UDC 616.12-008.46:615.03-092.6:615.036
DOI https://doi.org/10.63181/ujcvs.2025.33(4).94-105

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Efficacy of Sodium–Glucose Cotransporter 2 Inhibitors in Chronic Heart Failure: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Abstract

Background. Sodium–glucose cotransporter 2 (SGLT2) inhibitors are now a foundational therapy for heart failure (HF), yet uncertainties remain regarding their impact on mortality, recurrent events, patient-reported outcomes, and biomarkers.

Aim. To evaluate the efficacy and safety of sodium–glucose cotransporter 2 (SGLT2) inhibitors in patients with chronic heart failure across the spectrum of ejection fraction, based on evidence from randomized controlled trials.

Materials and Methods. We conducted a systematic review and meta-analysis in accordance with PRISMA 2020 (PROSPERO: CRD420251138644). PubMed, Embase, Cochrane CENTRAL, and ClinicalTrials.gov were searched through 25 June 2025. Eligible studies were randomized controlled trials (RCTs) of SGLT2 inhibitors versus placebo in adults with chronic HF. The primary endpoint was time to first cardiovascular (CV) death or HF hospitalization. Secondary outcomes included all-cause mortality, recurrent hospitalizations, quality of life, natriuretic peptides, and safety. Hazard ratios (HRs) were pooled using Hartung–Knapp random-effects models where definitions were consistent; other outcomes were narratively synthesized. Risk of bias was assessed with RoB 2, and the certainty of evidence with GRADE.

Results. Five RCTs (n = 16,222) were included: DAPA-HF, EMPEROR-Reduced, DELIVER, SOLOIST-WHF (providing recurrent-event analyses), and DEFINE-HF (mechanistic, biomarker-focused). SGLT2 inhibitors reduced the risk of CV death or HF hospitalization (pooled HR 0.79, 95% CI 0.74–0.83; I^2 = 0%). The reduction in hospitalization was consistent across trials (HRs ≈ 0.69–0.75), while all-cause mortality showed a modest but significant benefit (HR 0.90, 95% CI 0.83–0.98). Trials consistently demonstrated improvements in Kansas City Cardiomyopathy Questionnaire (KCCQ) scores and natriuretic peptide response rates. Safety findings were consistent with the established SGLT2 inhibitor profile, with no signals of serious adverse events.

Conclusions. SGLT2 inhibitors confer robust reductions in HF hospitalizations and provide supportive benefits on mortality, quality of life, and biomarkers across EF phenotypes, reinforcing their role as a cornerstone therapy in chronic HF.

Keywords: *cardiovascular death, hospital readmission, Kansas City Cardiomyopathy Questionnaire (KCCQ), NT-proBNP reduction, recurrent-event analysis, dapagliflozin, empagliflozin.*

Introduction. Heart failure (HF) is a major global cause of morbidity and mortality. Despite advances in guideline-directed therapy, outcomes remain poor, especially for patients with reduced ejection fraction (HFrEF). Sodium–glucose cotransporter 2 (SGLT2) inhibitors, originally developed as glucose-lowering drugs, have emerged as modulators of cardiovascular physiology with providing benefits beyond glycemic control. Landmark trials such as DAPA-HF and EMPEROR-Reduced showed that SGLT2 inhibitors significantly reduced cardiovascular death or HF hospitalization in HFrEF, irrespective of diabetes status [1,2]. These findings have led major societies, including the European Society of Cardiology and the American College of Cardiology/American Heart Association, to recommend them as first-line therapy [3,4].

Subsequent evidence extended benefits to HF with mildly reduced or preserved ejection fraction (HFmrEF and HFpEF). DELIVER and EMPEROR-Preserved demonstrated consistent reductions in HF hospitalization in these populations, which have historically been understudied [5,6]. Mechanistic studies highlighted pleiotropic effects – natriuresis, reduced ventricular loading, improved energetics, decreased stiffness, modulation of adipokines, and antifibrotic and antioxidative pathways [7,8] – that may explain the observed clinical benefits.

Nonetheless, gaps remain. While reductions in hospitalization are well established, uncertainty persists regarding the magnitude of mortality benefit, effects on recurrent hospitalizations, and improvements in quality

of life and biomarkers. Heterogeneity in trial designs, patient populations, and endpoint definitions further complicates interpretation and generalizability [9].

This systematic review and meta-analysis synthesize randomized evidence on SGLT2 inhibitors in chronic HF, prioritizing large outcome trials with adjudicated endpoints, incorporating mechanistic studies for biomarker and quality-of-life data, and excluding overlapping populations. Risk of bias (RoB 2) and GRADE certainty assessments were applied to ensure transparency and reproducibility.

Aim. To evaluate the efficacy and safety of sodium–glucose cotransporter 2 (SGLT2) inhibitors in patients with chronic heart failure across the spectrum of ejection fraction, based on evidence from randomized controlled trials.

Materials and Methods

Protocol and Registration. This systematic review and meta-analysis followed PRISMA 2020 and was prospectively registered on PROSPERO (CRD420251138644).

Search Strategy. PubMed/MEDLINE, Embase (Ovid), Cochrane CENTRAL, and ClinicalTrials.gov were searched from inception to 25 June 2025 using MeSH/Emtree terms and free-text keywords for SGLT2 inhibitors (e.g., "dapagliflozin," "empagliflozin," "sotagliflozin") and heart failure. Search strategies were tailored to each database with Boolean refinements. No language or date restrictions were applied. References of eligible trials and reviews were also screened. Full reproducible search strings are provided in Supplementary Table 1 (p. 101).

Eligibility Criteria. Inclusion:

- Randomized, double-blind, placebo-controlled trials in adults with chronic HF (HFrEF ≤40 %, HFmrEF 41-49 %, HFpEF ≥50 %), regardless of diabetes.
- Reporting cardiovascular death or HF hospitalization, or sufficient data to derive it.

