

Clinical Outcomes of SGLT2 Inhibitors in Heart Failure Patients Regardless of Diabetes Status: A Systematic Review

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HOW TO CITE:

Maha Abdul Rahim Muhammad Othman, Efdal Fadul Idrees Abdallah, Suliman Mohamed Ali Elkarouri, Khalid Saeed M Alqahtani, Rawiyah Mamoun Daffalla Abdalla, Yasser Yahya Alqadi, Safaa Ibrahim Alrawashdeh, Ali Mohammed A. Asiri, Yasmine Saad Ahmed Elkaliny, Dina Ahmed Abdelatty Abdelrahman, Ghada Ahmed Abdelatty Abdelrahman (2026). Clinical Outcomes of SGLT2 Inhibitors in Heart Failure Patients Regardless of Diabetes Status: A Systematic Review International Journal of Special Education, 41(22s),525-548

ABSTRACT

Background: Sodium-glucose cotransporter-2 (SGLT2) inhibitors were developed as glucose-lowering agents but have demonstrated profound cardiovascular benefits in patients with heart failure regardless of diabetes status. The landmark DAPA-HF, EMPEROR-Reduced, EMPEROR-Preserved, and DELIVER trials have collectively established SGLT2 inhibitors as foundational therapy across the entire spectrum of heart failure ejection fractions. This systematic review aimed to comprehensively evaluate the clinical outcomes of SGLT2 inhibitors in heart failure patients irrespective of diabetes status.

Methods: A systematic literature search was conducted in PubMed/MEDLINE, EMBASE, Cochrane Library, and Web of Science. Randomized controlled trials, systematic reviews, and meta-analyses reporting clinical outcomes of SGLT2 inhibitors in heart failure patients, with pre-specified subgroup data by diabetes status, were eligible. Quality assessment used the Cochrane Risk of Bias tool (RoB 2.0) for RCTs and AMSTAR-2 for systematic reviews. The GRADE approach was applied to evidence certainty.

Results: Ten studies met eligibility criteria: 4 landmark RCTs (DAPA-HF, EMPEROR-Reduced, EMPEROR-Preserved, DELIVER), 1 pre-specified meta-analysis of 2 HFrEF trials (Zannad et al., Lancet 2020), and 1 comprehensive meta-analysis of 5 trials (Vaduganathan et al., Lancet 2022), plus 4 additional subgroup analyses. SGLT2 inhibitors significantly reduced the composite primary outcome of cardiovascular death or worsening heart failure across all ejection fraction categories regardless of diabetes status. In HFrEF (DAPA-HF; HR 0.74; 95% CI 0.65–0.85): benefit was consistent in diabetic (HR 0.75) and non-diabetic patients (HR 0.73). In HFpEF (EMPEROR-Preserved): HR 0.79 (95% CI 0.69–0.90). The comprehensive 5-trial meta-analysis confirmed a pooled 23% relative risk reduction in CV death or HF hospitalization (HR 0.77; 95% CI 0.72–0.82; $p < 0.0001$) with no significant diabetes-status interaction.

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Conclusion: SGLT2 inhibitors provide consistent, diabetes-status-independent cardiovascular and heart failure benefits across the full ejection fraction spectrum. These agents should be considered standard of care for all eligible patients with heart failure, irrespective of the presence or absence of type 2 diabetes mellitus, consistent with current international guidelines.

Keywords: SGLT2 inhibitors; heart failure; dapagliflozin; empagliflozin; HFrEF; HFpEF; diabetes; cardiovascular outcomes; DAPA-HF; EMPEROR-Reduced; EMPEROR-Preserved; DELIVER; systematic review.

Background

Heart failure is a leading cause of morbidity and mortality worldwide, affecting more than 64 million people globally and representing one of the most common causes of cardiovascular hospitalization and death. Despite significant advances in pharmacological therapy over the past three decades—including the introduction of angiotensin-converting enzyme inhibitors, beta-blockers, mineralocorticoid receptor antagonists, and angiotensin receptor-neprilysin inhibitors—heart failure with reduced ejection fraction (HFrEF) continues to carry a five-year mortality rate exceeding 50%, and heart failure with preserved ejection fraction (HFpEF) has historically lacked evidence-based disease-modifying therapies [1].

Sodium-glucose cotransporter-2 (SGLT2) inhibitors were originally developed as oral glucose-lowering agents for the treatment of type

2 diabetes mellitus, operating through their mechanism of promoting urinary glucose excretion by blocking glucose reabsorption in the proximal renal tubule. The unexpected and striking cardiovascular benefits of this drug class emerged from cardiovascular safety outcome trials mandated by regulatory agencies following concern about cardiovascular risks of antidiabetic medications. The EMPA-REG OUTCOME trial (empagliflozin) and the DECLARE-TIMI 58 trial (dapagliflozin) demonstrated dramatic reductions in hospitalization for heart failure in patients with type 2 diabetes at high cardiovascular risk, even though these trials were not designed to enroll patients with established heart failure [2].

These observations from diabetes cardiovascular outcome trials catalyzed a paradigm shift in understanding the cardiovascular pharmacology of SGLT2 inhibitors. Rather than acting primarily

through glycemic reduction, the cardiovascular and renal benefits of these agents appeared to be mediated through multiple non-glycemic pathways including osmotic diuresis and natriuresis reducing cardiac preload and afterload, attenuation of maladaptive cardiac remodeling through mitochondrial energetics optimization and suppression of the sodium-hydrogen exchanger isoform 1 (NHE1) in cardiomyocytes, reduction of interstitial myocardial fibrosis via inhibition of the cardiac raas, attenuation of systemic and cardiac inflammation, and improvement of renal function [3].

The pivotal DAPA-HF trial by McMurray, Solomon, Inzucchi, Køber, Kosiborod, Martinez, Ponikowski, Sabatine, Anand et al. (2019) was the first dedicated heart failure trial of an SGLT2 inhibitor, enrolling 4,744 patients with HFrEF and demonstrating a 26% relative reduction in the primary composite endpoint of worsening heart failure or cardiovascular death with dapagliflozin compared with placebo, with strikingly consistent benefits in both diabetic and non-diabetic subpopulations [4]. This landmark trial fundamentally altered the therapeutic landscape for HFrEF and provided compelling evidence that the cardiovascular benefits of SGLT2 inhibitors were independent of their glucose-lowering effects.

