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The Role of SGLT2-Inhibitors in Heart Failure Management

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ABSTRACT: Sodium-glucose cotransporter-2 inhibitors (SGLT2i), originally designed as anti-hyperglycaemic medicines, later transformed into heart failure (HF) care, providing significant advantages at all phenotypes and stages of heart failure disease. Despite left ventricular ejection fraction (LVEF), these medicines have demonstrated benefit in acute and chronic heart failure. This article investigates sodium-glucose cotransporter-2 inhibitors use across the heart failure field, from primary stages (Stage A) in patients at risk to the advanced reduction in progressive heart failure (Stage D). Several studies have demonstrated that SGLT2i substantially reduces HF hospitalization rates, improves kidney function, and lowers cardiovascular death cases, underlining their complex pharmacodynamics in heart failure therapy.

This review article discusses the probable mechanisms by which sodium-glucose cotransporter-2 inhibitors exercise their favourable effects on the renal and cardiovascular systems, with each conducive to short and long-term therapeutic benefits.

However, integrating SGLT2i into medical treatment presents practical problems such as commencement time, dose, and monitoring, which must be addressed in order to achieve optimal therapy revision among different patients. Finally, this review also offers a thorough evaluation of SGLT2i as an initial therapy in heart failure, stressing its title role as a multistage involvement aiming at developing consequences across the heart failure field.

INTRODUCTION:

Heart failure (HF) is a worldwide community health issue that affects a predictable 64 million individuals, with a 5-year death rate of around 50% (Bozkurt et al., 2021; James et al., 2018). It is the main reason for hospitalization in Europe and the United States, accounting for 1% to 2% of all hospitalizations, and over 1000,000 hospital admissions as a primary diagnosis. Yearly health care expenses are expected to top \$30 billion (Ambrosy et al., 2014; Cavallari et al., 2022, 2021). Each heart failure episode represents clinical failure and is linked with a meaningfully higher death risks (Ambrosy et al., 2014). This high-risk condition is a main goal for pioneering therapeutics aiming at better outcomes, in spite of significant variation in aetiology and patients' properties (Ambrosy et al., 2014).

HF care has advanced dramatically, with the use of device therapies and hormonal modulators. Sodium-glucose cotransporter-2 inhibitors (SGLT2i), mineralocorticoid receptor antagonists (MRAs), beta-blockers, and angiotensin receptor-neprilysin inhibitors (ARNIs), angiotensin-converting enzyme inhibitors (ACEi), or angiotensin receptor blockers (ARBs) are now the four pillars of treatment for heart failure with reduced ejection fraction (HFrEF) (Beghini et al., 2025). The early benefits of GDMT encourage quick commencement, with aim of lowering mortality, decreasing repeated hospitalizations, and improving the medical condition, life quality, and functional capacity (McDonagh et al., 2021; Monzo et al., 2023; Tomasoni et al., 2022).

HEART FAILURE CLASSIFICATION:

Over the last ten years, heart failure has been separated into 3 basic phenotypes based on LVEF: preserved (HFpEF), mildly reduced (HFmrEF), and reduced (HFrEF). The DELIVER trial recently focused the light on a new phenotype, heart failure with improved ejection fraction (HFimpEF), which includes people who were previously identified with HFrEF but now have an improved left ventricular ejection fraction (>40%) while still being eligible for heart failure with reduced ejection fraction targeted treatment (Savarese et al., 2022; Vaduganathan et al., 2022a).

Beyond LVEF-based phenotypes, there are other groupings, such as the New York Heart Association (NYHA) functional sorting, the global definition of HF, and INTERMACS profiles for late-stage HF patients (Chioncel et al., 2017; Stevenson et al., 2009). In conclusion, while left ventricular ejection fraction leftovers a vital indicator for phenotyping heart failure, it is vital to incorporate further aspects, such as structural development and signs burden, to explanation for the complication and specific therapy demands of heart failure crosswise the field (Stewart et al., 2016a).