Exclusion:

- Non-randomized, observational, or post-hoc subgroup analyses.
- Trials without adequate outcome data or overlapping populations (most complete dataset retained).

Clarifications:

- *EMPEROR-Preserved* [6] was not pooled due to endpoint differences and overlap with *EMPEROR-Reduced* but is cited narratively.
- *SOLOIST-WHF* (sotagliflozin, dual SGLT1/2) was included for recurrent-event analyses; sensitivity analyses tested its impact.
- *DEFINE-HF* was used for biomarker and quality-of-life outcomes but excluded from time-to-event pooling.

Study Screening and Selection. Two reviewers independently screened titles, abstracts, and full texts; disagreements were resolved by consensus or, if necessary, a third reviewer. Reasons for exclusion were documented. The PRISMA flow diagram (Figure 1) illustrates the study selection process.

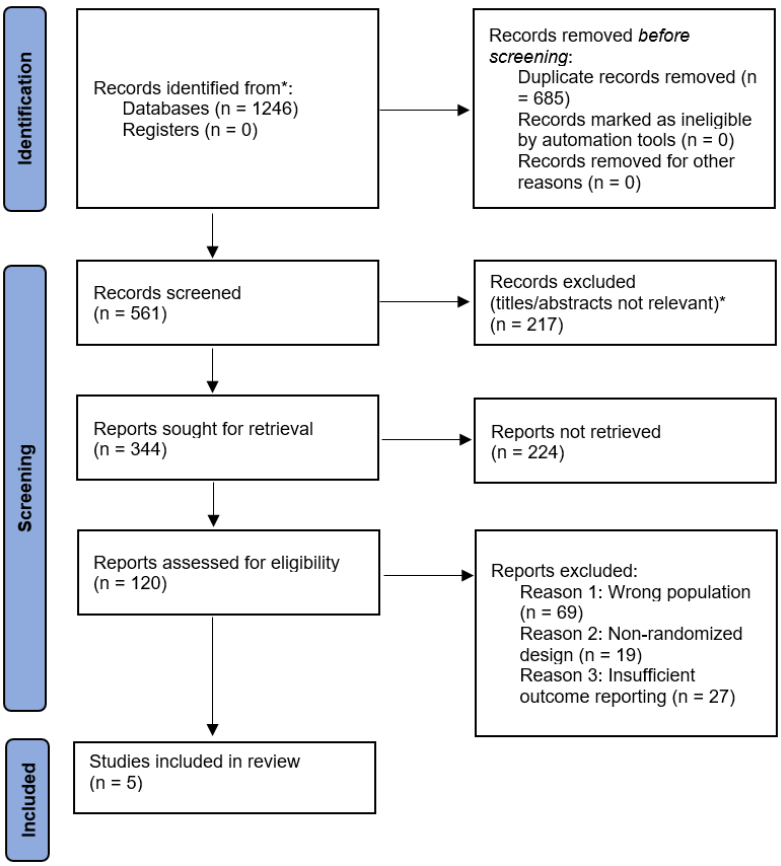

Figure 1. *PRISMA flow diagram*

Data Extraction. Two reviewers extracted study design, sample size, intervention, comparator, HF phenotype, comorbidities, follow-up, outcomes, risk of bias, and funding.

- Primary outcome: HR for cardiovascular death or HF hospitalization.
- Secondary outcomes: all-cause mortality, first/recurrent HF hospitalizations, Kansas City Cardiomyopathy Questionnaire (KCCQ) scores, natriuretic peptides, and safety.

No imputation was performed. Graphical data were digitized with WebPlotDigitizer v4.6, verified independently. Supplementary Table 2 (p. 101) lists extracted values; risk-of-bias details are in Supplementary Table 3 (p. 103).

Quality Assessment. Risk of bias was evaluated using the Cochrane RoB 2 tool (randomization, intervention adherence, missing data, outcome measurement, and selective reporting). Each domain was rated as "low risk," "some concerns," or "high risk." The certainty of evidence was assessed using GRADE. Summary of Findings table applied median control event rates to derive absolute risk estimates (Table 1).

Outcomes. The primary outcome was time-to-first cardiovascular death or HF hospitalization. Secondary outcomes:

- All-cause mortality.
- First and recurrent HF hospitalizations.
- KCCQ scores.
- Natriuretic peptide changes.

Table 1

Studies' Characteristics

Trial (first author, year)	Country / setting	N randomized (intervention / placebo)	Intervention (drug, dose)	Comparator	Population (EF, key inclusion)	Median follow-up	% with diabetes	Primary outcome (definition, harmonized)
DAPA-HF (McMurray 2019) [1]	Multinational (410 centers, 20 countries)	4744 (2373 / 2371)	Dapagliflozin 10 mg daily	Placebo	HFrEF (LVEF ⩽40%), NYHA II–IV; with/without T2D	18.2 months	45%	Time-to-first event composite of CV death or worsening HF (hospitalization or urgent visit requiring IV therapy)
EMPEROR-Reduced (Packer 2020) [2]	Multinational	3730 (1863 / 1867)	Empagliflozin 10 mg daily	Placebo	HFrEF (LVEF ⩽40%), NYHA II–IV; with/without T2D	16 months	50%	Time-to-first event composite of CV death or hospitalization for HF (adjudicated)
DELIVER (Solomon 2022) [5]	Multinational (353 centers, 20 countries)	6263 (3131 / 3132)	Dapagliflozin 10 mg daily	Placebo	HFmrEF/HFpEF (LVEF >40%), NYHA II–IV; with/without T2D	2.3 years	45%	Time-to-first event composite of CV death or worsening HF (hospitalization or urgent visit requiring IV therapy)
SOLOIST-WHF (Bhatt 2021) [10]	Multinational (306 sites, 32 countries)	1222 (608 / 614)	Sotagliflozin 200 mg daily (↑400 mg if tolerated)	Placebo	T2D with recent worsening HF (hospitalized, randomized before or ⩽3 days post-discharge)	9.2 months	100%	Modified during trial: total (first + recurrent) composite of CV death, HF hospitalizations, or urgent HF visits (investigator-reported)
DEFINE-HF (Nassif 2019) [11]	United States (26 sites)	263 (131 / 132)	Dapagliflozin 10 mg daily	Placebo	HFrEF (LVEF ⩽40%), NYHA II–III; elevated NT-proBNP	12 weeks	61%	Dual primary: (1) average NT-proBNP at 6–12 weeks; (2) proportion with clinically meaningful benefit (⩾5-point KCCQ-OS increase or ⩾20% NT-proBNP reduction)