The EMPEROR-Reduced trial by Packer, Anker, Butler, Filippatos, Pocock, Carson, Januzzi, Verma, Tsutsui et al. (2020) independently confirmed these findings in 3,730 patients with HFrEF randomized to empagliflozin or placebo, demonstrating a 25% relative reduction in the primary composite endpoint and a remarkably consistent treatment effect in patients with and without diabetes [5]. The convergent and mutually reinforcing evidence from DAPA-HF and EMPEROR-Reduced was subsequently synthesized in a pre-specified meta-analysis by Zannad, Ferreira, Pocock, Anker, Butler, Filippatos, Brueckmann, Ofstad, Pfarr, Jamal, and Packer (2020), establishing the pooled treatment effect of SGLT2 inhibition across both HFrEF trials and definitively confirming the

diabetes-status independence of the therapeutic benefit [6].

While the HFrEF evidence base was rapidly established, the question of whether SGLT2 inhibitors could benefit patients with HFpEF—a condition accounting for approximately half of all heart failure cases and for which pharmacological treatment options remained severely limited—was addressed by two dedicated trials. The EMPEROR-Preserved trial by Anker, Butler, Filippatos, Ferreira, Bocchi, Böhm, Brunner-La Rocca, Choi, Chopra, Chuquiere-Valenzuela, Giannetti et al. (2021) enrolled 5,988 patients with HFpEF (LVEF>40%) and demonstrated a significant 21% reduction in the primary composite endpoint with empagliflozin [7]. This represented the first pharmacological therapy to demonstrate a significant reduction in the primary endpoint of cardiovascular death or HF hospitalization in HFpEF.

The DELIVER trial by Solomon, McMurray, Claggett, de Boer, DeMets, Hernandez, Inzucchi, Kosiborod, Lam, Martinez, Shah, Desai, Jhund et al. (2022) independently confirmed SGLT2 inhibitor efficacy in HFmrEF and HFpEF (LVEF>40%), enrolling 6,263 patients and demonstrating a 18% relative reduction in the primary composite endpoint with dapagliflozin, again with consistent effects irrespective of diabetes status [8]. The comprehensive five-trial meta-analysis by Vaduganathan, Docherty, Claggett, Jhund, de Boer, Hernandez, Inzucchi, Kosiborod, Lam, Martinez, Shah, Desai, McMurray, and Solomon (2022) synthesized data from all five major SGLT2 inhibitor heart failure trials, providing the definitive pooled evidence base supporting this drug class across the ejection fraction spectrum [9].

The diabetes-status independence of SGLT2 inhibitor benefits in heart failure carries profound clinical implications. It reframes these agents not as antidiabetic drugs with cardiovascular benefits but as cardiovascular drugs with glycemic effects, fundamentally reshaping their positioning in heart failure treatment algorithms. Major international guidelines—including the 2021

ESC Heart Failure Guidelines, the 2022 AHA/ACC/HFSA Heart Failure Guidelines, and their subsequent focused updates—have incorporated SGLT2 inhibitors as Class I recommendations for patients with HFrEF regardless of diabetes status, reflecting this evidence-based paradigm shift [10].

The mechanisms underlying the diabetes-status-independent cardiovascular benefits of SGLT2 inhibitors remain an area of active investigation. The consistent treatment effect across glycemic strata suggests that glucose-lowering per se is not the primary mediator of benefit. Instead, the hemodynamic effects—including reduction in preload through natriuresis and osmotic diuresis without activation of the renin-angiotensin-aldosterone system or the sympathetic nervous system—and the direct cardioprotective effects mediated through suppression of the cardiac NHE1 exchanger, improvement of ketone body utilization as alternative myocardial fuel substrates, reduction in epicardial adipose tissue, and attenuation of inflammatory cytokine signaling are considered principal mechanisms [3].

Despite the compelling and consistent evidence from individual trials and meta-analyses, a comprehensive systematic review integrating the full evidence base from all landmark RCTs and high-quality meta-analyses—with specific attention to diabetes-status subgroup data across the full ejection fraction spectrum—has not been conducted in a manner that comprehensively addresses clinical outcomes in diabetic versus non-diabetic heart failure patients. The present systematic review therefore aimed to synthesize all available high-quality evidence on SGLT2 inhibitor clinical outcomes in heart failure, with a primary focus on delineating the consistency and magnitude of treatment effects regardless of diabetes status across all ejection fraction phenotypes [10].

2. Methodology

2.1 Study Design

This study was conducted as a systematic review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses

(PRISMA) 2020 guidelines. The review protocol was prospectively registered with PROSPERO. The primary objective was to synthesize all available high-quality evidence on the clinical outcomes of SGLT2 inhibitors in heart failure patients, with pre-specified focus on comparison of treatment effects between diabetic and non-diabetic patient subgroups across the full spectrum of left ventricular ejection fraction.

2.2 Eligibility Criteria

Studies were eligible for inclusion if they fulfilled the following criteria: (1) Study design: phase 3 randomized controlled trials with ≥ 500 patients, pre-specified meta-analyses of multiple RCTs, or systematic reviews with meta-analysis reporting diabetes-status subgroup data; (2) Population: adults (age ≥ 18 years) with a diagnosis of heart failure, regardless of LVEF (HFrEF, HFmrEF, or HFpEF) or diabetes status; (3) Intervention: any approved SGLT2 inhibitor (dapagliflozin, empagliflozin, canagliflozin, or sotagliflozin) at the approved dose compared with placebo; (4) Outcomes: primary composite endpoint of cardiovascular death or worsening heart failure (hospitalization or urgent visit), all-cause mortality, cardiovascular mortality, HF hospitalization, renal outcomes, or quality of life measures; (5) Pre-specified subgroup analysis by diabetes status (type 2 diabetes vs. no diabetes); (6) Language: English; (7) Publication: peer-reviewed journal publication without date restriction. Studies were excluded if they enrolled exclusively diabetic patients without reporting non-diabetic subgroup data, combined SGLT2 inhibitors with other investigational agents, or reported only surrogate endpoints without clinical outcome data.

2.3 Literature Search Strategy

Comprehensive searches were performed in PubMed/MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science. Search terms included: 'SGLT2 inhibitor,' 'sodium-glucose cotransporter-2,' 'dapagliflozin,' 'empagliflozin,' 'canagliflozin,' 'sotagliflozin,' 'heart failure,' 'reduced ejection fraction,' 'preserved ejection fraction,' 'HFrEF,' 'HFpEF,' 'HFmrEF,'

'cardiovascular outcomes,' 'diabetes,' 'non-diabetic,' combined using Boolean operators. The ClinicalTrials.gov registry was searched for registered trials. Reference lists of all included studies were hand-searched.

2.4 Study Selection

Records were imported into Rayyan software and duplicates removed. Two independent reviewers performed title/abstract screening followed by full-text review. Disagreements were resolved by consensus with adjudication by a senior reviewer as required. The selection process is documented in the PRISMA 2020 flow diagram.

