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Beyond glycemic control: SGLT2 inhibitors as foundational therapy in heart failure

Lawal Olutoyin Morenike, Hatem Seyid Ahmed, Mohamad Alazzeh, Mohamad Darwish, Aqsa Zafar, Afnan Chaudhry, Daniel Ratliff

Department of Internal Medicine, Phoenexville Hospital Towerhealth, Phoenixville, PA, USA

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Corresponding Author: Afnan Chaudhry, Afnan.chaudhry@towerhealth.org

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ABSTRACT

Heart failure affects over 64 million people worldwide and remains a leading cause of hospitalization, death, and health care costs. Despite advances with renin angiotensin aldosterone system inhibitors, beta blockers, and mineralocorticoid receptor antagonists, survival gains remain modest, and outcomes in preserved ejection fraction disease have historically been poor. This review examines how sodium glucose cotransporter 2 inhibitors, initially developed as glucose lowering agents, have redefined heart failure therapy. We synthesize mechanistic insights, pivotal trial data, and evolving guidelines to clarify their role as foundational treatment across the ejection fraction spectrum. Evidence was drawn from cardiovascular outcome studies, dedicated heart failure trials, mechanistic investigations, and international guidelines, with focus on physiologic mechanisms, efficacy, and safety. Sodium glucose cotransporter 2 inhibitors provide benefits that extend beyond glucose control. They promote sustained diuresis, improve myocardial energetics, reduce inflammation and fibrosis, and protect renal function. Landmark trials including DAPA HF, EMPEROR reduced, EMPEROR preserved, and DELIVER consistently reduced hospitalizations and cardiovascular death across reduced, mildly reduced, and preserved ejection fraction populations, regardless of diabetes status. Benefits emerge early, improve quality of life, and are supported by a favorable safety profile. These findings have rapidly reshaped international guidelines, positioning these drugs alongside renin angiotensin system inhibitors, beta blockers, and mineralocorticoid receptor antagonists as pillars of therapy.

Keywords: SGLT2 inhibitor, heart failure, mortality

INTRODUCTION

Heart failure (HF) affects more than 64 million people worldwide and remains a major driver of morbidity, mortality, and health care expenditures.[1-3] Despite decades of therapeutic innovation, ranging from renin–angiotensin–aldosterone system (RAAS) inhibition to β-blockade and mineralocorticoid receptor antagonism (MRA), survival gains have been modest, and hospitalization rates remain unacceptably high. The burden is particularly stark in heart failure with preserved ejection fraction (HFpEF), where traditional therapies have largely failed to improve outcomes.[3]

The epidemiologic backdrop underscores why emergent therapies are so urgently needed. HF is not only a disease of aging populations in high-income countries but a growing global challenge, affecting younger patients in low and middle income regions as well. The condition accounts for frequent hospital readmissions, reduced quality of life, and escalating healthcare costs.[2]

Against this backdrop, the discovery that sodium-glucose cotransporter-2 (SGLT2) inhibitors originally conceived as glucose-lowering agents for type 2 diabetes mellitus (T2DM) could dramatically reduce HF hospitalizations was nothing short of transformative.[4,5] What began as secondary findings in large cardiovascular outcomes trials (CVOTs) soon spurred dedicated investigations in HF populations, regardless of diabetes status. The arc from incidental observation to guideline-defining therapy has redefined the landscape of HF management. The aim of this mini review is to synthesize current mechanistic insights, pivotal clinical trial evidence, and evolving guideline recommendations to define the role of SGLT2 inhibitors as foundational therapy across the spectrum of HF.

MECHANISMS OF ACTION

The cardioprotective effects of SGLT2 inhibitors extend well beyond their modest glucose lowering properties. Their primary action blocking sodium and glucose reabsorption in the proximal renal tubule results in osmotic diuresis and natriuresis[6,7] (**Figure**). This dual effect reduces intravascular volume and blood pressure, thereby alleviating preload and afterload, two major drivers of HF progression. Unlike traditional loop diuretics, however, the volume reduction

induced by SGLT2 inhibitors is gentle, sustained, and not associated with neurohormonal activation, making them particularly attractive in the chronic HF setting.

