OPEN ACCESS

ISSN: 2835-9496

Caldeira Ruppen I, et al. (2025): 906
Ameri J Clin Med Re, 2025; 5(5): 100213
DOI: 10.71010/AJCMR.2025-e213

Research Article

American Journal of Clinical and Medical Research

The Importance of Using SGLT-2 Inhibitors in Heart Failure: An Updated Review

Ian Caldeira Ruppen[1*], Leandro Silva Pivato[2], Jerdal Micael Quilla Morsoletto[5], Mirla Mirtes Mastub de Paula[5], Lara Beatriz Dallaqua Bitiati[1], Camilla Antunes Zanini[3], Ana Luiza Romitti[1], Leticia de Paula Monteiro Oliveira[1], Ana Carolina Langendyk Rodrigues[1], Luhara Sechi Lorga Vieira[1], Leonardo Vieira Borchio Ribeiro[4], Daphine Ramella Marcon[1], Maisa Pivato Ziviani[1], Maria Rafaela Mahnic Colombo[1], Amanda Larissa Zotarelli Pasquali[1], Alan Henrique de Oliveira Torchi[1], Pedro Henrique Modelli[1], Otávio Antigo Orlandini[1]

[1]Centro Universitário Ingá – Uningá, Maringá, PR, Brazil.
[2]Hospital Santa Casa de Maringá, Brazil.
[3]Faculdade Morgana Potrich, Mineiros, GO, Brazil.
[4]Centro Universitário de Caratinga – UNEC, Brazil.
[5]Hospital Memorial Uningá - HMU, Maringá, PR, Brazil.

***Corresponding author:** Ian Caldeira Ruppen, Centro Universitário Ingá-Uningá, Maringá, Paraná, Brazil. Email: Ian2ruppen@gmail.com; ORCID: https://orcid.org/0000-0003-1706-1662

Citation: Caldeira Ruppen I**,** Silva Pivato L, Quilla Morsoletto JM, Mastub de Paula MM, Dallaqua Bitiati LB, et al. (2025) The Importance of Using SGLT-2 Inhibitors in Heart Failure: An Updated Review. Ameri J Clin Med Re: AJCMR-213.

Received Date: 22 April, 2025; **Accepted Date:** 28 April, 2025; **Published Date:** 01 May, 2025

Abstract

Sodium-glucose cotransporter 2 inhibitors (SGLT-2i) have emerged as revolutionary therapeutic agents in the management of heart failure, regardless of the presence of diabetes mellitus. Originally developed for glycemic control, SGLT-2 inhibitors have shown significant benefits in reducing heart failure hospitalizations and cardiovascular mortality. These effects extend to patients with both reduced and preserved ejection fraction. The mechanisms of action are diverse and include the reduction of oxidative stress, modulation of volume overload, and metabolic cardioprotective effects, as well as improved renal function. High-impact studies, such as the EMPA-REG, DAPA-HF, and EMPEROR-Reduced clinical trials, reinforce the efficacy and safety of this drug class, consolidating its role in current heart failure treatment guidelines.

Keywords: SGLT-2 Inhibitors; Heart Failure; Cardiovascular Therapy; Renal Function; Cardiometabolic Treatment.

Introduction

Heart failure (HF) is a complex clinical condition characterized by the heart's inability to adequately meet the body's metabolic demands, leading to symptoms such as dyspnea, fatigue, and fluid retention. Affecting millions of people worldwide, HF is one of the leading causes of morbidity and mortality, as well as a significant economic burden on healthcare systems. Despite therapeutic advances in recent decades, HF remains associated with high rates of hospitalization and mortality, highlighting the need for new therapeutic approaches. Sodium-glucose cotransporter 2 inhibitors (SGLT-2i), initially developed for the treatment of type 2 diabetes mellitus (T2DM), have demonstrated benefits beyond glycemic control, including reductions in cardiovascular and renal outcomes. These drugs inhibit glucose and sodium reabsorption in the proximal renal tubules, promoting glucosuria and natriuresis. Although essential in the management of T2DM, these effects prompted further investigation into the impact on cardiometabolic conditions, including HF. The EMPA-REG OUTCOME and CANVAS clinical trials, conducted in populations with T2DM and high cardiovascular risk, were the first to identify significant benefits of SGLT-2i in reducing HF hospitalizations and cardiovascular mortality. Subsequently, trials such as DAPA-HF and EMPEROR-Reduced expanded the application of this therapeutic class to patients with HF, regardless of diabetic status. This represented a milestone in cardiology, positioning SGLT-2i as one of the pillars in HF management, alongside beta-blockers, ACE inhibitors, angiotensin receptor blockers, and mineralocorticoid receptor antagonists.

