IOSR Journal of Research & Method in Education (IOSR-JRME)
e-ISSN: 2320–7388, p- ISSN: 2320-737x Volume 16, Issue 5 Ser. I (Sep. – Oct. 2026) 12-15
www.iosrjournals.org

Comparative Review of Sglt2 Inhibitors in Heart Failure Management

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Abstract

Sodium–glucose cotransporter 2 (SGLT2) inhibitors have rapidly evolved from glucose-lowering agents to cornerstone therapies in heart failure (HF) management, offering cardioprotective and renoprotective benefits independent of glycemic control. This review consolidates evidence from major clinical trials, including DAPA-HF, EMPEROR-Reduced, EMPEROR-Preserved, and DELIVER, comparing the efficacy and safety of agents such as dapagliflozin and empagliflozin across different HF phenotypes. SGLT2 inhibitors exert their therapeutic benefits through multifactorial mechanisms—reducing renal glucose and sodium reabsorption, promoting natriuresis, improving cardiac energy metabolism, and mitigating oxidative stress and inflammation. These effects translate into substantial reductions in HF hospitalizations, cardiovascular mortality, and renal function decline in both diabetic and non-diabetic populations. Contemporary guidelines from the ESC (2023) and AHA/ACC/HFSA (2022) now advocate SGLT2 inhibitors as a foundational class of heart failure therapy, alongside ARNIs, beta-blockers, and MRAs, across the spectrum of ejection fractions. Emerging studies such as EMPACT-MI and DAPA-MI continue to explore their role in acute coronary settings, while combination strategies with GLP-1 receptor agonists offer synergistic cardiometabolic benefits. Overall, SGLT2 inhibitors represent a transformative advance in heart failure management, integrating metabolic and cardiovascular benefits that re-define standard-of-care and future therapeutic directions.

Keywords*: SGLT2 inhibitors; Heart failure; Dapagliflozin; Empagliflozin; HFrEF; HFpEF; Cardiovascular outcomes; Renal protection; Natriuresis; Cardioprotection.*

Date of Submission: 27-08-2026 Date of Acceptance: 06-09-2026

I. INTRODUCTION

SGLT2 Inhibitors have recently emerged as pivotal agents in the management of heart failure , driven by compelling evidence from randomized clinical trials and systematic reviews.Their role is increasingly recognized not just in patients with diabetes mellitus, but also in those with preserved or reduced ejection fraction, regardless of underlying glycemic status. Traditionally used as antihyperglycaemic agents,SGLT2 inhibitors now hold clinical importance due to notable benefits on cardiovascular outcomes , renal function preservation , and quality of life for heart failure patients.

Recent clinical trials such as DAPA - HF and EMPEROR - Reduced have shown that SGLT2 inhibitors -when combined with standard heart failure therapies -can significantly reduce hospitalizations rates and cardiovascular mortality among both diabetic and non diabetic populations. The landmark EMPA-REG-OUTCOME study first demonstrated robust reductions in major adverse cardiovascular events among patients with type 2 diabetes , and subsequent heart failure - specific trials confirmed these findings among broader patient groups.

Meta analysis and comparative data consistently indicate that SGLT2 inhibitors such as dapagliflozin and empagliflozin yield substantial improvements in clinical endpoints , including reduced risk of heart failure progression , lowered hospitalizations rates , and decreased cardiovascular death.Furthermore, these agents help attenuate renal decline , supporting comprehensive management strategies for both chronic heart failure and comorbid diabetic nephropathy.

Overall, this review consolidates and analyzes current evidence regarding the efficacy, safety, and therapeutic impact of SGLT2 Inhibitors in heart failure , aiming to provide clinicians and researchers with an updated perspective on their integration into modern heart failure management protocols. Ongoing studies continue to explore optimal patient selection,combination therapy approaches and long-term outcomes, reinforcing the trans-formative potential of SGLT2 inhibitors in cardiovascular medicine.

SGLT2 INHIBITORS AS GLUCOSE - LOWERING AGENTS

SGLT2 inhibitors primarily target sodium-glucose co-transporters located in the proximal convoluted tubule of the kidney ,leading to reduced glucose and sodium reabsorption . This mechanism promotes glycosuria and facilitates improved glycemic control while inducing modest natriuresis. The early development of SGLT2 inhibitors was driven by promising resukts on lowering blood glucose and mitigating hyperglycemia in animal studies , leading to advanced clinical trials.

