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REVIEW ARTICLE

Unlocking Heart Failure's Secret Weapon: The Transformative Impact of Sodium-Glucose Cotransporter-2 Inhibitors on Heart Failure with Reduced Ejection Fraction

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ABSTRACT

Heart failure (HF) with reduced ejection fraction (EF) affects nearly half of HF patients and is associated with high mortality and morbidity rates, particularly among the elderly. Severe exercise intolerance is a primary chronic symptom in HF patients with reduced EF (HFrEF), significantly impairing their quality of life. Therefore, enhancing exercise capacity and overall quality of life remains a critical clinical objective for managing HFrEF. Recent randomized controlled trials (RCTs) and meta-analyses have demonstrated the cardiovascular benefits of sodium–glucose cotransporter 2 (SGLT-2) inhibitors in HFrEF patients. Despite multiple RCTs investigating SGLT-2 inhibitors in this population, results have shown inconsistency, partly attributed to limited statistical power. Further exploration of the mechanisms underlying the cardiovascular improvements associated with SGLT2 inhibitors in patients with HFrEF is warranted. This abstract underscores the importance of investigating the therapeutic potential of SGLT2 inhibitors in improving cardiovascular outcomes among HFrEF patients, thereby offering new insights for optimal management strategies.

Keywords: Heart failure, Ejection fraction, SGLT-2 inhibitors, Exercise intolerance, Cardiovascular outcomes

INTRODUCTION

Worldwide, the burden of heart failure has increased to an estimated 23 million people, and approximately 50% of cases are HF with reduced ejection fraction (HFrEF) **[1].**

Heart failure (HF) is a complex clinical syndrome that results from either functional or structural impairment of ventricles resulting in symptomatic left ventricle (LV) dysfunction. The symptoms come from an inadequate cardiac output, failing to keep up with the metabolic demands of the body. It is a leading cause of cardiovascular morbidity and mortality worldwide despite the advances in therapies and prevention. It can result from disorders of the pericardium, myocardium, endocardium, heart valves, great vessels, or some metabolic abnormalities **[2].**

Three main phenotypes describe HF according to the measurement of the left ventricle ejection fraction (EF), and the differentiation between these types is important due to different demographics, comorbidities, and responses to therapies:

1-Heart failure with reduced ejection fraction (HFrEF): EF less than or equal to 40%

2-Heart failure with preserved EF (HFpEF): EF is greater than or equal to 50%

3-Heart failure with mid-range EF (HFmrEF) (other names are: HFpEF-borderline and HFpEF-improved when EF in HFrEF improves to greater than 40%): EF is 41% to 49% per European guidelines and 40 to 49% per the US guidelines **[3].**

Multiple conditions can cause HF, including systemic diseases, a wide range of cardiac

conditions, and some hereditary defects. Etiologies of HF vary between high-income and developing countries, and patients may have mixed etiologies. More than two-thirds of all cases of HF are attributable to ischemic heart disease, COPD, hypertensive heart disease, and rheumatic heart disease **[4].**

The pathophysiology of HF is complex and includes structural, neuro-hormonal, cellular, and molecular mechanisms activation to maintain physiologic functioning (maladaptation, myocyte hypertrophy, myocyte death/apoptosis/regeneration, and remodeling **[5].**

Sodium–glucose co-transporter 2 (SGLT2) inhibitors have recently been recommended as a foundational therapy for patients with heart failure (HF) and reduced ejection fraction (HFrEF) because of their favourable effects on mortality, clinical events and quality of life **[6].**

Sodium-glucose co-transporter-2 (SGLT2) inhibitors are glucose-lowering agents that eliminate excess glucose through a glucosuric effect by reducing glucose reabsorption from the renal filtrate **[7].**

There are four SGLT-2 inhibitors: canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin that are approved by Food Drug Administration (FDA) for their use in adults. The indications for use vary per agent, but all four agents are approved for use in adults with type 2 diabetes mellitus (DM) to improve blood sugar control adjunct to diet and exercise **[8].**