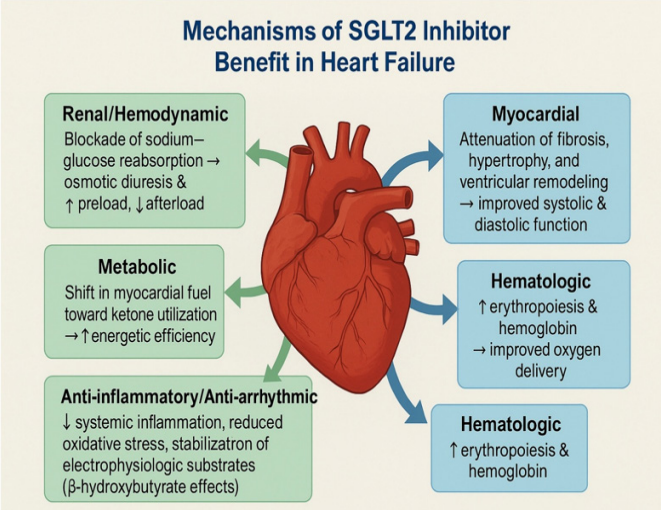

Figure. Mechanisms of SGLT2 inhibitor benefit in heart failure

Beyond volume management, SGLT2 inhibition reshapes cardiac metabolism. The failing myocardium is metabolically inflexible, often unable to efficiently utilize glucose or free fatty acids. By promoting mild ketosis, these agents shift myocardial substrate preference toward ketone bodies, which provide a more energy-efficient fuel for the stressed heart.[7] This "metabolic reprogramming" improves myocardial work efficiency and may explain the rapid symptomatic gains observed in clinical trials.

The pleiotropic effects extend to structural remodeling. Experimental studies suggest that SGLT2 inhibitors attenuate myocardial fibrosis, reduce oxidative stress, and downregulate pro-inflammatory cytokines. β-hydroxybutyrate, a ketone body elevated under SGLT2 inhibition, exerts direct anti-inflammatory and anti-arrhythmic effects, potentially reducing sudden cardiac death risk.[8]

Systemically, SGLT2 inhibitors enhance oxygen delivery by stimulating erythropoietin production, increasing hematocrit and hemoglobin levels.[9,10] This effect may mitigate anemia, a common comorbidity in HF, and further improve functional capacity. Renally, they lower intraglomerular pressure and prevent hyperfiltration, thus protecting against chronic kidney disease (CKD), a frequent companion of HF and an amplifier of poor prognosis.

Collectively, these multidimensional mechanisms establish SGLT2 inhibitors as comprehensive organ-protective therapies, simultaneously modulating hemodynamic, metabolic, renal, and hematologic pathways.

EVIDENCE IN HEART FAILURE WITH REDUCED EJECTION FRACTION (HFrEF)

The paradigm-shifting DAPA-HF trial, published in 2019, enrolled patients with symptomatic HFrEF (LVEF ≤40%), with and without diabetes, and showed that dapagliflozin reduced the composite of worsening HF or cardiovascular death by 26%.[11] Importantly, the benefit emerged early within weeks of initiation, underscoring a direct and rapid disease modifying effect. Subgroup analyses confirmed efficacy across diabetic and non-diabetic populations, cementing the notion that cardioprotection is independent of glycemic control.

The EMPEROR-Reduced trial extended these observations with empagliflozin, demonstrating reductions not only in HF hospitalizations but also in the rate of decline in renal function.[12] This renal protection is particularly relevant since CKD is both highly prevalent in HFrEF and a major driver of adverse outcomes.

Meta-analysis of DAPA-HF and EMPEROR-Reduced confirmed consistent reductions in cardiovascular mortality and HF hospitalizations.[13] The pooled data reinforce the robustness of benefit and highlight class effects rather than drug-specific actions.

Beyond hard clinical endpoints, trials also documented meaningful improvements in patient-centered outcomes. DEFINE-HF demonstrated improvements in health status and quality of life measures, reflecting symptomatic relief that translates into tangible patient benefit.[14] EMPA-TROPISM, a mechanistic study in non-diabetic HFrEF patients, provided structural evidence: empagliflozin induced reverse left ventricular remodeling, reduced volumes, and improved systolic function, thereby offering imaging correlates of clinical benefit.[8]

The cumulative evidence has firmly established SGLT2 inhibitors as one of the four foundational therapies for HFrEF, alongside ARNIs, β-blockers, and MRAs. Their inclusion represents not just an incremental advance but a leap forward in the comprehensive management of systolic HF.

EVIDENCE IN HF WITH PRESERVED AND MILDLY REDUCED EF (HFpEF, HFmrEF)

HFpEF has long been considered a therapeutic void, with numerous trials of RAAS inhibition, ARBs, and ARNIs failing to produce consistent outcome improvements. SGLT2 inhibitors have changed this narrative.

The EMPEROR-preserved trial demonstrated that empagliflozin significantly reduced the composite of cardiovascular death or HF hospitalization in patients with LVEF >40%, a Landmark achievement given decades of trial failures in this domain.[15] Importantly, the benefits were consistent across prespecified subgroups, including those without diabetes.