Over the past decade , randomized controlled trials have established the glycemic efficacy of SGLT2 inhibitors, with agents such as empagliflozin, dapagliflozin, and canagliflozin now widely incorporated into type 2 diabetes management guidelines . Following the identification of safety concerns with certain antidiabetic drugs, regulatory agencies (such as FDA)have required new therapies to demonstrate positive cardiovascular outcomes , shaping the evidence base that supports the use of SGLT2 inhibitors in both diabetes and heart failure treatment.

MECHANISM OF ACTION OF SGLT2 INHIBITORS IN CARDIOMETABOLIC DISEASE

SGLT2 inhibitors or sodium -glucose -co transporter 2 inhibitors have a multifaceted mechanism of action in cardio-metabolic disease that extends beyond glucose control. The primary effects as well as their secondary benefits relevant to the heart,kidneys and metabolism.

PRIMARY RENAL MECHANISM

BLOCK RENAL GLUCOSE REABSORPTION :

SGLT2 inhibitors act on the SGLT2 proteins in the proximal renal tubules , inhibiting the reabsorption of about 90% of filtered glucose back into the bloodstream. This induces glycosuria (urinary glucose excretion) and subsequently lowers blood glucose levels independently of insulin secretions or action.

NATRIURESIS AND DIURESIS :

Along with glucose, sodium reabsorption is blocked , promoting osmotic diuresis and mild natriuresis, reducing plasma volume and preload on the heart.

CARDIOVASCULAR AND METABOLIC EFFECTS

- BLOOD PRESSURE REDUCTION :

Osmotic diuresis and natriuresis reduce blood pressure , which benefits patients with heart failure and reduces cardiovascular risk.

- IMPROVED CARDIAC AND VASCULAR FUNCTION :

SGLT2 inhibitors reduce glomerular and vascular pressure lower inflammation , decrease oxidative stress and improve endothelial function contributing to vascular and myocardial protection.

- SHIFT IN SUBSTRATE UTILIZATION :

The drugs promote a shift from glucose to fatty acid and ketone metabolism in cardiac cells , which is thought to benefit energy efficiency in the falling heart.

- REDUCED WEIGHT AND INSULIN RESISTANCE :

Loss of calories through glucosuria leads to modest weight loss and improved insulin sensitivity and lipid metabolism.

RENAL PROTECTION :

-RESTORE TUBULOGLOMERULAR FEEDBACK
By allowing more sodium to reach the macula densa , SGLT2 inhibitors restore tubuloglomerular feedback , reduce3 intra glomerular pressure and mitigate kidney hyper filtration , thus showing the progression of nephropathy.
-INHIBITION OF NHE3 :
SGLT2 inhibitors may inhibit sodium/hydrogen exchanger 3 (NHE3) further promoting natriuresis and reno protection.

ADDITIONAL MECHANISMS
Other proposed mechanisms include reduced serum uric acid levels, increased erythropoiesis improving oxygen delivery and decreased epicardial fat mass.

HEART FAILURE WITH REDUCED EJECTION FRACTION

(HFrEF)Studies investigating cardiovascular outcomes in individuals with type 2 diabetes revealed a decreased risk of cardiovascular death and heart failure hospitalizations, resulting in dedicated evaluation of SGLT2 inhibitors within heart failure treatment. The DAPA-HF trial was the first to examine dapagliflozin in those with HFrEF (left ventricular ejection fraction [LVEF]<40%), involving 4744 subjects and a median follow-up of 18 months. The trial found dapagliflozin substantially lowered the composite outcome of cardiovascular death, hospitalizations for heart failure, and urgent heart failure visits compared to placebo, with the majority of the benefit arising from a reduction in hospitalizations.Results were consistent regardless of diabetes status, and similar findings emerged from the EMPEROR-Reduced study with empagliflozin in 3730 patients with diminished LVEF. This study showed a 21% relative risk reduction in the combined endpoint of cardiovascular death and heart failure hospitalization, with much of the effect related to fewer hospitalizations. A pooled analysis of these trials further verified a meaningful decrease in both overall mortality and the composite endpoint, demonstrating the strong effectiveness of SGLT2 inhibitors in HFrEF.

