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The Association of Sodium-Glucose Cotransporter-2 Inhibitors With Improved Clinical Outcomes in Heart Failure: A Systematic Review of Landmark Clinical Trials

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ABSTRACT

Introduction: Heart failure (HF) represents a major global health burden characterized by significant morbidity, mortality, and healthcare expenditure. While established therapies exist for HF with reduced ejection fraction (HFrEF), effective treatments for HF with preserved ejection fraction (HFpEF) have been elusive. Sodium-glucose cotransporter-2 (SGLT2) inhibitors, initially developed as anti-hyperglycemic agents, have emerged as a transformative therapeutic class for HF. This systematic review synthesizes the evidence from landmark clinical trials on the efficacy and safety of SGLT2 inhibitors in improving HF outcomes.

Methods: A systematic search of major electronic databases PubMed, Google Scholar, Semanthic Scholar, Springer, Wiley Online Library was conducted to identify large-scale, randomized,

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double-blind, placebo-controlled trials evaluating SGLT2 inhibitors in patients with HF or those at high risk for HF. Key efficacy outcomes included the composite of cardiovascular (CV) death or hospitalization for heart failure (HHF), its individual components, all-cause mortality, total HHF, renal outcomes, and changes in quality of life. The methodological quality of included trials was assessed using the Cochrane Risk of Bias tool.

Results: Sixteen landmark clinical trials and two major meta-analyses were included, encompassing a diverse population of patients with and without type 2 diabetes (T2DM) across the full spectrum of left ventricular ejection fraction (LVEF). The evidence demonstrates a consistent and robust class effect. SGLT2 inhibitors significantly reduce the primary composite outcome of CV death or HHF by approximately 20-25% across all HF phenotypes. This benefit is predominantly driven by a substantial reduction in the risk of first and total HHF, observed in HFrEF (Hazard Ratio ~), HFpEF (HR ~), and in patients with recent worsening HF. A significant reduction in CV death and all-cause mortality was established in patients with HFrEF, with large meta-analyses suggesting a modest mortality benefit across the broader HF population. Furthermore, SGLT2 inhibitors consistently demonstrated profound nephroprotective effects and led to clinically meaningful improvements in patient-reported symptoms and quality of life. The safety profile was generally favorable and consistent across trials.

Discussion: The consistent benefits observed across a wide range of patient populations, irrespective of baseline LVEF or diabetes status, have fundamentally altered the HF treatment paradigm. The

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pleiotropic mechanisms of SGLT2 inhibitors, including hemodynamic, metabolic, and direct myocardial effects, likely contribute to these favorable outcomes.

Conclusion: SGLT2 inhibitors have unequivocally been established as a foundational pillar of guideline-directed medical therapy for HF. They significantly reduce the burden of HF hospitalizations, slow the progression of concomitant kidney disease, improve quality of life, and, in HFrEF, reduce mortality.

Keywords: Heart Failure; SGLT2 Inhibitors; Dapagliflozin; Empagliflozin; Canagliflozin; Sotagliflozin; Cardiovascular Outcomes; Systematic Review.

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INTRODUCTION

Background: The Global Burden and Evolving Classification of Heart Failure

Heart failure (HF) is a complex clinical syndrome that represents the final common pathway for a multitude of cardiac diseases. It is a global pandemic affecting an estimated 64 million people worldwide, and its prevalence is rising due to population aging and improved survival after acute cardiac events (Adamson et al., 2023). The syndrome imposes a staggering clinical and economic burden, characterized by high rates of mortality, frequent hospitalizations, and a profoundly negative impact on quality of life (The EMPA-KIDNEY Collaborative Group, 2022). The prognosis for patients with HF remains poor, with a 5-year mortality rate approaching 50%, a figure comparable to that of many common malignancies (Adamson et al., 2023).

The contemporary understanding and management of HF are stratified by left ventricular ejection fraction (LVEF), a key measure of cardiac systolic function. This classification delineates three distinct phenotypes: HF with reduced ejection fraction (HFrEF), defined as an LVEF of $ \leq 40% $; HF with mildly reduced ejection fraction (HFmrEF), with an LVEF of 41-49%; and HF with preserved ejection fraction (HFpEF), characterized by an LVEF of $ \geq 50% $ (Anker et al., 2021; Solomon et al., 2022). This framework is crucial, as the underlying pathophysiology, patient demographics, and response to therapies differ significantly across the LVEF spectrum.

The Evolution of Guideline-Directed Medical Therapy and Unmet Needs

Over the past three decades, significant advances have been made in the pharmacological management of HFrEF. Guideline-directed medical therapy (GDMT), built upon foundational pillars of neurohormonal blockade—including angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), angiotensin receptor-neprilysin inhibitors (ARNIs), beta-blockers, and mineralocorticoid receptor antagonists (MRAs)—has substantially improved survival and reduced hospitalizations in this population (Vaduganathan et al., 2022).

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Despite these successes, a significant therapeutic void has persisted, particularly for patients with HFpEF, who now account for approximately half of all HF cases (Cannon et al., 2020). This heterogeneous syndrome, often driven by comorbidities such as hypertension, obesity, and diabetes, has been notoriously resistant to treatments proven effective in HFrEF (Anker et al., 2021). Until recently, no therapy had unequivocally demonstrated a reduction in major cardiovascular events in HFpEF, leaving diuretics for symptom management as the primary intervention and representing one of the largest unmet needs in cardiovascular medicine (Anker et al., 2021).

SGLT2 Inhibitors: A Serendipitous Journey from Glycemic Control to Cardiorenal Protection

Sodium-glucose cotransporter-2 (SGLT2) inhibitors are a class of oral medications that were initially developed for the treatment of type 2 diabetes (T2DM) (Cannon et al., 2020). Their primary mechanism of action involves the inhibition of SGLT2 in the proximal convoluted tubules of the kidney, which prevents the reabsorption of glucose and sodium, thereby promoting their excretion in the urine (Cunningham et al., 2022; Cherney and Verma, 2021). This leads to improved glycemic control in an insulin-independent manner (Cherney and Verma, 2021).