The mechanisms of action of SGLT-2i in HF are multifactorial and go beyond glucosuria, as they exert hemodynamic, metabolic, and anti-inflammatory effects, improving myocardial function, reducing ventricular filling pressure, and preserving renal function. The reduction of oxidative stress, improved cardiac metabolic efficiency, and decreased volume overload are some of the mechanisms contributing to the observed benefits. These effects are particularly relevant in patients with heart failure with reduced ejection fraction (HFrEF), but recent evidence suggests benefits in patients with preserved ejection fraction (HFpEF) as well. Current international guidelines, including those from the European Society of Cardiology (ESC) and the American Heart Association (AHA), now recommend SGLT-2i as part of first-line treatment for HF with reduced ejection fraction, regardless of the presence of diabetes. However, challenges remain, such as the practical implementation of this approach, the identification of specific populations that benefit the most from treatment, and the monitoring of potential adverse effects such as urinary tract infections and euglycemic ketoacidosis. Given the significant global burden of HF and the transformative potential of SGLT-2i in managing this condition, reviewing the latest evidence and studies on their clinical benefits and exploring the underlying mechanisms of these effects is essential.

Objectives

This article aims to synthesize the main advances in the use of SGLT-2i for heart failure, focusing on clinical outcomes, future perspectives, and implications for clinical practice.

Materials and Methods

A bibliographic review was performed, including articles published in the PubMed, ScienceDirect, and SciELO databases to support the study.

Discussion

The advent of sodium-glucose cotransporter 2 inhibitors (SGLT-2i) has brought a paradigm shift in the management of heart failure (HF), particularly in patients with reduced ejection fraction (HFrEF). Trials such as EMPEROR-Reduced and DAPA-HF have shown that these agents significantly reduce HF hospitalizations and cardiovascular mortality. Although originally developed for the treatment of type 2 diabetes mellitus (T2DM), the benefits of SGLT-2i appear to be independent of glycemic control, suggesting unique cardioprotective mechanisms. The therapeutic effects of SGLT-2i in HF are diverse and extend beyond glycemic reduction. By promoting glucosuria and natriuresis, they reduce volume overload and blood pressure, which are crucial factors in HF management. In addition, SGLT-2i improve endothelial function, reduce oxidative stress, and modulate systemic inflammation. A particularly interesting aspect is the improvement in cardiac metabolic efficiency through increased ketone body oxidation, which provides a more efficient energy source for the heart during myocardial dysfunction.

Clinical evidence has demonstrated compelling benefits of SGLT-2i in HF. For example, the DAPA-HF trial showed that dapagliflozin reduced the risk of HF hospitalization by 30% and cardiovascular death by 18% in patients with HFrEF. Similarly, EMPEROR-Reduced, which evaluated empagliflozin, confirmed similar reductions in cardiovascular outcomes. Both studies included patients with and without T2DM, reinforcing the broader applicability of this class of drugs. In addition to HFrEF, more recent evidence, such as from EMPEROR-Preserved, indicates benefits of SGLT-2i in patients with HF with preserved ejection fraction (HFpEF). These findings are significant, given the limited efficacy of other therapies in this population. The renal benefits observed in SGLT-2i studies are also relevant in the context of heart failure. Chronic kidney disease (CKD) progression is often associated with worsening HF, and SGLT-2i have been shown to slow CKD progression by preserving glomerular filtration rate (GFR) and reducing the risk of adverse renal events. This intersection of cardiovascular and renal protection is a key distinguishing feature of this drug class. It is worth noting that, despite substantial benefits, the use of SGLT-2i is not without challenges. These include adverse effects such as urinary tract infections, euglycemic ketoacidosis, and, rarely, dehydration. These effects require close monitoring, especially in more vulnerable populations such as the elderly and patients with advanced renal disease. Another challenge is adherence and practical implementation, particularly in low- and middle-income countries where medication costs can be a significant barrier.

Conclusion

SGLT-2 inhibitors represent a revolutionary advance in the treatment of heart failure (HF), transcending their original use in the management of type 2 diabetes mellitus (T2DM). The accumulated evidence of the past decades has established this therapeutic class as one of the most effective and safest interventions to reduce HF hospitalizations, improve quality of life, and prolong survival in patients with both reduced (HFrEF) and preserved (HFpEF) ejection fraction. The observed benefits of SGLT-2i in HF are driven by multifaceted mechanisms of action that go beyond glycemic control, including reductions in volume overload, improved cardiac and renal function, decreased oxidative stress, and anti-inflammatory effects. These properties not only optimize cardiac function but also have a systemic impact that contributes to the clinical improvement of HF patients. Although progress is promising, challenges remain. Practical implementation faces barriers such as high medication costs, the need for close monitoring of adverse effects, and limited awareness among healthcare professionals. Furthermore, specific patient subgroups, such as those with advanced renal disease or end-stage heart failure, require additional studies to assess the safety and efficacy of SGLT-2i.

Future perspectives for SGLT-2i include research on their impact in the early stages of HF, as well as in combination with other emerging therapeutic classes, such as GLP-1 receptor agonists and neprilysin inhibitors. There is also substantial interest in the preventive potential of these medications, particularly in high-risk populations for HF development, such as individuals with obesity, hypertension, and metabolic syndrome.