2.5 Data Extraction

Standardized data extraction was performed independently by two reviewers capturing: trial name, first author, year, drug and dose, sample size (total and per arm), baseline LVEF category, proportion with diabetes at baseline, follow-up duration, primary endpoint definition and result (HR/RR, 95% CI, p-value), diabetes and non-diabetes subgroup results for the primary endpoint, key secondary endpoints, safety outcomes (volume depletion, genital mycotic infection, DKA, renal outcomes), and risk of bias rating.

2.6 Quality Assessment

All four primary RCTs were assessed using the Cochrane Risk of Bias 2.0 (RoB 2.0) tool across five domains. Systematic reviews and meta-analyses were evaluated using AMSTAR-2. The overall certainty of evidence for each primary outcome was rated using the GRADE approach (high, moderate, low, or very low certainty). Quality assessments were performed in duplicate with disagreements resolved by consensus.

2.7 Data Synthesis

A narrative synthesis organized by ejection fraction category and diabetes status was performed as the primary analytic approach. For outcomes reported across multiple studies, pooled effect estimates from the highest-quality included meta-analyses (Zannad et al., 2020;

Vaduganathan et al., 2022) were presented directly rather than re-pooled, to avoid double-counting. Diabetes-status interaction p-values from each trial and meta-analysis were extracted and tabulated. Subgroup analyses examining outcomes in patients with and without type 2 diabetes were the primary focus of evidence synthesis.

2.8 Ethical Considerations

As a systematic review of previously published peer-reviewed literature, this study did not require institutional review board approval or patient informed consent. All included primary studies had obtained appropriate ethical approval and patient consent at their originating institutions.

3. Results

The systematic database search retrieved 4,214 records across PubMed/MEDLINE (n=1,743), EMBASE (n=1,102), CENTRAL (n=892), and Web of Science (n=477). After removal of 1,384 duplicates, 2,830 records underwent title and abstract screening, of which 2,747 were excluded. Eighty-three full-text articles were assessed for eligibility, and 73 were excluded: no pre-specified diabetes subgroup data (n=29), not a phase 3 RCT, pre-specified meta-analysis, or high-quality SR (n=24), exclusively diabetic population without non-diabetic comparator (n=12), and insufficient sample size or surrogate endpoints only (n=8). Ten studies fulfilled all eligibility criteria.

3.1 Characteristics of Included Studies

The 10 included studies comprised 4 landmark phase 3 randomized controlled trials, 2 pre-specified meta-analyses, and 4 pre-specified diabetes-status subgroup analyses from the primary trials. Studies were published between 2019 and 2022. The 4 primary RCTs collectively enrolled 20,725 patients across the full ejection fraction spectrum. Table 1 presents the verified characteristics of all 10 included studies with their exact confirmed authors.

Table 1. Characteristics of included studies with verified exact authors

Author(s) (Year) / Trial	Journal	Design	N	EF Category	Drug Dose	& Key Focus
McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, Ponikowski P, Sabatine MS, Anand IS, Bělohávek J, Böhm M, Chiang CE, Chopra VK, de Boer RA, Desai AS, ... Langkilde AM; DAPA-HF Trial Committees and Investigators (2019) / DAPA-HF	N Engl J Med	Phase 3 RCT	4,744	HFrEF (LVEF ≤40%)	Dapagliflozin 10 mg OD vs placebo	Primary endpoint: CV death or worsening HF; diabetes-status pre-specified subgroup; PMID: 31535829
Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, Januzzi J, Verma S, Tsutsui H, Brueckmann M, Jamal W, Kimura K, Schnee J, Zeller C, Cotton D, Bocchi E, Böhm M, Choi DJ, Chopra V, Chuquiure E, Giannetti N, Janssens S, Zhang J,	N Engl J Med	Phase 3 RCT	3,730	HFrEF (LVEF <40%)	Empagliflozin 10 mg OD vs placebo	Primary endpoint: CV death or HF hospitalization; diabetes-status subgroup; PMID: 32865377

Author(s) (Year) / Trial	Journal	Design	N	EF Category	Drug Dose	& Key Focus
Gonzalez Juanatey JR, Kaul S, Brunner-La Rocca HP, Merkely B, Nicholls SJ, Perrone S, Pina I, Ponikowski P, Sattar N, Senni M, Seronde MF, Spinar J, Squire I, Taddei S, Wanner C, Zannad F; EMPEROR -Reduced Trial Investigators (2020) / EMPEROR -Reduced						
Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, Brunner-La Rocca HP, Choi DJ, Chopra V, Chuquiere- Valenzuela E, Giannetti N, Gomez- Mesa JE, Janssens S, Januzzi JL, Gonzalez- Juanatey JR, Merkely B, Nicholls SJ, Perrone SV, Piña IL, Ponikowski P, Senni M, Sim D,	N Engl J Med	Phase 3 RCT	5,988	HFpEF (LVEF >40%)	Empaglifloz in 10 mg OD vs placebo	First positive phase 3 trial in HFpEF; diabetes- status subgroup; PMID: 34449189

Author(s) (Year) / Trial	Journal	Design	N	EF Category	Drug Dose	& Key Focus
Spinar J, Squire I, Taddei S, Tsutsui H, Verma S, Vinereanu D, Zhang J, Carson P, Lam CSP, Marx N, Zeller C, Sattar N, Jamal W, Schnaidt S, Schnee JM, Brueckmann M, Pocock SJ, Zannad F, Packer M; EMPEROR -Preserved Trial Investigators (2021) / EMPEROR -Preserved						
Solomon SD, McMurray JJV, Claggett B, de Boer RA, DeMets D, Hernandez AF, Inzucchi SE, Kosiborod MN, Lam CSP, Martinez F, Shah SJ, Desai AS, Jhund PS, Belohlavek J, Chiang CE, Borleffs CJW, Comin- Colet J, Dobreanu D, Drozd J,	N Engl J Med	Phase 3 RCT	6,263	HFmrEF/HFp EF (LVEF >40%)	Dapagliflozi n 10 mg OD vs placebo	Second positive phase 3 trial in HFpEF; consistent diabetes- status independenc e confirmed; PMID: 36027570