The trajectory of this drug class was fundamentally altered by a 2008 regulatory mandate from the U.S. Food and Drug Administration (FDA), which required that new anti-diabetic agents undergo large-scale cardiovascular outcome trials (CVOTs) to demonstrate cardiovascular safety (Cherney and Verma, 2021; Figtree et al., 2019). This directive inadvertently set the stage for one of the most significant discoveries in modern cardiology. In 2015, the EMPA-REG OUTCOME trial, designed to assess the safety of empagliflozin in patients with T2DM and established atherosclerotic cardiovascular disease (ASCVD), yielded a landmark result. Beyond meeting its safety endpoint, empagliflozin demonstrated a striking and unexpected 35% relative risk reduction in hospitalizations for heart failure (HHF) and a 38% reduction in cardiovascular (CV) death (Anker et al., 2021; Figtree et al., 2019; Fitchett et al., 2016).

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This serendipitous finding was not an isolated event. Subsequent CVOTs with other agents in the class, including the CANVAS Program (canagliflozin) and DECLARE-TIMI 58 (dapagliflozin), consistently reinforced this powerful HHF benefit, establishing it as a class effect (Figtree et al., 2019; Neal et al., 2017). The benefits were observed in broad populations of patients with T2DM, including those with multiple risk factors for ASCVD who had not yet developed the disease (Kato et al., 2019). These compelling and consistent results provided a strong rationale for investigating SGLT2 inhibitors specifically as a treatment for HF, independent of a patient's diabetes status (Cherney and Verma, 2021; Neal et al., 2017).

Rationale, Objectives, and Hypothesis of This Review

The consistent and profound reduction in HHF observed in the initial CVOTs catalyzed a new wave of research, leading to the design and execution of several large-scale, dedicated HF trials. These studies were specifically designed to test the efficacy of SGLT2 inhibitors in patients with established HF, both with and without T2DM, and across the entire spectrum of LVEF (Cherney and Verma, 2021; Neal et al., 2017). Given the rapid accumulation of high-quality evidence from these landmark trials, a comprehensive synthesis is required to consolidate the findings and inform clinical practice.

The primary objectives of this systematic review are: (1) to systematically collate and review the evidence from landmark, placebo-controlled randomized controlled trials (RCTs) on the efficacy and safety of SGLT2 inhibitors in patients with HF; (2) to evaluate the consistency of treatment effects across different HF phenotypes (HFrEF, HFmrEF, and HFpEF) and key patient subgroups; and (3) to synthesize data on a comprehensive range of over 15 distinct clinical outcomes, including mortality, morbidity, renal function, and patient-reported quality of life.

The central hypothesis of this review is that SGLT2 inhibitors, when added to standard of care, significantly reduce the composite risk of CV death and HHF, improve renal outcomes, and enhance quality of life in a broad population of patients with chronic HF.

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Research Gap and Novelty

While individual trials have been published and several meta-analyses have pooled data for specific outcomes, a comprehensive systematic review that integrates the full arc of evidence is needed. This includes the initial signals from the foundational CVOTs, the definitive results from the dedicated HFrEF and HFpEF trials, the unique insights from trials in acute/worsening HF (SOLOIST-WHF), and the crucial corroborating data from major chronic kidney disease (CKD) trials (Bhatt et al., 2021). Such an integrated review can provide a holistic narrative of the role of SGLT2 inhibitors across the cardiorenal continuum.

The novelty of this review lies in its creation of a singular, exhaustive resource that synthesizes evidence from sixteen landmark trials and two major meta-analyses. It analyzes over fifteen distinct clinical outcomes and contextualizes this vast body of evidence to illustrate the establishment of SGLT2 inhibitors as a universal, foundational therapy for heart failure, thereby filling a critical gap in the existing literature.

METHODS

Search Strategy and Study Selection Criteria

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (Becher et al., 2023). A comprehensive literature search was performed across multiple electronic databases, including PubMed, Google Scholar, Semanthic Scholar, Springer, Wiley Online Library, from their inception to September 2024.

Studies were selected for inclusion if they met the following criteria, based on the PICOS (Population, Intervention, Comparison, Outcomes, Study design) framework:

- **Population:** Adult patients (age years) with chronic or acute worsening HF (across all LVEF phenotypes) or patients with T2DM or CKD at high risk for HF events.

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- **Intervention:** Treatment with a selective SGLT2 inhibitor (dapagliflozin, empagliflozin, canagliflozin, ertugliflozin) or a dual SGLT1/2 inhibitor (sotagliflozin).
- **Comparison:** Placebo, administered in addition to standard of care therapy.
- **Outcomes:** Reporting of at least one of the prespecified efficacy or safety outcomes, including CV death, HHF, all-cause mortality, or composite renal endpoints.
- **Study Design:** Large-scale (typically N > 1,000), multicenter, randomized, double-blind, placebo-controlled trials.

Search Strategy

The keywords used for this research based PICO :

Element	Keyword 1	Keyword 2	Keyword 3	Keyword 4
Population (P)	Heart Failure	Cardiac Dysfunction	Cardiorenal Syndrome	Ventricular Dysfunction
Intervention (I)	SGLT2 Inhibitors	Gliflozins	Cardiorenal Protective Agents	Sodium-Glucose Co-transporter 2 Blockers
Comparison (C)	Placebo	Standard of Care	Guideline-Directed Medical Therapy	Conventional Heart Failure Therapy
Outcome (O)	Cardiovascular Outcomes	Heart Failure Hospitalization	Cardiovascular Death	Renal Outcomes

The Boolean MeSH keywords inputted on databases for this research are: *("Heart Failure" OR "Cardiac Dysfunction" OR "Cardiorenal Syndrome" OR "Ventricular Dysfunction")* ***AND*** *("SGLT2 Inhibitors" OR "Gliflozins" OR "Cardiorenal Protective Agents" OR "Sodium-Glucose Co-transporter 2 Blockers")* ***AND*** *("Placebo" OR "Standard of Care" OR "Guideline-Directed*