In 2019, DAPA-HF (Dapagliflozin and Prevention of Adverse outcome in Heart Failure) was the first trial demonstrating a significant benefit of a SGLT2 inhibitor in patients with established HFrEF, regardless of diabetes history, with a 26% reduction in the risk of the composite endpoint of CV death or worsening HF (hospitalization or an urgent visit requiring intravenous therapy for HF) **[9].**

In 2020, the EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction) trial confirmed the results of DAPA-HF in a population with slightly different eligibility criteria, recruiting patients with more severe HF than in DAPA-HF **[10].**

More recently, the EMPULSE (a study to test the effect of empagliflozin in patients who are in hospital for acute HF) trial was concluded. This trial tested safety and efficacy of in-hospital initiation of empagliflozin, soon after initial stabilization, in patients with acute decompensated HF, regardless of their LVEF **[11].**

The beneficial effects of SGLT2 inhibition on heart failure (Figure 1):

1) Blood pressure lowering:

Although the exact mechanism(s) for the antihypertensive effects of SGLT2 inhibition are not fully understood, they are probably mediated by the osmotic and diuresis effects of SGLT2 inhibitors because of an inhibition of sodium reabsorption in the proximal tubules of the kidney. SGLT2 inhibition can result in a 30% to 60% increase in urinary sodium excretion **[12].**

By lowering blood pressure, SGLT2 inhibitors may lower cardiac afterload, with resultant improvement in ventricular arterial coupling and cardiac efficiency **[13].**

2) Increasing diuresis/natriuresis:

In a study comparing dapagliflozin and hydrochlorothiazide, for example, a reduction in plasma volume and increase in erythrocyte mass was observed with dapagliflozin but not with hydrochlorothiazide **[14].**

It has therefore been speculated that SGLT2 inhibition may afford a differential effect in regulating interstitial fluid (vs. intravascular volume), which may limit the reflex neurohumoral stimulation that occurs in response to intravascular volume contraction with traditional diuretics **[13].**

3) Improving cardiac energy metabolism.

Dramatic changes in energy metabolism occur in the failing heart. As heart failure progresses, a continual decline in mitochondrial oxidative metabolism occurs, and the heart becomes more reliant on glycolysis as a source of energy **[15].** The uncoupling between glycolysis and glucose oxidation in the failing heart also leads to increased proton production that leads to a decrease in cardiac efficiency (cardiac work / O_2 consumed) **[16].**

4) Preventing inflammation:

The SGLT2 inhibitors, empagliflozin, canagliflozin,and dapagliflozin have been shown to attenuate or ameliorate the inflammatory profile in patients with diabetes. This decrease in anti-inflammatory properties of SGLT2 inhibitors has the potential to decrease molecular processes related to

inflammation, such as extracellular matrix turnover and fibrosis **[17].**

5) Weight loss:

The excretion of glucose by the kidney with SGLT2 inhibitor treatment results in a loss of calories. As a result of this, there is a subsequent decrease in body weight as fatty acids are mobilized from adipose tissue stores. Clinical studies have consistently shown body weight reduction in patients treated with SGLT2 inhibitors **[18].**

6) Inhibiting the sympathetic nervous system:

The observation that SGLT2 inhibitors reduce blood pressure in the absence of increasing heart rate suggests, indirectly, that these agents may be associated with a reduction in sympathetic nervous system (SNS) activity. In fact, accumulating data indicates that SGLT2 inhibition may lead to a reduction in sympathetic nerve activity, inhibit norepinephrine turnover in brown adipose tissue, and reduce tyrosine hydroxylase production **[19].**

7) Preventing adverse cardiac remodeling:

Inhibition of the mammalian target of rapamycin pathway, a major pathway involved in cardiac hypertrophy, by SGLT2 inhibition may also be involved. Prevention of adverse remodeling with SGLT2 inhibition is also associated with a decreased fibrosis, which may in part be mediated by the anti-inflammatory actions of SGLT2 inhibition (see reduction in inflammation discussion). As a result, SGLT2 inhibition may reverse the cardiac remodeling seen in heart failure, thereby reducing LV wall stress and improving cardiac function **[20].**

8) Preventing ischemia/reperfusion injury:

Recent experimental evidence suggests that SGLT2 inhibition has a cardioprotective effect against ischemia/reperfusion injury in both diabetic and nondiabetic. This beneficial effect of SGLT2 inhibition on ischemia/reperfusion injury is associated with a decrease in calmodulin kinase II activity, resulting in improved sarcoplasmic reticulum $Ca2^{+}$ flux and increased contractility**[21].**

9) Inhibiting the cardiac Na^{+}/H^{+} exchanger:

Inhibition of the Na^{+}/H^{+} exchanger has also been demonstrated to protect the heart in several experimental models of heart failure **[22].**

Inhibition of the Na^{+}/H^{+} exchanger has been proposed to explain the beneficial effects of SGLT2 inhibitors in heart failure The cardiac Na^{+}/H^{+} exchanger is inhibited by SGLT2 inhibitors, which can lower myocardial Na^{+} levels **[23].**

10) Increasing autophagy and lysosomal degradation:

By driving catabolic rates due to constant glycosuria, it has been proposed that SGLT2 inhibition can promote autophagy and lysosomal degradation, thereby improving mitochondrial morphology and function **[24].**

11) Decreasing epicardial fat mass:

Epicardial adipose tissue can produce several bioactive molecules that can negatively affect heart function and contribute to coronary artery disease. In addition, SGLT2 inhibitors reduce the accumulation and inflammation of peri-vascular adipose tissue, thus minimizing the secretion of leptin and its paracrine actions on the heart to promote fibrosis **[25].**

12) Improving vascular function:

Vascular smooth muscle and endothelial dysfunction contribute to the pathophysiology of heart failure. Its existence in patients with heart failure increases morbidity and mortality. SGLT2 inhibition has been shown to improve vascular function by attenuating endothelial cell activation, inducing direct vasorelaxation, reducing endothelial cell dysfunction and molecular changes associated with early atherogenesis decreasing arterial wall stiffness, and decreasing vascular resistance **[26].**

CONCLUSION

This review offers a comprehensive overview on the effect of SGLT2i on improving cardiovascular outcomes in patients with heart failure with reduced ejection fraction (HFrEF).

CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

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REFRENCES

1. Murphy SP, Ibrahim NE, Januzzi JL. Heart Failure With Reduced Ejection Fraction: A Review. JAMA, 2020; 324(5), 488–504.

2. Hajouli S, Ludhwani D. Heart failure and ejection fraction, 2022.

3. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur. Heart J., 2016; 37(27), 2129–2200.

4. Yusuf S, Rangarajan S, Teo K, Islam S, Li W, Liu L, et al. Cardiovascular risk and events in 17 low-, middle-, and high-income countries. N Engl J Med, 2014; 371(9), 818–827.

5. Tanai E, Frantz S. Pathophysiology of Heart Failure. Compr. Physiol., 2015; 6(1), 187–214.

6. Tomasoni D, Fonarow GC, Adamo M, Anker SD, Butler J, Coats AJS, et al. Sodium-glucose co-transporter 2 inhibitors as an early, first-line therapy in patients with heart failure and reduced ejection fraction. Eur. J. Heart Fail., 2022; 24(3), 431–441.

7. Ghezzi C, Loo DDF, Wright EM. Physiology of renal glucose handling via SGLT1, SGLT2 and GLUT2. Diabetol., 2018; 61(10), 2087–2097.

8. Nespoux J, Vallon V. Renal effects of SGLT2 inhibitors: an update. Curr. Opin. Nephrol. Hypertens., 2020; 29(2), 190–198.

9. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. NEW ENGL J MED, 2019; 381(21), 1995–2008.

10. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. NEW ENGL J MED, 2020; 383(15), 1413–1424

11. Tromp J, Ponikowski P, Salsali A, Angermann CE, Biegus J, Blatchford J, et al. Sodium-glucose co-transporter 2 inhibition in patients hospitalized for acute decompensated heart failure: rationale for and design of the EMPULSE trial. Eur. J. Heart Fail., 2021; 23(5), 826–834.