DELIVER, evaluating dapagliflozin in a similar population, not only confirmed reductions in HF hospitalizations but also demonstrated benefit in patients with mildly reduced EF (HFmrEF, LVEF 41–49%).[16] Together, EMPEROR-Preserved and DELIVER established that SGLT2 inhibitors deliver consistent clinical benefit across the entire EF spectrum.

Symptom-oriented trials such as DEFINE-Preserved and PRESERVED-HF further reinforced their role, showing improvements in patient-reported outcomes including quality of life and symptom burden.[17,18] While EMPERIAL-Preserved failed to demonstrate significant gains in six-minute walk distance, this likely reflects the heterogeneity

of HFpEF, where symptom improvement does not always translate to measurable functional capacity.[19]

A meta-analysis synthesizing these findings by Jaiswal et al.[20] confirmed that SGLT2 inhibitors reduce HF hospitalizations across HFpEF and HFmrEF, cementing them as the first truly effective pharmacologic class in this setting. The implication is profound as HFpEF is no longer a therapeutic void, but a condition with an evidence-based treatment option (**Table**).

GUIDELINE PERSPECTIVES

The rapid accumulation of evidence has translated into equally rapid changes in guideline recommendations. The 2021 European Society of Cardiology (ESC) guidelines awarded SGLT2 inhibitors a class I recommendation for HFrEF, but at the time refrained from extending this to HFpEF or HFmrEF given the lack of trial data.[21]

Just a year later, the 2022 AHA/ACC/HFSA guidelines incorporated results from EMPEROR-preserved and DELIVER, providing SGLT2 inhibitors with a class IIa recommendation for both HFmrEF and HFpEF.[22] This shift underscores how quickly clinical practice has been reshaped.

In 2024, the ACC Expert consensus placed further emphasis on the early initiation of SGLT2 inhibitors in HFrEF, advocating for rapid sequencing of all four pillars of therapy, informed by data from the STRONG-HF trial.[23,24] This reflects a broader cultural change in HF management: moving away from sequential uptitration toward aggressive, early, multidrug initiation to maximize survival gains.

SAFETY AND SPECIAL POPULATIONS

The tolerability of SGLT2 inhibitors has been key to their widespread uptake. Adverse events are generally mild and manageable. Genital mycotic infections are the most common but rarely necessitate discontinuation.[25] Volume-related effects, such as dizziness or hypotension, can occur but are usually mild.

Concerns about euglycemic diabetic ketoacidosis are limited to a small subset of insulin-dependent patients, where education and monitoring mitigate risk.[26] The CANVAS program's signal of increased amputations and fractures with canagliflozin has not been observed consistently across other agents.[5]

Importantly, renal function should not preclude use. Although SGLT2 inhibitors cause an early, modest dip in estimated glomerular filtration rate (eGFR), long-term effects are renoprotective. Clinical trials support their use down to eGFR thresholds of 20–25 mL/min/1.73 m^2. Elderly and frail populations, often underrepresented in clinical research, have not demonstrated excess harm, supporting generalizability.[27]

This safety profile allows SGLT2 inhibitors to be applied broadly across diverse HF populations, including those with advanced CKD, frailty, and polypharmacy.

LIMITATIONS

Despite their transformative impact, several limitations of the current SGLT2 inhibitor evidence base must be acknowledged. First, most pivotal trials were designed with composite endpoints driven largely by reductions in HF hospitalizations, while the effect on all-cause mortality remains more modest. Although meta-analyses suggest a survival benefit, longer-term follow-up is needed to fully establish their impact on mortality.[13,20]

Second, patients enrolled in Landmark trials may not fully represent the broader HF population. Individuals with advanced HF (NYHA IV), those requiring inotropes, and patients with severe renal impairment were often underrepresented or excluded. Similarly, frail elderly patients and those with multiple comorbidities—who constitute a substantial proportion of real-world HF—require further study.

Third, while safety signals have been generally reassuring, questions remain. The risk of euglycemic diabetic ketoacidosis, though rare, is clinically significant in insulin-treated patients.[26] Observations of amputation risk in CANVAS[5] have not been replicated, but residual uncertainty persists, particularly in populations with peripheral arterial disease.