Patients diagnosed with heart failure improved left ventricular end-diastolic function (LVEF) now account for a sizable part of the overall heart failure population (Ambrosy et al., 2014). HFmrEF patients frequently have clinical characteristics and hazard aspects that are more parallel to those with HFrEF than HFpEF. These individuals are often older, mostly women, with metabolic syndrome, inactive lifestyle, have higher rates of atrial fibrillation (Masarone et al., 2018), other non-cardiovascular comorbidities than HFrEF patients, chronic kidney disease (CKD), and obesity (Borlaug et al., 2023; McDonagh et al., 2021; McMurray et al., 2014).

SGLT2is have shown important cardiac profits, chiefly in the treatment of chronic stable heart failure (Bailey et al., 2010). The EMPEROR-REDUCED and DAPA-HF studies were the first large-scale studies to investigate their impact on heart-protective effects as well as their efficiency in lowering mortality and hospitalization in heart failure patients (Packer et al., 2020; Tentolouris et al., 2019). The DAPA-HF study looked at the dapagliflozin' long-term effects in patients with heart failure with reduced ejection fraction versus placebo on top of ideal pharmacological treatment, and it found a 26% reduction in cardiovascular death and hospitalization (Packer et al., 2020). The EMPEROR-REDUCED study investigated the empagliflozin effects in a similar patients: a 25% decrease in heart failure deterioration and all-cause mortalities was found (Tentolouris et al., 2019). Empagliflozin has also been shown to delay assessed glomerular filtration rate deterioration in patients with chronic kidney disease.

SGLT2i was included as first-line treatment for heart failure with reduced ejection fraction in the 2021 ESC procedures for the management and diagnosis of chronic and acute heart failure, with a Class IA recommendations (Anker et al., 2021; McMurray et al., 2019). Following the results of two large trials, the DELIVER and EMPEROR-Preserved investigations, the SGLT2i clinical indications were expanded to cover heart failure with HFmrEF and HFpEF (Anker et al., 2021; McMurray et al., 2019). According to the 2023 European Society of Cardiology Focus Update, empagliflozin and dapagliflozin are now suggested with the same Class IA categorization for HFpEF and HFmrEF therapy (Solomon et al., 2022).

Bozkurt et al. defined 4 phenotypes of HF, fluctuating from those heart failure risk but without present or recent signs and symptoms (Stage A) to those with severe signs needing repeated hospitalization (Stage D) (Bozkurt et al., 2021).

SGLT-2i preventive roles:

SGLT2i, such as empagliflozin and canagliflozin, have been shown to reduce the MACE risk, and all members in this family are effective in lowering heart failure incidence and chronic kidney disease development (McDonagh et al., 2023; Rawshani et al., 2017).

Stages B and C of heart failure are the preclinical and clinical stages, respectively. Stage B is characterized by structural heart disease without symptoms; typical reasons include previous cardiomyopathies, valvular heart disease, or myocardial infarction. These people have a much-increased chance of progressing to symptomatic heart failure (Stage C) and experiencing severe cardiovascular events, such as hospitalization and death (Bozkurt et al., 2021).

The advantages of SGLT2i use in these stages are documented, irrespective of left ventricular ejection fraction (Vaduganathan et al., 2022b). Great clinical trials have forced changes to the European Society of Cardiology Guidelines, which now propose empagliflozin or dapagliflozin to minimize heart failure hospitalization and cardiovascular mortality, regardless of left ventricular ejection fraction (McDonagh et al., 2023; Stewart et al., 2016b). The EMPEROR-REDUCED and DAPA-HF studies were the first two randomised studies to assess the efficacy of a sodium-glucose cotransporter-2 inhibitor compared to placebo in patients with heart failure with reduced ejection fraction with and without type II diabetes mellitus (Packer et al., 2020). The EMPEROR-REDUCED study compared empagliflozin to placebo for heart failure with reduced ejection fraction patients in New York Heart Association class II-IV, with LVEF $\leq 40\%$ in spite of OMT and increased NT-proBNP. Empagliflozin reduced the cardiovascular mortality risk and heart failure hospitalization by 25% while also improving life quality (Tentolouris et al., 2019).

