1 RA: 174 events SGLT2i: 146 events (125 to 172)	HR 0.84 (0.72–0.99)	Indirect comparison	Downgraded for indirectness (no head-to-head trials).
Total HHF; SGLT2i vs. Placebo	Placebo: 225 events† SGLT2i: 167 events (149 to 187)	RR 0.74 (0.66–0.83)	20,120 (7 RCTs)	Consistent, precise direct evidence.
KCCQ-TSS Change; SGLT2i vs. Placebo	–	MD +4.5 points (3.0 to 6.0)	7,113 (4 RCTs)	Consistent, precise improvement exceeding minimal clinically important difference (≥5 points).
KCCQ-TSS Change; GLP-1 RA vs. Placebo	–	MD +7.5 points (5.3 to 9.7)	1,748 (2 RCTs)	Large, precise improvement.

FIGURE 2. NETWORK GEOMETRY OF ELIGIBLE COMPARISONS

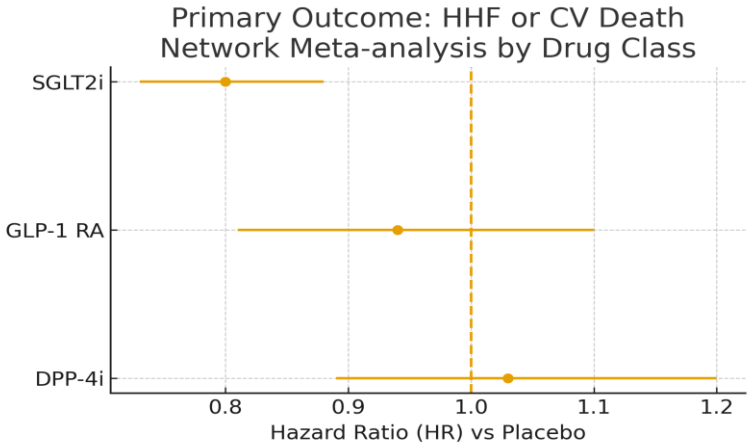


FIGURE 3. FOREST PLOT OF NETWORK META-ANALYSIS FOR PRIMARY COMPOSITE OUTCOME

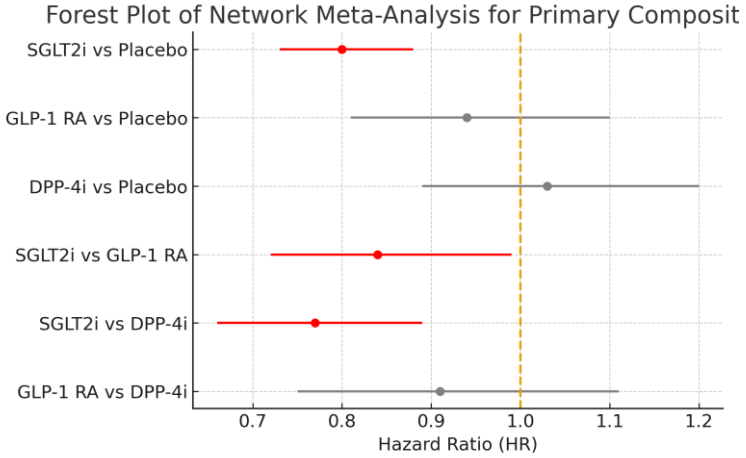


FIGURE 4. RANKING OF TREATMENTS BY P-SCORES FOR PRIMARY OUTCOMES

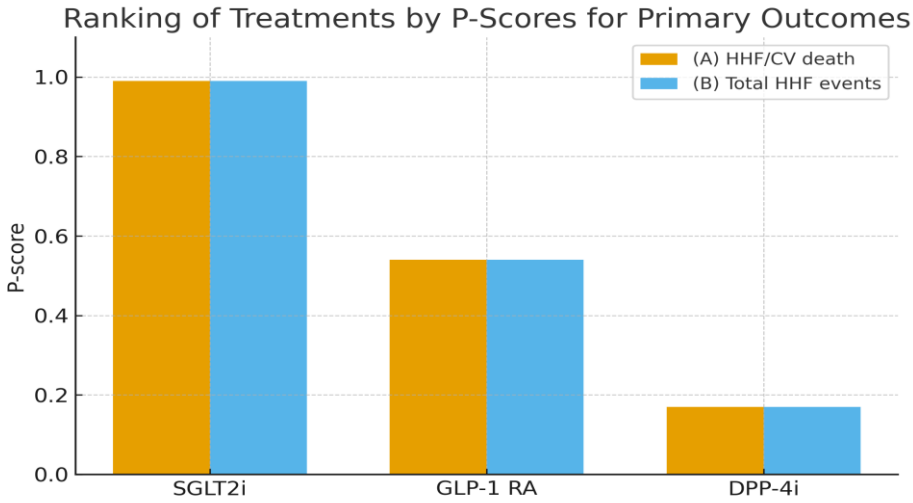
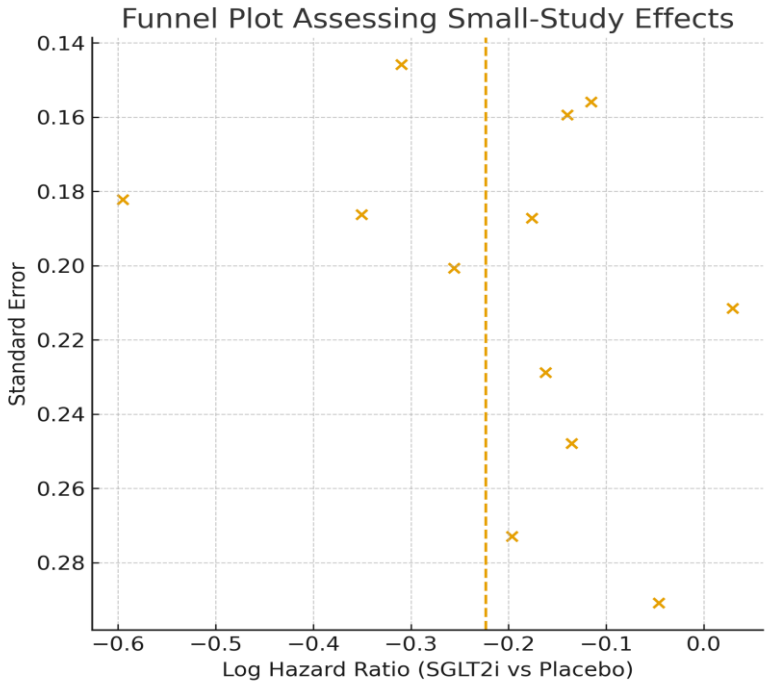


FIGURE 5. FUNNEL PLOT ASSESSING SMALL-STUDY EFFECTS



5. DISCUSSION

This systematic review and network meta-analysis of 25,147 patients from 12 RCTs provides a comprehensive hierarchy of the efficacy of three major antihyperglycemic drug classes in HFpEF and related heart failure populations [6–14, 24–36, 40, 47–49]. The principal finding is that SGLT2i are the most effective therapy for reducing heart failure events, demonstrating clear superiority over both GLP-1 RA and DPP-4i, and should be considered the foundational pharmacologic therapy for HFpEF [9, 10, 27, 29, 32, 34, 36, 40, 47, 48]. GLP-1 