- Safety (renal events, hypoglycemia, genital infections).

Statistical Analysis. Log HRs and SEs were pooled using inverse-variance random-effects models. Both DerSimonian–Laird and REML with Hartung–Knapp adjustment were applied; Hartung–Knapp was prioritized. Heterogeneity was assessed with Q, τ^2, and I^2, and prediction intervals were calculated.

- *SOLOIST-WHF* contributed only recurrent-event rate ratios due to early termination.
- *DEFINE-HF* was excluded from event meta-analyses.
- Recurrent events were analyzed with pooled log-transformed RRs. Sensitivity analyses included leave-one-out and exclusion of *SOLOIST-WHF*.

Analyses were conducted in Stata 17.0 and Python 3.11; $p<0.05$ was considered significant.

Ethics Statement. Only published data were used; institutional review board approval and consent were not required.

Results

Study Selection and Characteristics. From 1,246 records, five randomized, double-blind placebo-controlled trials met inclusion (Figure 1). Three evaluated dapagliflozin (*DAPA-HF, DELIVER, DEFINE-HF*), one empagliflozin (*EMPEROR-Reduced*), and one sotagliflozin (*SOLOIST-WHF*) (Table 2).

- *DAPA-HF* and *EMPEROR-Reduced* were large HFrEF outcome trials with median follow-up of

Table 2

Studies' Characteristics

Trial (first author, year)	Country / setting	N randomized (intervention / placebo)	Intervention (drug, dose)	Comparator	Population (EF, key inclusion)	Median follow-up	% with diabetes	Primary outcome (definition, harmonized)
DAPA-HF (McMurray 2019) [1]	Multinational (410 centers, 20 countries)	4744 (2373 / 2371)	Dapagliflozin 10 mg daily	Placebo	HFrEF (LVEF ⩽40%), NYHA II–IV; with/without T2D	18.2 months	45%	Time-to-first event composite of CV death or worsening HF (hospitalization or urgent visit requiring IV therapy)
EMPEROR-Reduced (Packer 2020) [2]	Multinational	3730 (1863 / 1867)	Empagliflozin 10 mg daily	Placebo	HFrEF (LVEF ⩽40%), NYHA II–IV; with/without T2D	16 months	50%	Time-to-first event composite of CV death or hospitalization for HF (adjudicated)
DELIVER (Solomon 2022) [5]	Multinational (353 centers, 20 countries)	6263 (3131 / 3132)	Dapagliflozin 10 mg daily	Placebo	HFmrEF/HFpEF (LVEF >40%), NYHA II–IV; with/without T2D	2.3 years	45%	Time-to-first event composite of CV death or worsening HF (hospitalization or urgent visit requiring IV therapy)
SOLOIST-WHF (Bhatt 2021) [10]	Multinational (306 sites, 32 countries)	1222 (608 / 614)	Sotagliflozin 200 mg daily (↑400 mg if tolerated)	Placebo	T2D with recent worsening HF (hospitalized, randomized before or ⩽3 days post-discharge)	9.2 months	100%	Modified during trial: total (first + recurrent) composite of CV death, HF hospitalizations, or urgent HF visits (investigator-reported)
DEFINE-HF (Nassif 2019) [11]	United States (26 sites)	263 (131 / 132)	Dapagliflozin 10 mg daily	Placebo	HFrEF (LVEF ⩽40%), NYHA II–III; elevated NT-proBNP	12 weeks	61%	Dual primary: (1) average NT-proBNP at 6–12 weeks; (2) proportion with clinically meaningful benefit (⩾5-point KCCQ-OS increase or ⩾20% NT-proBNP reduction)

~16–18 months, assessing HF hospitalization and cardiovascular death.

- *DELIVER* enrolled HFmrEF/HFpEF (LVEF >40 %) with 2.3 years' follow-up.
- *SOLOIST-WHF* enrolled recently hospitalized diabetic patients with HF and reported investigator-adjudicated total events after early termination.
- *DEFINE-HF* was a 12-week mechanistic study focused on biomarkers and health status.

Differences in EF range, diabetes enrichment, outcome definitions, and follow-up informed prespecified subgroup and sensitivity analyses.

Risk of bias assessment: DAPA-HF, EMPEROR-Reduced, and DELIVER were judged to be at low risk of bias across all domains. DEFINE-HF also met low-risk criteria despite its small sample size and short duration. SOLOIST-WHF raised some concerns due to early termination, endpoint modifications, and reliance on non-adjudicated events. Full details are in Supplementary Table 3 (p. 103).

Primary Composite Outcome. Across 16,222 participants, SGLT2 inhibitors reduced cardiovascular death or HF hospitalization (pooled HR 0.79, 95 % CI 0.74–0.83; I^2 = 0 %; Figure 2). All individual trials favored active therapy.