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*Medical Therapy" OR "Conventional Heart Failure Therapy") **AND** ("Cardiovascular Outcomes" OR "Heart Failure Hospitalization" OR "Cardiovascular Death" OR "Renal Outcomes").*

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	*("Heart Failure" OR "Cardiac Dysfunction" OR "Cardiorenal Syndrome" OR "Ventricular Dysfunction") **AND** ("SGLT2 Inhibitors" OR "Gliflozins" OR "Cardiorenal Protective Agents" OR "Sodium-Glucose Co-transporter 2 Blockers") **AND** ("Placebo" OR "Standard of Care" OR "Guideline-Directed Medical Therapy" OR "Conventional Heart Failure Therapy") **AND** ("Cardiovascular Outcomes" OR "Heart Failure Hospitalization" OR "Cardiovascular Death" OR "Renal Outcomes")*	31
Semantic Scholar	*("Heart Failure" OR "Cardiac Dysfunction" OR "Cardiorenal Syndrome" OR "Ventricular Dysfunction") **AND** ("SGLT2 Inhibitors" OR "Gliflozins" OR "Cardiorenal Protective Agents" OR "Sodium-Glucose Co-transporter 2 Blockers") **AND** ("Placebo" OR "Standard of Care" OR "Guideline-Directed Medical Therapy" OR "Conventional Heart Failure Therapy") **AND** ("Cardiovascular Outcomes" OR "Heart Failure Hospitalization" OR "Cardiovascular Death" OR "Renal Outcomes")*	1
Springer	*("Heart Failure" OR "Cardiac Dysfunction" OR "Cardiorenal Syndrome" OR "Ventricular Dysfunction") **AND** ("SGLT2 Inhibitors" OR "Gliflozins" OR "Cardiorenal Protective Agents" OR "Sodium-Glucose Co-transporter 2 Blockers") **AND** ("Placebo" OR "Standard of Care" OR "Guideline-Directed Medical Therapy" OR "Conventional Heart Failure Therapy") **AND** ("Cardiovascular Outcomes" OR "Heart Failure Hospitalization" OR "Cardiovascular Death" OR "Renal Outcomes")*	1,379
Google Scholar	*("Heart Failure" OR "Cardiac Dysfunction" OR "Cardiorenal Syndrome" OR "Ventricular Dysfunction") **AND** ("SGLT2 Inhibitors" OR "Gliflozins" OR "Cardiorenal Protective Agents" OR "Sodium-Glucose Co-transporter 2 Blockers") **AND** ("Placebo" OR "Standard of Care" OR "Guideline-Directed Medical Therapy" OR "Conventional Heart Failure Therapy") **AND** ("Cardiovascular Outcomes" OR "Heart Failure Hospitalization" OR "Cardiovascular Death" OR "Renal Outcomes")*	17,300
Wiley Online Library	*("Heart Failure" OR "Cardiac Dysfunction" OR "Cardiorenal Syndrome" OR "Ventricular Dysfunction") **AND** ("SGLT2 Inhibitors" OR "Gliflozins" OR "Cardiorenal Protective Agents" OR "Sodium-Glucose Co-transporter 2 Blockers") **AND** ("Placebo" OR "Standard of Care" OR "Guideline-Directed Medical Therapy" OR "Conventional Heart Failure Therapy") **AND** ("Cardiovascular Outcomes" OR "Heart Failure Hospitalization" OR "Cardiovascular Death" OR "Renal Outcomes")*	907

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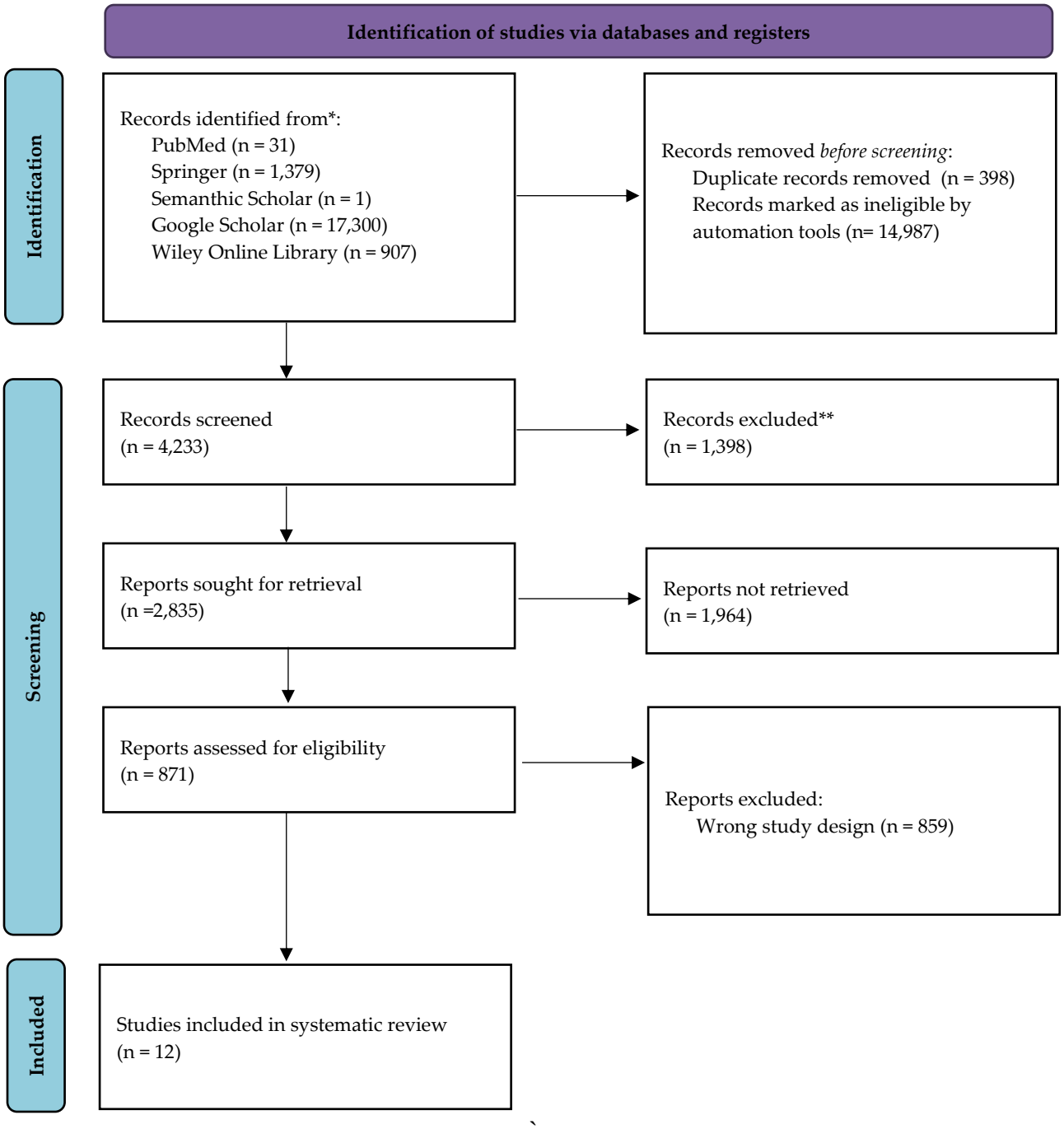