Author(s) (Year) / Trial	Journal	Design	N	EF Category	Drug Dose &	Key Focus
Fang JC, Alcocer-Gamba MA, Al Habeeb W, Han Y, Cabrera Honorio JW, Janssens SP, Katova T, Kitakaze M, Merkely B, O'Meara E, Saraiva JFK, Tereshchenko SN, Thierer J, Vaduganathan M, Vardeny O, Verma S, Pham VN, Wilderäng U, Zaozerska N, Bachus E, Lindholm D, Petersson M, Langkilde AM; DELIVER Trial Committees and Investigators (2022) / DELIVER						
Zannad F, Ferreira JP, Pocock SJ, Anker SD, Butler J, Filippatos G, Brueckmann M, Ofstad AP, Pfarr E, Jamal W, Packer M (2020)	Lancet	Pre-specified MA (2 RCTs)	8,474	HFrEF	Dapagliflozin & empagliflozin	Pooled DAPA-HF + EMPEROR-Reduced; all-cause death; diabetes-status; PMID: 32877652

Author(s) (Year) / Trial	Journal	Design	N	EF Category	Drug Dose &	Key Focus
Vaduganathan M, Docherty KF, Claggett BL, Jhund PS, de Boer RA, Hernandez AF, Inzucchi SE, Kosiborod MN, Lam CSP, Martinez F, Shah SJ, Desai AS, McMurray JJV, Solomon SD (2022)	Lancet	Comprehensive MA (5 RCTs)	21,947	Full spectrum EF	Dapagliflozin & empagliflozin	Pooled all 5 HF SGLT2 trials; CV death or HF hospitalization; all ejection fractions; diabetes-status; PMID: 36041474
Docherty KF, Jhund PS, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, de Boer RA, Desai AS, Sabatine MS, Bengtsson O, Sjöstrand M, Langkilde AM, Solomon SD, McMurray JJV; DAPA-HF Trial Committees and Investigators (2020)	Eur Heart J	Pre-specified subgroup (DAPA-HF)	4,744	HF _r EF	Dapagliflozin 10 mg OD	Diabetes-status pre-specified subgroup analysis from DAPA-HF; PMID: 32006625
Anker SD, Butler J, Filippatos G, Khan MS, Marx N,	Circulation	Pre-specified subgroup (EMPEROR-Reduced)	3,730	HF _r EF	Empagliflozin 10 mg OD	Diabetes-status pre-specified subgroup from

Author(s) (Year) / Trial	Journal	Design	N	EF Category	Drug Dose	& Key Focus
Lam CSP, Schnaidt S, Ofstad AP, Brueckmann M, Jamal W, Bocchi EA, Ponikowski P, Perrone SV, Januzzi JL, Verma S, Böhm M, Ferreira JP, Pocock SJ, Zannad F, Packer M; EMPEROR-Reduced Trial Committees and Investigators (2021)						EMPEROR-Reduced; PMID: 33175585
Filippatos G, Butler J, Farmakis D, Zannad F, Ofstad AP, Ferreira JP, Green JB, Rosenstock J, Schnaidt S, Brueckmann M, Pocock SJ, Packer M, Anker SD; EMPEROR-Preserved Trial Committees and Investigators (2022)	Circulation	Pre-specified subgroup (EMPEROR-Preserved)	5,988	HFpEF	Empagliflozin 10 mg OD	Diabetes-status subgroup from EMPEROR-Preserved: with and without diabetes; PMID: 35762322
Butt JH, Jhund PS, Belohlávek J, Chiang CE, Chopra VK, de Boer RA, Desai AS,	JAMA Cardiol	Pre-specified subgroup (DELIVER)	6,263	HFmrEF/HFpEF	Dapagliflozin 10 mg OD	Diabetes-status pre-specified subgroup from DELIVER; PMID: 36308735

Author(s) (Year) / Trial	Journal	Design	N	EF Category	Drug Dose	& Key Focus
Hernandez AF, Inzucchi SE, Kosiborod MN, Lam CSP, Martinez F, O'Meara E, Shah SJ, Vaduganath an M, Langkilde AM, Lindholm D, Petersson M, Claggett BL, McMurray JJV, Solomon SD; DELIVER Trial Committees and Investigators (2022)						

HFrEF = Heart Failure with Reduced Ejection Fraction (LVEF $\leq 40\%$); HFpEF = Heart Failure with Preserved Ejection Fraction (LVEF $\geq 50\%$); HFmrEF = Heart Failure with Mildly Reduced Ejection Fraction (LVEF 41–49%); MA = Meta-Analysis; EF = Ejection Fraction; OD = Once Daily; CV = Cardiovascular; PMID = PubMed Identifier.

3.2 Quality Assessment

All four primary RCTs were double-blind, placebo-controlled, multicenter trials with event-driven designs and PROBE or central adjudication committees for outcomes, and were

rated as low risk of bias on RoB 2.0. The two meta-analyses by Zannad et al. (2020) and Vaduganathan et al. (2022) were both rated as high confidence on AMSTAR-2, with pre-specified analysis plans, complete datasets, and transparent reporting. The four diabetes-status subgroup analyses were all pre-specified in their respective trial protocols, rated as low risk of bias. The overall certainty of evidence for the primary outcome of CV death or HF hospitalization was rated as high by GRADE for both HFrEF and HFpEF, reflecting large sample sizes, low risk of bias, consistent direction of effect, and precise confidence intervals.

Table 2. Quality assessment of included studies

Study (First Author, Year)	Study Design	Quality Tool	Assessment Result	Overall Quality
McMurray et al. (2019) / DAPA-HF	Phase 3 RCT (n=4,744)	RoB 2.0	Low risk – double-blind; central endpoint adjudication; pre-specified SAP; NEJM	High
Packer et al. (2020) / EMPEROR-Reduced	Phase 3 RCT (n=3,730)	RoB 2.0	Low risk – double-blind; independent DSMB; pre-specified subgroups; NEJM	High
Anker et al. (2021) / EMPEROR-Preserved	Phase 3 RCT (n=5,988)	RoB 2.0	Low risk – double-blind; adjudication committee; event-driven design; NEJM	High
Solomon et al. (2022) / DELIVER	Phase 3 RCT (n=6,263)	RoB 2.0	Low risk – double-blind; pre-registered SAP; largest HFpEF trial; NEJM	High
Zannad et al. (2020)	Pre-specified MA (2 RCTs)	AMSTAR-2	High confidence – pre-specified MA; IPD-level pooling; Lancet; complete datasets	High
Vaduganathan et al. (2022)	Comprehensive MA (5 RCTs)	AMSTAR-2	High confidence – 21,947 patients; 5 trials; pre-specified; GRADE-rated; Lancet	High
Docherty et al. (2020) / DAPA-HF subgroup	Pre-specified subgroup RCT	RoB 2.0	Low risk – pre-specified in SAP; Eur Heart J; complete reporting	High
Anker et al. (2021) / EMPEROR-Reduced subgroup	Pre-specified subgroup RCT	RoB 2.0	Low risk – pre-specified; Circulation; independent adjudication	High
Filippatos et al. (2022) / EMPEROR-Preserved subgroup	Pre-specified subgroup RCT	RoB 2.0	Low risk – pre-specified; Circulation; no qualitative differences in effect	High

Study (First Author, Year)	Study Design	Quality Tool	Assessment Result	Overall Quality
Butt et al. (2022) / DELIVER subgroup	Pre-specified subgroup RCT	RoB 2.0	Low risk – pre-specified in SAP; JAMA Cardiol; event-driven consistent outcome	High

3.3 Primary Endpoint Outcomes: SGLT2 Inhibitors in HFrEF

Primary endpoint outcomes from studies evaluating SGLT2 inhibitors in HFrEF are summarized in Table 3.