Subgroup and sensitivity analyses:

- By EF: HFrEF trials (HR 0.77, 95 % CI 0.72-0.84) and DELIVER (HR 0.82, 95 % CI 0.73-0.92) showed consistent benefit with no heterogeneity (Figure 3).
- Exclusions: Removing DEFINE-HF (HR 0.78) or SOLOIST-WHF (HR 0.79) did not alter results.
- By drug: Dapagliflozin HR 0.78; empagliflozin HR 0.75; sotagliflozin HR 0.77; no heterogeneity (p>0.10).

Recurrent-Events Analysis. Four trials reported total HF events. Pooled RR was 0.73 (95 % CI 0.67-0.79; I^2 = 0%; Figure 4). Results were unchanged when excluding *SOLOIST-WHF* (RR 0.74).

Mechanistic Trial (DEFINE-HF). Among 263 participants, dapagliflozin improved health status (KCCQ-Overall +3.7, Clinical +4.6) and increased odds of ≥20 % NT-proBNP reduction (44.0 % vs 29.4 %; OR ~1.9).

Secondary Outcomes. Comprehensive trial-level secondary outcomes are summarized in Supplementary Table 4 (p. 103).

- **All-cause mortality:** *DAPA-HF, EMPEROR-Reduced,* and *DELIVER* pooled HR 0.90 (95 % CI 0.83–0.98; I^2 = 0 %; Figure 5).
- **Hospitalizations:** First-event HRs clustered 0.69-0.75; recurrent events reduced consistently.
- **Quality of life:** KCCQ improved across trials, strongest in *DEFINE-HF*.
- **Natriuretic peptides:** Higher likelihood of NT-proBNP reduction, though average changes are modest.
- **Safety:** Class effects included mild genital infections and occasional hypoglycemia; no signal for serious renal harm.

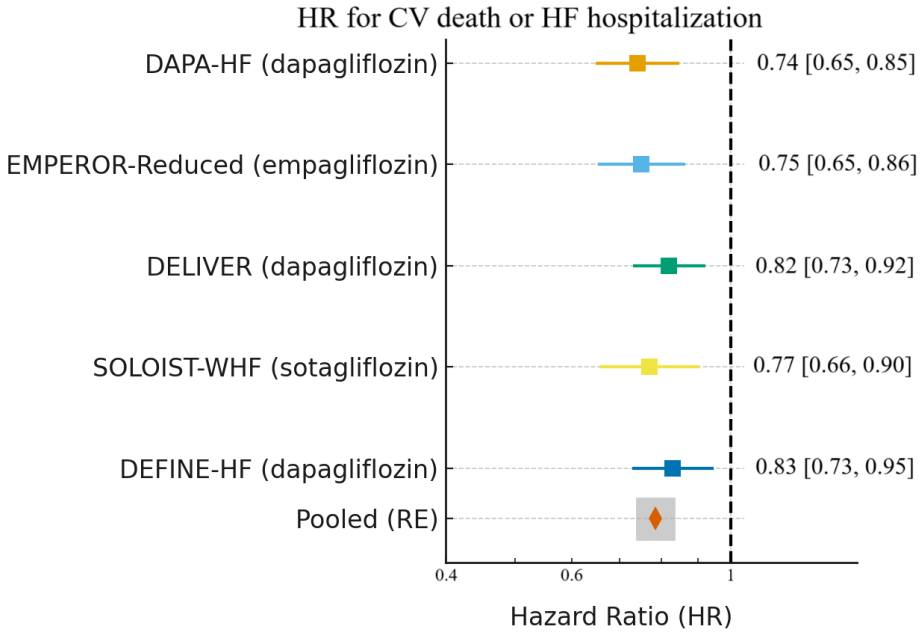

Figure 2. *Forest plot of the effect of SGLT2 inhibitors versus placebo on the composite of cardiovascular death or hospitalization for heart failure across five randomized controlled trials. Squares represent hazard ratios (HRs) for individual trials, with sizes proportional to study weight; horizontal lines indicate 95 % confidence intervals (CIs). The diamond represents the pooled summary effect from a random-effects model (HR 0.79, 95 % CI 0.74–0.83; I^2=0 %), which lies entirely to the left of the line of no effect (HR=1). The 95 % prediction interval (0.75-0.84) suggests a consistent benefit in future settings.*