12. Ferrannini E, Baldi S, Frascerra S, Astiarraga B, Barsotti E, Clerico A, et al. Renal Handling of Ketones in Response to Sodium-Glucose Cotransporter 2 Inhibition in Patients With Type 2 Diabetes. Diabetes care, 2017; 40(6), 771–776.

13. Lopaschuk GD, Verma S. Mechanisms of Cardiovascular Benefits of Sodium Glucose Co-Transporter 2 (SGLT2) Inhibitors: A State-of-the-Art Review. JACC. Basic Trans Science, 2020; 5(6), 632–644.

14. Lambers Heerspink HJ, de Zeeuw D, Wie L, Leslie B, List J. Dapagliflozin a glucose-regulating drug with diuretic properties in subjects with type 2 diabetes. Diabetes Obes. Metab., 2013; 15(9), 853–862.

15. Lopaschuk GD, Ussher JR, Folmes CD, Jaswal JS, Stanley WC. Myocardial fatty acid metabolism in health and disease. Physiol. Rev., 2010; 90(1), 207–258.

16. Wang W, Zhang L, Battiprolu PK, Fukushima A, Nguyen K, Milner K, et al. Malonyl CoA Decarboxylase Inhibition Improves Cardiac Function Post-Myocardial Infarction. JACC. Basic Trans Science, 2019; 4(3), 385–400.

17. Lee TM, Chang NC, Lin SZ. Dapagliflozin, a selective SGLT2 Inhibitor, attenuated cardiac fibrosis by regulating the macrophage polarization via STAT3 signaling in infarcted rat hearts. Free Radic. Biol. Med., 2017; 104, 298–310.

18. Cai X, Yang W, Gao X, Chen Y, Zhou L, Zhang S, et al. The Association Between the Dosage of SGLT2 Inhibitor and Weight Reduction in Type 2 Diabetes Patients: A Meta-Analysis. Obesity (Silver Spring, Md.), 2018; 26(1), 70–80.

19. Jordan J, Tank J, Heusser K, Heise T, Wanner C, Heer M, et al. The effect of empagliflozin on muscle sympathetic nerve activity in patients with type II diabetes mellitus. Am. J. Hypertens.: JASH, 2017; 11(9), 604–612.

20. Verma S, Garg A, Yan AT, Gupta AK, Al-Omran M, Sabongui A, et al. Effect of Empagliflozin on Left Ventricular Mass and Diastolic Function in Individuals With Diabetes: An Important Clue to the EMPA-REG OUTCOME Trial?. Diabetes care, 2016; 39(12), e212–e213

21. Lim VG, Bell RM, Arjun S, Kolatsi-Joannou M, Long DA, Yellon DM. SGLT2 Inhibitor, Canagliflozin, Attenuates Myocardial Infarction in the Diabetic and Nondiabetic Heart. JACC. Basic Trans Science., 2019; 4(1), 15–26.

22. Wakabayashi S, Hisamitsu T, Nakamura TY. Regulation of the cardiac Na^+/H^+ exchanger in health and disease. J Mol Cell Cardiol, 2013; 61, 68–76.

23. Baartscheer A, Schumacher CA, Wust CA. Empagliflozin decreases myocardial cytoplasmic Na^+ through inhibition of the cardiac Na^+/H^+ exchanger in rats and rabbits. Diabetol.. 2017; 60:568–573

24. Esterline RL, Vaag A, Oscarsson J, Vora J. MECHANISMS IN ENDOCRINOLOGY: SGLT2 inhibitors: clinical benefits by restoration of normal

diurnal metabolism?. Eur. J. Endocrinol., 2018; 178(4), R113–R125

25. Iborra-Egea O, Santiago-Vacas E, Yurista SR, Lupón J, Packer M, Heymans S, et al. Unraveling the Molecular Mechanism of Action of Empagliflozin in Heart Failure With Reduced Ejection Fraction With or Without Diabetes. JACC. Basic Trans Science, 2019; 4(7), 831–840.

26. Gaspari T, Spizzo I, Liu H, Hu Y, Simpson RW, Widdop RE, et al. Dapagliflozin attenuates human vascular endothelial cell activation and induces vasorelaxation: A potential mechanism for inhibition of atherogenesis. Diabetes Vasc. Dis. Res., 2018; 15(1), 64–73.