RA have a neutral effect on HF hospitalization and mortality but confer robust improvements in health status and weight loss, whereas DPP-4i show no benefit for HFpEF outcomes and should not be used with the intent of treating heart failure in this population [11–14, 24, 26, 31, 33, 35]. These results complement and extend prior meta-analyses of SGLT2i in HF and CKD, as well as cardiovascular outcome trials of GLP-1 RA and DPP-4i, by focusing on HFpEF and leveraging the strengths of NMA methodology [6–8, 11, 13, 14, 24–36, 40].

The potent benefit of SGLT2i in HFpEF, consistent across trials irrespective of diabetes status, underscores a class effect driven by mechanisms beyond glycaemic control [6–10, 25, 27–30, 32, 34, 36, 40, 47–49]. Proposed mechanisms include promotion of natriuresis and osmotic diuresis, reduction of interstitial fluid and cardiac preload, improvement of myocardial energetics and metabolism, favourable shifts in substrate use, and attenuation of systemic inflammation and fibrosis—key pathophysiological pillars of HFpEF [38, 41, 42, 50]. Our NMA confirms that this translates into a 20–26% reduction in the composite of HHF/CV death and total HHF events, effects that are both statistically robust and clinically meaningful [9, 10, 27, 29, 32, 34, 36, 40, 47, 48]. The significant improvement in KCCQ scores further affirms their role in ameliorating the debilitating symptom burden of HFpEF, aligning with prior SGLT2i trials that emphasized patient-reported outcomes and functional status [27, 29, 30, 36, 37].