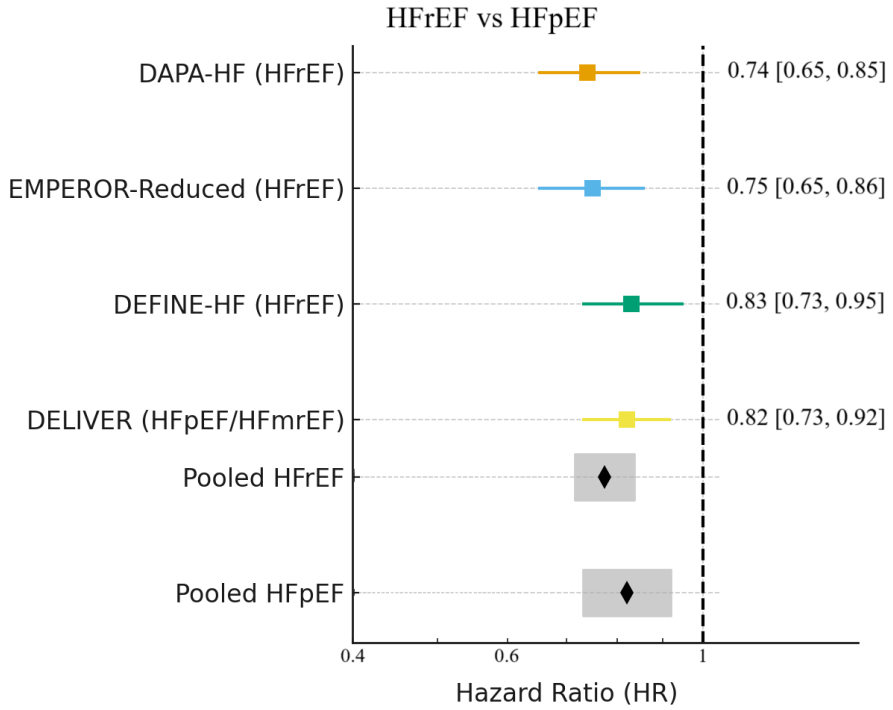

Figure 3. *Subgroup forest plot of SGLT2 inhibitors versus placebo stratified by heart failure phenotype. In three HFrEF trials (DAPA-HF, EMPEROR-Reduced, DEFINE-HF), the pooled HR was 0.77 (95 % CI 0.72-0.84; I^2=0 %). In the DELIVER trial (HFmrEF/HFpEF), the HR was 0.82 (95 % CI 0.73-0.92). The pooled summary estimates (diamonds) indicate consistent treatment benefit across the EF spectrum, with no evidence of subgroup heterogeneity (p-interaction >0.10). The 95 % prediction interval for the overall effect was 0.74-0.85.*

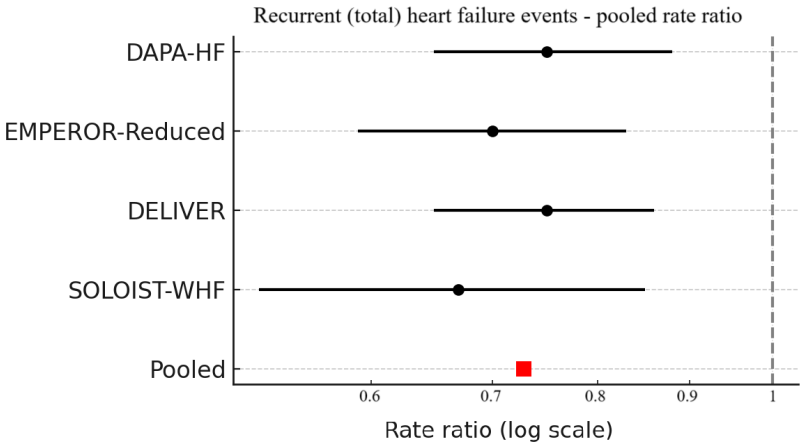

Figure 4. *Forest plot of the effect of SGLT2 inhibitors versus placebo on recurrent (total) heart-failure hospitalizations across four randomized controlled trials (DAPA-HF, EMPEROR-Reduced, DELIVER, SOLOIST-WHF). Squares represent study-specific rate ratios (RRs), with sizes proportional to study weights; horizontal lines denote 95 % confidence intervals (CIs). The diamond indicates the pooled summary effect (random-effects REML model with Hartung–Knapp adjustment). Pooled analysis demonstrated a 27 % relative reduction in recurrent HF events (RR 0.73, 95 % CI 0.67-0.79), with a 95 % prediction interval of 0.61-0.87, suggesting reproducible benefit in future studies.*

Publication Bias. Funnel plots were not generated given <10 RCTs.

Summary. In >16,000 patients across five RCTs, SGLT2 inhibitors reduced cardiovascular death or HF hospitalization, lowered recurrent events, modestly reduced mortality, improved quality of life and biomarkers, and had an acceptable safety profile.

Discussion. In this meta-analysis of five RCTs including >16,000 patients with chronic HF, SGLT2 inhibitors consistently reduced the composite of cardiovascular

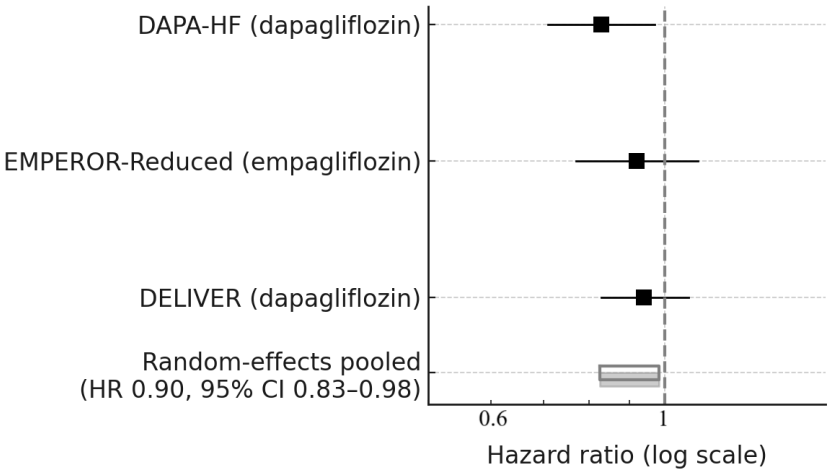

Figure 5. *Pooled analysis of all-cause mortality with SGLT2 inhibitors in heart failure.*

HRs and 95 % CIs are shown for DAPA-HF, EMPEROR-Reduced, and DELIVER, each reporting all-cause death as a time-to-first event. A random-effects meta-analysis (DerSimonian–Laird) demonstrated a 10 % relative reduction in the hazard of death from any cause with SGLT2 inhibitors compared with placebo (HR 0.90, 95 % CI 0.83-0.98). Between-trial heterogeneity was low (Q=1.54, df=2; τ^2=0.000; I^2=0 %). The 95 % prediction interval (0.82-0.99) supports a robust mortality benefit across future studies.

death or HF hospitalization compared with placebo. Benefits were evident across the EF spectrum, with reproducible ~30 % reductions in recurrent hospitalizations, highlighting a substantial impact on morbidity and healthcare utilization. Sensitivity analyses confirmed robustness despite variations in endpoint definitions. Although pooled mortality analyses suggested a modest benefit (HR ~0.90), trials were not uniformly powered for this outcome, particularly in HFpEF. Complementary findings included improved patient-reported health status (KCCQ), favorable biomarker responses, and a reassuring safety profile. Together, these reinforce SGLT2 inhibitors as effective, well-tolerated therapy across EF phenotypes.

