

# The Promise and Challenges of SGLT2 Inhibitors in Heart Failure Management

Arav Jain \*

Department of Cardiology, Ghent University, Ghent, Belgium

## DESCRIPTION

Heart Failure (HF) represents a global pandemic affecting over 64 million people worldwide, with rising prevalence due to an aging population and improved survival following acute cardiovascular events. Despite significant advances in pharmacological and device-based therapies over recent decades, the prognosis for patients with heart failure remains poor, with high rates of hospitalization and mortality. The persistent burden of this syndrome has driven the search for novel therapeutic approaches beyond traditional neurohormonal antagonists.

Sodium-Glucose Cotransporter 2 (SGLT2) inhibitors have emerged as a groundbreaking class of medications that have transformed the treatment landscape for heart failure. Initially developed as glucose-lowering agents for Type 2 Diabetes Mellitus (T2DM), these medications have demonstrated remarkable cardiovascular benefits that extend well beyond glycemic control. The unexpected cardiovascular protection observed in initial diabetes trials prompted dedicated heart failure trials that have firmly established SGLT2 inhibitors as a basis therapy for heart failure management.

The Dapagliflozin and Prevention of Adverse outcomes in Heart Failure (DAPA-HF)-reduced trials demonstrated that dapagliflozin and empagliflozin, respectively, significantly reduced the composite outcome of cardiovascular death or heart failure hospitalization in patients with Heart Failure with reduced Ejection Fraction (HFrEF), regardless of diabetes status. The magnitude of benefit observed with these agents was comparable to that of established neurohormonal antagonists, with a rapid onset of action and favorable safety profile. The mechanism through which SGLT2 inhibitors exert their beneficial effects in heart failure is multifaceted and not fully elucidated. While the primary action of these agents is to inhibit glucose reabsorption in the proximal tubule of the kidney, leading to glucosuria, their cardiovascular benefits appear to be largely independent of glucose control. Proposed mechanisms include favorable effects on cardiac energetics through increased ketone production, reduced cardiac preload and afterload *via*

osmotic diuresis and natriuresis, decreased sympathetic activity, improved myocardial ionic homeostasis, reduced inflammation and oxidative stress, and attenuated adverse cardiac remodeling.

The clinical implementation of SGLT2 inhibitors in heart failure management does come with challenges. Despite their proven benefits and inclusion in major clinical guidelines, adoption of these agents in clinical practice has been slower than anticipated. Barriers to implementation include clinical inertia, concerns about adverse effects (particularly genital mycotic infections and volume depletion), lack of familiarity with their use among cardiologists, and cost considerations. Additionally, the optimal timing and sequencing of SGLT2 inhibitors with other heart failure therapies, particularly in newly diagnosed patients, remains uncertain.

The expanding role of SGLT2 inhibitors has also raised questions about their impact on specific populations and clinical scenarios. Their efficacy appears consistent across age groups, sex, and baseline renal function, though patients with very advanced chronic kidney disease were excluded from major trials. The safety and efficacy of SGLT2 inhibitors in acute decompensated heart failure is being investigated in ongoing trials, with preliminary data suggesting potential benefits in this setting as well.

Cost-effectiveness analyses have generally supported the value of SGLT2 inhibitors in heart failure management, with improvements in quality-adjusted life years that justify their cost in most healthcare systems. However, affordability remains a concern, particularly in resource-constrained settings and for patients with limited insurance coverage. The recent availability of generic SGLT2 inhibitors in some markets may help address this challenge.

Looking ahead, several ongoing trials are exploring the role of SGLT2 inhibitors in other cardiovascular conditions, including acute coronary syndromes and arrhythmias. Additionally, combination therapy with SGLT2 inhibitors and other novel agents, such as soluble guanylate cyclase stimulators and cardiac myosin activators, holds promise for further improving outcomes in heart failure.

**Correspondence to:** Arav Jain, Department of Cardiology, Ghent University, Ghent, Belgium, E-mail: aravjain089@gmail.com

**Received:** 03-Feb-2025, Manuscript No. JCEC-25-37165; **Editor assigned:** 05-Feb-2025, PreQC No. JCEC-25-37165 (PQ); **Reviewed:** 19-Feb-2025, QC No. JCEC-25-37165; **Revised:** 26-Feb-2025, Manuscript No. JCEC-25-37165 (R); **Published:** 05-Mar-2025, DOI:10.35248/2155-9880.25.16.939

**Citation:** Jain A (2025). The Promise and Challenges of SGLT2 Inhibitors in Heart Failure Management. J Clin Exp Cardiol. 16:939.

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The remarkable story of *SGLT2* inhibitors in heart failure underscores the value of careful post-marketing surveillance and the potential for drug repurposing in cardiovascular medicine. What began as agents for glycemic control in diabetes have evolved into cornerstone therapies for heart failure management, benefiting millions of patients worldwide. As our understanding of their mechanisms and optimal use continues to evolve, *SGLT2* inhibitors represent one of the most significant advances in heart failure therapy in recent decades.

The integration of *SGLT2* inhibitors into routine clinical practice requires a collaborative approach involving cardiologists, primary care physicians, endocrinologists, and pharmacists. Education about their benefits, appropriate patient selection, and management of potential adverse effects is essential to overcome implementation barriers. With their proven efficacy across the spectrum of heart failure, regardless of ejection

fraction or diabetes status, *SGLT2* inhibitors have truly revolutionized our approach to this challenging syndrome.

## CONCLUSION

As we continue to refine heart failure management strategies, the success story of *SGLT2* inhibitors serves as inspiration for ongoing research into novel pathways and therapeutic targets. The future of heart failure therapy will likely involve personalized approaches based on specific phenotypes and biomarker profiles, with *SGLT2* inhibitors playing a central role in many treatment algorithms. Their discovery and development highlight the serendipitous nature of medical advances and the importance of remaining open to unexpected benefits of medications beyond their primary indications.