Hence, the impact of SGLT-2 inhibitors in HF treatment is not limited to the clinical outcomes demonstrated thus far. They represent a new era in cardiology, offering an innovative and effective therapeutic solution for a condition that affects millions of people worldwide. Ongoing research and the development of policies that ensure equitable access to this therapy are essential to maximize its benefits and transform global heart failure care.

References

1. ANKER, S. D.; BUTLER, J.; FILIPPATOS, G. et al. Empagliflozin in heart failure with a preserved ejection fraction. *The New England Journal of Medicine*, v. 385, n. 16, p. 1451–1461, 2021. DOI: https://doi.org/10.1056/NEJMoa2107038.
2. COSENTINO, F.; GRANT, P. J.; ABOYANS, V. et al. 2019 ESC guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *European Heart Journal*, v. 41, n. 2, p. 255–323, 2020. DOI: https://doi.org/10.1093/eurheartj/ehz486.
3. DOCHERTY, K. F.; JHUND, P. S.; INZUCCHI, S. E. et al. Effects of dapagliflozin in DAPA-HF according to background heart failure therapy. *European Heart Journal*, v. 41, n. 25, p. 2379–2392, 2020. DOI: https://doi.org/10.1093/eurheartj/ehaa183.
4. FITCHETT, D.; ZINMAN, B.; WANNER, C. et al. Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: results of the EMPA-REG OUTCOME® trial. *European Heart Journal*, v. 37, n.

19, p. 1526–1534, 2019. DOI: https://doi.org/10.1093/eurheartj/ehw110.

5. HEERSPINK, H. J. L.; STEFÁNSSON, B. V.; CORREA-ROTTER, R. et al. Dapagliflozin in patients with chronic kidney disease. *The New England Journal of Medicine*, v. 383, n. 15, p. 1436–1446, 2020. DOI: https://doi.org/10.1056/NEJMoa2024816.
6. MARTENS, P.; MULLENS, W. Heart failure with preserved ejection fraction. *Heart*, v. 105, n. 14, p. 1001–1012, 2019. DOI: https://doi.org/10.1136/heartjnl-2018-314195.
7. MCMURRAY, J. J. V.; SOLOMON, S. D.; INZUCCHI, S. E. et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *The New England Journal of Medicine*, v. 381, n. 21, p. 1995–2008, 2019. DOI: https://doi.org/10.1056/NEJMoa1911303.
8. NASSIF, M. E.; WINDSOR, S. L.; TANG, F. et al. Dapagliflozin effects on biomarkers, symptoms, and functional status in patients with heart failure with reduced ejection fraction. *JACC: Heart Failure*, v. 8, n. 10, p. 811–822, 2021. DOI: https://doi.org/10.1016/j.jchf.2020.06.006.
9. NEUEN, B. L.; YOUNG, T.; HEERSPINK, H. J. L. et al. SGLT2 inhibitors for the prevention of kidney failure in patients with type 2 diabetes: a systematic review and meta-analysis. *The Lancet Diabetes & Endocrinology*, v. 7, n. 11, p. 845–854, 2019. DOI: https://doi.org/10.1016/S2213-8587(19)30256-6.
10. PACKER, M.; ANKER, S. D.; BUTLER, J. et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. *The New England Journal of Medicine*, v. 383, n. 15, p. 1413–1424, 2020. DOI: https://doi.org/10.1056/NEJMoa2022190.
11. PERKOVIC, V.; JARDINE, M. J.; NEAL, B. et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *The New England Journal of Medicine*, v. 380, n. 24, p. 2295–2306, 2019. DOI: https://doi.org/10.1056/NEJMoa1811744.
12. SEFEROVIC, P. M.; PONIKOWSKI, P.; ANKER, S. D. et al. Clinical practice update on heart failure 2019: pharmacotherapy, procedures, devices and patient management. An expert consensus meeting report of the Heart Failure Association of the European Society of Cardiology. *European Journal of Heart Failure*, v. 22, n. 2, p. 231–255, 2020. DOI: https://doi.org/10.1002/ejhf.1744.
13. VADUGANATHAN, M.; CLAGGETT, B. L.; JHUND, P. S. et al. Estimating lifetime benefits of comprehensive disease-modifying pharmacological therapies in heart failure with reduced ejection fraction: a comparative analysis of three randomized controlled trials. *The Lancet*, v. 396, n. 10244, p. 121–128, 2020. DOI: https://doi.org/10.1016/S0140-6736(20)30728-0.
14. VERMA, S.; MCMURRAY, J. J. V. SGLT2 inhibitors and mechanisms of cardiovascular benefit: a state-of-the-art review. *Diabetologia*, v. 61, n. 10, p. 2108–2117, 2018. DOI: https://doi.org/10.1007/s00125-018-4670-7.
15. ZINMAN, B.; WANNER, C.; LACHIN, J. M. et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *The New England Journal of Medicine*, v. 373, n. 22, p. 2117–2128, 2015. DOI: https://doi.org/10.1056/NEJMoa1504720.