Table 3. Primary composite endpoint outcomes in HFrEF: overall and by diabetes status

Study Trial	N	EF Category	Primary Endpoint	Overall HR (95% CI)	Diabetes HR (95% CI)	No-DM HR (95% CI)	Interaction p-value
McMurray et al. (2019) / DAPA-HF	4,744	HFrEF ($\leq 40\%$)	CV death or worsening HF	0.74 (0.65–0.85)	0.75 (0.63–0.90)	0.73 (0.60–0.88)	p=0.80 (no significant interaction)
Packer et al. (2020) / EMPEROR-Reduced	3,730	HFrEF ($< 40\%$)	CV death or HF hospitalization	0.75 (0.65–0.86)	0.72 (0.60–0.87)	0.78 (0.64–0.97)	p=0.53 (no significant interaction)
Docherty et al. (2020) / DAPA-HF subgroup	4,744	HFrEF	CV death or worsening HF (subgroup)	0.74 (0.65–0.85)	0.75 (0.63–0.90); absolute risk reduction 3.4%	0.73 (0.60–0.88); absolute risk reduction 3.2%	p=0.80; consistent benefit confirmed
Anker et al. (2021) / EMPEROR-Reduced subgroup	3,730	HFrEF	CV death or HF hospitalization (subgroup)	0.75 (0.65–0.86)	0.72 (0.60–0.87)	0.78 (0.64–0.97)	p=0.53; benefit consistent DM and non-DM
Zannad et al. (2020) / Pooled HFrEF MA	8,474	HFrEF (pooled)	CV death or HF hospitalization	0.74 (0.68–0.82)	0.73 (0.65–0.82)	0.75 (0.65–0.86)	p=0.72; no diabetes-status heterogeneity

Study Trial	/ N	EF Category	Primary Endpoint	Overall HR (95% CI)	Diabetes HR (95% CI)	No-DM HR (95% CI)	Interaction p-value
Zannad et al. (2020) / All-cause death	8,474	HF _r EF	All-cause mortality	0.92 (0.82–1.03)	0.90 (0.77–1.04)	0.95 (0.80–1.12)	p=0.60; consistent trend; not significant overall
Pooled HF_rEF Summary	8,474	HF_rEF	CV death or HF hospitalization	HR 0.74–0.75	HR ~0.72–0.75	HR ~0.73–0.78	All p-interaction >0.50: consistent DM-independent benefit

Table 3 demonstrates that SGLT2 inhibitors produce consistent and highly statistically significant reductions in the primary composite endpoint in HF_rEF patients, with no significant interaction by diabetes status in either primary trial or their pooled meta-analysis. In DAPA-HF (McMurray, Solomon, Inzucchi, Køber, Kosiborod, Martinez et al., 2019), dapagliflozin reduced the primary endpoint by 26% overall (HR 0.74; 95% CI 0.65–0.85), with nearly identical hazard ratios in the diabetic subgroup (HR 0.75; 95% CI 0.63–0.90) and the non-diabetic subgroup (HR 0.73; 95% CI 0.60–0.88; interaction p=0.80). In EMPEROR-Reduced (Packer, Anker, Butler, Filippatos et al., 2020), empagliflozin produced a 25% relative reduction

in the primary endpoint (HR 0.75; 95% CI 0.65–0.86), again with consistent effects in diabetic (HR 0.72) and non-diabetic (HR 0.78) patients (interaction p=0.53). The pre-specified meta-analysis by Zannad, Ferreira, Pocock, Anker, Butler et al. (2020) confirmed a pooled HR of 0.74 (95% CI 0.68–0.82) for CV death or HF hospitalization, with no significant diabetes-status heterogeneity (p=0.72).

3.4 Primary Endpoint Outcomes: SGLT2 Inhibitors in HF_pEF/HF_{mr}EF

Primary endpoint outcomes from studies evaluating SGLT2 inhibitors in HF_pEF and HF_{mr}EF are presented in Table 4.

Table 4. Primary composite endpoint outcomes in HF_pEF/HF_{mr}EF: overall and by diabetes status

Study Trial	/ N	EF Category	Primary Endpoint	Overall HR (95% CI)	Diabetes HR (95% CI)	No-DM HR (95% CI)	Interaction p-value
Anker et al. (2021) /	5,988	HF _p EF (>40%)	CV death or HF hospitalization	0.79 (0.69–0.90)	0.79 (0.68–0.93)	0.78 (0.62–0.99)	p=0.87 (no significant interaction)

Study Trial	N	EF Category	Primary Endpoint	Overall HR (95% CI)	Diabetes HR (95% CI)	No-DM HR (95% CI)	Interaction p-value
EMPEROR-Preserved							
Solomon et al. (2022) / DELIVER	6,263	HFmrEF/HFpEF (>40%)	CV death or worsening HF	0.82 (0.73–0.92)	0.80 (0.69–0.93)	0.84 (0.70–1.01)	p=0.57 (no significant interaction)
Filippatos et al. (2022) / EMPEROR-Preserved subgroup	5,988	HFpEF	CV death or HF hospitalization (subgroup)	0.79 (0.69–0.90)	0.79 (0.68–0.93)	0.78 (0.62–0.99)	p=0.87; empagliflozin effective with and without DM
Butt et al. (2022) / DELIVER subgroup	6,263	HFmrEF/HFpEF	CV death or worsening HF (subgroup)	0.82 (0.73–0.92)	0.80 (0.69–0.93)	0.84 (0.70–1.01)	p=0.57; consistent benefit irrespective of DM status
Pooled HFpEF Summary	12,251	HFpEF/HFmrEF	CV death or HF hospitalization	HR 0.79–0.82	HR 0.79–0.80	HR 0.78–0.84	All p-interaction >0.50: consistent DM-independent benefit

Table 4 demonstrates that SGLT2 inhibitors produce statistically significant and clinically meaningful reductions in the primary composite endpoint in HFpEF and HFmrEF, with consistent treatment effects across diabetes status. EMPEROR-Preserved (Anker, Butler, Filippatos, Ferreira, Bocchi, Böhm, Brunner-La Rocca et al., 2021) demonstrated a 21% reduction in CV death or HF hospitalization (HR 0.79; 95% CI 0.69–0.90), with nearly identical benefit in diabetic (HR 0.79) and non-diabetic patients (HR 0.78; interaction p=0.87). The DELIVER trial (Solomon, McMurray, Claggett, de Boer, DeMets, Hernandez, Inzucchi, Kosiborod, Lam et al., 2022) demonstrated an 18% relative

reduction (HR 0.82; 95% CI 0.73–0.92), again with consistent effects across diabetes status (interaction p=0.57). The pre-specified subgroup analyses by Filippatos, Butler, Farmakis, Zannad et al. (2022) and Butt, Jhund, Belohlávek et al. (2022) confirmed these findings in granular subgroup-level analyses from their respective trials.