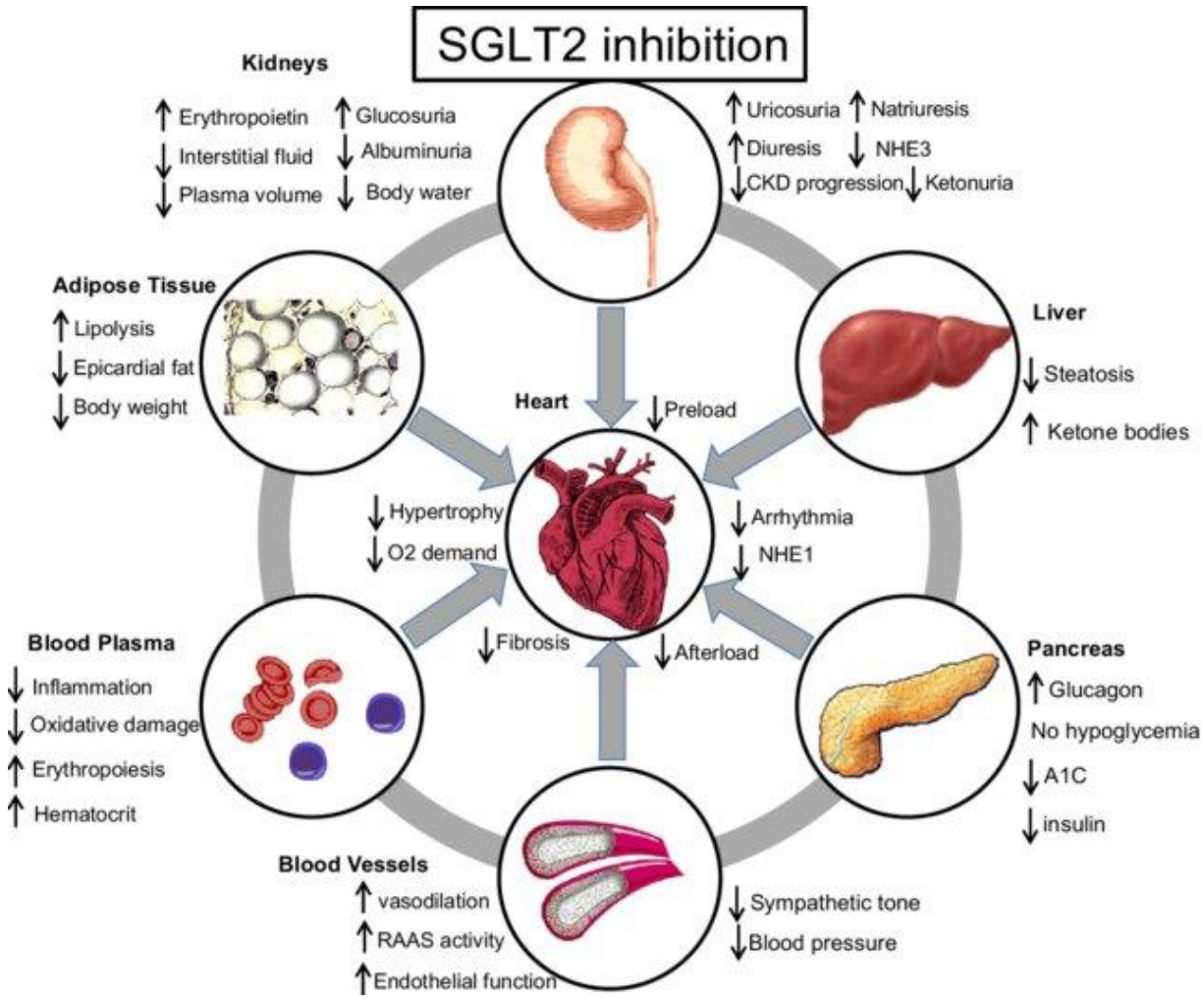

Fig. 1 The beneficial effects of SGLT2 inhibition on heart failure **[13].**

Citation

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