Our results align with pivotal trials such as DAPA-HF [1] and EMPEROR-Reduced [2], as well as their extension to HFmrEF/HFpEF populations in DELIVER [5] and EMPEROR-Preserved [6]. Earlier pooled analyses confirmed reductions in the primary composite outcome [12], and contemporary guidelines now endorse SGLT2 inhibitors as foundational therapy for heart failure [3,4]. More recent meta-analyses incorporating DELIVER and EMPEROR-Preserved similarly report robust reductions in HF hospitalizations but only modest effects on mortality [13,14]. Specific trials, such as SOLOIST-WHF [15], support early initiation to reduce recurrent events, whereas DEFINE-HF provides mechanistic evidence of improved symptoms and NT-proBNP response.

The consistent reduction in hospitalizations makes SGLT2 inhibitors an essential part of routine HF management. Event prevention directly translates into better quality of life and reduced system burden. Combination with other guideline-directed agents, including ARNI, appears additive and safe [16-18]. Future priorities include longer follow-up to clarify mortality and renal effects, head-to-head comparisons between agents, and pragmatic trials addressing timing, sequencing, and adherence. Mechanistic research into hemodynamic, metabolic, and antifibrotic pathways may identify biomarkers of response and opportunities for personalization [9].

Strengths and Limitations

Strengths: comprehensive search, strict prespecified criteria, inclusion of all large RCTs across EF phenotypes, consistent endpoint definitions where possible, and robust quantitative synthesis.

Limitations: heterogeneity in endpoint definitions, limited power for mortality and secondary outcomes, early termination and non-adjudicated events in *SOLOIST-WHF*, short duration of *DEFINE-HF*, and too few trials to formally assess publication bias.

Across >16,000 patients, SGLT2 inhibitors reduced cardiovascular death or HF hospitalization, with robust reductions in recurrent events, modest mortality benefit, improved quality of life and biomarkers, and favorable safety. These findings establish SGLT2 inhibitors as cornerstone therapy in chronic heart failure.

Conclusion. SGLT2 inhibitors consistently reduce the risk of cardiovascular death or hospitalization for heart failure, with robust effects on recurrent hospitalizations and supportive benefits for mortality, quality of life, and biomarkers, without excess safety concerns. These findings establish SGLT2 inhibition as a cornerstone therapy across the spectrum of ejection fraction in patients with chronic heart failure. Longer follow-up and comparative studies are warranted to clarify their effects on mortality and to define optimal integration with other disease-modifying therapies.

Declarations

Prospects for Further Research

Future research may expand upon the findings summarized in this review by incorporating emerging evidence and clinical data from ongoing studies.

Conflict of Interest

The author declares that he has no competing interests.

Compliance with Ethical Standards

The author certifies that the preparation of this review article was based exclusively on published scientific literature. The work did not involve human participants, animals, or any unpublished clinical data. Therefore, ethical approval was not required. The study was conducted in accordance with good scientific practice and the ethical standards outlined by the Committee on Publication Ethics (COPE).

Use of Artificial Intelligence

No generative artificial intelligence or AI-assisted tools were used in the writing or preparation of this manuscript.

Primary Data and Materials

Data sharing not applicable to this article as no data-sets were generated or analyzed during the current study.

Funding Information: not applicable.

Supplementary Materials

Supplementary Table 1

Full Electronic Search Strategies

Database	Search Strategy	Limits	Date of Last Search
PubMed/MEDLINE	("Sodium-Glucose Transporter 2 Inhibitors"[Mesh] OR "sodium glucose cotransporter 2 inhibitor*" OR "SGLT2 inhibitor*" OR dapagliflozin OR empagliflozin OR sotagliflozin OR canagliflozin OR ertugliflozin) AND ("Heart Failure"[Mesh] OR "heart failure" OR "cardiac failure" OR "congestive heart failure" OR "HFrEF" OR "HFpEF" OR "HFmrEF") AND (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomly[tiab] OR placebo[tiab] OR trial[tiab]) NOT (animals[mh] NOT humans[mh])	No date or language restrictions	June 25, 2025
Embase (Ovid)	('sodium glucose cotransporter 2 inhibitor'/exp OR 'sodium glucose cotransporter 2 inhibitor*':ti,ab OR 'sglt2 inhibitor*':ti,ab OR dapagliflozin:ti,ab OR empagliflozin:ti,ab OR sotagliflozin:ti,ab OR canagliflozin:ti,ab OR ertugliflozin:ti,ab) AND ('heart failure'/exp OR 'heart failure':ti,ab OR 'cardiac failure':ti,ab OR 'congestive heart failure':ti,ab OR HFrEF:ti,ab OR HFpEF:ti,ab OR HFmrEF:ti,ab) AND ('randomized controlled trial'/exp OR 'controlled clinical trial'/exp OR random*:ti,ab OR placebo:ti,ab OR trial:ti,ab) NOT ([animals]/lim NOT [humans]/lim)	No date or language restrictions	June 25, 2025
Cochrane CENTRAL	("SGLT2 inhibitor" OR dapagliflozin OR empagliflozin OR sotagliflozin OR canagliflozin OR ertugliflozin) AND ("heart failure" OR HFrEF OR HFpEF OR HFmrEF)	No date or language restrictions	June 25, 2025
ClinicalTrials.gov	Condition or disease: "heart failure"; Intervention: "SGLT2 inhibitor" OR dapagliflozin OR empagliflozin OR sotagliflozin OR canagliflozin OR ertugliflozin; Study type: Interventional studies (clinical trials)	No date or language restrictions	June 25, 2025