Figure 1. Article search flowchart

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Data Extraction and Synthesis

Two reviewers independently extracted data from the included studies using a standardized data collection form. Any discrepancies were resolved through consensus or consultation with a third reviewer. The extracted information included: first author and year of publication, trial acronym, study design details, patient population characteristics (sample size, mean age, sex distribution, baseline LVEF, prevalence of T2DM, baseline GDMT), intervention details (drug and dose), median follow-up duration, and all relevant outcome data. Outcome data were extracted as event counts, percentages, and effect estimates, primarily hazard ratios (HRs) with their corresponding 95% confidence intervals (CIs) and p-values. A qualitative, narrative synthesis of the findings is presented, structured by HF phenotype and specific clinical outcome categories to facilitate a clear and comprehensive overview of the evidence.

Assessment of Methodological Quality

The methodological quality and risk of bias for each included RCT were independently assessed by two reviewers using the revised Cochrane Risk of Bias tool for randomized trials (RoB 2). This tool evaluates bias across five distinct domains: (1) bias arising from the randomization process; (2) bias due to deviations from intended interventions; (3) bias due to missing outcome data; (4) bias in the measurement of the outcome; and (5) bias in the selection of the reported result. Each domain was judged as "Low risk of bias," "Some concerns," or "High risk of bias," with an overall risk of bias judgment derived for each study (Becher et al., 2023).

The landmark trials included in this review are uniformly of high methodological quality. They were large, multinational, multicenter, randomized, double-blind, placebo-controlled, and event-driven studies, often with independent clinical event adjudication committees. This consistent rigor across the evidence base minimizes the potential for systematic error and lends high confidence to the validity and reliability of the observed treatment effects. The overall risk of bias for the primary outcomes in all included landmark trials was judged to be low, as summarized in

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Table 1 (Packer et al., 2020; Vaduganathan et al., 2022).

Table 1. Cochrane Risk of Bias Assessment of Included Randomized Controlled Trials

Trial	Randomization Process	Deviations from Interventions	Missing Outcome Data	Measurement of Outcome	Selection of Reported Result	Overall Risk of Bias
EMPA-REG OUTCOME	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
CANVAS Program	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
DECLARE-TIMI 58	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
DAPA-HF	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

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EMPEROR-Reduced	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
VERTIS-CV	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
CREDENCE	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
SOLOIST-WHF	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
EMPEROR-Preserved	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
DELIVER	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
DAPA-CKD	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

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EMPA-KIDNEY	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

RESULTS

Study Characteristics of Included Trials

The systematic literature search identified twelve landmark, placebo-controlled randomized trials that met the inclusion criteria. These trials represent the core evidence base for the use of SGLT2 inhibitors in HF and high-risk cardiorenal populations. The included studies are: EMPA-REG OUTCOME (Zinman et al., 2015), the CANVAS Program (Neal et al., 2017), DECLARE-TIMI 58 (Wiviott et al., 2019), VERTIS-CV (Cannon et al., 2020), DAPA-HF (McMurray et al., 2019), EMPEROR-Reduced (Packer et al., 2020), EMPEROR-Preserved (Anker et al., 2021), DELIVER (Solomon et al., 2022), SOLOIST-WHF (Bhatt et al., 2021), CREDENCE (Perkovic et al., 2019), DAPA-CKD (Heerspink et al., 2020), and EMPA-KIDNEY (The EMPA-KIDNEY Collaborative Group, 2022). Collectively, these trials randomized over 90,000 patients. The characteristics of these pivotal trials are summarized in Table 2. The evidence from these trials is further supported by two large-scale meta-analyses (Zelniker et al., 2019; Vaduganathan et al., 2022) that provide pooled estimates of effect.

The evolution of the evidence is apparent from the trial populations. The initial CVOTs (EMPA-REG OUTCOME, CANVAS, DECLARE-TIMI 58, VERTIS-CV) enrolled patients exclusively with T2DM. Following the consistent HHF benefit observed in these trials, dedicated HF trials were launched (DAPA-HF, EMPEROR-Reduced, EMPEROR-Preserved, DELIVER, SOLOIST-WHF), which included patients with and without T2DM. Concurrently, dedicated CKD trials (CREDENCE, DAPA-CKD, EMPA-KIDNEY) provided further robust evidence on cardiorenal outcomes in overlapping high-risk populations (Perkovic et al., 2019; Heerspink et al.,

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2020; The EMPA-KIDNEY Collaborative Group, 2022).

