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ADVANCES IN HEART FAILURE MANAGEMENT: SGLT2 INHIBITORS BEYOND DIABETES

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Annotation: This article reviews the emerging role of sodium-glucose cotransporter 2 (SGLT2) inhibitors in the treatment of heart failure (HF), extending beyond their original use in managing type 2 diabetes mellitus. Recent landmark clinical trials have demonstrated that SGLT2 inhibitors such as dapagliflozin and empagliflozin significantly reduce cardiovascular mortality and hospitalization for heart failure in both diabetic and non-diabetic patients.

Key Words: *device-based therapies, glucose-lowering properties, systemic inflammation, cardiovascular safety, cardiovascular medicine*.

INTRODUCTION

Heart failure (HF) is a progressive clinical syndrome resulting from structural or functional impairment of ventricular filling or ejection of blood, leading to inadequate systemic perfusion and a constellation of symptoms such as dyspnea, fatigue, and fluid retention. It represents a major global public health challenge, affecting over 64 million people worldwide, with high rates of hospitalization, morbidity, and mortality. Despite advances in pharmacological and device-based therapies, the burden of HF continues to grow due to aging populations and increasing prevalence of risk factors such as hypertension, obesity, and diabetes mellitus. Traditionally, heart failure management has focused on neurohormonal modulation through agents like angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), beta-blockers, and mineralocorticoid receptor antagonists. While these therapies improve survival and reduce hospitalizations, residual risk remains substantial, especially in patients with heart failure with preserved ejection fraction (HFpEF), a subgroup for which effective treatments have long been elusive.

LITERARY ANALYSIS

The advent of sodium-glucose cotransporter 2 (SGLT2) inhibitors marks a significant milestone in the management of cardiovascular diseases. Originally developed to improve glycemic control in patients with type 2 diabetes mellitus (T2DM), SGLT2 inhibitors have

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unexpectedly demonstrated powerful cardioprotective effects independent of their glucose-lowering properties. Large-scale randomized controlled trials have consistently shown that these agents reduce heart failure hospitalizations and cardiovascular mortality not only in diabetic patients but also in non-diabetic individuals with heart failure. This expanding body of evidence has sparked a paradigm shift, positioning SGLT2 inhibitors as a novel cornerstone in heart failure therapy. Their unique mechanisms, which involve modulation of renal sodium handling, cardiac metabolism, and systemic inflammation, offer new hope for patients with both heart failure with reduced ejection fraction (HFrEF) and HFpEF. This article aims to explore the advances in heart failure management brought about by SGLT2 inhibitors beyond diabetes, highlighting their mechanisms of action, clinical trial data, safety considerations, and future prospects in cardiovascular medicine.

Heart failure (HF) and type 2 diabetes mellitus (T2DM) often occur together with an associated increased risk of adverse outcomes. HF is one of the most common cardiovascular conditions and one of the major causes of mortality in patients with T2DM. Furthermore, T2DM is frequent in patients with HF, occurring in almost 40% of patients hospitalised for HF and up to 30% of those with chronic HF. Despite numerous available treatments for HF, the prognosis remains poor, with a small increase in survival over the last decade. Concomitant T2DM confers a worse prognosis in HF, as the risks of cardiovascular and all-cause mortality are significantly increased, independent of other factors.

Over the last decade, cardiovascular outcome trials have investigated several classes of new glucose-lowering agents, including dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 receptor agonists and sodium–glucose co-transporter 2 (SGLT2) inhibitors, and all have demonstrated cardiovascular safety in patients with T2DM. Furthermore, some of these agents have been proven to have beneficial effects in reducing both major adverse cardiovascular events (MACE), as well as hospitalisation for HF, and a few of these drugs have also reduced cardiovascular mortality (i.e. empagliflozin in EMPA-REG OUTCOME7 and liraglutide in LEADER). Of particular importance has been the consistent finding of a reduction in HF hospitalisations in trials with SGLT2 inhibitors (empagliflozin, canagliflozin, and dapagliflozin) in patients with T2DM. Also, there was a consistent finding of renal protection in T2DM with these drugs. The safety profile and position of the new glucose-lowering agents in T2DM in general has been described in the 2019 European Society of Cardiology guidelines on diabetes, pre-diabetes, and cardiovascular diseases, the 2019 Heart Failure Association (HFA) position paper on the role and safety of new glucose-lowering medications, and the HFA

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clinical practice update on HF. These documents suggest that SGLT2 inhibitors, empagliflozin, canagliflozin and dapagliflozin, can be used to prevent HF hospitalisation in patients with T2DM.

RESULT AND DISCUSSION

In addition to clinical outcomes, a potential for an improvement in functional status has been recently explored with SGLT2 inhibitors. The effect of SGLT2 inhibitors on exercise tolerance in patients with HFrEF with and without T2DM is still under debate as the DEFINE-HF trial has not shown a significant effect of dapagliflozin on mean NT-proBNP levels, but increased the proportion of patients achieving a combined endpoint of improved functional status (as measured by the KCCQ), or ≥20% reduction in NT-proBNP. The results of DEFINE-HF trial could be considered as hypothesis generating. In contrast to these results, according to the recent press release, the EMPERIAL Reduced and Preserved trials failed to demonstrate an effect of empagliflozin on functional status in patients with HFrEF and HF with preserved ejection fraction (HFpEF), with and without T2DM over a period of 3 months. After these disappointing head-line results became known, the DETERMINE Reduced and Preserved trials (testing the impact of dapagliflozin vs. placebo on quality of life and functional capacity over 3 months) changed their primary endpoint to be quality of life-focused (rather than relying on 6-min walking test distance as originally planned) and they were somewhat increased in size to improve power. Quality of life improvement may, however, need longer periods of time to become apparent (i.e. 8 months in DAPA-HF), but if achieved, would lend support to a possibility of decreasing the burden of HF symptoms with SGLT2 inhibitor treatment.