HEART FAILURE WITH PRESERVED EJECTION FRACTION

(HFpEF)Heart failure with preserved ejection fraction (HFpEF) is a complex syndrome, often linked to impaired relaxation of the heart and commonly seen among older adults with interconnected heart and kidney comorbidities. Representing roughly half of all heart failure presentations, HFpEF is distinct from HFrEF with its own therapeutic challenges. Initial evidence for SGLT2 inhibitors in HFpEF came from the SOLOIST-WHF study, which indicated these drugs could reduce major cardiovascular events among patients with both HFpEF and diabetes.This was supported by the EMPEROR-Preserved trial, which specifically assessed empagliflozin in 5988 individuals with HFpEF (LVEF>40%, NYHA class II-IV). Empagliflozin achieved a 19% reduction in the primary endpoint of cardiovascular death and heart failure hospitalization, mainly driven by a 27% decrease in heart failure hospitalizations, with improvements seen as soon as 18 days after starting therapy. The benefit was less pronounced in those with LVEF greater than 60%, implying the most substantial effect occurred within the lower range of preserved EF. Importantly, the benefit was observed regardless of diabetes status.The DELIVER trial further explored dapagliflozin in those with both HFrEF and HFpEF, including patients whose LVEF had recovered beyond 40% with therapy. Enrolling 6263 subjects and a median follow-up of 2.3 years, DELIVER demonstrated that dapagliflozin reduced the composite of unplanned heart failure hospitalizations, urgent visits, and cardiovascular death by 18% compared to placebo, with the majority of benefit attributed to a 21% reduction in hospitalizations and urgent visits. In contrast with EMPEROR-Preserved, the reduction in the composite outcome was maintained even in those with LVEF ≥ 60%, pointing to a broader efficacy profile for dapagliflozin within the HFpEF population.

CURRENT PRACTICE GUIDELINES FOR HEART FAILURE

Modern guidelines for the management of heart failure (HF), including the 2023 ESC update, highlight an evidence-driven and patient-centered approach tailored to HF subtypes and disease stages. The 2022 AHA/ACC/HFSA heart failure guidelines provide comprehensive recommendations spanning prevention, diagnosis, and therapeutic strategies, all reflecting the latest research evidence.The ICARDIO Alliance Global Implementation Guidelines (2025) address global disparities in HF care, integrating advances in therapy while accounting for resource constraints to improve patient outcomes worldwide. The 2023 ESC guideline revision emphasizes rapid initiation and up-titration of guideline-directed therapy, particularly the foundational four classes for HFrEF—SGLT2 inhibitors, angiotensin receptor neprilysin inhibitors (ARNIs), beta-blockers, and mineralocorticoid receptor antagonists (MRAs). These same classes now underpin recommendations for patients

with mildly reduced or preserved ejection fraction (HFmrEF/HFpEF), reflecting strong evidence for SGLT2 inhibitors across the spectrum of HF phenotypes.

II. FUTURE DIRECTIONS

Emerging research continues to expand the scope of SGLT2 inhibitors in CV medicine. Studies such as EMPACT-MI and DAPA-MI are investigating the role of these agents in acute and post-myocardial infarction settings, with a focus on reducing adverse cardiovascular events and improving survival. Mechanistic studies further suggest benefits that go beyond glycemic and volume effects, including anti-inflammatory actions, improved myocardial energetics, cardiac metabolism, and protection against adverse remodeling.Notably, SGLT2 inhibitors are now recognized as the only drug class recommended for all heart failure patients to improve prognosis regardless of ejection fraction. Long-term studies will clarify optimal timing, dosing, and combinations with other therapies to maximize both cardiac and renal outcomes.

Role of SGLT2 inhibitors in the management of heart Combination therapy using SGLT2 inhibitors with GLP-1 receptor agonists is emerging as an innovative approach that may offer synergistic effects. This strategy leverages multiple metabolic pathways, with the potential to improve glycemic regulation, support weight loss, and amplify protective benefits for cardiovascular and renal systems. Evidence from clinical trials such as DURATION-8 and AWARD-10 has indicated that combining these agents is both safe and effective, but further studies are necessary to better understand long-term outcomes and to refine criteria for patient selection.Additionally, new agents and dual-action compounds that offer superior selectivity and safetyprofiles are under development, aiming to expand treatment options. Preferentially tailored therapies, such as individualized use of SGLT2 inhibitors and GLP-1 agonists, incorporate patient-specific risk profiles and underlying comorbid conditions—this personalized medicine approach may shape the future of cardiovascular and metabolic care.

III. CONCLUSION

Looking ahead, the failure and cardiovascular disease is expected to broaden, with expanding clinical applications, combined regimens, and a greater focus on mechanistic precision medicine to optimize patient outcomes. These agents are now established as essential therapeutics for reducing morbidity and mortality in heart failure patients, irrespective of left ventricular ejection fraction. While the mechanisms underpinning their benefits are still under investigation, current research points to various metabolic and biomolecular pathways that contribute to their cardioprotective and renoprotective effects.SGLT2 inhibitors demonstrate efficacy not only in heart failure, but also in patients with type 2 diabetes and chronic kidney disease. Maximizing the appropriate use of these drugs across relevant populations is vital for improving event-free survival and reducing overall health care costs.

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