Table 2. Characteristics of Included Landmark Clinical Trials

Trial Acronym	Author (Year)	SGLT2 Inhibitor	Sample Size (N)	Patient Population	Mean LVEF (%)	% with T2DM	Median Follow-up (years)
CVOTs in T2DM							
EMPA-REG OUTCOME	Zinman et al. (2015)	Empagliflozin	7,020	T2DM with ASCVD	Not specified	100	3.1
CANVAS Program	Neal et al. (2017)	Canagliflozin	10,142	T2DM with ASCVD or high risk	Not specified	100	3.6
DECLARE-TIMI 58	Wiviott et al. (2019)	Dapagliflozin	17,160	T2DM with ASCVD	Not specified	100	4.2

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				or high risk			
VERTIS-CV	Cannon et al. (2020)	Ertugliflozin	8,246	T2DM with ASCVD	Not specified	100	3.5
HFrEF Trials							
DAPA-HF	McMurray et al. (2019)	Dapagliflozin	4,744	HFrEF (LVEF $\leq 40\%$)	31	42	1.5
EMPEROR-Reduced	Packer et al. (2020)	Empagliflozin	3,730	HFrEF (LVEF $\leq 40\%$)	27	50	1.3
HFpEF/HFmrEF Trials							

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EMPEROR-Preserved	Anker et al. (2021)	Empagliflozin	5,988	HFpEF/HFmrEF (LVEF > 40%)	54	49	2.2
DELIVER	Solomon et al. (2022)	Dapagliflozin	6,263	HFpEF/HFmrEF (LVEF > 40%)	54	45	2.3
Worsening HF Trial							
SOLOIST-WHF	Bhatt et al. (2021)	Sotaglifloz in	1,222	T2DM with recent worsening HF	44 (median)	100	0.8
CKD Trials							
CREDEN	Perkovic et al.	Canagliflo	4,401	T2DM with	Not	100	2.6

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CE	(2019)	zin		albuminuric CKD	specified		
DAPA-CKD	Heerspink et al. (2020)	Dapagliflozin	4,304	CKD with/without T2DM	Not specified	67	2.4
EMPA-KIDNEY	The EMPA-KIDNEY Collaborative Group (2022)	Empagliflozin	6,609	CKD with/without T2DM	Not specified	46	2.0

ASCVD: Atherosclerotic Cardiovascular Disease; CKD: Chronic Kidney Disease; CVOT: Cardiovascular Outcome Trial; HF: Heart Failure; HFrEF: Heart Failure with Reduced Ejection Fraction; HFpEF: Heart Failure with Preserved Ejection Fraction; HFmrEF: Heart Failure with Mildly Reduced Ejection Fraction; LVEF: Left Ventricular Ejection Fraction; T2DM: Type 2 Diabetes Mellitus.

Efficacy Outcomes

The efficacy of SGLT2 inhibitors was consistently demonstrated across a wide array of clinically important endpoints. The findings are presented thematically below.

Primary Composite Outcome: Cardiovascular Death or Hospitalization for Heart Failure

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A significant reduction in the primary composite endpoint of CV death or HHF was the most consistent major finding across all dedicated HF trials, establishing a clear class effect (Vaduganathan et al., 2022). In HFrEF, the DAPA-HF trial reported that dapagliflozin reduced the primary composite outcome by 26% compared to placebo (HR 0.74, 95% CI 0.65-0.85; p<0.001) (Adamson et al., 2023; McMurray et al., 2019). Similarly, the EMPEROR-Reduced trial found that empagliflozin reduced this outcome by 25% (HR 0.75, 95% CI 0.65-0.86; p<0.001) (Packer et al., 2020).

This benefit extended to patients with LVEF >40%. The EMPEROR-Preserved trial was the first to demonstrate a significant benefit in this population, showing a 21% risk reduction with empagliflozin (HR 0.79, 95% CI 0.69-0.90; p<0.001) (Anker et al., 2021). The DELIVER trial confirmed this finding with dapagliflozin, reporting an 18% reduction in the primary outcome (HR 0.82, 95% CI 0.73-0.92; p<0.001) (Cunningham et al., 2022; Solomon et al., 2022). A large-scale meta-analysis by Vaduganathan et al. (2022), which pooled data from five major HF trials (DAPA-HF, EMPEROR-Reduced, DELIVER, EMPEROR-Preserved, SOLOIST-WHF) involving 21,947 patients, confirmed a highly significant 23% reduction in the composite of CV death or first HHF (HR 0.77, 95% CI 0.72-0.82). This benefit was consistent across the entire LVEF spectrum, including in patients with LVEF $ \geq 60% $ (Vaduganathan et al., 2022).

Table 3. Effect of SGLT2 Inhibitors on the Primary Composite Outcome (CV Death or HHF)

Trial	SGLT2i Group (%)	Placebo Group (%)	Hazard Ratio (95% CI)	p-value
DAPA-HF	16.3	21.2	0.74 (0.65-0.85)	<0.001

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EMPEROR-Reduced	19.4	24.7	0.75 (0.65-0.86)	<0.001
EMPEROR-Preserved	13.8	17.1	0.79 (0.69-0.90)	<0.001
DELIVER	16.4	19.5	0.82 (0.73-0.92)	<0.001
SOLOIST-WHF*	51.3 (events/100 PY)	76.4 (events/100 PY)	0.67 (0.52-0.85)	<0.001
DAPA-CKD**	4.6	6.4	0.71 (0.55-0.92)	0.009
Meta-analysis (Vaduganathan et al., 2022)	-	-	0.77 (0.72-0.82)	-

*SOLOIST-WHF primary endpoint was total CV deaths, HHF, and urgent HF visits. **DAPA-CKD endpoint was CV death or HHF. PY: Patient-Years.