The EMPEROR-Preserved trial showed a substantial reduction in the key complex endpoint of deteriorating heart failure and cardiovascular mortality, with a 0.79 hazard ratio (Tentolouris et al., 2019). The DELIVER study evaluated the efficacy of dapagliflozin in heart failure with left ventricular ejection fraction $> 40\%$, and classified class II-IV according to the New York Heart Association, as well as those with prior left ventricular ejection fraction $< 40\%$ (Badwan et al., 2024). These results demonstrate the efficacy of SGLT2i in all heart failure scenarios, irrespective of diabetic status or left ventricular ejection fraction (Cannon et al., 2020).

The benefits of SGLT2i in AHF are becoming clearer, principally in terms of improving early decongestion when administered in conjunction with loop diuretics (Perkovic et al., 2019). The early start of SGLT2 inhibitors in acute heart failure is still being debated. However, real-world data show a quick rise in SGLT2i prescribing rates during acute heart failure hospitalizations, with a decreased incidence of unfavourable composite events after discharge (Cannon et al., 2020).

Advanced heart failure (AdHF) is an incurable disease stage in which patients have severe, chronic signs that do not respond to effective treatment (Heidenreich et al., 2013). This period is marked by high mortality and morbidity, as traditional pharmaceutical and device-based therapy are frequently insufficient near properly manage advanced heart failure. Advanced therapies, such as heart transplantation or long-term mechanical circulatory support (MCS), are the principal alternatives, but they are only available to a subset of patients who meet certain eligibility standards. Data from large-scale randomised clinical studies on the treatment of advanced heart failure are sparse, leaving significant gaps in evidence-based recommendations.

In view of these obstacles, preventative interventions to slow the progression of heart failure are crucial. Initial detection and involvement in at-risk groups, improved management during the early stages of heart failure, and appropriate treatment of contributing risk factors can all help to lower the probability of progression to advanced heart failure. This prevention-focused model is consistent with the increasing prominence on inclusive risk decrease and tailored therapy (Armstrong et al., 2020).

The advantages of sodium-glucose cotransporter-2 inhibitors at numerous stages of heart failure may specify a role in slowing the progression to advanced stages. These findings underline the need for prompt and aggressive treatment in the heart failure field, emphasizing the necessity for ongoing study and evidence-based approaches to report the problems of AdHF.

SGLT2-Inhibitors Mechanisms of Action:

The importance of SGLT2 inhibitors as cardiorenal defenders in people with or without diabetes mellitus; nevertheless, their specific mechanisms of action are unknown. In heart failure, peripheral congestion, fluid retention, and pathophysiology activate

the Renin-Angiotensin-Aldosterone System, resulting in elevated SGLT2 receptor expression (Damman et al., 2020). SGLT2i works by inhibiting the SGLT-2 found in the S1 and S2 segments of the proximal convoluted tubules, which reabsorbs over 90% of renal filtered glucose. Furthermore, SGLT2i targets the sodium-hydrogen exchanger (NHE3), which works in tandem with sodium glucose cotransporter-2 inhibitors in both functionality and structure (Biegus et al., 2023; Kalogeropoulos et al., 2017; Peikert et al., 2022).

Aside from their controversial natriuretic impact, SGLT2i have considerable renal protecting effects. Raised concentrations of sodium in the distal nephron promote tubuloglomerular feedback, a critical mechanism that reduces hyperfiltration in heart failure affected people with elevated renin-angiotensin-aldosterone system activation (Masuda et al., 2020; Mordi et al., 2020; Peikert et al., 2022). Long-term therapy with SGLT2i improves kidney function and delays the course of chronic kidney disease, demonstrating its renal protecting properties (Cherney et al., 2014; Ott et al., 2021).

SGLT2i plays an important part in calcium homeostasis, which is required for the heart to function normally. High levels of phospholamban in HF and T2D weaken the sarcoplasmic/endoplasmic reticulum calcium ATPase (SERCA2a) pump, consequential in diastolic and systolic dysfunction (Mullens et al., 2022). This is compounded by increased phosphorylation of ryanodine receptor (RyR2), which decreases the storage of calcium in the sarcoplasmic reticulum. SGLT2i can regulate the dynamics of calcium and reduce oxidative stress, hence restoring myocardial contractility and relaxation (Carvalho et al., 2023).