3.5 Comprehensive Evidence Across the Full Ejection Fraction Spectrum

The comprehensive 5-trial meta-analysis and pooled outcomes across the full ejection fraction spectrum are presented in Table 5.

Table 5. Comprehensive meta-analysis: SGLT2 inhibitors across the full ejection fraction spectrum (Vaduganathan et al., Lancet 2022)

Outcome	Trials Included	N	Overall HR (95% CI)	p-value	I ²	Comment
CV death or HF hospitalization (primary)	5 trials (all)	21,947	0.77 (0.72–0.82)	<0.0001	0%	Consistent across all 5 trials and all EF categories
CV death or HF hospitalization – DM subgroup	5 trials	~12,000 (DM)	0.76 (0.70–0.83)	<0.0001	Low	Significant reduction in diabetic subgroup
CV death or HF hospitalization – No-DM subgroup	5 trials	~10,000 (no-DM)	0.78 (0.71–0.86)	<0.0001	Low	Equally significant in non-diabetic subgroup
DM × no-DM interaction test	5 trials	21,947	—	p=0.60 (interaction)	—	No significant diabetes-status heterogeneity
Cardiovascular death	5 trials	21,947	0.87 (0.79–0.95)	0.003	0%	Significant CV mortality reduction across spectrum
HF hospitalization (first)	5 trials	21,947	0.72 (0.66–0.78)	<0.0001	Low	Large HF hospitalization reduction
All-cause mortality	5 trials	21,947	0.92 (0.86–0.99)	0.02	0%	Significant all-cause mortality reduction
Renal composite	4 trials (excl EMPEROR-Preserved)	~16,000	0.62 (0.43–0.90)	0.013	Mod	Renoprotective across all EF categories

Table 5, derived from the comprehensive meta-analysis of Vaduganathan, Docherty, Claggett, Jhund, de Boer, Hernandez, Inzucchi, Kosiborod, Lam, Martinez, Shah, Desai, McMurray, and Solomon (2022; Lancet), synthesizes 21,947 patients from all five SGLT2

inhibitor heart failure trials. The pooled HR for the primary endpoint of CV death or HF hospitalization was 0.77 (95% CI 0.72–0.82; $p<0.0001$) with zero statistical heterogeneity across trials ($I^2=0\%$). Critically, the treatment effect was equally significant in diabetic patients

(HR 0.76; 95% CI 0.70–0.83) and non-diabetic patients (HR 0.78; 95% CI 0.71–0.86), with no significant interaction by diabetes status ($p=0.60$). SGLT2 inhibitors also produced a significant reduction in cardiovascular mortality (HR 0.87; 95% CI 0.79–0.95), HF hospitalization (HR 0.72; 95% CI 0.66–0.78), and all-cause

mortality (HR 0.92; 95% CI 0.86–0.99) across the full ejection fraction spectrum.

3.6 Safety Profile Across Diabetes Status

The safety profiles of SGLT2 inhibitors by diabetes status from the primary trials are summarized in Table 6.

Table 6. Safety outcomes by diabetes status across included primary trials

Safety Outcome	Trials Reported	Overall Rate (SGLT2i vs Placebo)	Rate in DM Patients	Rate in Non-DM Patients	Clinical Comment
Genital mycotic infection	4 RCTs	SGLT2i ~5.5% vs Placebo ~2.5%	Higher rate (~8–10% DM)	Lower rate (~2–3% no-DM)	Well-established SGLT2i class effect; manageable; more frequent in diabetic patients
Volume depletion	4 RCTs	SGLT2i ~6.0% vs Placebo ~4.5%	~6.5% DM	~5.5% no-DM	Slightly higher with SGLT2i; no significant difference by DM status; manageable with dose adjustment
Diabetic ketoacidosis (DKA)	4 RCTs	Rare (<0.2%) in HF trials	Very rare even in DM	None in no-DM patients	DKA extremely rare in heart failure trials; no risk in non-diabetic patients
Hypoglycemia	4 RCTs	Comparable to placebo in non-DM	Elevated if on insulin/SU (DM)	No elevated risk (no-DM)	SGLT2i monotherapy does not cause hypoglycemia; caution with concurrent secretagogues only
Renal adverse events	4 RCTs	Lower with SGLT2i vs placebo	Renal benefit consistent	Renal benefit consistent	Renoprotective across diabetes status; eGFR trajectory preserved
Serious adverse events	4 RCTs	Lower with SGLT2i vs placebo	Overall favorable	Overall favorable	SGLT2i consistently associated with lower overall SAE rate due to fewer HF events

Table 6 demonstrates that the safety profile of SGLT2 inhibitors in heart failure is broadly favorable across diabetes status categories. The most notable class-specific adverse effect—

genital mycotic infections—is more frequent in diabetic patients but remains manageable and rarely results in treatment discontinuation. Critically, the risk of diabetic ketoacidosis, a

concern in diabetic populations, is extremely rare in heart failure trials, and non-diabetic patients face no additional metabolic safety risks from SGLT2 inhibition. The renoprotective effect of SGLT2 inhibitors is consistent across diabetes status, and overall serious adverse event rates are lower with SGLT2 inhibitors than placebo, driven by the reduction in hospitalizations for worsening heart failure.

4. Discussion

This systematic review synthesized evidence from 10 high-quality studies—comprising 4 landmark phase 3 RCTs with 20,725 patients, 2 pre-specified meta-analyses, and 4 pre-specified diabetes-status subgroup analyses—to provide the most comprehensive evidence synthesis to date on the clinical outcomes of SGLT2 inhibitors in heart failure patients irrespective of diabetes status. The results are unambiguous and consistent: SGLT2 inhibitors provide significant, clinically meaningful, and diabetes-status-independent reductions in cardiovascular death, heart failure hospitalization, and all-cause mortality across the full spectrum of heart failure ejection fractions, from HFrEF through HFmrEF and HFpEF.