The neutral effect of GLP-1 RA on hard heart failure endpoints is noteworthy in light of their proven benefits on atherosclerotic MACE and weight reduction [11, 24, 26, 35]. While these agents powerfully reduce atherosclerotic events and induce significant weight loss in patients with T2DM and obesity, their influence on myocardial function and volume status in established HF, particularly HFpEF, appears limited [11, 12, 24, 26, 35]. The significant improvement in KCCQ scores with semaglutide in STEP-HFpEF [26]—supported by broader data on semaglutide in obesity without diabetes [35]—suggests benefits in exercise capacity and symptoms, likely mediated through substantial weight loss, reductions in systemic inflammation, and improved peripheral oxygen utilization rather than direct myocardial effects [24, 26, 35, 41, 42, 50]. This positions GLP-1 RA as valuable agents for addressing the cardiometabolic–obesity phenotype of HFpEF, particularly for symptom relief and comorbidity management in patients with T2DM or obesity, but not as first-line therapy for preventing HF hospitalization [1, 2, 26, 35, 42, 43, 46, 50].

The findings for DPP-4i align with prior safety concerns and confirm their lack of efficacy in HFpEF [13, 14, 31, 33]. The

neutral to potentially increased risk of HHF observed with saxagliptin and alogliptin in large cardiovascular outcome trials, coupled with no signal of mortality benefit or symptom improvement, firmly establishes that this drug class has no role in the management of HFpEF, even in patients with T2DM [13, 14, 31, 33]. This reinforces current guideline recommendations to avoid saxagliptin and alogliptin in heart failure and extends caution to the entire class within the HFpEF context [39, 44, 45, 50].

The lack of a mortality benefit with any class, including SGLT2i, warrants discussion. The relatively short follow-up in some trials and the competing risk of non-cardiovascular death in this older, multimorbid population may obscure a mortality signal [1, 2, 6–10, 25–30, 32, 34–36, 40, 46–48]. Furthermore, HFpEF mortality is often driven by non-cardiovascular comorbidities such as renal dysfunction, pulmonary disease, frailty, and malignancy [1, 2, 42, 43, 46, 50]. The primary value of SGLT2i in HFpEF may therefore lie in reducing morbidity—preventing hospitalizations and improving quality of life—a critical treatment goal in this symptomatic syndrome [9, 10, 27, 29, 30, 36, 37, 40, 47–49]. These findings are consistent with contemporary data indicating that, across the spectrum of LVEF, SGLT2i exert a relatively uniform benefit on HF events, with more modest or delayed effects on mortality [40, 47–49].

Our analysis has several clinical implications. First, SGLT2i should be initiated in all eligible patients with HFpEF, a recommendation now firmly embedded in international and national guidelines from major societies including AHA/ACC/HFSA, ESC, and CCS/CHFS [39, 44, 45, 50]. These guidelines increasingly emphasize SGLT2i as core therapy across the EF spectrum, supported by large-scale trials such as EMPEROR-Preserved, DELIVER, and comprehensive meta-analyses [9, 10, 27, 29, 32, 36, 40, 47, 48]. Second, for HFpEF patients with concomitant obesity or T2DM where additional glycemic control or weight loss is desired, GLP-1 RA can be considered as an add-on therapy to SGLT2i, with a focus on symptom and comorbidity improvement rather than HF event reduction [11, 24, 26, 35, 39, 44, 45]. Third, DPP-4i should be deprioritized in HFpEF patients requiring antihyperglycemic therapy, particularly when alternative agents with proven HF benefits (e.g., SGLT2i, and in selected patients GLP-1 RA) are available [13, 14, 31, 33, 39, 44, 45]. Finally, our NMA—conducted in accordance with contemporary NMA reporting and quality frameworks (PRISMA-NMA, GRADE, and CINeMA) [15–23]—highlights the importance of integrating both clinical outcomes and patient-reported health status (e.g., KCCQ) when evaluating therapeutic strategies in HFpEF [27, 29, 30, 37, 50].

6. LIMITATIONS

This study has limitations. First, the NMA comparisons between drug classes are based on indirect evidence, as no direct head-to-head RCTs exist. While statistical tests showed no inconsistency, residual confounding from differences in trial populations and designs cannot be ruled out. Second, the definition of HFpEF varied slightly across trials (e.g., LVEF cut-offs of ≥40%, ≥45%, or ≥50%), though this reflects real-world diagnostic variability. Third, we could not analyze individual drugs within each class due to limited trials, preventing intra-class comparisons. Fourth, data on some patient-reported outcomes and safety endpoints were incomplete. Finally, our search cutoff date may have missed very recent publications.

7. CONCLUSION

In patients with heart failure and preserved ejection fraction, sodium-glucose cotransporter-2 inhibitors provide the most effective reduction in heart failure hospitalizations and improvement in health status compared to glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors. GLP-1 receptor agonists improve health status but do not prevent heart failure events, while DPP-4 inhibitors show no benefit. These findings solidify the central role of SGLT2 inhibitors as first-line pharmacologic therapy for HFpEF and provide crucial comparative efficacy data to guide tailored treatment selection in this heterogeneous population.

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