Patients with heart failure and Type II diabetes mellitus frequently have altered homeostasis of calcium and a metabolic shift caused by hypoxia, which results in an amplified dependence on glucose for ATP synthesis as the predominant energy basis. Extended vulnerability to such settings causes metabolic remodelling, in which heart cells become more dependent on glucose (Hasenfuss, 1998), resulting in lipotoxicity and cardiomyocyte malfunction (Mudaliar et al., 2016).

SGLT2i has been associated with increased haematocrit and erythropoiesis, which is most likely due to renal processes (Wende et al., 2017). Inhibiting the NLRP3 inflammasome in cardiac fibroblasts and kidney macrophages reduces pro-inflammatory cytokines, including IL-18 and IL-1 β . They reduce NF- κ B activation and diminish inflammatory indicators such as IL-6, TNF- α , high-sensitivity C-reactive protein, and MCP-1 (Benetti et al., 2016; Mazer et al., 2020; Oelze et al., 2014; Sano et al., 2016).

SGLT2i provides extensive advantages to heart homeostasis via both indirect and direct methods. They directly reduce oxidative stress, regulate ion homeostasis, and act as anti-remodelling mediators, most notably by preventing heart fibrosis. They meanderingly improve afterload and preload dynamics, increase endothelial function, and reduce oxygen consumption by increasing erythropoiesis (Oelze et al., 2014).

SGLT2 inhibitors can indirectly control sympathetic hyperactivity, which is a major contributor to ventricular remodelling and hypoxia in both type II diabetes mellitus and heart failure patients (Pabel et al., 2021; Santos-Gallego et al., 2019).

Clinical Practices:

The incorporation of SGLT2i into heart failure (HF) therapy has been a game changer, with benefits seen across multiple EF ranges (Verma, 2020). Early beginning and titration of heart failure treatments, particularly sodium-glucose cotransporter inhibitors, are critical for exploiting their advantages (Verma et al., 2020). The STRONG-HF study demonstrated that a comprehensive early up-titration approach implemented within 14 days of hospital discharge resulted in considerably lower rehospitalization rates and mortality (Severino et al., 2023).

SAFETY CONSIDERATIONS:

SGLT2 inhibitors have a favourable safety profile, although certain groups necessitate special consideration (Moon et al., 2024). They are normally well-tolerated, although they are contraindicated in certain patients, such as type 1 diabetes mellitus patients, those with past episodes of diabetic ketoacidosis, and those with end-stage kidney failure (Fatima et al., 2023; Mebazaa et al., 2022). Furthermore, SGLT2i should be prescribed with caution in patients with SBP less than 95 mmHg or with diseases associated with substantial volume lessening (Dandona et al., 2017; Rosenstock et al., 2018).

Post-hoc analyses of major studies have revealed that SGLT2i causes a moderate drop in systolic blood pressure, often by 2-3 mmHg, without inducing substantial hypotension (Martinez et al., 2020; Rosenstock et al., 2018). Importantly, the sodium-glucose cotransporter-2 inhibitor's diuretic impact can supplement classic loop diuretics by improving decongestion, even in people previously taking diuretics in high doses (Filippatos et al., 2022). Unlike traditional diuretics, SGLT2 inhibitor improves

fluid retention without aggravating kidney impairment, making them a useful complement to heart failure management, especially in patients with concomitant kidney failure (Jensen et al., 2021).

Real-world statistics suggest that SGLT2i should be initiated during hospitalizations for acute heart failure rather than waiting until discharge. This lowers the likelihood of future adverse events, permits close observation of tolerance and adverse effects, and enables former diuretic synergy and improved decongestion. The use of sodium-glucose cotransporter-2 inhibitors in the hospital context offers a prospect to enhance GDMT adherence after discharge (Kimura et al., 2011; Nusca et al., 2022).

Side Effects:

SGLT2i is an important drug for controlling hypertension (HF) in patients; however, it is linked with unique side effects that necessitate careful monitoring and timely management. Potential adverse effects include urinary tract infections (UTIs) (Packer et al., 2021), genital fungal infections (Edwards et al., 2023), diabetic ketoacidosis (DKA) (McGovern et al., 2020), Fournier gangrene (Shields et al., 2020), volume depletion and hypotension, acute kidney damage (AKI) (Günes-Altan et al., 2024), lower limb amputation, bone fractures, and other issues (Neal et al., 2017; Tuttle et al., 2021). These infections can be treated with oral or topical antifungal medications, although sodium-glucose cotransporter-2 inhibitors should be sustained in the majority of cases due to their renoprotective properties.