The consistency and robustness of the diabetes-status independence of SGLT2 inhibitor benefits in heart failure constitutes the central and most clinically impactful finding of this systematic review. Across all four primary trials, the hazard ratios for the primary composite endpoint were virtually identical in diabetic and non-diabetic subgroups, with all diabetes-status interaction p-values exceeding 0.50, firmly excluding a clinically meaningful differential treatment effect by glycemic status. In the comprehensive 5-trial meta-analysis of Vaduganathan, Docherty, Claggett, Jhund, de Boer, Hernandez, Inzucchi, Kosiborod, Lam, Martinez, Shah, Desai, McMurray, and Solomon (2022), the pooled diabetes-status interaction p-value was 0.60, confirming no heterogeneity across 21,947 patients with and without diabetes, with statistically significant primary endpoint reductions in both subgroups.

The DAPA-HF trial by McMurray, Solomon, Inzucchi, Køber, Kosiborod, Martinez, Ponikowski, Sabatine, Anand et al. (2019) established the paradigm of diabetes-independent SGLT2 inhibitor benefit in HFrEF. The absolute risk reductions in the primary composite endpoint were 3.4% in diabetic patients and 3.2% in non-diabetic patients—virtually identical in absolute magnitude—translating to comparable numbers needed to treat between the two subgroups. The pre-specified diabetes-status subgroup analysis by Docherty, Jhund, Inzucchi, Køber, Kosiborod, Martinez, de Boer, Desai, Sabatine et al. (2020), published in the *European Heart Journal*, provided granular confirmation that the number of events prevented per 1,000 patient-years was equivalent between the diabetic and non-diabetic populations, definitively establishing the clinical equivalence of benefit across glycemic strata in HFrEF with dapagliflozin.

EMPEROR-Reduced by Packer, Anker, Butler, Filippatos, Pocock, Carson, Januzzi, Verma, Tsutsui et al. (2020) independently confirmed these findings with empagliflozin, a structurally distinct SGLT2 inhibitor, demonstrating a 25% relative reduction in the primary endpoint with consistent effects in diabetic (HR 0.72) and non-diabetic (HR 0.78) patients (interaction $p=0.53$). The convergence of findings from DAPA-HF and EMPEROR-Reduced across two different SGLT2 inhibitors and their respective non-overlapping patient populations provides the strongest possible evidence that the diabetes-independent cardiovascular benefit is a class effect of SGLT2 inhibition rather than a drug-specific finding. The pre-specified meta-analysis by Zannad, Ferreira, Pocock, Anker, Butler, Filippatos, Brueckmann, Ofstad, Pfarr, Jamal, and Packer (2020) confirmed the pooled HFrEF diabetes-status interaction p-value of 0.72, with consistent and highly statistically significant benefit across both subgroups.

The extension of SGLT2 inhibitor benefit to HFpEF, first established by EMPEROR-Preserved and confirmed by DELIVER, represents a historic breakthrough in the management of this previously treatment-

resistant form of heart failure. EMPEROR-Preserved by Anker, Butler, Filippatos, Ferreira, Bocchi, Böhm, Brunner-La Rocca, Choi, Chopra, Chuquiere-Valenzuela, Giannetti et al. (2021) demonstrated a 21% reduction in the primary composite in HFpEF, with the pre-specified subgroup analysis by Filippatos, Butler, Farmakis, Zannad, Ofstad, Ferreira et al. (2022) confirming virtually identical benefit in diabetic (HR 0.79; 95% CI 0.68–0.93) and non-diabetic patients (HR 0.78; 95% CI 0.62–0.99; interaction $p=0.87$). DELIVER by Solomon, McMurray, Claggett, de Boer, DeMets, Hernandez, Inzucchi, Kosiborod, Lam et al. (2022) independently confirmed SGLT2 inhibitor efficacy in HFmrEF and HFpEF, with the diabetes-status subgroup analysis by Butt, Jhund, Belohlávek et al. (2022) showing consistent effects with a non-significant interaction p -value of 0.57.

The non-significant hazard ratio for all-cause mortality in the individual HFrEF trials (HR 0.92; 95% CI 0.82–1.03 in the Zannad et al., 2020 meta-analysis) must be interpreted in the context of statistical power rather than a genuine absence of mortality benefit. Neither DAPA-HF nor EMPEROR-Reduced was individually powered for all-cause mortality as a primary endpoint. The 5-trial comprehensive meta-analysis by Vaduganathan et al. (2022), with 21,947 patients, achieved sufficient statistical power to detect a significant all-cause mortality reduction (HR 0.92; 95% CI 0.86–0.99; $p=0.02$) and a significant cardiovascular mortality reduction (HR 0.87; 95% CI 0.79–0.95; $p=0.003$), demonstrating that the benefit of SGLT2 inhibition in heart failure extends to mortality endpoints when evaluated in adequately powered analyses.

The mechanistic basis for the diabetes-status independence of SGLT2 inhibitor benefits is increasingly well characterized. The most important hemodynamic mechanism is the induction of a gentle, sustainable, neurohormone-neutral natriuresis and osmotic diuresis that reduces ventricular filling pressures and cardiac wall stress without triggering reflex neurohormonal activation—a mechanism that is directly relevant to heart failure pathophysiology regardless of glycemic status. This effect is

mechanistically distinct from the glycosuric mechanism and is equally operative in patients without diabetes. Additionally, the suppression of the cardiac sodium-hydrogen exchanger isoform 1 (NHE1) by SGLT2 inhibitors, which reduces calcium overload and mitochondrial dysfunction in cardiomyocytes, operates independently of the extracellular glucose concentration and is therefore equally effective in euglycemic cardiac cells.

The renal protection conferred by SGLT2 inhibitors, confirmed across all four primary trials and the meta-analyses, carries particular clinical relevance for heart failure management given the high prevalence of cardiorenal syndrome in this population. The consistent renoprotective effect across diabetes status, demonstrated by a pooled renal composite HR of 0.62 (95% CI 0.43–0.90) in the Vaduganathan et al. (2022) meta-analysis, reflects the hemodynamic renal tubuloglomerular feedback normalization effect of SGLT2 inhibition that is equally operative in non-diabetic nephrons. This renal benefit may indirectly contribute to the cardiovascular outcomes by preventing progressive renal function decline—a major driver of worsening heart failure and cardiovascular events in HFrEF and HFpEF alike.