Trial	Population	Drug	Diabetes Status	Primary Outcome	Relative Risk Reduction (RRR)	Hazard Ratio (HR)	P-Value
DAPA-HF (2019)	HFrEF (EF ≤ 40%), n=4,744	Dapagliflozin	45% non-diabetic	CV death or HF hospitalization	26%	0.74	<0.001

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Trial	Population	Drug	Diabetes Status	Primary Outcome	Relative Risk Reduction (RRR)	Hazard Ratio (HR)	P-Value
EMPEROR-Reduced (2020)	HFrEF (EF ≤ 40%), n=3,730	Empagliflozin	~50% non-diabetic	CV death or HF hospitalization	25%	0.75	<0.001
EMPEROR-Preserved (2021)	HFpEF (EF > 40%), n=5,988	Empagliflozin	~50% non-diabetic	HF hospitalization	21%	0.79	<0.001
DELIVER (2022)	HFmrEF/HFpEF (EF > 40%), n=6,263	Dapagliflozin	44% non-diabetic	CV death or HF hospitalization	18%	0.82	0.009
SOLOIST-WHF (2020)	Acute HF with T2DM, n=1,222	Sotagliflozin	100% diabetic	CV death, HF hospitalization, urgent HF visit	33%	0.67	<0.001

Table 1 summarizes the pivotal clinical trials evaluating the efficacy of SGLT2 inhibitors in patients with heart failure (HF), both with and without type 2 diabetes mellitus (T2DM). The evidence across all major studies consistently demonstrates significant cardiovascular benefits of SGLT2 inhibitors beyond glycemic control. In the DAPA-HF trial, involving 4,744 patients with HFrEF, dapagliflozin led to a 26% relative risk reduction in the composite outcome of cardiovascular (CV) death or worsening heart failure, with a hazard ratio (HR) of 0.74 (p<0.001). Notably, this benefit was independent of diabetic status, with approximately 45% of the cohort being non-diabetic. Similarly, the EMPEROR-Reduced trial showed that empagliflozin reduced the risk of CV death or HF hospitalization by 25% (HR 0.75, p<0.001) in patients with HFrEF, of whom nearly half were non-diabetic. This trial also demonstrated renal protective effects, with a slower decline in eGFR in the treatment group.

A key turning point in heart failure management came with the EMPEROR-Preserved trial, which enrolled patients with HFpEF (EF >40%). Empagliflozin significantly reduced the risk of HF hospitalization by 21% (HR 0.79, p<0.001), making it the first therapy to show meaningful benefit in HFpEF—a condition historically resistant to treatment. These benefits were again observed across both diabetic and non-diabetic populations. The deliver trial confirmed these findings in a similar population (EF >40%) using dapagliflozin. Among the 6,263 patients enrolled, the drug reduced the risk of CV death or HF hospitalization by 18% (HR 0.82, p=0.009), with consistent results in subgroups regardless of ejection fraction or diabetes status. Finally, the SOLOIST-WHF trial focused on patients with acute worsening HF and T2DM. Sotagliflozin, a dual SGLT1/SGLT2 inhibitor, achieved a 33% risk reduction in a composite endpoint of CV death, HF hospitalization, or urgent HF visits (HR 0.67, p<0.001). Although this study involved only diabetic patients, it reinforced the cardiovascular benefits of SGLT inhibition even in the acute setting.

CONCLUSION

The emergence of SGLT2 inhibitors as a cornerstone therapy in heart failure represents one of the most significant therapeutic advances in recent cardiovascular medicine. Originally developed as glucose-lowering agents for type 2 diabetes mellitus, SGLT2 inhibitors have demonstrated robust, consistent, and clinically meaningful benefits in reducing cardiovascular mortality, hospitalization for heart failure, and renal disease progression—independent of glycemic status. Large-scale clinical trials such as DAPA-HF, EMPEROR-Reduced, EMPEROR-Preserved, and DELIVER have established the efficacy of dapagliflozin and empagliflozin across the full spectrum of ejection fraction, with benefits extending equally to diabetic and non-diabetic patients. These findings confirm that the mechanisms of action of SGLT2 inhibitors are pleiotropic, involving hemodynamic, metabolic, and cellular effects that go far beyond glucose control. International guidelines now recommend SGLT2 inhibitors as first-line or adjunctive therapy for patients with HFrEF and HFpEF, marking a shift toward more comprehensive, patient-centered management. Furthermore, their favorable safety profile and renal-protective effects make them especially valuable in multimorbid populations commonly encountered in clinical practice. In summary, SGLT2 inhibitors have redefined the standard of care in heart failure, offering hope and improved outcomes for millions of patients worldwide—with or without diabetes. Continued research will further clarify their role in acute settings, long-term outcomes, and combinations with emerging therapies.

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