Supplementary Table 2

Trial-level extracted data (values used / verified for the meta-analysis)

Trial (first author, year)	N (treatment / placebo)	Median follow-up	Primary composite (time-to-first) – HR (95% CI)	Primary events (treatment / placebo)	All-cause mortality – HR (95% CI) (events t / p)	Cardiovascular death – HR (95% CI) (events t / p)	First HF hospitalization – HR (95% CI) (events t / p)	Recurrent / total events (reported)	Key QoL / NT-proBNP results (timepoint)
DAPA-HF (McMurray 2019)	4744 (2373 / 2371)	18.2 months	HR 0.74 (0.65–0.85)	386 / 502	HR 0.83 (0.71–0.97); 276 / 329	HR 0.82 (0.69–0.98); 227 / 273	HR 0.70 (0.59–0.83); 231 / 318	Total (first + recurrent) events: rate-ratio 0.75 (0.65–0.88); 567 vs 742 total events	KCCQ (month 8): greater increase with dapagliflozin; proportion with ⩾5-point improvement 58.3% vs 50.9% (odds ratio 1.15, 95% CI 1.08–1.23). (See main trial tables.)

Continuation of Supplementary Table 2

Trial (first author, year)	N (treatment / placebo)	Median follow-up	Primary composite (time-to-first) – HR (95% CI)	Primary events (treatment / placebo)	All-cause mortality – HR (95% CI) (events t / p)	Cardiovascular death – HR (95% CI) (events t / p)	First HF hospitalization – HR (95% CI) (events t / p)	Recurrent / total events (reported)	Key QoL / NT-proBNP results (timepoint)
EMPEROR-Reduced (Packer 2020)	3730 (1863 / 1867)	16 months (median)	HR 0.75 (0.65–0.86)	361 / 462	HR 0.92 (0.77–1.10); (no significant reduction)	HR ≈0.92 (0.75–1.12) (events reported in paper)	HR ≈0.69 (0.59–0.81) for first hospitalization (events reported in trial tables)	Recurrent events analyses reported favorable RR (trial reported recurrent-event analyses)	QoL: modest/ variable benefits across analyses (reported in paper; not a simple pooled mean). NT-proBNP: modest mean changes reported.
DELIVER (Solomon 2022)	6263 (3131 / 3132)	2.3 years	HR 0.82 (0.73–0.92)	512 / 610	HR 0.94 (0.83–1.07) (death from any cause – not statistically significant)	HR 0.88 (0.74–1.05); 231 / 261	HR 0.79 (0.69–0.91) for worsening HF (events 368 / 455)	Total events / total worsening HF + CV deaths: rate ratio and counts reported (trial reports lower total events with dapagliflozin)	KCCQ: small but consistent improvements (mean placebo-corrected difference among survivors ~2.4 points at month 8); NT-proBNP: small mean changes.
SOLOIST-WHF (Bhatt 2021) – sotagliflozin (SGLT1/2)	1222 (608 / 614)	~9.0 months (median)	Primary was changed to total (first + recurrent) events – reported as rate ratio: 0.67 (0.52–0.85) for total CV deaths + HF hospitalizations/ urgent visits (events 245 vs 355; rate 51.0 vs 76.3 per 100 PY)	245 total events (t) / 355 (p) – (primary reported as total events)	Death (any cause) – HR/rate reported: 0.82 (0.59–1.14) (rate 13.5 vs 16.3 per 100 PY)	CV death rate HR 0.84 (0.58–1.22) (rates 10.6 vs 12.5)	First-event HR (reported in paper) ~0.71 (95% CI reported in figures, see paper)	Primary and hierarchical secondary endpoints were reported as total events/ rates (used investigator-reported events due to early termination)	KCCQ-12: least-squares mean change to month 4: 17.7 vs 13.6 (LS mean difference 4.1, 95% CI 1.3–7.0). Safety: higher severe hypoglycemia (1.5% vs 0.3%).
DEFINE-HF (Nassif 2019) – mechanistic trial	263 (131 / 132)	12 weeks (trial duration)	Not powered for clinical composite (no time-to-first primary composite like the others)	Very few clinical events (reported)	Deaths: very few (not powered)	–	Hospitalizations: not powered / few events	NT-proBNP / KCCQ (key mechanistic endpoints): at 12 weeks – proportion with ⩾20% NT-proBNP reduction 44.0% vs 29.4% (adjusted OR ≈1.9); KCCQ-OS mean change ≈ +3.7 and KCCQ-CS ≈ +4.6 at 12 weeks; responder rates (⩾5-point) at 6 weeks and 12 weeks reported (e.g., 6-week KCCQ-OS ⩾5 pts: 59/126 [46.8%] vs 46/128 [35.9%], adjusted OR 1.83).	Biomarker and QoL endpoints are reported in the trial tables with explicit counts/means.

Supplementary Table 3

Risk of Bias assessment (RoB 2) for included trials

Trial (first author, year)	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of outcomes	Selection of reported results	Overall judgment	Justification (short)
DAPA-HF (McMurray 2019)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Central randomization, double-blind; very low dropout; outcomes adjudicated by blinded committee; prespecified outcomes reported in full.
EMPEROR-Reduced (Packer 2020)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Adequate randomization and concealment; blinded; minimal missing data; independent adjudication; consistent reporting across sources.
DELIVER (Solomon 2022)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Large multicenter RCT, good balance at baseline, blinded; very complete follow-up; outcomes prespecified and fully reported.
SOLOIST-WHF (Bhatt 2021)	Some concerns	Some concerns	Low risk	High risk	Some concerns	Some concerns	Randomization adequate, but trial stopped early for loss of funding; investigator-reported (not centrally adjudicated) outcomes may bias measurement; reporting impacted by premature termination.
DEFINE-HF (Nassif 2019)	Low risk	Low risk	Some concerns	Low risk	Some concerns	Some concerns	Small mechanistic trial; randomization appropriate; higher attrition than large trials (esp. at 12 weeks); outcomes prespecified but some exploratory analyses reported.