Fourth, mechanistic explanations, though compelling, are still incompletely understood. The relative contributions of hemodynamic unloading, metabolic remodeling, renal

Table. Landmark clinical trials of SGLT2 inhibitors in heart failure

Trial	Population (n)	EF range	Key outcome	Main findings
DAPA-HF (2019)[11]	4744	HFrEF (≤40%), ±DM	CV death or HF hospitalization	↓ risk by 26%; benefit irrespective of diabetes
EMPEROR-reduced (2020)[12]	3730	HFrEF (≤40%), ±DM	CV death or HF hospitalization	↓ risk by 25%; slower eGFR decline
DEFINE-HF (2019)[14]	263	HFrEF (≤40%), ±DM	KCCQ health status	Improved symptoms/quality of life
EMPA-TROPISM (2021)[15]	84 (non-DM)	HFrEF (≤40%)	LV remodeling	Reverse remodeling, improved LVEF
EMPEROR-preserved (2021)[16]	5988	HFpEF (≥50%)±HFmrEF	CV death or HF hospitalization	↓ risk by 21%, driven by ↓ HF hospitalization
DELIVER (2022)[17]	6263	HFpEF (≥40%), HFmrEF	CV death or HF hospitalization	↓ risk consistent across EF spectrum
PRESERVED-HF (2021)[19]	324	HFpEF (≥45%)	KCCQ health status	Improved QoL and functional status
DEFINE-preserved (2021)[18]	289	HFpEF (≥45%)	NT-proBNP & KCCQ	Symptom and biomarker improvement
EMPERIAL-preserved (2020)[20]	315	HFpEF (≥45%)	6MWT distance	Neutral; no improvement in exercise capacity

CV: Cardiovascular, HF: Heart failure, HFrEF: HF with reduced EF, HFmrEF: HF with mildly reduced EF, HFpEF: HF with preserved EF, KCCQ: Kansas City Cardiomyopathy Questionnaire, LVEF: Left ventricular ejection fraction, EF: Ejection fraction, eGFR: Estimated glomerular filtration rate

protection, and hematologic effects remain debated. Translational studies are needed to clarify how these pathways interact and to identify biomarkers predictive of response.

Finally, implementation challenges cannot be ignored. Cost, access disparities, and therapeutic inertia may limit uptake. In many regions, access to newer HF therapies is constrained by socioeconomic and health system factors, threatening to widen existing disparities in care.[29]

Addressing these limitations through dedicated research, registry data, and health policy initiatives will be essential to realizing the full promise of SGLT2 inhibitors in HF.

FUTURE DIRECTIONS

The therapeutic frontier continues to expand. The EMMY trial suggested that early post-myocardial infarction initiation of SGLT2 inhibitors improves biomarkers of remodeling, raising the possibility that these drugs may prevent HF onset after acute coronary events.[28] Ongoing large trials such as EMPACT-MI and DAPA-MI will test whether these early signals translate into reductions in clinical HF or recurrent ischemic events.

Other areas of interest include advanced HF requiring device therapy or inotropes, where the safety and efficacy of SGLT2 inhibitors remain under investigation. Their potential to modulate anemia and improve outcomes in cardiorenal syndromes is also under study.[9]

Beyond disease treatment, prevention is a tantalizing prospect. Given their efficacy across diabetic and non-diabetic populations, SGLT2 inhibitors could be deployed in high-risk individuals to forestall the development of overt HF. Cost-effectiveness analyses suggest that reduced hospitalizations offset drug costs, making widespread adoption both clinically and economically viable.[30]

The next decade will likely see integration of SGLT2 inhibitors into broader preventive and precision medicine strategies, guided by biomarkers, imaging phenotypes, and individualized risk profiles.

CONCLUSION

Few drug classes in modern medicine have transformed clinical practice as swiftly as SGLT2 inhibitors. Originally conceived as glucose lowering agents through the simple mechanism of inducing glucosuria, they have rapidly emerged as a cornerstone of HF therapy. Today, they sit at the very center of HF management, consistently reducing hospitalizations, mortality, and symptom burden, while simultaneously safeguarding renal function and improving systemic physiology across the entire ejection fraction spectrum.

Their ascent is more than the sum of trial outcomes. It is a story of serendipity meeting translational science, brought to life by rigorous clinical validation. What began as a metabolic therapy has become a paradigm shifting discovery that redefines the boundaries of cardiometabolic care. The task ahead is no longer to prove efficacy but to ensure these benefits reach all patients equitably, overcoming barriers to access, adoption, and the exploration of new indications.

Together with ARNIs, beta blockers, and MRAs, SGLT2 inhibitors now anchor the modern foundation of HF therapy. Yet their trajectory is far from complete. With expanding applications across the spectrum of cardiovascular and metabolic disease, they are poised to stand among the most influential therapeutic breakthroughs of the twenty first century, an exemplar of how science can reshape lives when opportunity, innovation, and persistence converge.

ETHICAL DECLARATIONS

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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