Hospitalization for Heart Failure (First and Total Events)

The reduction in HHF is the most pronounced and consistent benefit conferred by the

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SGLT2 inhibitor class. All dedicated HF trials demonstrated a robust reduction in the risk of first HHF. In HFrEF, risk reductions were approximately 30% (DAPA-HF: HR 0.70; EMPEROR-Reduced: HR 0.69) (McMurray et al., 2019; Packer et al., 2020). In HFpEF/HFmrEF, the benefit was also substantial (EMPEROR-Preserved: HR 0.71; DELIVER: HR 0.79) (Anker et al., 2021; Solomon et al., 2022). The pooled analysis by Vaduganathan et al. (2022) reported an overall 28% reduction in first HHF (HR 0.72, 95% CI 0.67-0.78).

Beyond preventing the first event, SGLT2 inhibitors also reduce the burden of recurrent hospitalizations. In EMPEROR-Reduced, empagliflozin reduced the total number of HHF events by 30% (HR 0.70, 95% CI 0.58-0.85) (Packer et al., 2020). In EMPEROR-Preserved, total hospitalizations were significantly lower in the empagliflozin group (407 vs. 541 events, $p<0.001$) (Anker et al., 2021). This effect on total disease burden is a critical patient-centric outcome, as recurrent hospitalizations are a primary driver of poor quality of life and high healthcare costs in HF. The benefit on HHF is remarkably rapid. The SOLOIST-WHF trial, which enrolled patients with T2DM during or shortly after a hospitalization for worsening HF, showed that sotagliflozin achieved a statistically significant reduction in the composite of total HHF and urgent HF visits within 28 days of randomization (Bhatt et al., 2021).

Table 4. Effect of SGLT2 Inhibitors on Hospitalization for Heart Failure (First and Total Events)

Trial	Outcome	Hazard Ratio (95% CI)	p-value
DAPA-HF	First HHF	0.70 (0.59-0.83)	<0.001

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EMPEROR-Reduced	First HHF	0.69 (0.59-0.81)	-
	Total HHF	0.70 (0.58-0.85)	<0.001
EMPEROR-Preserved	First HHF	0.71 (0.60-0.83)	-
	Total HHF	Rate Ratio 0.73 (0.61-0.88)	<0.001
DELIVER	First HHF	0.79 (0.69-0.91)	-
SOLOIST-WHF	Total HHF & Urgent HF Visits	0.67 (0.52-0.85)	<0.001
Meta-analysis (Vaduganathan et al., 2022)	First HHF	0.72 (0.67-0.78)	-

Mortality Outcomes: Cardiovascular and All-Cause Death

The effect of SGLT2 inhibitors on mortality varies by HF phenotype in individual trials, but a clearer picture emerges from pooled analyses. In HFrEF, a significant mortality benefit has been firmly established. The DAPA-HF trial demonstrated an 18% reduction in CV death (HR 0.82, 95%

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CI 0.69-0.98) and a 17% reduction in all-cause mortality (HR 0.83, 95% CI 0.71-0.97) (Adamson et al., 2023). While EMPEROR-Reduced showed a non-significant trend towards benefit for both outcomes (CV death HR 0.92; all-cause mortality HR 0.92) (Packer et al., 2020), a prespecified meta-analysis of the two trials confirmed a significant 14% reduction in CV death (HR 0.86, 95% CI 0.76-0.98) and a 13% reduction in all-cause mortality (HR 0.87, 95% CI 0.77-0.98) (Packer et al., 2020).

In HFmrEF/HFpEF, the individual landmark trials, EMPEROR-Preserved and DELIVER, did not demonstrate a statistically significant reduction in either CV death or all-cause mortality (Anker et al., 2021; Solomon et al., 2022). This is likely attributable to the lower overall event rates for CV death and the higher proportion of non-CV deaths in the HFpEF population compared to HFrEF, reducing the statistical power to detect a mortality benefit. However, when data are pooled across the entire HF spectrum, a modest but significant mortality benefit emerges. The meta-analysis by Vaduganathan et al. (2022) found a 13% relative risk reduction for CV death (HR 0.87, 95% CI 0.79-0.95) and an 8% reduction for all-cause mortality (HR 0.92, 95% CI 0.86-0.99).

Table 5. Effect of SGLT2 Inhibitors on Cardiovascular and All-Cause Mortality

Trial	Outcome	SGLT2i Group (%)	Placebo Group (%)	Hazard Ratio (95% CI)
DAPA-HF	CV Death	9.6	11.5	0.82 (0.69-0.98)
	All-Cause Death	11.6	13.9	0.83 (0.71-0.97)

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EMPEROR-Reduced	CV Death	10.0	10.8	0.92 (0.75-1.12)
	All-Cause Death	13.4	14.2	0.92 (0.77-1.10)
EMPEROR-Preserved	CV Death	7.3	8.2	0.91 (0.76-1.09)
	All-Cause Death	13.4	14.2	0.92 (0.77-1.10)
DELIVER	CV Death	7.4	8.3	0.88 (0.74-1.05)
	All-Cause Death	15.9	16.8	0.94 (0.83-1.07)
Meta-analysis (Vaduganathan et al., 2022)	CV Death	-	-	0.87 (0.79-0.95)
	All-Cause Death	-	-	0.92 (0.86-0.99)

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Renal Outcomes

A profound nephroprotective effect is another cornerstone benefit of the SGLT2 inhibitor class, consistently observed in both HF and dedicated CKD trials. The dedicated CKD trials provided definitive evidence. In DAPA-CKD, dapagliflozin reduced the primary composite renal outcome (sustained $ \geq 50% $ eGFR decline, end-stage kidney disease, or renal/CV death) by 39% (HR 0.61, 95% CI 0.51-0.72) (Heerspink et al., 2020). In CREDENCE, canagliflozin reduced a similar endpoint by 30% (HR 0.70, 95% CI 0.59-0.82) (Perkovic et al., 2019). Most recently, EMPA-KIDNEY showed a 28% reduction in kidney disease progression or CV death with empagliflozin (HR 0.72, 95% CI 0.64-0.82) (The EMPA-KIDNEY Collaborative Group, 2022).