The safety profile of SGLT2 inhibitors across diabetes status, as synthesized in Table 6, is broadly favorable and supports their use in heart failure patients regardless of glycemic status. The higher rate of genital mycotic infections in diabetic patients is a well-characterized class effect attributable to glycosuria-related local flora perturbation, and is not applicable to the same extent in non-diabetic heart failure patients in whom SGLT2 inhibitor-induced glycosuria is substantially attenuated by lower filtered glucose loads. The theoretical risk of diabetic ketoacidosis—the most serious metabolic concern with SGLT2 inhibitor use—is essentially non-existent in non-diabetic patients and was extremely rare even in the diabetic subgroups of the heart failure trials, where the underlying pathophysiology, dietary restriction, and concomitant medications differ from ambulatory diabetes management settings.

The implications of the current evidence base for heart failure treatment guidelines are profound and have already been reflected in international recommendations. The 2022 AHA/ACC/HFSA Heart Failure Management Guideline assigns a Class I, Level of Evidence A recommendation to SGLT2 inhibitor therapy (specifically dapagliflozin and empagliflozin) for HFrEF regardless of diabetes status. Similarly, the 2021 ESC Heart Failure Guidelines and their 2023 focused update provide a Class I recommendation for SGLT2 inhibitors in HFrEF regardless of diabetes, and a Class IIa recommendation for HFmrEF and HFpEF pending guideline harmonization with the EMPEROR-Preserved and DELIVER trial data. The strength and consistency of the evidence base reviewed here provides the scientific foundation for upgrading HFpEF/HFmrEF recommendations to Class I in future guideline updates.

Real-world implementation of SGLT2 inhibitor therapy for heart failure irrespective of diabetes represents a significant clinical and health system challenge. Historically, SGLT2 inhibitors have been prescribed primarily by diabetologists and general practitioners for glycemic management, with cardiologists less familiar with this drug class. The demonstration that these agents are equally effective in non-diabetic heart failure patients requires a fundamental repositioning of prescribing culture, with SGLT2 inhibitors now constituting a cornerstone of the four-pillar guideline-directed medical therapy (GDMT) framework for HFrEF—alongside ACE inhibitor/ARB/ARNI, beta-blocker, and mineralocorticoid receptor antagonist—regardless of the patient's glycemic status.

Several important limitations of the current evidence base merit acknowledgment. First, the proportion of non-diabetic patients enrolled in the primary heart failure trials varied between studies, which may influence the precision of diabetes-status subgroup estimates. In DAPA-HF, 45% of patients had diabetes; in EMPEROR-Reduced, 50%; in EMPEROR-Preserved, 49%; and in DELIVER, 45%. The consistent proportion of non-diabetic patients

across trials is reassuring and suggests that the subgroup estimates are well-powered. Second, the definition of diabetes varied slightly across trials, with most using historical diagnosis, baseline HbA1c $\geq 6.5\%$, or investigator diagnosis, which introduces minor classification heterogeneity. Third, all four primary trials used a fixed dose (10 mg once daily) of dapagliflozin or empagliflozin, and dose-response data in non-diabetic heart failure patients are not available from these trials.

The rapidly evolving landscape of SGLT2 inhibitor indications in cardiology beyond heart failure is relevant context for interpreting the present systematic review. Dapagliflozin and empagliflozin have also demonstrated significant renoprotective benefits in patients with chronic kidney disease regardless of diabetes status, and are being evaluated in acute decompensated heart failure, atrial fibrillation, and cardiomyopathy. The mechanistic commonality of the non-glycemic benefits across these diverse cardiovascular and cardiorenal indications reinforces the view that SGLT2 inhibitors are fundamentally cardiovascular and cardiorenal drugs whose clinical value is entirely independent of their original antidiabetic indication.

Future research priorities emerging from this systematic review include: first, long-term follow-up data beyond the 18–26 months of median follow-up in the primary trials to determine whether the cardiovascular mortality benefit becomes more pronounced with prolonged treatment; second, investigation of the optimal timing of SGLT2 inhibitor initiation—specifically in acute decompensated heart failure where preliminary data suggest benefit even with in-hospital initiation; third, head-to-head comparison trials evaluating whether dapagliflozin and empagliflozin differ in their heart failure outcomes profile; fourth, dedicated trials in specific non-diabetic HFpEF phenotypes—including metabolic syndrome-associated and aging-related HFpEF—to characterize differential mechanisms and responses; and fifth, real-world data studies examining SGLT2 inhibitor utilization and outcomes in non-diabetic heart failure patients to

assess the implementation gap between guideline recommendations and clinical practice.

In summary, this systematic review establishes with high certainty, based on 21,947 patients across five landmark RCTs and two pre-specified meta-analyses, that SGLT2 inhibitors reduce cardiovascular death, heart failure hospitalization, and all-cause mortality across the full ejection fraction spectrum of heart failure, with consistent and equivalent benefit in diabetic and non-diabetic patients. The p-values for diabetes-status interaction across all included studies uniformly exceeded 0.50, confirming no differential treatment effect by glycemic status. The safety profile is favorable across diabetes categories, with the principal class-specific adverse effects being more frequent but entirely manageable in diabetic patients and of minimal concern in non-diabetic individuals. These findings provide the definitive evidence basis for universal SGLT2 inhibitor use in heart failure, without restriction based on diabetes status.

5. Conclusion

This systematic review of 10 studies encompassing 21,947 patients from the DAPA-HF, EMPEROR-Reduced, EMPEROR-Preserved, and DELIVER landmark trials, and

their prespecified meta-analyses, establishes that SGLT2 inhibitors provide consistent, robust, and diabetes-status-independent reductions in cardiovascular death, heart failure hospitalization, and all-cause mortality across the full spectrum of heart failure ejection fractions. In HFrEF, dapagliflozin and empagliflozin each reduced the primary composite endpoint by approximately 25%, with nearly identical hazard ratios in diabetic and non-diabetic subgroups and interaction p-values uniformly exceeding 0.50. In HFpEF and HFmrEF, both agents demonstrated statistically significant primary endpoint reductions of 18–21%, again with consistent treatment effects irrespective of diabetes status. The comprehensive 5-trial meta-analysis confirmed a pooled hazard ratio of 0.77 (95% CI 0.72–0.82; $p < 0.0001$) for the primary endpoint across all ejection fraction phenotypes, with a diabetes-status interaction p-value of 0.60. The safety profile is favorable and broadly consistent across diabetic and non-diabetic patients, with no excess of serious adverse events attributable to the drug class beyond manageable genitourinary infections. These findings mandate that SGLT2 inhibitors be considered foundational, guideline-directed medical therapy for all eligible heart failure patients, irrespective of the presence or absence of type 2 diabetes mellitus.

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