Supplementary Table 4

Secondary Endpoints Reported by Included Trials

Trial (Year)	All-Cause Mortality	HF Hospitalizations (First)	HF Hospitalizations (Recurrent / Total)	KCCQ (Quality of Life)	Natriuretic Peptides	Safety
DAPA-HF (2019)	276/2373 (11.6%) vs 329/2371 (13.9%); HR 0.83 (95% CI 0.71–0.97)	231/2373 (9.7%) vs 318/2371 (13.4%); HR 0.70 (95% CI 0.59–0.83)	RR 0.75 (95% CI 0.65–0.88)	Greater improvement in KCCQ total symptom score at 8 months; higher % with ⩾5-point gain	Modest NT-proBNP reductions; higher % responders	↑ genital infections; no excess renal events
EMPEROR-Reduced (2020)	HR 0.92 (95% CI 0.77–1.10); NS	HR 0.69 (95% CI 0.59–0.81)	Similar benefits for recurrent events; RR ~0.73	Modest improvements in KCCQ; variable across analyses	Small NT-proBNP differences; responder advantage	↑ genital infections; no excess renal events
DELIVER (2022)	HR 0.94 (95% CI 0.83–1.07); NS	Consistent reduction in first worsening HF events	Significant reduction in recurrent HF events (HR ~0.82)	Small but consistent improvements in KCCQ	Small NT-proBNP differences; responder benefit	Safety profile consistent with class
SOLOIST-WHF (2021)	Not powered; numerical reduction (HR for CV/all-cause death <1, NS)	Not primary endpoint	Total HF events: 51.0 vs 76.3 per 100 patient-years; HR 0.67 (95% CI 0.52–0.85)	Not systematically assessed	Not systematically assessed	↑ diarrhea; ↑ genital infections; early termination limits inference
DEFINE-HF (2019)	Very few deaths (12-week trial)	Not powered for HF hospitalization	Not reported (short trial)	+3.7 KCCQ-OS; +4.6 KCCQ-CS; higher % ⩾5-point improvements	44% vs 29% ⩾20% NT-proBNP reduction; OR ~1.9	Well tolerated; expected ↑ genital infections

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Ефективність інгібіторів натрій-глюкозного котранспортера 2 при хронічній серцевій недостатності: систематичний огляд і метааналіз рандомізованих контрольованих досліджень

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Резюме

Вступ. Інгібітори натрій-глюкозного котранспортера 2 (SGLT2) нині є базисною терапією серцевої недостатності (СН), однак залишаються невизначеності щодо їх впливу на смертність, повторні події, показники, що повідомляються пацієнтами, та біомаркери.

Мета. Оцінити ефективність і безпеку інгібіторів SGLT2 у пацієнтів із хронічною серцевою недостатністю в усьому діапазоні фракції викиду, на основі доказів рандомізованих контрольованих досліджень.

Матеріали та методи. Проведено систематичний огляд і метааналіз відповідно до рекомендацій PRISMA 2020 (PROSPERO: CRD420251138644). Бази даних PubMed, Embase, Cochrane CENTRAL та ClinicalTrials.gov були проаналізовані станом на 25 червня 2025 року. До аналізу включалися рандомізовані контрольовані дослідження (РКД), у яких порівнювали інгібітори SGLT2 із плацебо в дорослих пацієнтів із хронічною СН. Первинною кінцевою точкою був час до першої серцево-судинної (СС) смерті або госпіталізації з приводу СН. Вторинні кінцеві точки включали загальну смертність, повторні госпіталізації, якість життя, рівні натрійуретичних пептидів і безпеку. Відношення ризиків (HR) об'єднували за допомогою моделі випадкових ефектів Гартунга–Кнаппа, якщо визначення показників збігалися; інші результати описувалися наративно. Ризик упередженості оцінювали за допомогою інструменту RoB 2, а достовірність доказів – за системою GRADE.

Результати. До аналізу включено п'ять РКД (n=16,222): DAPA-HF, EMPEROR-Reduced, DELIVER, SOLOIST-WHF (яке надало дані повторних подій) та DEFINE-HF (механістичне, зосереджене на біомаркерах). Інгібітори SGLT2 зменшували ризик СС смерті або госпіталізації з приводу СН (сукупний HR 0,79; 95 % ДІ 0,74-0,83; $I^2 = 0$ %). Зменшення частоти госпіталізацій було узгодженим у всіх дослідженнях (HR ≈ 0,69-0,75), тоді як загальна смертність продемонструвала помірну, але статистично значущу користь (HR 0,90; 95 % ДІ 0,83-0,98). У дослідженнях послідовно спостерігалося покращення показників опитувальника Канзаського міста щодо кардіоміопатії (KCCQ) та відповідь натрійуретичних пептидів. Профіль безпеки відповідав уже відомому для інгібіторів SGLT2, без сигналів серйозних побічних явищ.

Висновки. Інгібітори SGLT2 забезпечують значне зниження частоти госпіталізацій через СН і сприятливо впливають на смертність, якість життя та біомаркери у пацієнтів з різними фенотипами фракції викиду, підтверджуючи їхнє ключове значення в лікуванні хронічної серцевої недостатності.

Ключові слова: *серцево-судинна смертність, повторна госпіталізація, опитувальник Канзаського міста (KCCQ), зниження NT-proBNP, аналіз повторних подій, дапагліфлозин, емпагліфлозин.*

Стаття надійшла в редакцію / Received: 29.09.2025
Після доопрацювання / Revised: 06.10.2025
Прийнято до друку / Accepted: 16.10.2025