The HF trials corroborated these findings. Empagliflozin significantly slowed the rate of eGFR decline compared to placebo in both EMPEROR-Reduced (vs. mL/min/1.73m²/year) and EMPEROR-Preserved (vs. mL/min/1.73m²/year) (Packer et al., 2020; Anker et al., 2021). This preservation of kidney function is critically important in the HF population, where cardiorenal syndrome is common and progressive renal dysfunction is associated with poor prognosis (Wheeler et al., 2021).

Table 6. Effect of SGLT2 Inhibitors on Key Renal Outcomes

Trial	Outcome	Hazard Ratio (95% CI)	p-value
DAPA-CKD	Composite Renal Outcome	0.61 (0.51-0.72)	<0.001
CREDENCE	Composite Renal	0.70 (0.59-0.82)	<0.001

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	Outcome		
EMPA-KIDNEY	Kidney Disease Progression or CV Death	0.72 (0.64-0.82)	<0.001
EMPEROR-Reduced	Composite Renal Outcome	0.50 (0.32-0.77)	<0.01
EMPEROR-Preserved	Change in eGFR slope (mL/min/1.73m²/year)	+1.36 vs. Placebo	<0.001

Patient-Reported Outcomes and Quality of Life

Beyond improving hard clinical endpoints, SGLT2 inhibitors consistently enhance patients' quality of life. This was measured in the HF trials using the Kansas City Cardiomyopathy Questionnaire (KCCQ), a well-validated, disease-specific instrument. In DAPA-HF, patients treated with dapagliflozin had a greater improvement in the KCCQ total symptom score (Adamson et al., 2023). In EMPEROR-Reduced and EMPEROR-Preserved, empagliflozin led to early and sustained improvements in the KCCQ-Clinical Summary Score compared to placebo (Packer et al., 2020; Anker et al., 2021). In DELIVER, dapagliflozin also improved KCCQ total symptom scores, with greater benefits seen in more frail patients and those with higher body mass index (BMI) (Solomon et al., 2022). These patient-centric benefits are a crucial component of the value proposition of SGLT2 inhibitors in managing a chronic, symptomatic condition like HF.

Table 7. Effect of SGLT2 Inhibitors on Patient-Reported Outcomes (Kansas City Cardiomyopathy Questionnaire)

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Trial	KCCQ Domain	Mean Difference vs. Placebo (Points)	p-value
DAPA-HF	Total Symptom Score	+2.8	<0.001
EMPEROR-Reduced	Clinical Summary Score (at 52 weeks)	+1.61	<0.05
EMPEROR-Preserved	Clinical Summary Score (at 52 weeks)	+1.50	<0.01
DELIVER	Total Symptom Score (at 8 months)	+2.4	<0.001

Other Key Efficacy Outcomes

The benefits of SGLT2 inhibitors extend to a wide range of other important clinical outcomes. In EMPA-KIDNEY, empagliflozin was the first SGLT2 inhibitor in a CKD trial to demonstrate a significant 14% reduction in all-cause hospitalizations (HR 0.86, 95% CI 0.78-0.95) (The EMPA-KIDNEY Collaborative Group, 2022). An analysis of DAPA-HF showed that dapagliflozin reduced the composite of ventricular arrhythmia, resuscitated cardiac arrest, or sudden death (HR 0.79, 95% CI 0.63-0.99; p=0.037) (McMurray et al., 2019). Furthermore, patients on SGLT2 inhibitors were significantly less likely to require outpatient intensification of diuretic therapy, and pooled analyses showed a reduced risk of hyperkalemia, which may facilitate the use

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of other GDMT (Packer et al., 2020).

Safety and Tolerability

Across this large body of evidence, SGLT2 inhibitors have demonstrated a consistent and favorable safety profile. They are generally well-tolerated, with discontinuation rates due to adverse events comparable to placebo in most trials (Adamson et al., 2023). The most frequently reported adverse event was an increased incidence of genital mycotic infections, which were typically mild to moderate in severity and rarely led to treatment discontinuation (Anker et al., 2021; Zinman et al., 2015).

Despite their diuretic and natriuretic effects, SGLT2 inhibitors did not significantly increase the rates of adverse events related to volume depletion, hypotension, or acute kidney injury compared to placebo (Adamson et al., 2023; Wheeler et al., 2021). Diabetic ketoacidosis (DKA) is a rare but serious adverse event, with a low incidence across the trials (Wiviott et al., 2019). An increased risk of lower-limb amputation was observed with canagliflozin in the CANVAS Program but has not been consistently observed with other SGLT2 inhibitors in subsequent large-scale trials (Neal et al., 2017; Heerspink et al., 2020; Wiviott et al., 2019).

Table 8. Summary of Key Safety Outcomes Across Major Trials

Adverse Event	SGLT2i Group (Typical Incidence)	Placebo Group (Typical Incidence)	Key Finding
Genital Mycotic Infections	3-8%	1-2%	Increased risk, but typically mild and manageable.

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Volume Depletion	~7-9%	~7-9%	No significant increase compared to placebo.
Acute Kidney Injury	~2-5%	~2-6%	No significant increase compared to placebo.
Diabetic Ketoacidosis (DKA)	<0.5%	<0.2%	Rare, but a recognized risk, primarily in T2DM.
Lower-Limb Amputation	~0.6-1.5%	~0.5-1.5%	Risk signal seen with canagliflozin in CANVAS, not confirmed with other agents.

DISCUSSION

Summary of Principal Findings: A Class Effect Across the HF Spectrum

The totality of evidence from more than a dozen landmark clinical trials presents a clear and compelling conclusion: SGLT2 inhibitors represent a fundamental advance in the management of heart failure. This systematic review confirms a powerful class effect characterized by three core pillars of benefit. First, SGLT2 inhibitors produce a rapid, robust, and consistent reduction in hospitalizations for heart failure, a benefit that extends across the entire spectrum of LVEF, from HFrEF to HFpEF (Vaduganathan et al., 2022). Second, they confer a significant survival benefit, which is most clearly established in patients with HFrEF but is also suggested by large meta-

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analyses to extend across the broader HF population (Vaduganathan et al., 2022). Third, they provide profound and consistent cardiorenal protection, slowing the inexorable decline in kidney function that so often complicates HF (Heerspink et al., 2020). Crucially, these benefits are independent of baseline diabetes status, firmly repositioning these agents from their origins as anti-diabetic drugs to true, universal heart failure therapies (Neal et al., 2017; Anker et al., 2021; Figtree et al., 2019).