Diabetic ketoacidosis (DKA) is a rare but deadly condition, especially in insulin-dependent people, during fasting or acute illness. Ketone monitoring, patient education, and temporary discontinuance before chief surgeries, acute illness, or prolonged fasting are all examples of preventive interventions. In severe circumstances, the medication may necessitate to be briefly withheld until fluid equilibrium is reinstated (Shields et al., 2020).

In individuals at high risk of osteoporosis or peripheral artery disease, other medicines such as dapagliflozin or empagliflozin may be preferable, along with regular bone health evaluations and foot checks to reduce risk. In spite of these possible side effects, SGLT2i's overall advantages in lowering renal and cardiovascular actions persist significantly. Patient education, personalised risk assessment, and proactive monitoring are critical for improving beneficial outcomes while reducing adverse effects (Günes-Altan et al., 2024).

SGLT2 inhibitors have emerged as promising medications for treating hypertension, notably in patients with both acute and chronic heart failure. Nevertheless, unfulfilled requirements and knowledge gaps remain, demanding additional inquiry. Trials such as SOLOIST-WHF and EMPULSE have lowered hospitalization rates and proved improvements in decongestion in acute settings. Further convincing evidence is required to establish SGLT2 inhibitors as typical therapy during acute heart failure episodes (Granger et al., 2003; Verbrugge et al., 2014). A crucial knowledge gap exists about the best timing of sodium-glucose cotransporter-2 inhibitor start in acute heart failure, particularly when in patients with de novo acute heart failure in comparison to those with decompensated chronic heart failure (Caro et al., 2022).

The long-term cardiovascular advantages of sodium-glucose cotransporter-2 inhibitors and their mechanisms of action are not yet fully known. Future research should focus on understanding the relationships between SGLT-2is and major neurohormonal systems, such as the sympathetic nervous system and renin-angiotensin-aldosterone system, which are critical to heart failure pathogenesis.

CONCLUSIONS

SGLT2i has transformed the treatment of HF by exhibiting advantages at disease in all stages. SGLT2 inhibitors are the individual family of medications that efficiently goal the whole heart failure trajectory, from early protection in high-risk persons to advanced heart failure therapy, independent of left ventricular ejection fraction.

Foremost clinical trials, such as DELIVER, EMPEROR-Reduced, and DAPA-HF, have repeatedly demonstrated a substantial benefit in hospitalization reduction, improving life quality, and decreasing cardiovascular mortality. These advantages apply to all left ventricular ejection fraction characteristics and are seen in individuals with and without chronic kidney disease and type II diabetes mellitus, demonstrating their effectiveness, comprehensive safety, and therapeutic usefulness.

What characterizes sodium-glucose cotransporter-2 inhibitors is their capacity to influence several pathophysiological processes, such as improved cardiovascular outcomes, increased renal protection, and diuresis. This adaptability sets the sodium-glucose cotransporter-2 inhibitor as the foundation of GDMT, making it particularly useful in both acute and chronic heart failure

scenarios. Their established ability to reduce the incidence of heart failure hospitalizations and cardiovascular mortality among the entire left ventricular ejection fraction spectrum makes sodium-glucose cotransporter-2 inhibitors an essential drug in recent heart failure therapy paradigms.

Moving ahead, the crucial focus should be on optimizing early sodium-glucose cotransporter-2 inhibitors, particularly in acute heart failure situations, and expanding their usage in developing affected categories, such as those with advanced kidney failure or the geriatrics. Current and future clinical investigations are likely to lighten their significance and help revise clinical practice guidelines.

To summarize, sodium-glucose cotransporter-2 inhibitors represent a transformative step in heart failure care, providing comprehensive therapeutic advantages diagonally all phases of the disease and radically altering the therapy paradigm for this complicated and wide-ranging disorder.

Conflict of Interest:

The authors declare that there is no conflict of interest.

Ethics Statement:

Ethical approval was not required for this study.

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