Mechanistic Insights: Unraveling the Pleiotropic Cardioprotective Effects

The profound clinical benefits of SGLT2 inhibitors cannot be explained solely by their glucose-lowering effects. Instead, they are attributed to a complex interplay of multiple pleiotropic mechanisms that favorably impact cardiac and renal pathophysiology (Cunningham et al., 2022). The initial and most rapid benefits are likely driven by hemodynamic changes. The natriuresis and osmotic diuresis induced by SGLT2 inhibition lead to a modest reduction in plasma volume and interstitial fluid, thereby decreasing both cardiac preload and afterload (Anker et al., 2021; Cunningham et al., 2022). This reduction in cardiac loading conditions alleviates congestion and improves ventricular wall stress without the detrimental neurohormonal activation typically seen with loop diuretics (Packer et al., 2021).

On a cellular level, SGLT2 inhibitors induce a metabolic shift in the failing heart. By promoting mild, persistent ketonemia, they provide the myocardium with ketone bodies, a more energy-efficient fuel source than fatty acids or glucose (Cunningham et al., 2022; Packer et al., 2021). Emerging evidence also suggests direct effects on the heart and vasculature. SGLT2 inhibitors have been shown to modulate the myocardial sodium-hydrogen exchanger (NHE-1), leading to reduced intracellular sodium and calcium concentrations, which can mitigate cytotoxicity and improve mitochondrial function (Packer et al., 2021). Furthermore, they have been demonstrated to reduce oxidative stress, inflammation, and myocardial fibrosis—key drivers of adverse cardiac remodeling in HF (Cunningham et al., 2022; Packer et al., 2021).

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Clinical Implications: A Paradigm Shift in Heart Failure Management

The overwhelming evidence from these trials has precipitated a paradigm shift in HF management. Major international clinical practice guidelines have rapidly incorporated SGLT2 inhibitors as a foundational pillar of GDMT (Vaduganathan et al., 2022). For HFrEF, they now carry a Class I (strongest) recommendation for all symptomatic patients to reduce HHF and mortality (Vaduganathan et al., 2022). For HFpEF and HFmrEF, where therapeutic options have been historically limited, SGLT2 inhibitors are the first drug class to demonstrate a consistent and significant reduction in major HF outcomes, leading to strong recommendations for their use in these populations as well (Anker et al., 2021).

A key advantage facilitating their widespread adoption is their simplicity of use. They are administered as a once-daily oral tablet, do not require titration, and have a favorable safety profile that does not necessitate intensive electrolyte or renal function monitoring (Solomon et al., 2022). This ease of use makes them highly suitable for initiation and management in diverse clinical settings, including primary care, which is critical for ensuring broad and equitable access to this life-saving therapy (Solomon et al., 2022).

Nuances and Heterogeneity of Treatment Effect

While the benefit on HHF is remarkably consistent, the effect on mortality shows some heterogeneity. The clear survival benefit in HFrEF trials versus the neutral effect in individual HFpEF trials likely reflects fundamental differences in the underlying pathophysiology of these conditions (Vaduganathan et al., 2022). HFrEF is largely a syndrome of pump failure and progressive adverse remodeling, where interventions that improve cardiac function can directly impact CV mortality. In contrast, HFpEF is a more heterogeneous syndrome where mortality is often driven by a wider range of non-cardiac comorbidities (Vaduganathan et al., 2022). In this context, a therapy that primarily targets cardiac congestion and remodeling would have its survival benefit diluted by competing risks. The fact that a modest but significant mortality benefit emerges

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in large pooled analyses suggests the effect is real but smaller in magnitude in the HFpEF population (Vaduganathan et al., 2022).

Despite this nuance in mortality, the consistency of benefit across nearly all other prespecified subgroups—including age, sex, race, background HF therapies, and baseline renal function—is a testament to the broad applicability and robustness of SGLT2 inhibitors as a cornerstone HF therapy (McMurray et al., 2019; Vaduganathan et al., 2022; Wiviott et al., 2019).

CONCLUSION AND FUTURE DIRECTIONS

Conclusion

The evidence from a comprehensive portfolio of landmark clinical trials unequivocally establishes sodium-glucose cotransporter-2 inhibitors as a transformative therapeutic class for patients with heart failure. They consistently and significantly reduce the burdensome outcome of hospitalizations for heart failure across the entire spectrum of left ventricular ejection fraction. They provide profound nephroprotection, slowing the progression of chronic kidney disease, a common and devastating comorbidity. Furthermore, they lead to clinically meaningful improvements in patients' symptoms and quality of life. In patients with HFrEF, they also confer a significant survival benefit. These multifaceted benefits are observed in patients with and without type 2 diabetes, cementing the role of SGLT2 inhibitors as a foundational, universal pillar in the modern management of heart failure.

Recommendations for Clinical Practice and Future Research

For Clinical Practice: Based on the robust and consistent evidence, SGLT2 inhibitors should be initiated in all eligible patients with symptomatic chronic HF (NYHA class II-IV), regardless of their LVEF or diabetes status, unless a specific contraindication exists. Their favorable safety profile and ease of use support early and broad implementation to reduce the global burden of heart failure.

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For Future Research: While the current evidence is practice-changing, important questions remain. Further research is needed to define the role of SGLT2 inhibitors in patients with advanced, end-stage HF (NYHA Class IV) and in those who are acutely decompensated. The potential benefit of initiating therapy in the immediate post-myocardial infarction period to prevent the subsequent development of HF is an area of active investigation. Finally, research aimed at identifying specific HFpEF phenotypes that may derive the greatest benefit from SGLT2 inhibition could help to further personalize therapy in this heterogeneous population.

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